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Nanosymposium

010. Stem Cell Reprograming and Differentiation

Location: 150A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***010.01

**Topic: ***A.03. Stem Cells and Reprogramming

Title: *In vivo* brain organoid model for generation of vascularized and functional PSC-Derived human brain organoids

Authors: *A. MANSOUR[1], J. GONÇALVE[3], C. BLOYD[4], H. LI[4], S. FERNANDIS[4], X. JIN[5], F. H. GAGE[2]
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Abstract: Stem cells have the remarkable ability to self-organize in three-dimensional (3D) space into organ-like structures termed Organoids. By harnessing this property, researchers have been able to create such organoids for several tissues that better recapitulate the complexity and physiological properties of tissues and organs. Despite many reports describing the generation of human neural organoids, the generation of vascularized and functional neural organoid graft is not described yet. Here we describe the generation of vascularized, and electrophysiologically active, human cerebral-organoids by transplantation of organoids grown in vitro to an adult mouse brain. Engrafted mice were viable, and exhibit long and high survival rates. Moreover, histological and immunostaining analysis revealed intact grafts with mature neurons, and extensive axonal trajectories from the implant to multiple regions of the host mouse brain. Importantly, live imaging on of the implanted organoids using two-photon microscopy revealed neuronal activity, and intensive vascular network with active blood flow within the organoid. Moreover, our method creates opportunities for noninvasive recording of neuronal activity with high spatial and temporal resolution deep within organoid-brain chimera. This powerful combination of in vitro 3D human neural structures, and an in vivo rich environment in the animal brain provides a promising novel approach with broad applications for degenerative and regenerative medicine.

Disclosures: A. Mansour: None. **J. Gonçalve:** None. **C. Bloyd:** None. **H. Li:** None. **S. Fernandis:** None. **X. Jin:** None. **F.H. Gage:** None.

Nanosymposium

010. Stem Cell Reprograming and Differentiation

Location: 150A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***010.02

**Topic: ***A.03. Stem Cells and Reprogramming

Support: ALS Association
Travis Roy Foundation
Massachusetts Department of Health-SCI cure

Title: Directed differentiation of corticofugal projection neurons from endogenous cortical progenitors

Authors: *A. OZKAN[1], H. K. PADMANABHAN[1], S. L. SHIPMAN[1], V. SAHNI[1], P. KUMAR[1], W. EBINA[1], A. N. BASAK[2], J. D. MACKLIS[1]
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Abstract: Specific classes of neurons are selectively vulnerable in distinct neurodegenerative, developmental, and acquired diseases of the CNS, resulting in irreversible functional deficits. In particular, for this work, corticospinal motor neurons (CSMN) degenerate in amyotrophic lateral sclerosis (ALS) and other motor neuron diseases, and loss of motor function in spinal cord injury results from damage to CSMN axons. Directed differentiation of new neurons with appropriate identity, maturity, circuit connectivity, and function from endogenous local progenitors offers a potential therapeutic approach for functional repair of diseased or injured neuronal circuitry. Recent work by our lab and others has begun to identify central elements of a combinatorial "molecular logic" of stage-, state-, and area-specific controls over development of broad classes and specific subtypes of cortical projection neurons. Here, we target endogenous cortical progenitors present in postnatal and adult brain to direct their differentiation into corticofugal (cortical output) projection neurons; CSMN belong to this class. Application of a select combination of central and complementary transcriptional controls in cultured cortical progenitors directs acquisition of cardinal morphological, molecular, and electrophysiological features of corticofugal projection neurons. We employ synthetic modified RNA technology to enable temporal and dose control to mimic the *in vivo* expression dynamics of the relevant transcriptional regulators. Ongoing work will further assess fidelity of their differentiation, integration, and connectivity within complex cortical circuitry in mice. These findings demonstrate the feasibility of achieving subtype-specific differentiation of cortical projection neurons from a widely distributed *in vivo* neocortical progenitor population.

Disclosures: A. Ozkan: None. **H.K. Padmanabhan:** None. **S.L. Shipman:** None. **V. Sahni:** None. **P. Kumar:** None. **W. Ebina:** None. **A.N. Basak:** None. **J.D. Macklis:** None.

Nanosymposium

010. Stem Cell Reprograming and Differentiation

Location: 150A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***010.03

**Topic: ***A.03. Stem Cells and Reprogramming

Support: EDUC2-08391 CIRM bridges 2.0 to ZP

Title: Novel induction of neural-ectoderm and differentiation of neural progenitors from human iPSCs using pressure

Authors: Z. PAPPALARDO[1,2], L. CASSEREAU[2], *B. A. ADAMS[2], B. DOWNEY[2], J. LIM[2]
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Abstract: Induced pluripotent stem cells (iPSCs) can be used for autologous regenerative medicine to treat conditions such as spinal cord injuries and neuropathology-associated genetic disease. iPSCs can differentiate to neural progenitor cells (NPCs), a multipotent population that can give rise to all lineages of adult neural cells. However, a confounding limitation of neurons derived from iPSC-derived NPCs is that they are not genetically and functionally equivalent to adult neurons in vivo, rendering in vitro systems as sub-optimal surrogates. Furthermore, maturation of iPSC-derived neurons for regenerative medicine may improve clinical efficacy of neural cell transplants. Recent studies highlight the significance of micro-environmental factors such as hypoxia and mechanical force / pressure on stem cell maintenance and directed-differentiation to specific cell lineages, yet none have evaluated the combined contribution of these factors towards differentiation of iPSCs to NPCs and subsequent maturation of differentiated neurons. We demonstrate the biological impact of oxygen and atmospheric pressure on differentiation to NPCs from human iPSCs. Also, we explore how atmospheric pressure-mediated force can act with soluble factors to promote differentiation of NPCs to mature neurons. We used the AVATAR™, which allows tunable control of the microenvironment *ex vivo*, to allow precise control of physiologically-relevant levels of oxygen and pressure simultaneously. We demonstrate that combinatorial oxygen and pressure are significant drivers of NPC differentiation from iPSCs. We used settings for oxygen concentration (5% vs normoxia) and atmospheric pressure (2 PSI + atmospheric) during re-programming of fibroblasts to iPSCs and identified pressure-dependent increases in genes involved in re-modeling of the extra-cellular matrix and neural differentiation. We further show that in the absence of soluble differentiating factors, oxygen and pressure are sufficient to fully differentiate iPSCs to NPCs expressing PAX6, NES, and SOX2. When evaluating the effects of oxygen/pressure plus soluble factors for neural induction of iPSCs we see an increase in efficiency relative to a standard CO2 incubator workflow. We now are leveraging the differentiation potential of combinatorial oxygen and atmospheric pressure towards maturation

of CNS neurons, astrocytes, and motor neurons. Our findings suggest that oxygen and pressure are important drivers of neural differentiation from human iPSCs, and that these factors have the potential to induce maturation of neurons such that they are better suited for translational studies in vitro and in the clinic.

Disclosures: Z. Pappalardo: A. Employment/Salary (full or part-time):; Xcell Biosciences Inc. **L. Cassereau:** A. Employment/Salary (full or part-time):; Xcell Biosciences Inc. **B.A. Adams:** A. Employment/Salary (full or part-time):; Xcell Biosciences Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Xcell Biosciences Inc. **B. Downey:** A. Employment/Salary (full or part-time):; Xcell Biosciences Inc. **J. Lim:** A. Employment/Salary (full or part-time):; Xcell Biosciences Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Xcell Biosciences Inc.

Nanosymposium

010. Stem Cell Reprograming and Differentiation

Location: 150A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***010.04

**Topic: ***A.03. Stem Cells and Reprogramming

Support: NIH NEI RO1 EY024940

Title: Analysis of retinal ganglion cell development and maturation using human pluripotent stem cells

Authors: *S. OHLEMACHER[1], A. SRIDHAR[1], Y. XIAO[1], V. SLUCH[2], D. J. ZACK[2], A. J. BAUCUM[1,3], T. R. CUMMINS[1,3], J. S. MEYER[1,3]
[1]Biol., Indiana Univ. Purdue Univ. at Indianapolis Dept. of Biol., Indianapolis, IN; [2]Wilmer Eye Inst., John Hopkins, Baltimore, MD; [3]Stark Neurosciences Res. Inst., Indiana Univ., Indianapolis, IN

Abstract: Retinal ganglion cells (RGCs) serve as the primary connection from the eye to the brain, allowing for normal visual processing. Loss of RGCs leads to devastating blinding disorders termed optic neuropathies. Human pluripotent stem cells (hPSCs) allow for the development of a variety of translational applications for optic neuropathies, including cell replacement, drug screening, and disease modeling. To date, however, little attention has been paid to the degree of maturation of these hPSC-derived RGCs, limiting their ability to serve as effective tools for the study and/or treatment of optic neuropathies. To address this shortcoming, efforts were undertaken to identify those factors leading to an enhanced state of maturation of

hPSC-derived RGCs. hPSCs were directed to differentiate toward a retinal lineage in a stepwise manner as previously described. Within the first 40 days of differentiation, RGCs could be definitively identified by gene expression and morphological characteristics. RGCs were grown in culture for up to 12 weeks, at which point the degree of maturation of these RGCs was monitored over time by immunocytochemistry, electrophysiology, and western blot analyses. Throughout this timecourse, the degree of dendritic and axonal extensions was analyzed and quantified, with corresponding increases in complexity over time. Additionally, the survival and proliferation of RGCs was monitored by the expression of activated caspase-3 and Ki-67, respectively. Furthermore, these RGCs were able to develop advancing features of synaptogenesis over time. Ongoing experiments aim to test the ability to enhance the timing and efficacy of RGC maturation from hPSCs. The results presented above demonstrate the ability to reliably and efficiently derive RGCs from hPSCs. Prolonged differentiation of these RGCs resulted in increased complexity of RGC morphologies, as well as a temporal increase in the expression of synaptic markers. Overall, the results of this study indicate the ability of hPSC-derived RGCs to acquire advancing features of maturation, with important implications for disease modeling, drug screening, and cellular replacement therapies.

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Nanosymposium

010. Stem Cell Reprograming and Differentiation

Location: 150A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***010.05

**Topic: ***A.03. Stem Cells and Reprogramming

Support: MOST 105-2314-B-281-002 -

Title: Knocking down of heat-shock protein 27 and one of the members of S100 superfamily induces differentiation of functional glutamatergic neurons and astrocytes from placenta-derived multipotent cells

Authors: *C.-C. CHIEN[1,3], Y.-C. CHENG[2,3,4], C.-J. HUANG[2,5], L.-T. TIEN[3], Y.-J. LEE[3]
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Abstract: The neural lineage differentiation capacity of placenta-derived multipotent cells (PDMCs) under the induction of 1-methyl-3-isobutylxanthine (IBMX) *in vitro* has been well-

demonstrated previously. To identify molecules involved in this process, we applied both genomics and proteomics approaches to generate a panel of molecules consistently expressed. After serial verification, total four most promising genes were finally selected. Among them, the heat-shock protein 27 (HSP27, also termed HSPβ1 or HSP25) was first examined. The results demonstrated that overexpression of HSP27 in PDMCs led to the arrest of neuronal differentiation. However, the knockdown of HSP27 by specific short-hairpin RNA yielded a substantially enhanced ability to differentiate PDMCs into functional glutamatergic neurons under the induction of IBMX and formed neuron synaptic networks *(published in July 2016 in Scientific Reports,6:30314, DOI: 10.1038/srep30314*). We therefore extend our previous works to test all gene combinations applying similar genetic manipulation as described in our previous publication. The preliminary results demonstrated that, by knocking down HSP27 and one of the members of S100 superfamily, PDMCs were induced to differentiate into functional glutamatergic neurons and astrocytes while IBMX is no longer required in this process. The differentiated cells co-expressed the N-methyl-D-aspartate receptor, vesicular glutamate transporter, synaptosomal-associated protein 25 and glial fibrillary acidic protein while did not show expression of choline acetyltransferase, tyrosine hydroxylase or glutamate decarboxylase 67. Furthermore, the induced neurons showed increasing intracellular calcium influx upon glutamate and thrombin treatment. Therefore, we concluded that the co-silence of these two genes is sufficient to induce PDMCs to differentiate into neurons possessing the characteristics of functional glutamatergic neurons and astrocytes.

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Nanosymposium

010. Stem Cell Reprograming and Differentiation

Location: 150A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***010.06

**Topic: ***A.03. Stem Cells and Reprogramming

Support: AMED
KAKENHI
Takeda Science Foundation

Title: Investigation of excitatory and inhibitory neuronal phenotypes in Angelman syndrome neurons using rapid-single step neuronal differentiation methods

Authors: *M. ISHIKAWA
Dept. Physiol., Keio Univ. Sch. Med., Tokyo, Japan

Abstract: Genomic imprinting is an epigenetic phenomenon by which certain genes are expressed in parent–of–origin-specific manner. Angelman syndrome (AS) is one of the most famous imprinting disorders which shows sever neurodevelopmental deficit, speech impairments, intellectual disability, epilepsy, prognathism, abnormal sleep patterns, and hyperactivity. In most cases, AS is caused by large deletion of maternally inherited human chromosome 15q11–q13, which contains UBE3A (ubiquitin protein ligase E3A) cording region. In this study, we established novel iPS cells from T lymphocytes of seven different AS individuals, including not only a large genomic deletion of maternal 15q11-13 region, but also uniparental disomy, or imprinting defect or epimutation in the imprinting center in 15q11-13 region, which can also cause AS pathogenesis. To investigate the AS–specific neuronal phenotypes, we performed the several single–step neural induction method and analyzed the expression levels of synapse-related genes. All the AS–specific iPSC lines were successfully differentiated into functional glutamatergic and inhibitory neurons. Interestingly, UBE3A gene expression levels were different in the each class-specific neurons, which probably generates a variety of phenotype among the AS classes. We are now investigating the functional differentiation between healthy control and AS neurons, and performing a drug screening for restoring the UBE3A gene expression.

Disclosures: M. Ishikawa: None.

Nanosymposium

010. Stem Cell Reprograming and Differentiation

Location: 150A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***010.07

**Topic: ***A.03. Stem Cells and Reprogramming

Title: Transcriptional comparisons of iPSC-derived striatal cell models delineate gene network interactions among physical time in culture, cellular maturation, age, and Huntington’s disease

Authors: *V. B. MATTIS[1], R. HO[2], C. TOM[2], P. MATHKAR[3], R. G. LIM[5], C. GEATER[5], N. ALLEN[6], P. J. KEMP[6], L. M. THOMPSON[7], C. N. SVENDSEN[4]
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Abstract: Induced pluripotent stem cell (iPSC) models of Huntington's disease (HD) provide an opportunity to study the mechanisms underlying disease pathology in patient tissues relevant to

disease. These human-based studies are critical, due to inherent differences in brain development and timing between humans and rodent animal models. The striatum of HD patients exhibits the most prominent loss of cells, specifically medium spiny neurons (MSNs). iPSC modeling of the striatum aims to reenact embryogenesis, maturation, and aging of the relevant striatal cell types *in vitro*. Studies have identified molecular pathways affected by HD in post-mortem human striata, and it is the primary goal of iPSC-based modeling to recapitulate the molecular etiology of HD leading to those events found in human end stage samples. However, the molecular fidelity of iPSC-derived MSNs (iMSNs) grown *in vitro* compared to human MSNs *in vivo* remains largely unaddressed; it is unclear to what extent this *in vitro* system captures critical aspects of MSN development, maturation, aging, and molecular signatures associated with HD. Because HD is a late onset disease that affects mature and aged MSNs in adults, we addressed whether iMSNs *in vitro* differentiated from iPSCs up to 800 days could recapitulate the differentiation process *in vivo* by comparing transcriptomes among human iPSCs, iMSNs, fetal striata, and adult striata. Principal component analysis produced a maturation scale revealing that iMSNs differentiate towards fetal striata, but extended time in culture drives their expression profiles to diverge away from the *in vivo* fetal profile while stalling neuronal maturation towards adult striata. Additionally, we resolved gene networks and pathways associated with iMSN time in culture, MSN embryonic development, maturation, and aging. These networks enriched for proteins that directly interact with CAG-expanded HTT, and were also affected in caudate nuclei of HD patients. Altogether, our findings test and establish the fidelities and limitations of extended time in culture to capture aspects of *in vivo* striatal development, maturation, aging, and disease phenotypes in iPSC models of HD.

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Nanosymposium

010. Stem Cell Reprograming and Differentiation

Location: 150A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***010.08

**Topic: ***A.03. Stem Cells and Reprogramming

Support: National Science Centre, Poland, Grant No 2016/22/M/NZ2/00548
German Federal Ministry of Education and Research (BMBF)AZ. 031A318.

Title: Inactivation of neurotoxic CAG expansion repeats in patient iPSC-derived neurons using highly specific Cas9 gene editing system

Authors: *P. LISOWSKI[1,2], B. MLODY[3], P. KANNAN[3], J. PRILLER[4], E. WANKER[3], R. KÜHN[1], A. PRIGIONE[3]
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Abstract: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by a progressive loss of GABAergic medium spiny neurons (MSNs) in the striatum. The disease is caused by a mutation in the CAG repeat tract of the huntingtin gene HTT, which leads to an expanded polyglutamine stretch (polyQ) in the huntingtin protein HTT. The presence of 40 CAG repeats or more give rise to the disease, with longer repeats associated with juvenile more aggressive forms. Several lines of evidence implicate a prominent involvement of mitochondrial dysfunction and impaired energy metabolism in HD pathogenesis. Thus the objective of presented study was to (1) uncover the early alterations of the mitochondrial energy metabolism using human neurons differentiated from induced pluripotent stem cells (iPSCs) derived from HD patients; (2) clearly dissect the impact of the disease-causing mutation, using Cas9-based editing technologies that allow for the generation of isogenic lines carrying a healthy length of CAG repeats within the same nuclear background of the patients; (3) test whether the N-terminal truncated protein is able to support normal neuronal development; (4) assess in a first approximation whether the improved Cas9 variants in comparison to wildtype Cas9 nuclease might be suitable for a application in somatic gene therapy. HD iPSC lines were first confirmed to exhibit normal karyotype and lack of de novo mutations and CNVs in comparison to the parental fibroblasts. In order to clearly dissect the impact of the disease-causing HTT mutation, we have taken an advantage of genome editing technology that allowed for generation of isogenic lines within the same nuclear background of the patients generated from precisely corrected iPSC clones by homologous recombination (HR) and NHEJ mediated excision of the Q/P repeat region by reannealing of the DSB resulted into an in-frame HTT coding region lacking the N-terminal Q/P repeat as well as iPSC clones with introduced 180 CAG repeats to fast forward disease phenotype. Edited iPSC clones were characterized for the potential modification at predicted off-target sites and differentiated MSNs were subjected for the functional studies with high-content screening and energy metabolism profiling.

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Nanosymposium

010. Stem Cell Reprograming and Differentiation

**Location: ***150A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***010.09

**Topic: ***A.03. Stem Cells and Reprogramming

Support: Brace Cove Health Foundation
Maryland Stem Cell Research Fund

Title: Using human induced pluripotent stem cells to model Pitt-Hopkins Syndrome

Authors: *D. J. HILER[1], S. SRIPATHY RAO[1], A. TUTTLE[1], B. J. MAHER[1,2,3]
[1]The Lieber Inst. For Brain Develop., Baltimore, MD; [2]The Solomon H. Snyder Dept. of Neurosci., [3]Dept. of Psychiatry and Behavioral Sci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Pitt-Hopkins Syndrome (PTHS) is a rare and relatively understudied autism spectrum disorder that is caused by an autosomal dominant mutation or deletion in gene transcription factor 4 (TCF4). TCF4 is a basic helix-loop-helix (bHLH) transcription factor that plays a critical role in neuronal development through known interactions with other proneural bHLH proteins. In our animal models of PTHS, we have identified a deficit in the excitability of prefrontal cortical neurons through the upregulation of a voltage-gated sodium channel gene (SCN10a, $Na_v1.8$). We hypothesize that this deficit in excitability is also present in human cortical neurons and may potentially represent a common pathophysiology in autism spectrum disorders. To validate this hypothesis, we have generated human cortical neurons from induced pluripotent stem cells derived from both PTHS patients and controls in an effort to create a developmental profile of neuron maturation in PTHS. Using whole-cell patch clamp, immunohistochemistry, RNA-seq, and imaging analysis, we have characterized the intrinsic excitability of human cortical neurons from PTHS patients in an effort to validate the phenotype observed in our animal models. We have paired this phenotypic characterization with a RNA-Seq molecular profile of neural progenitor cells and early maturing cortical neurons to identify additional therapeutic targets and develop a understating of how normal neuronal maturation is altered in PTHS patients.

Disclosures: D.J. Hiler: None. **S. Sripathy Rao:** None. **A. Tuttle:** None. **B.J. Maher:** None.

Nanosymposium

010. Stem Cell Reprograming and Differentiation

Location: 150A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***010.10

**Topic: ***A.03. Stem Cells and Reprogramming

Support: CIRM Grant LA1-08015

Title: Differentiation and single cell RNA sequencing of V2a interneurons from human pluripotent stem cells

Authors: *J. BUTTS[1], D. A. MCCREEDY[2], J. A. MARTINEZ-VARGAS[3], C. A. GIFFORD[4], L. J. NOBLE-HAEUSSLEIN[5], T. C. MCDEVITT[4]
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Abstract: V2a interneurons (INs) are a critical population of neurons found in the hindbrain and spinal cord that are necessary for coordinated motor function, including control of breathing and locomotion. V2a INs span several spinal cord segments and relay excitatory information to adjacent INs and downstream motor neurons. While studies of murine V2a INs have provided critical early characterization of this population, there is no robust source of human V2a INs to phenotypically characterize this cell population *in vitro* as a potential therapy for human motor dysfunction. Therefore, we recently described a protocol to differentiate V2a INs, marked by the CHX10 transcription factor, from human pluripotent stem cells (hPSCs). Drawing inspiration from neural tube development, the critical signaling molecules retinoic acid (RA), Purmorphamine (Pur, a Shh agonist), and DAPT (a Notch inhibitor) were varied systematically until a $CHX10^+$ population of approximately 30% was obtained with 100nM RA, 100nM Pur, and 1μM DAPT. After starting with human ESCs (H7), the protocol was reproduced in three additional hPSC lines (H1 ESCs, WTC and WTB induced PSCs), to yield CHX10 percentages between 25-50%. Expression of V2a IN lineage markers (*CHX10*, *SOX14*) was highly upregulated (~100-fold) when compared to a published motor neuron protocol. Single cell RNA sequencing was performed to identify the cell populations in the V2a IN differentiation. K-means clustering of twelve principle components revealed seven distinct cell populations including mature neurons, progenitor neurons, and glial cells. The cluster containing the majority of *CHX10*-expressing cells also expressed other markers of V2a interneurons (*SOX21* and *SHOX2*), as well as genes associated with a glutamatergic phenotype (*PCP4* and *OAT*). V2a cultures expressed a mature glutamatergic neuronal phenotypic ($NeuN^+$ and $VGlut2^+$) and demonstrated increased action potential frequency when cultured for up to 60 days. To determine if V2a

interneuron cultures could integrate with the endogenous spinal cord, dissociated cultures were transplanted into T9 vertebrae of uninjured mice and resulted in survival and neurite extension greater than 5mm rostral and caudal to the transplantation site. Transplanted cells expressed the presynaptic maker synaptophysin on neurite terminals adjacent to host $NeuN^+$ neurons, indicating integration with host circuitry. In summary, we have developed the first protocol to differentiate V2a INs from hPSCs that will allow for further characterization of novel phenotypic and electrophysiological properties of these cells.

Disclosures: J. Butts: None. **D.A. McCreedy:** None. **J.A. Martinez-Vargas:** None. **C.A. Gifford:** None. **L.J. Noble-Haeusslein:** None. **T.C. McDevitt:** None.

Nanosymposium

011. Autophagy and Degradation

Location: 150B

**Time: ***Saturday, November 11, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***011.01

**Topic: ***B.07. Synaptic Transmission

Support: NIH Grant DK094980

Title: Autophagy regulates drug-responsive behaviors to cannabinoids and cocaine

Authors: *C. HE, S. YAMAMOTO, K. KURAMOTO, W. ZHANG, S. HUANG, A. ROCCHI
Northwestern Univ. - Chicago, Chicago, IL

Abstract: The mechanisms of behavioral responses to abusive substances are not fully understood. For example, cannabinoids and related drugs generate profound analgesic effects through activating the cannabinoid receptor type 1 (CB1R). However, repeated cannabinoid administration triggers lysosomal degradation of the receptor and rapid development of analgesic tolerance, limiting the medical use of marijuana in chronic diseases. Here we show that autophagy, an essential conserved lysosomal degradation pathway, plays a role in the regulation of signaling and animal behaviors in response to drugs, including cannabinoids. We found that an autophagy-related protein, Becn2/Beclin 2, mediates analgesic tolerance to cannabinoids by preventing CB1R recycling and resensitization after prolonged agonist exposure, and deletion of Becn2 rescues CB1R activity in mouse brain and enhances the analgesic effects of cannabinoids. To target Becn2 therapeutically, we established a competitive recruitment model of Becn2 and identified novel synthetic, natural or physiological stimuli of autophagy that sequester Becn2 from its binding with GPCR-associated sorting protein 1 (GASP1), an adaptor protein for CB1R degradation. Co-administration of these autophagy inducers effectively restores the level and signaling of brain CB1R and enhances cannabinoid analgesia in wild-type mice. In addition to

cannabinoids, we found that Becn2 knockout mice are protected from the stimulant effects of cocaine. We generated a mutant Becn2 mouse line that loses interaction with GASP1 by CRISPR, and found that these mice also display ameliorated behavioral responses to cocaine stimulation. Thus, understanding the role of autophagy in behavioral regulation is necessary for improving medical efficacy of cannabinoids and preventing detrimental effects of cocaine overdose. Overall, our studies demonstrate a functional link among autophagy, receptor signaling and animal behaviors regulated by psychoactive drugs, and provide experimental evidence that autophagy-modulating agents can alter the animal behaviors in response to drugs.

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Nanosymposium

011. Autophagy and Degradation

Location: 150B

**Time: ***Saturday, November 11, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***011.02

**Topic: ***B.07. Synaptic Transmission

Support: JPB foundation
NIGMS T32 GM007367

Title: Macroautophagy controls striatal circuit development via regulation of Kir2 channels

Authors: *O. LIEBERMAN[1], M. FRIER[1], E. SANTINI[2], A. BORGKVIST[4], D. SULZER[3]
[2]Neurol., [3]Psychiatry, [1]Columbia Univ., New York, NY; [4]Neurol., Columbia Univ. Med. Ctr., New York, NY

Abstract: Dysfunction of the striatum has been proposed to play a role in the pathophysiology of neurodevelopmental disorders such as autism. Genetic lesions in the mTOR pathway have been linked to syndromic forms of autism and reduce levels of ongoing autophagy. Here, we investigated the role of autophagy in striatal development and maturation. We developed conditional knockouts of autophagy in D1- and D2-MSNs, the principle neurons of the striatum. Loss of autophagy in MSNs led to the disruption in the ontogenetic reduction in MSN excitability during postnatal development. In contrast to loss of autophagy in the cortex and hippocampus, no effect was found on spine density, dendritic arborization of spontaneous synaptic activity. Furthermore, no cell death or neuroinflammation was observed in conditional knockouts, arguing for a role of autophagy in neural function independent of its role in neurodegenerative pathology. Using voltage-clamp recordings, we found that Kir2.X currents are decreased in MSNs without autophagy. This was associated with elevated total Kir 2.X protein,

Kir2.X ubiquitination and decreased synaptosomal localization. Future work will characterize the behavioral effects on loss of autophagy in the striatum. Thus, we report here the first example of autophagic regulation of an ion channel in neurons and the consequence of loss of autophagy on a neural circuit implicated in neuropsychiatric disease.

Disclosures: O. Lieberman: None. **M. Frier:** None. **E. Santini:** None. **A. Borgkvist:** None. **D. Sulzer:** None.

Nanosymposium

011. Autophagy and Degradation

Location: 150B

**Time: ***Saturday, November 11, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***011.03

**Topic: ***B.07. Synaptic Transmission

Support: NIMH K01 MH096956
DOD W81XWH-16-1-0263
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DOD W81XWH-15-1-0112
SFARI 345915
SFARI 402220

Title: A role for macroautophagy in postnatal dendritic spine synapse development

Authors: *G. TANG[1], H. LI[1], H. ZHANG[2], X. WU[3], O. ARANCIO[2]
[1]Columbia University, Dept of Neurol., New York, NY; [2]Pathology and cell biology, [3]Neurosurg., Columbia Univ., New York, NY

Abstract: Components of the mammalian target of rapamycin (mTOR) signaling pathway are key players in the pathogenesis of autism spectrum disorder (ASD). mTOR regulates protein homeostasis by promoting protein synthesis and inhibiting macroautophagy (autophagy thereafter), a homeostatic degradation process whereby cellular proteins and organelles are engulfed by autophagosomes, digested in lysosomes, and recycled to sustain cellular metabolism. We recently discovered that, in response to hyperactive mTOR, autophagy is impaired in excitatory neurons in brains of a subset of ASD patients. Impaired mTOR-autophagy is associated with an increase in the density of dendritic spine synapses and a blockade in dendritic spine synapse pruning, a postnatal developmental process during which unnecessary excessive excitatory synapses are eliminated. Using a neuronal specific autophagy gene Atg7 conditional knockout mouse line, we found that autophagy regulates postnatal hippocampal CA1 excitatory synapse development, synaptic plasticity and cognitive function. Autophagy deficiency resulted

in redundant excitatory synapses, impaired hippocampal CA3-CA1 long term potentiation (LTP) and long term depression (LTP), and impaired learning and memory. Our studies thus provide the first evidence that autophagy is required for postnatal excitatory dendritic spine synapse development, and autophagy deficiency contributes to excitatory synapse pathology in ASD. Further study of the mechanism by which autophagy regulates synaptic structure and function will suggest novel therapeutic targets.

Disclosures: **G. Tang:** None. **H. Li:** None. **H. Zhang:** None. **X. Wu:** None. **O. Arancio:** None.

Nanosymposium

011. Autophagy and Degradation

Location: 150B

Time: *Saturday, November 11, 2017, 1:00 PM - 2:45 PM

Presentation Number: *011.04

Topic: *B.07. Synaptic Transmission

Support: NIH 5 P50 DA00266
Brain and Behavior Foundation YIG-25360

Title: Basp1 mediates cocaine's locomotor stimulant effect via autophagy

Authors: ***M. M. HARRAZ**, P. GUHA, I. KANG, A. MALLA, P. CORTES, S. H. SNYDER
Dept. of Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: The locomotor stimulant actions of cocaine are thought to reflect potentiation of synaptic dopamine mediate by inhibiting its reuptake inactivation. In this context, cocaine binds the dopamine transporter (DAT) and inhibits its function, an effect that occurs at micromolar concentrations of the drug. While cocaine concentrations range from the nanomolar to the low micromolar levels in vivo, the drug binds multiple proteins limiting its bioavailability to a small fraction of the total. Here we show that cocaine, at subnanomolar concentrations, elicits autophagy in cortical neurons and other cell types. We find that DAT is rapidly depleted in the nucleus accumbens following cocaine treatment in mice. Degradation of DAT by cocaine is abolished by blocking autophagy. Furthermore, autophagy inhibitors block the locomotor stimulant effect of cocaine. We used affinity pull down to identify a putative cocaine receptor as the protein BASP1, whose depletion prevents the autophagic actions of cocaine. Stereotaxic injection of BASP1 shRNA in the ventral tegmental midbrain inhibits cocaine's locomotor stimulant effect in mice. Our findings support a model wherein cocaine acts through BASP1 to induce autophagy, which enhances dopamine signaling by degrading DAT. These findings identify novel therapeutic targets for cocaine addiction.

Disclosures: **M.M. Harraz:** None. **P. Guha:** None. **I. Kang:** None. **A. Malla:** None. **P. Cortes:** None. **S.H. Snyder:** None.

Nanosymposium

011. Autophagy and Degradation

Location: 150B

Time: *Saturday, November 11, 2017, 1:00 PM - 2:45 PM

Presentation Number: *011.05

Topic: *B.07. Synaptic Transmission

Title: Selective autophagy degrades protein inclusions in the soma and dendrites of CNS neurons

Authors: ***K. PURTELL**, J. LIM, Y. ZHANG, L. LACHENMAYER, Z. YUE
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Abstract: Macroautophagy (herein referred to as autophagy) is an essential homeostatic process whereby large protein complexes and damaged organelles are engulfed into double-membraned structures called autophagosomes and broken down via fusion with the lysosome. In most cells of the body, autophagy is induced in response to nutrient starvation and used as a means of recycling essential amino acids. Autophagy in neurons, however, does not respond to starvation and is therefore regulated differently than other cells in the body. Constitutively active, or 'basal', autophagy in nutrient-rich conditions is required for neuronal homeostasis and impairment of this process in autophagy-deficient transgenic mice causes accumulation of toxic protein aggregates and neurodegeneration. Studies of autophagy in neurons have primarily focused on the regulation of autophagosomes in the axon, which are differentially regulated from autophagosomes in the soma and dendrites. Here we show that rescue of basal autophagy *in vivo* in neuron-specific ATG7-deficient mice can clear large protein aggregates in the soma and dendrites. We found that pathogenic proteins, such as β-amyloid and phosphorylated-tau, co-localize with the autophagy receptor, p62 in large proteinaceous inclusions. We also demonstrate that rescue of autophagy in the midbrain restores the functionality of dopaminergic neurons and that impaired autophagy may affect synapse formation. We recapitulated our findings in an *in vitro* primary neuron cell culture system that can be used for mechanistic studies to advance our understanding of the formation and clearance of protein aggregates in neurodegenerative disease.

Disclosures: **K. Purtell:** None. **J. Lim:** None. **Y. Zhang:** None. **L. Lachenmayer:** None. **Z. Yue:** None.

Nanosymposium

011. Autophagy and Degradation

Location: 150B

**Time: ***Saturday, November 11, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***011.06

**Topic: ***B.07. Synaptic Transmission

Support: NINDS
Parkinson's disease foundation

Title: Parkinson's disease gene SYNJ1 contributes to impaired dopamine transmission and dopamine neuron vulnerability through regulating PIP2 levels

Authors: P.-Y. PAN, *Z. YUE, P. SHEEHAN, Q. WANG, Y. ZHANG, D. CAI
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Abstract: Parkinson's disease (PD) is the most common movement disorder with a high incidence in aged people and it is known to be caused by selective loss of Substantia Nigra dopamine neurons. While majority of the clinical cases are sporadic, over 20 genetic variants and many environmental factors have been reported to associate with disease risk, among which, aging is considered the greatest contributor. Identifying genetic changes for disease-vulnerable dopamine neurons in the context of aging is therefore crucial for understanding PD etiology. We now report midbrain dopamine neuron-specific down-regulation of PARK20/SYNJ1 gene expression due to aging. Synaptojanin1 (encoded by SYNJ1) is an important inositol phosphatase enriched at nerve terminals for regulating inositol phosphates metabolism and synaptic transmission. It has also recently been implicated in autophagy regulation in *Drosophila* NMJ. Homozygous missense mutations were identified in families with early-onset Atypical Parkinsonism with unknown mechanism. Our study shows that aging-related decrease in synaptojanin1 (synj1) expression results in 2-fold elevation of PIP2 levels in the midbrain compared to the cortex in 1-year old mice. The impaired PIP2 metabolism sensitizes dopamine neurons to pathological synj1 deficiency. Primary cultured midbrain neurons display a reverse SYNJ1 gene dose-dependent increase in calcium entry along the axon during synaptic activity. Aged $SYNJ1^{+/-}$ mice exhibit reduced dopamine levels in the striatum accompanied by behavioral deficits and loss of dopaminergic nerve terminals. Our analysis of public data set also reveals a significant reduction of SYNJ1 transcripts in subgroups of sporadic PD patients, further suggesting that synj1 down-regulation predisposes aged people to PD pathogenesis likely via lipids deregulation and autophagy impairments.

Disclosures: P. Pan: None. **Z. Yue:** None. **P. Sheehan:** None. **Q. Wang:** None. **Y. Zhang:** None. **D. Cai:** None.

Nanosymposium

011. Autophagy and Degradation

Location: 150B

**Time: ***Saturday, November 11, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***011.07

**Topic: ***D.01. Sensory Disorders

Support: NIH Grant EY024232

Title: Isoform-selective Hsp90 inhibition rescues model of hereditary open-angle glaucoma

Authors: *J. KOREN, III[1], A. SUNTHARALINGAM[1], V. M. CROWLEY[2], B. S. J. BLAGG[2], L. BLAIR[1]
[1]MDC36, Mol. Med., Tampa, FL; [2]The Univ. of Kansas, Lawrence, KS

Abstract: The heat shock protein 90 (Hsp90) family of molecular chaperones regulates protein homeostasis, folding, and degradation. The ER-resident Hsp90 isoform, glucose-regulated protein 94 (Grp94), promotes the aggregation of mutant forms of myocilin, a protein associated with primary open-angle glaucoma. While inhibition of Grp94 promotes the degradation of mutant myocilin *in vitro*, to date no Grp94-selective inhibitors have been investigated *in vivo*. Here, a Grp94-selective inhibitor facilitated mutant myocilin degradation and rescued phenotypes in a transgenic mouse model of hereditary primary open-angle glaucoma. Ocular toxicities previously associated with pan-Hsp90 inhibitors were not evident with our Grp94-selective inhibitor, 4-Br-BnIm. Our study suggests that selective inhibition of a distinct Hsp90 family member holds translational promise for ocular and other diseases associated with cell stress and protein misfolding.

Disclosures: J. Koren: None. **A. Suntharalingam:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder. **V.M. Crowley:** None. **B.S.J. Blagg:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder. **L. Blair:** None.

Nanosymposium

012. Cognitive Dysfunction in Alzheimer's Disease and Related Dementias

Location: 152B

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***012.01

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

Support: Department of Biotechnology (BT/PR3996/MED/97/57/2011), Government of India

Title: Analysis of Arc interacting proteins in mouse hippocampus during amnesia and its restoration

Authors: *A. GAUTAM[1], S. KAUL[2], M. THAKUR[3]
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Abstract: Our earlier studies show that Activity-regulated cytoskeleton-associated protein (Arc) is involved in memory dysfunction as well as in its restoration, though the underlying molecular mechanism still remains vague. We assume that Arc mediates in such memory-related disorder through the recruitment of a number of other crucial proteins. To prove this, we tried to identify various Arc interacting proteins in the hippocampus of control, scopolamine-induced amnesic and Ashwagandha leaf extract pre-treated amnesic mice using co-immunoprecipitation technique followed by MALDI-MS/MS and bioinformatical analysis. In the present study, we found nine Arc interacting partners; with the varying interaction level during amnesia and its restoration as compared to the control. The bio-informatics scanning for Arc protein-protein interactions at the confidence score > 0.5 showed 11 Arc interacting proteins, out of which three were obtained in our co-IP experiments also. In-silico analysis of these proteins indicated conformation based interaction through the common type of secondary structures having the alpha helical, extended beta strand and random coil. Analysis of their unique tryptic peptides by the motif-scan software revealed that most of the interacting partners were containing sites for the Casein kinase II phosphorylation, N-glycosylation, phosphokinase C phosphorylation, Tyrosine kinase phosphorylation, cAMP- and cGMP-dependent protein kinase phosphorylation and N-myristoylation as the consensus binding motifs. Thus, the present study gives an insight into the Arc interacting proteins through their specific conformations and consensus sites which may be helpful to regulate Arc mediated signaling during memory related disorders like amnesia.

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Nanosymposium

012. Cognitive Dysfunction in Alzheimer's Disease and Related Dementias

Location: 152B

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***012.02

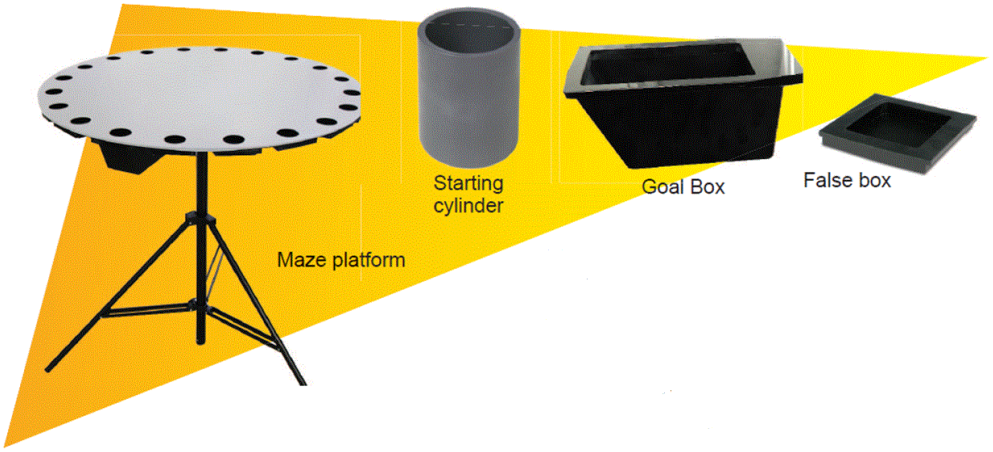
**Topic: ***C.02. Alzheimer's Disease and Other Dementias

Support: SDU2020

Title: Modeling progressive cognitive impairment in the $APP_{swe}/PS1_{dE9}$ mouse model of amyloidosis by using the Barnes maze test

Authors: *A. METAXAS[1], R. VAITHEESWARAN[1], S. LI[2], K. L. LAMBERTSEN[1], B. FINSEN[1]
[1]Univ. of Southern Denmark, Odense C, Denmark; [2]Chinese Acad. of Sci., Beijing, China

Abstract: Spatial learning and memory in Alzheimer's disease (AD) mouse models are commonly evaluated under the influence of strong aversive stimuli and food deprivation. Here, we report that progressive cognitive decline can be monitored in the $APP_{swe}/PS1_{\Delta E9}$ model of familial AD by using the Barnes maze (BM) test, a dry-land assay employing light as a weak aversive stimulus. Male, wild-type (WT) and littermate transgenic (TG) mice were tested in the BM arena at 6-8, 12-14, and 18-20 months of age (n=7-11/genotype & age). Following 5 days of handling and a habituation session, animals were trained to escape from the brightly lit BM arena towards a dark recessed goal box, located under 1 of the 20 maze holes. The training trials began by placing mice in a non-transparent cylinder in the center of the arena. The arena was illuminated, the box lifted, and mice were allowed to explore the maze for a period of 3 min. Each acquisition trial ended after 3 min, or when mice had entered the escape chamber. Time to reach (primary latency) and enter (total latency) the goal box was measured for each animal. Each mouse received 5 trials/day during the acquisition phase, which was conducted over three consecutive days. Short- and long-term memory retention was evaluated for a period of 90 s, 24 h and 7 days following the acquisition phase, respectively. For the memory probing trials, the escape box was removed and replaced by a false goal box. Primary latency, number of hole-pokes, and time-spent in the quarter of the arena where the escape box used to be located measured (target block time). All sessions were videotaped, and data analysis performed by two observers blinded to genotype. There were no behavioral differences between 6 month old WT and TG animals. Twelve month old TG mice spent less time in the target block compared to age-matched controls, 7 days after the end of the acquisition phase. Eighteen month old TG mice did not learn the task, and were impaired compared to WT mice on probe days 4 and 11. These results highlight the sensitivity of the BM test to detect cognitive decline in the $APP_{swe}/PS1_{\Delta E9}$ model of amyloidosis.



Disclosures: **A. Metaxas:** None. **R. Vaitheeswaran:** None. **S. Li:** None. **K.L. Lambertsen:** None. **B. Finsen:** None.

Nanosymposium

012. Cognitive Dysfunction in Alzheimer's Disease and Related Dementias

Location: 152B

Time: *Saturday, November 11, 2017, 1:00 PM - 3:00 PM

Presentation Number: *012.03

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

Support: Birdsong Foundation, Suffolk, VA

Title: Individual computer access improves advanced dementia & MCI

Authors: ***P. F. ARAVICH**[1], A. ORD[4], A. AZHER[5], A. P. CHIDESTER[5], M. S. BINDER[2], S. SAUTTER[3]
[1]Pathology/Anatomy, [3]Psyychiatry & Behavioral Sci. & Glennan Ctr., [2]Eastern Virginia Med. Sch., Norfolk, VA; [4]Psychology, Regent Univ., Virginia Beach, VA; [5]Westminster-Canterbury on Chesapeake Bay, Virginia Beach, VA

Abstract: There is growing interest in computer engagement strategies for cognitively impaired older adults. These randomized control trials determined the effects of individual computer access on old-old subjects with advanced all-cause dementia (n=10, MoCA 10; 12 wk study duration) and with mild cognitive impairment (MCI) (n=10, MoCA 21; 6 wk duration). Individual computer access was defined as guided computer engagement (5hr/wk) combined with free individual computer access. Subjects were randomized into independent computer access groups and control groups and tested in their assisted living/long-term care units. A

customized large touch screen computer with various applications (e.g., music, games) was used: It's Never Too Late (IN2L) computer platform (Denver, CO). The guided sessions began with preferred music followed by a limited number of other applications. Standard of care for all conditions included group IN2L activities. Results. 1) In both the advanced dementia and MCI experiments individual computer access scores were reliably increased compared to baselines on the Affect Balance Scale, a measure of overall well-being; there were no reliable increases in the control groups. Contrary to a previous report (Chidester et al. Alzheimer's & Dementia, 2016; 12(7): 259-60), there were no reliable effects on challenging behaviors or antipsychotic use. 2) In both experiments overall CNA Perceived Stress Scale scores were reliably reduced vs pre-test baselines. And 3) MoCA and Geriatric Depression Scale scores in the computer access group were reliably improved compared to baselines in the MCI study but not the advanced dementia study; no reliable changes were seen in the control groups. Conclusions. Individual computer access improved the overall well-being of subjects with advanced all-cause dementia and with MCI. Cognitive and depression scores also improved in MCI subjects, unlike subjects with advanced dementia; the lack of a mood effect is attributed to impaired awareness and the scale used. The failure to reduce antipsychotic use in advanced dementia may be due to the small number of subjects on these drugs in this sample; further research with larger sample sizes is needed to address this issue. Also to be determined is if the beneficial effects reported here are due to guided IN2L computer engagement, free computer access or a combination. Importantly, this study showed that assisting with this research reduced CNA stress, which has implications for CNA wellness and for CNA cooperation in future clinical trials. Finally, this study showed a productive academic-long-term care/assisted living collaboration in a naturalistic setting.

Disclosures: P.F. Aravich: None. **A. Ord:** None. **A. Azher:** None. **A.P. Chidester:** None. **M.S. Binder:** None. **S. Sautter:** None.

Nanosymposium

012. Cognitive Dysfunction in Alzheimer's Disease and Related Dementias

Location: 152B

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***012.04

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

Title: Murine amyloid-beta disrupts the consolidation, but not retrieval, of contextual memories in C57BL/6J mice

Authors: *J. D. WHITE[1], C. URBANO[1], J. TAYLOR[1], J. L. PETERMAN[1], M. COOKSEY[1], B. COOPER[1], M. J. CHUMLEY[2], G. W. BOEHM[1]
[1]Dept. of Psychology, [2]Dept. of Biol., Texas Christian Univ., Fort Worth, TX

Abstract: The presence of soluble Aβ oligomers alters synaptic function and is implicated in cognitive dysfunction. Furthermore, established research in rodents indicates that intracerebroventricular (ICV) injections of human Aβ alters both the acquisition and consolidation of associative memories, but little is understood about how Aβ impacts the retrieval of those memories. Murine and human Aβ differ by three amino acids (R5G, Y10F, H13R) which alter aggregation efficacy and appear to diminish toxicity. The purpose of the present experiments was to determine how oligomeric murine Aβ impacts the consolidation and retrieval of associative memories. Using a contextual fear-conditioning (CFC) paradigm, three experiments were carried out to disentangle which phase of learning, consolidation and/or retrieval is impacted in the presence of murine Aβ oligomers. In Experiments 1 and 2, animals received an injection of Aβ or sterile saline immediately following training, or 6 hours post-training, and were tested in the same context 42-48 hours later. Results indicate that Aβ infusions immediately after training lead to decreased freezing behavior, indicating that murine Aβ disrupted the consolidation and possibly the retrieval of the context-shock pairing. In Experiment 3, animals were trained in CFC and received injections of Aβ or sterile saline 46 hours later. Two hours after infusions, freezing behavior was assessed in the same context. Results from Experiment 3 revealed that Aβ infusions 2 hours prior to testing had no impact on freezing behavior. Together these results indicate that Aβ is disrupting the consolidation of new memories, but is not impacting the recovery of previously consolidated information. This research suggests that despite differences between murine and human Aβ, e.g., the diminished aggregation properties of mAβ compared to hAβ, the functional outcomes on consolidation are strikingly similar. Thus, the use of mAβ may serve as a more ethologically valid model in which to explore subtle ways in which Aβ oligomers alter synaptic functioning.

Disclosures: **J.D. White:** None. **C. Urbano:** None. **J. Taylor:** None. **J.L. Peterman:** None. **M. Cooksey:** None. **B. Cooper:** None. **M.J. Chumley:** None. **G.W. Boehm:** None.

Nanosymposium

012. Cognitive Dysfunction in Alzheimer's Disease and Related Dementias

Location: 152B

Time: *Saturday, November 11, 2017, 1:00 PM - 3:00 PM

Presentation Number: *012.05

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

Support: NIH R01 NS088514
Alzheimer's Association New Investigator Research Grant NIRG-14-321722
NIA grant T32 AG 020494

Title: The effects of testosterone in chronic intermittent hypoxia induced neurodegeneration

Authors: *B. SNYDER[1], R. L. CUNNINGHAM[2]
[1]Univ. of North Texas Hlth. Sci. Ctr., Ft Worth, TX; [2]Ctr. for Alzheimer's and Neurodegenerative Dis. Res., Univ. North Texas Hlth. Sci. Ctr., Fort Worth, TX

Abstract: The recent failure of major drug trials to halt the progression of AD highlights the importance of identifying early contributors to the development of neurodegeneration to improve therapeutic outcomes. Sleep apnea is a common comorbidity of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) and may increase the risk of developing neurodegeneration. Sex differences in the onset and progression of these diseases implicate a role for sex hormones in the epidemiology of these diseases. Sleep apnea occurs more frequently in men and is associated with a decrease in the male sex hormone, testosterone (T). Our rodent model of mild chronic intermittent hypoxia (CIH) mimics the hypoxia experienced by patients with mild sleep apnea and has previously been shown to elevate oxidative stress and pro-inflammatory signals in the entorhinal cortex (ETC) and substantia nigra (SN), brain regions implicated in pre-clinical stages of AD and PD, respectively. Additionally, a decrease in testosterone is observed in our model. We hypothesize mild CIH will result in behavioral deficits associated with the SN and ETC, whereas maintaining T levels will prevent those deficits. To investigate this hypothesis, male Long-Evans rats were assigned to either intact, gonadectomy + T, or intact + T groups. Two weeks after hormone replacement, rats were exposed to CIH or room air (AHI = 8) for 12 days. During the last 5 days of CIH, cognitive and motor behavioral assessments were conducted. We observed a reduction in cognitive behaviors linked to ETC function, but not with hippocampal function. Further, fine motor skills were impaired but not gross motor skills. This suggests mild CIH induces deficits in brain regions associated with pre-clinical neurodegenerative pathology. Maintaining physiological levels of T reduced these outcomes. Thus, mild sleep apnea may be one early contributor to the risk of developing AD or PD.

Disclosures: B. Snyder: None. **R.L. Cunningham:** None.

Nanosymposium

012. Cognitive Dysfunction in Alzheimer's Disease and Related Dementias

Location: 152B

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***012.06

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

Support: NSFC grant 81400874
NSFC grant 31171080
NSFC grant 51136002

Michael Smith Foundation for Health Research
The Pacific Alzheimer Research Foundation

Title: Formaldehyde facilitates diabetes-related cognitive deficits

Authors: *Y. ZHANG[1], T. TAN[2], W. LUO[3], J. LV[4], C. HAN[5], J. N. HAMLIN[5], H. LUO[3], H. LI[3], Y. WAN[6], X. YANG[7], Z. TONG[2], W. SONG[1]
[1]Univ. of British Columbia, Vancouver, BC, Canada; [2]Capital Med. Univ., Beijing, China; [3]Shantou Univ. Med. Col., Guangdong, China; [4]Beijing Geriatric Hosp., Beijing, China; [5]McGill Univ., Montreal, QC, Canada; [6]Peking Univ., Beijing, China; [7]Central China Normal Univ., Wuhan, China

Abstract: Abstract: Patients suffering from type 2 diabetes mellitus (T2DM) often experience a significant decline in cognitive function. Hyperglycemia is one of the most prominent characteristics of diabetes, but how glycemic state contributes to cognitive dysfunction in T2DM remains elusive. Mitochondrial aldehyde dehydrogenase (ALDH2) is the major enzyme responsible for oxidizing FA and is ubiquitously expressed to promptly metabolize excess FA. Here, we report that T2MD patients with mutations in *ALDH2* gene had higher levels of FA associated with more severe dementia. Ablation of *ALDH2* gene expression induced abnormally high levels of FA, leading to hyperglycemia and cognitive impairments in mice. In addition, we found that excess FA interacts with insulin and impairs insulin signaling pathway, which contributes to memory decline in diabetic rodents. Reduction of FA by transgenic overexpression of hALDH2 attenuates hyperglycemia and alleviates cognitive deficits in different diabetic mouse models. These findings indicate the deleterious role of excess FA in mediating diabetic-related dementia. Targeting FA and its metabolizing enzyme ALDH2 may be a promising approach for preventing and treating dementia in diabetics.

Disclosures: Y. Zhang: None. **T. Tan:** None. **W. Luo:** None. **J. Lv:** None. **C. Han:** None. **J.N. Hamlin:** None. **H. Luo:** None. **H. Li:** None. **Y. Wan:** None. **X. Yang:** None. **Z. Tong:** None. **W. Song:** None.

Nanosymposium

012. Cognitive Dysfunction in Alzheimer's Disease and Related Dementias

Location: 152B

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***012.07

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

Support: National Natural Science Foundation of China (81671268)

Title: Activity CA3 pyramidal neuron improve cognitive functions via restoring synaptic deficits in Alzheimer's disease

Authors: D. SONG[1], Q. YANG[1], *H. QING[2]
[1]Beijing Inst. of Technol., Beijing, China; [2]Beijing Inst. of Technol., China

Abstract: Alzheimer's Disease (AD) is a neurodegenerative disorder, which feature shows memory deficits and synaptic dysfunction. It is reported that short-term memory is impaired significantly in AD pathogenesis. The CA3 region of hippocampus is important for rapid encoding of memory. Astrocytes are now viewed as key elements of neuronal communication and important synaptic modulator. However, the precise relationship between short term memory decline in early AD and synaptic modulation in CA3 is unknown. Here we report that photostimulation of pyramidal neuron with channelrhodopsin-2 in CA3 reverses the decline of short term memory, a delayed matching-to-place version of the Morris water in rapid one-trial learning maze task, in AD mouse. Photostimulation of pyramidal neuron restore synaptic density and also activate astrocyte, but not decrease the number of Aβ plaque. Moreover, we found that knockdown of astrocyte via shRNA and then activation of CA3 pyramidal neurons could not restore short-term memory, which indicated that activation of pyramidal neurons did not induce synaptic restore and memory rescue directly. Astrocyte maybe act a key role in middle process. Therefore, we activate astrocytes directly by optogenetics can restore short-term memory in AD mice, in which the synapses are increased as well. The results revealed that astrocyte is crucial to rescuing short-term memory decline and recovery of synaptic functions. Thus, induced neural activity to rescue synaptic functions via activation of astrocyte may provide a new treatment strategy of Alzheimer's disease. (Qinghu Yang and Da Song contibute equally to this work and will present the meeting together.)

Disclosures: **D. Song:** None. **Q. Yang:** None. **H. Qing:** None.

Nanosymposium

012. Cognitive Dysfunction in Alzheimer's Disease and Related Dementias

Location: 152B

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Presentation Number: *****012.08

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

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NHMRC-ARC Dementia Research Development Fellowship APP1097026
ARC Future Fellowship FT160100096
NHMRC Senior Research Fellowship APP1103258

Title: Cerebellar atrophy and its contribution to cognitive dysfunction in frontotemporal dementia subtypes

Authors: *Y. CHEN[1,3,4], F. KUMFOR[1,3,4], R. LANDIN-ROMERO[1,3,4], M. IRISH[1,3,4], J. HODGES[2,3,4], O. PIGUET[1,3,4]
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Abstract: Cerebellar degeneration is thought to primarily impact on motor function integrity. Emerging evidence, however, suggests that it also leads to cognitive deficits. The nature and patterns of cerebellar atrophy in dementia syndromes remains unclear. Frontotemporal dementia (FTD) refers to a heterogeneous group of neurodegenerative disorders primarily affecting the frontal and/or temporal lobes. Currently, three main subtypes are recognised: behavioural-variant FTD (bvFTD) is characterized by personality and behavioural changes, and impaired social cognition; semantic dementia (SD) is typified by an amodal loss of semantic knowledge and single-word comprehension; and progressive nonfluent aphasia (PNFA) presents impaired speech production and/or apraxia of speech. This study examined cerebellar grey matter integrity on MRI in FTD, and the relations between cerebellar degeneration and patterns of cognitive deficits in FTD subtypes. Forty-five bvFTD, 28 SD and 23 PNFA patients, meeting current clinical diagnostic criteria, and 35 age-, sex- and education-matched controls were included. Cerebellar grey matter integrity was investigated using voxel based morphometry. Each FTD subtype showed a specific pattern of cerebellar changes. Compared with controls, bvFTD showed intensity decrease in the right lobule VIIb with widespread changes in the cerebellar hemispheres and posterior vermis bilaterally. In SD, intensity decrease was found in the right Crus II extending into bilateral cerebellar posterior hemispheres. Finally, in PNFA, intensity decrease was observed in the right Crus II extending into bilateral cerebellar posterior and inferior hemispheres. Between group comparisons revealed greater intensity decrease in bvFTD in the right lobule VIIIa extending into right posterior and inferior hemisphere compared with SD, and in the right lobules VI and I-V compared with PNFA. Correlational analyses revealed that cerebellar grey matter degeneration in the bilateral hemispheres and the posterior vermis was associated with attention and working memory capacity in bvFTD. The bilateral cerebellar posterior and inferior hemispheres were associated with deficits in word repetition task in PNFA. Finally, the bilateral cerebellar posterior hemispheres were associated with semantic loss in SD, which were anatomically distinct from the regions found related to the word repetition task in PNFA. This study is the first to identify distinct patterns of cerebellar grey matter changes across FTD phenotypes, and provide evidence that cerebellar degeneration contributes to their cognitive deficits.

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Nanosymposium

013. Alpha-Synuclein, Tau, and PRP Aggregation and Transmission: Models and Therapeutics

Location: 140A

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**Topic: ***C.03. Parkinson's Disease

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Title: Therapeutic antibodies to alpha-synuclein targeting both truncated and full length alpha-synuclein forms bind to fibril seeds and attenuate seeding of alpha-synuclein aggregation by alpha-synuclein fibrils *In vitro* and *In vivo*

Authors: *P. KALLUNKI[1], A.-L. BERGSTROM[1], I. J. MALIK[1], F. SOTTY[1], L. B. VESTERAGER[1], K. JUST ANDERSEN[1], L. ØSTERGAARD PEDERSEN[1], J. B. STAVENHAGEN[1], P. PARREN[2], R. RADEMAKER[2], E. VAN DEN BRINK[2], T. VINK[2], D. SATIJN[2], J. EGEBJERG[1], K. FOG[1]
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Abstract: Alpha-synuclein (alpha-syn) is genetically linked to Parkinson's disease (PD) and intracellular aggregates of alpha-syn are the pathological hallmark of idiopathic PD. Secretion of alpha-syn into extracellular space and toxicity, and transmission of alpha-syn pathology between neurons is believed to contribute to disease progression. Antibodies to be used as immunotherapy against alpha-syn toxic forms are promising as therapeutic approach for slowing disease progression. Several post-translational modifications have been identified in alpha-syn, including phosphorylation, nitration, oxidation, ubiquitination and proteolytic truncations in amino and carboxy terminus of the protein. We have identified and characterized fully human antibodies against alpha-syn for the clinical development of an immunotherapy for Parkinson's disease (PD). The antibodies were produced against different forms of alpha-syn. Hybridomas from mice were screened for antibodies binding to the human alpha-synuclein secreted from mammalian cells. The antibodies were cloned and selected for specificity to alpha-synuclein and for having high affinity binding to monomeric and aggregated forms of alpha-syn, as well as all major post-translationally modified forms of the protein. The antibodies bind to preformed alpha-synuclein fibrils, are taken into cells with the fibrils and inhibit proteolysis of fibrils to truncated fragments, and inhibit seeding of alpha-syn aggregation in primary neuronal cultures. The effects of antibodies on alpha-syn seeding in vivo was assessed in mouse models where mice were intracerebrally inoculated with alpha-syn fibrils. In the in vivo mouse model antibodies attenuated the seeding of alpha-syn pathology, reducing the amount of cells with phosphorylated alpha-syn inclusions. The preclinical data supports that these antibodies can be developed for the treatment and prevention of PD.

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Nanosymposium

013. Alpha-Synuclein, Tau, and PRP Aggregation and Transmission: Models and Therapeutics

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Topic: *C.03. Parkinson’s Disease

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Title: The molecular tweezer CLR01 shows promise as a therapeutic agent in a mouse model of multiple system atrophy

Authors: *G. BITAN[1], M. HERRERA VAQUERO[2], M. KALLAB[2], D. BOUQUIO[1], K. BIGGS[1], J. OCHOA[1], W. POEWE[2], G. WENNING[2], F.-G. KLÄRNER[3], T. SCHRADER[3], N. STEFANOVA[2]
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Abstract: Multiple system atrophy (MSA) is characterized by deposition of fibrillar α-synuclein in glial cytoplasmic inclusions (GCIs) in oligodendrocytes. Similarly to other synucleinopathies, α-synuclein self-assembly is thought to be a key pathologic event in MSA and therefore, it is a prominent target for disease modification in MSA. We have been developing "molecular tweezers" which act as broad-spectrum nanochaperones that prevent formation of toxic protein oligomers and aggregates and enhance their clearance. Our current lead molecular tweezer, CLR01, has been shown to inhibit α-synuclein aggregation and toxicity in vitro and in vivo. Therefore, we asked if it could reduce α-synuclein load in a transgenic mouse model of MSA and ameliorate the disease phenotype. To answer this question, we applied CLR01 in the PLP-aSYN mouse model of MSA, which overexpresses human α-synuclein in oligodendroglia under control of the proteolipid protein promoter. To ensure exposure of the mouse brain to CLR01 in proof-of-concept experiments, we used intracerebroventricular administration of the compound by mini-osmotic pumps over one month. In follow-up experiments, we administered CLR01 continuously for two months via subcutaneously implanted pellets. CLR01 was found to restore an anxiety phenotype of MSA mice in the open-field test to wild-type control levels. Neuropathological analysis showed significant, dose-dependent reduction in α-synuclein-positive GCI density in brains of MSA mice receiving CLR01. The results demonstrate the therapeutic effect of CLR01 in the MSA mouse model and support development of the compound for human therapy.

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Nanosymposium

013. Alpha-Synuclein, Tau, and PRP Aggregation and Transmission: Models and Therapeutics

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**Topic: ***C.03. Parkinson's Disease

Support: Van Andel Research Institute

Title: Preformed alpha-synuclein fibrils induced synucleinopathy in organotypic brain slice cultures

Authors: A. ROUX, X. WANG, *J. MA
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Abstract: Alpha-synuclein (asyn), mostly in the serine 129 phosphorylated form (PS129asyn), is the major component of Lewy body and Lewy neurites, the pathological hallmark of synucleinopathies including Parkinson's disease. Despite strong evidence connecting asyn to neurodegeneration, the molecular mechanism responsible for asyn caused neurotoxicity remains unknown. Taking advantage of the "prion-like" spread of asyn aggregates, we established a chronic model of synucleinopathy by adding exogenous asyn aggregates to organotypic brain slice cultures, which results in asyn aggregation and neurotoxicity in a time-dependent manner. Rat organotypic brain slices were cultured and treated with murine pff (preformed recombinant asyn fibrils). A time-dependent PS129asyn accumulation was clearly detected with both immunofluorescent stain and immunoblot analyses. The same protocol was successfully applied to brain slice culture prepared from genetically modified mice. Using asyn knockout mice, we demonstrated that the accumulated PS129asyn was from endogenous asyn, which was completely absent in asyn knockout brain slices. Using brain slices derived from transgenic mice expressing human asyn on mouse asyn null background, the human pff similarly induced PS129asyn accumulation. In both rat and mouse slices, the PS129asyn was aggregated, appearing in the pellet fraction. More interestingly, the accumulation of aggregated PS129asyn was accompanied with a significant reduction in punctate staining of synaptophysin, which was aggravated in a time-dependent manner. Notably, the loss of synaptophysin staining pattern depends on the expression of endogenous asyn and was absent in pff-treated asyn knockout slices. These findings suggest to us that the synaptic toxicity results from pff-induced change of endogenous asyn, but not directly from pff. Overall, our system recapitulates the *in vivo* pathogenic changes in synucleinopathies, PS129asyn aggregation and accompanied neurotoxicity, in a relatively short time frame. The versatility of this system would allow us to elucidate the pathogenic mechanisms of synucleinopathies, and develop novel therapies against these devastating neurodegenerative disorders.

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Title: Inhibition of membrane-induced alpha-synuclein aggregation as a potential therapeutic strategy in Parkinson's disease

Authors: S. DUTTA[1], D. YSSELSTEIN[1], R. ARLINGHAUS[1], L.-K. LIN[2], C. J. GILPIN[3], L. A. STANCIU[2], *J.-C. ROCHET[1]
[1]Medicinal Chem. &Molecular Pharmacol, [2]Schools of Materials Engin. and Biomed. Engin., [3]LifeScience Microscopy Facility, Purdue Univ., West Lafayette, IN

Abstract: Genetic and neuropathological data suggest that aggregation of the presynaptic protein alpha-synuclein (aSyn) plays a central role in PD pathogenesis. Multiple lines of evidence suggest that the rate of aSyn self-assembly is markedly increased in the presence of phospholipid vesicles. Moreover, we have found that aSyn variants with an enhanced ability to undergo membrane-induced aggregation compared to wild-type aSyn elicit greater neuronal cell loss in primary midbrain cultures and have a high propensity to trigger vesicle permeabilization. These observations suggest that inhibiting membrane-induced aSyn aggregation and aSyn-mediated vesicle disruption could be a viable strategy to alleviate aSyn neurotoxicity in PD. To address this hypothesis, we used a phage-display screening approach to identify a set of heptapeptides with the ability to bind membrane-associated aSyn. Strikingly, four peptides were found to inhibit membrane-induced aSyn aggregation and aSyn-mediated vesicle disruption without affecting aSyn-lipid binding or aSyn fibrillization in the absence of lipids. Moreover, stabilized derivative forms of these peptides were found to penetrate neuronal cell membranes and alleviate aSyn neurotoxicity in primary midbrain cultures. Current efforts are focused on characterizing a library of five- and six-residue truncated forms of the initial heptapeptides in terms of their effects on membrane-induced aSyn aggregation and aSyn-mediated vesicle disruption, with the goal of identifying derivatives that retain inhibitory activity but could potentially have increased

brain bioavailability in vivo. Additional efforts are aimed at screening libraries of drug-like compounds to identify small molecules with the ability to inhibit aSyn-mediated membrane permeabilization and neurodegeneration. Collectively, our findings provide strong support for the hypothesis that membrane-induced aSyn self-assembly plays a central role in PD pathogenesis, and they lay the foundation for developing therapies to interfere with aSyn neurotoxicity in the brains of patients.

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Nanosymposium

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Title: α-synuclein fibril-induced inclusion spread in rats and mice correlates with dopaminergic neurodegeneration

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Abstract: Proteinaceous inclusions in neurons, composed primarily of α-synuclein, define the pathology in several neurodegenerative disorders. Neurons can internalize α-synuclein fibrils that can seed new inclusions from endogenously expressed α-synuclein. The factors contributing to the spread of pathology and subsequent neurodegeneration are not fully understood. Further, the relationship between inclusions and neurodegeneration is not clear. On the one hand, neurodegeneration may inhibit spread of inclusions to other neurons. Alternatively, neurodegeneration may precipitate spread of inclusions to other neurons. Here, we tested the relationship between inclusion spread and neurodegeneration in evaluating mice and rats injected with fibrils at either dopaminergic terminals in the dorsal striatum or in the substantia nigra at dopamine neuron cell bodies. In mice, fibril injections in the dorsal striatum resulted in dopaminergic neurodegeneration that correlated with the spread of the pathology outside of the striatum. Unexpectedly, C3H/HeJ mice were much more sensitive to inclusion formation and neurodegeneration than C57BL/6J mice. In rats, injection of fibrils into the substantia nigra pars

compacta (SNpc) resulted in a gradual spread of pathology to medium spiny neurons in the dorsal striatum, and this closely correlated with dopaminergic neurodegeneration. Thus, in both mice and rats, inclusion spread, particularly from the SNpc to the striatum, positively correlates with dopaminergic neurodegeneration. These results suggest that inclusion spread in the brain may be promoted by the loss of neurons.

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013. Alpha-Synuclein, Tau, and PRP Aggregation and Transmission: Models and Therapeutics

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**Topic: ***C.03. Parkinson's Disease

Support: Parkinson Disease Association of Alabama
Michael J. Fox Foundation

Title: Neuronal defects caused by early formation of alpha-synuclein inclusions

Authors: *L. A. VOLPICELLI-DALEY[1], J. M. FROULA[1], B. W. HENDERSON[1], J. GONZALEZ[2], J. H. VADEN[2], L. OVERSTREET-WADICHE[2], J. H. HERSKOWITZ[1]
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Abstract: Abundant evidence suggests that pathologic aggregates of alpha-synuclein contribute to the progression and symptoms of Parkinson's disease (PD). These inclusions appear throughout the nervous system including the enteric nervous system, sympathetic ganglion, nerves of the cardiac conduction system, dorsal motor nucleus of the vagus nerve, spinal cord, brainstem, hypothalamus, amygdala, hippocampus, and cortex. Although it is clear that loss of dopamine neurons in the substanta nigra pars compacta causes the cardinal motor symptoms of PD, many brain regions with abundant alpha-synuclein inclusions do not show obvious neuron loss. But, alpha-synuclein inclusions in these neurons could contribute to neuronal dysfunction, leading to some of the non-motor features of PD such as cognitive dysfunction. Furthermore, understanding how alpha-synuclein aggregates impact neuronal function at the early stages of their formation will help identify potential therapeutics that could enhance neuron function and/or prevent alpha-synuclein aggregation before the irreversible onset of neuron death. We previously showed that addition of alpha-synuclein fibrils to primary neurons causes formation

of inclusions that closely resemble those found in PD brains. We will present phenotypes in neurons caused by the early formation of fibril-induced alpha-synuclein inclusions at time points well before the neurons begin to die. Such phenotypes include selective defects in trafficking of endosomes, defects in calcium influx and neuronal synchronization, changes in presynaptic function, and altered synaptic structure. These findings could help researchers by providing additional assays of neuronal dysfunction caused by abnormal alpha-synuclein. These findings may also help determine mechanisms by which alpha-synuclein aggregates could cause defects in neuron subtypes that do not show obvious degeneration.

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013. Alpha-Synuclein, Tau, and PRP Aggregation and Transmission: Models and Therapeutics

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Title: Pharmacological inhibition of the NLRP3 inflammasome protects against synuclein pathology and dopaminergic degeneration

Authors: *R. GORDON[1], E. A. ALBORNOZ[2], D. C. CHRISTIE[2], M. R. LANGLEY[4], V. KUMAR[2], S. MANTOVANI[2], A. A. B. ROBERTSON[2], M. S. BUTLER[3], L. A. O'NEILL[5], A. G. KANTHASAMY[4], K. SCHRODER[2], M. A. COOPER[3], T. M. WOODRUFF[2]
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Abstract: Parkinson's disease (PD) pathology is characterized by a profound loss of nigral dopaminergic neurons that is accompanied by chronic neuroinflammation and extensive α-synuclein inclusions in the form of Lewy-bodies. Fibrillar synuclein has recently been shown to be the major neurotoxic species in PD, mediating cell-to-cell transmission and neuropathology. However, the mechanisms by synuclein pathology and spread contributes to dopaminergic degeneration remain unclear. Chronic activation of the NLRP3 inflammasome in the CNS by

insoluble protein aggregates, is emerging as a major pathological mechanism that can drive progressive neurodegeneration. Herein, we demonstrate that activation of the microglial NLRP3 inflammasome is a common pathway triggered by both fibrillar synuclein and by dopaminergic degeneration in the absence of synuclein aggregates. Key hallmarks of inflammasome activation including cleaved caspase-1 p20, and ASC upregulation are evident in the substantia nigra of PD patients. Similarly, we also found extensive NLRP3 inflammasome in multiple pre-clinical mouse models of PD. Our mechanistic studies with primary microglia demonstrate that fibrillar Syn activates the NLRP3 inflammasome with delayed kinetics compared to canonical NLRP3 agonists. Crucially, we demonstrate that the potent NLRP3 inhibitor, MCC950, is active in the central nervous system following oral dosing, and can effectively block inflammasome activation and neuropahtology in PD models. Significantly, chronic daily oral dosing of MCC950 effectively protected against motor deficits and nigrostriatal dopaminergic degeneration induced by synuclein fibrils in the pre-formed fibril model of synuclein pathology. Collectively, these findings suggest that the microglial NLRP3 inflammasome pathway could be a sustained source of neuroinflammation that drives PD pathology, and highlights microglial NLRP3 as a novel therapeutic target for PD.

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013. Alpha-Synuclein, Tau, and PRP Aggregation and Transmission: Models and Therapeutics

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**Topic: ***C.03. Parkinson's Disease

Title: Differential distribution of alpha-synuclein disease-causing mutants in extracellular vesicles

Authors: *M. INGELSSON[1,2], G. GUSTAFSSON[1], D. SEHLIN[1], A. ERLANDSSON[1], J. BERGSTRÖM[1], T. F. OUTEIRO[3], X. O. BREAKEFIELD[2], B. T. HYMAN[2], C. LÖÖV[2]
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Abstract: Background Observations indicate that propagation of pathology in the Parkinson's disease brain may be caused by spreading of α-synuclein (α-syn) between cells. The underlying

mechanisms are largely unknown, although evidence suggest that exosomes or other extracellular vesicles (EVs) may be involved. In this context, disease-causing α-syn mutants may lead to accelerated pathology by promoting their distribution in EVs. **Objective** To investigate whether the different α-syn mutants are more readily incorporated into EVs than wild type α-syn. **Methods** The human neuroblastoma SH-SY5Y cell line, cultured in media with vesicle-depleted serum, was either non-transfected or transfected with expression constructs for wild type α-syn or any of the six different disease-causing α-syn mutants (A30P, E46K, H50Q, G51D, A53E and A53T). Ultracentrifugation of cell-free conditioned media at 100,000 x *g* generated EV and extracellular (EC) fractions. Western blot and electron microscopy were used to assess the presence of vesicular proteins/structures in the respective fractions. All samples, including cell lysates, were measured by ELISA for total α-syn levels. The EV fractions were analyzed with or without addition of detergent (RIPA) to assess the levels within and on the outside of the EVs, respectively.
Results The EV fractions displayed vesicles of 100-300 nm that were positive for EV marker flotillin-1. Nano- to picomolar levels of α-syn could be detected in cell lysates and in the two different fractions released from transfected cells. Approximately 0.1-2% of secreted α-syn was found to be associated with vesicles. The major part of EV-associated α-syn was attached to the outside of the particles, whereas a smaller fraction was found in their lumen. Among the six different disease-causing α-syn mutants, A53T led to a significant increase of α-syn levels in the EV fraction, as compared to the wild type protein. For two other mutants, H50Q and G51D, there was a redistribution of α-syn from the outside to the inside of the vesicles. **Conclusions** Our data suggest that human neuroblastoma cells secrete α-syn both as free-floating protein and via EVs. Moreover, we found that the A53T mutant was especially directed into EVs released from cells, whereas two other mutations, H50Q and G51D, seemed to promote internalization of α-syn into EVs. Taken together, our findings suggest that a mutation-induced loss of physiological function or altered aggregation properties of α-syn may shift cellular processing of some mutants towards vesicular release. Our findings thus lend further support to the theory that EVs are mediators of extracellular spreading of pathological α-syn species.

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Nanosymposium

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Title: Pathological tau strains from human brains recapitulate the diversity of tauopathies in nontransgenic mouse brain

Authors: *S. NARASIMHAN, J. L. GUO, L. CHANGOLKAR, J. D. MCBRIDE, L. V. SILVA, Z. HE, B. ZHANG, R. J. GATHAGAN, J. Q. TROJANOWSKI, V. M.-Y. LEE
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Abstract: Pathological tau aggregates occur in Alzheimer's disease (AD) and other neurodegenerative tauopathies. It is not clearly understood why tauopathies vary greatly in the neuroanatomical and histopathological patterns of tau aggregation, which may contribute to clinical heterogeneity in these disorders. Recent studies have shown that tau aggregates may form distinct structural conformations, known as tau strains, similar to prion protein strains. Here, we developed a novel model to test the hypothesis that cell-to-cell transmission of different tau strains occurs in non-transgenic (non-Tg) mice. By injecting pathological tau extracted from postmortem brains of AD (AD-tau), progressive supranuclear palsy (PSP-tau) and corticobasal degeneration (CBD-tau) patients into different brain regions of non-Tg mice, we demonstrated the induction and propagation of endogenous mouse tau aggregates. Specifically, we identified differences in tau strain potency corresponding to different rates of propagation between AD-tau, CBD-tau and PSP-tau in non-Tg mice. Moreover, differences in cell-type specificity of tau aggregate transmission were observed between the tau strains such that only PSP-tau and CBD-tau strains induced astroglial and oligodendroglial tau inclusions, recapitulating the diversity of neuropathology in human tauopathies. Furthermore, CBD-tau and PSP-tau injected mice showed spatiotemporal transmission of glial tau pathology over time, suggesting glial tau transmission contributes to the progression of tauopathies. Finally, we demonstrated the neuronal connectome, but not the tau strain, determines which brain regions develop tau pathology. Taken together, our data suggest that different tau strains determine seeding potency and cell-type specificity of tau pathology formation that underlie the diversity of human tauopathies.

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**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases -dementias, and Prion diseases

Support: NIH Grant AG021601
NIH Grant AG02132

Title: Sequelae of anti-prion therapeutics and the appearance of drug resistance

Authors: *K. GILES, N.-T. T. NGUYEN, D. B. BERRY, C. CONDELLO, A. OEHLER, B. N. DUGGER, S. B. PRUSINER
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Abstract: There are no therapeutics that halt or slow any neurodegenerative disease, presenting a growing socioeconomic challenge as the population ages. The prototypical prion diseases are caused by self-templated aggregation of the prion protein (PrP) in the brain. Moreover, distinct PrP conformations, or strains, produce unique biochemical and neuropathological phenotypes characterized by vacuolation, PrP deposition, and robust astrocytic gliosis as evidenced by upregulation of glial fibrillary acid protein (Gfap). A mounting body of evidence suggests that Alzheimer's and Parkinson's diseases propagate by a similar conformational templating mechanism of other endogenous proteins. We have developed a range of compounds that extend survival of PrP prion-infected mice. In most instances, these compounds also lead to the development of new strains, some of which showed resistance to the compound used for the initial treatment. The appearance of such drug resistance is a major challenge to drug development efforts. We previously reported that the compound IND125 extends survival of prion-infected mice up to 3-fold and reduces the neuropathological hallmarks of prion disease. Interestingly, we observed a difference in efficacy of IND125 between wild-type (wt) mice and those overexpressing PrP, suggesting prion propagation kinetics may play a role in efficacy and the development of drug resistance. To help develop more effective anti-prion therapeutics, we determined the changes occurring upon IND125 treatment of wt and PrP-overexpressing mice. We monitored disease progression in vivo by bioluminescence imaging using a luciferase reporter driven by the Gfap promoter and observed a sustained suppression of Gfap signal in treated mice, rising only shortly before clinical onset. To define further the spatiotemporal changes in gliosis, we analyzed a time course series of prion-infected mice treated with IND125. Using Western blotting and immunohistochemistry, we quantified levels of astroglial and microglial markers. In addition, we characterized the levels and distribution of vacuolation and disease-associated PrP in the brains of treated mice. To investigate the appearance of drug

resistance following treatment with IND125, we infected cell cultures with brain homogenate from time course samples and treated them with increasing concentrations of IND125. Our studies provide insight into the sequelae of therapeutic intervention in PrP prion diseases. The common mechanistic principles of conformational templating suggest this work may aid in the generation of new drugs to treat more prominent neurodegenerative diseases.

Disclosures: K. Giles: None. **N.T. Nguyen:** None. **D.B. Berry:** None. **C. Condello:** None. **A. Oehler:** None. **B.N. Dugger:** None. **S.B. Prusiner:** None.

Nanosymposium

013. Alpha-Synuclein, Tau, and PRP Aggregation and Transmission: Models and Therapeutics

Location: 140A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***013.11

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Title: Anti-tau antibodies reduce tau seeding induced by pathological tau species and Alzheimer-like tauopathy in primary neurons from rTg4510 mice

Authors: *C. VOLBRACHT, L. HELBOE, L. ØSTERGAARD PEDERSEN, J. FALSIG PEDERSEN, N. ROSENQVIST, J. TORLEIF PEDERSEN
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Abstract: The abnormal hyperphosphorylation of the microtubule-associated protein tau plays a crucial role in neurodegeneration in Alzheimer's disease (AD) and aggregation of hyperphosphorylated tau into neurofibrillary tangles (NFTs) is a hallmark in AD. The mechanisms underlying the transformation of highly soluble normal tau into insoluble NFTs remain unclear. We established an assay in primary neurons isolated from tau transgenic rTg4510 mice in which NFT-like tau aggregates develop to investigate mechanisms of tau pathogenesis and tau-based therapeutics *in vitro*. The rTg4510 mouse strain overexpresses an inducible human mutant P301L tau and displays age-dependent tau pathology including NFTs. Primary cortical cultures isolated from embryonic rTg4510 mice were expressing human mutant P301L tau without presenting tau pathology and were incubated with low concentrations of pathological tau species isolated from AD or aged rTg4510 brains. Sarkosyl-insoluble hyperphosphorylated tau species were spontaneously taken up by cortical neurons and initiated seeding of normal endogenous human tau in rTg4510 cortical cultures over long term incubation periods. Tau seeding in neurons was characterized by recruitment of soluble endogenous tau into inclusions of aggregated and hyperphosphorylated tau displayed as mobility shifted tau bands at higher molecular weight on SDS page recapitulating some features of Alzheimer-like tauopathy

in neurons *in vitro.* Anti-total tau and anti-phosphorylated tau (P-tau) antibodies significantly reduced tau seeding and aggregation in rTg4510 cortical cultures. These findings indicate that low amounts of exogenous pathological tau species can corrupt normal endogenous tau and induce tau seeding and pathology in primary neurons *in vitro*, suggesting a seeding and recruitment process as a possible mechanism underlying NFT formation *in vivo*. Further, our findings suggest that anti-tau antibodies can obstruct the tau seeding and aggregation process *in vitro*.

Disclosures: C. Volbracht: A. Employment/Salary (full or part-time):; H.Lundbeck A/S. **L. Helboe:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **L. Østergaard Pedersen:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **J. Falsig Pedersen:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **N. Rosenqvist:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **J. Torleif Pedersen:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S.

Nanosymposium

013. Alpha-Synuclein, Tau, and PRP Aggregation and Transmission: Models and Therapeutics

Location: 140A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***013.12

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant AG043415
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ADDF Funds

Title: MW150, a novel isoform selective p38αMAPK inhibitor drug candidate, protects against memory loss in mouse models of tauopathy

Authors: *O. ARANCIO[1], A. STANISZEWSKI[2], J. SCHAVOCKY[3], S. ROY[3], J. PELLETIER[3], M. WINDISCH[4], D. M. WATTERSON[3]
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Abstract: Synaptic dysfunction is a common denominator for dementia in neurodegenerative diseases and brain injury. An accumulating body of clinical and preclinical evidence implicates stress related kinases in CNS disease progression, with brain p38αMAPK directly implicated as a potential neurotherapeutic target for synaptic dysfunction. Activation of p38αMAPK in both

neurons and glia, the interacting cellular components of the synaptic pathophysiological axis, offers a potential for enhanced pharmacological efficacy via pleiotropic action of a single drug working through a single target. However, achieving the neurotherapeutic goal was not possible prior to the availability of MW01-18-150SRM (a.k.a. MW150), a novel, blood brain barrier penetrant, highly selective, small molecule drug candidate that is functional in multiple animal models of Alzheimer's disease (AD). Congruent with this potential novel mechanism, MW150 improves synaptic/memory outcomes in distinct AD models based on amyloid-beta deposition when used in preventive or disease stage dosing paradigms without altering amyloid-beta levels. MW150 efficacy and pharmacodynamic effects in animal models are consistent with its known mechanisms of action and link the engaged target to pathophysiology progression. However, MW150 targets distinct pathways from current AD drugs or those in late stage clinical trials. Therefore, we have extended our efficacy investigations to preclinical models based on tau in order to provide proof of concept for MW150 potential for future trials in tauopathies. Specifically, we tested the efficacy of MW150 against memory loss in two distinct mouse models. In the first study, we determined whether a single i.p. injection of the inhibitor rescues both the defect in associative memory during a contextual fear learning paradigm and that in short-term spatial memory assessed through the 2-day radial arm water maze due to a brief infusion of tau oligomers onto hippocampus of wild-type mice. In the second study, we determined whether the prolonged oral administration for 45 days of the inhibitor rescued the same memory defects in the rTg4510 mouse model of tauopathies. Both studies showed that MW150 was capable of improving the tau dependent cognitive impairments. Thus, these findings extend the possibility of MW150 use for prevention and treatment of tauopathies. The animal model efficacy outcomes, combined with the previously reported candidate selection criteria and recent positive outcomes of IND-enabling safety pharmacology and toxicity analyses, make MW150 a unique choice for future clinical investigations.

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Nanosymposium

013. Alpha-Synuclein, Tau, and PRP Aggregation and Transmission: Models and Therapeutics

Location: 140A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***013.13

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Title: Global *In vivo* repression of endogenous mouse tau with systemic delivery of a zinc-finger protein transcription factor

Authors: *S. DEVOS[1], B. ZEITLER[2], S. WEGMANN[1], K. MARLEN[2], H.-O. NGUYEN[2], Q. YU[2], D. MACKENZIE[1], C. COMMINS[1], B. CORJUC[1], M. C. HOLMES[2], B. RILEY[2], S. ZHANG[2], B. T. HYMAN[1]
[1]Massachusetts Gen. Hosp., Charlestown, MA; [2]Sangamo Therapeutics, Inc., Richmond, CA

Abstract: The neuronal microtubule associated protein tau is associated with neurodegeneration in many disease contexts. Several studies have suggested the use of tau lowering agents as a possible therapeutic treatment for primary tauopathy disorders, including Alzheimer's Disease (AD), Progressive Supranuclear Palsy, Corticobasal Degeneration, and others. The genetic ablation of mouse tau or its transient decrease with antisense oligonucleotides have demonstrated the functional benefit of tau reduction in mice. Here we describe the results from a single intravenous (IV) administration of a zinc-finger protein transcription factor (ZFP-TF) designed to repress endogenous mouse tau. Recent advances in the field of AAV engineering have yielded vector varaints capable of widespread central nervous system (CNS) transduction following IV delivery, including AAV-PHP.B (CREATE system), AAV-AS, and AAV-BR1. To evaluate ZFP-TF mediated tau reduction upon systemic AAV delivery, we coupled a highly specific and potent ZFP-TF targeting tau with the AAV9-derived CNS trophic capsid, AAV-PHP.B. A single IV administration of the ZFP-TF delivered with an AAV PHP.B vector to adult mice achieved greater than 50% global CNS sustained neuronal repression of mouse tau mRNA and protein across multiple brain and spinal cord regions. The extensive tau mRNA and protein reduction throughout the CNS provided an opportunity to monitor the impact of ZFP-TF treatment on tau levels in the cerebrospinal fluid (CSF). Studies are currently underway to evaluate the efficacy of a systemically delivered ZFP-TF on global tau reduction in AD mouse models. These results support the further study of potent and exquisitely specific ZFP-TFs and novel CNS-trophic AAV serotypes for use in tauopathy diseases.

Disclosures: **S. DeVos:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Sangamo Therapeutics, Inc. **B. Zeitler:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sangamo Therapeutics, Inc. **S. Wegmann:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Sangamo Therapeutics, Inc. **K. Marlen:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics, Inc. **H. Nguyen:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics, Inc. **Q. Yu:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics, Inc.. **D. MacKenzie:** None. **C. Commins:** None. **B. Corjuc:** None. **M.C. Holmes:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics, Inc. **B. Riley:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics, Inc. **S. Zhang:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics, Inc. **B.T. Hyman:** 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.; Sangamo

Therapeutics, Inc. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Sangamo Therapeutics, Inc..

Nanosymposium

014. Neuroinflammation: Virus and Infections

Location: 147B

Time: *Saturday, November 11, 2017, 1:00 PM - 2:45 PM

Presentation Number: *014.01

Topic: *C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: K02DA027374
R01Da033200
R01DA018633
R01DA034231

Title: $GABA_A$ agonist muscimol reverses morphine and HIV-Tat-induced calcium overload in hippocampal neurons

Authors: *V. D. MCLANE[1], P. E. KNAPP[2], K. F. HAUSER[1]
[1]Pharmacol. and Toxicology, [2]Anat. and Neurobio., Virginia Commonwealth Univ., Richmond, VA

Abstract: Human immunodeficiency virus (HIV)-1 infiltrates the central nervous system (CNS) early in infection, leading to the production of neurotoxic HIV-1 proteins such as *transactivator of transcription* (Tat) and the development of HIV-associated neurocognitive disorders. Opiates such as morphine exacerbate HIV-induced neuropathogenesis in multiple regions of the CNS, including the hippocampus. Transgenic Tat expression in mice correlated to reduced spine density, impaired long-term potentiation and a decline in specific inhibitory interneuron populations within the CA1 region of the hippocampus. Morphine has been shown to amplify Tat-induced calcium overload and inhibit GABAergic neurotransmission in striatal neurons, but morphine's effects on Tat-induced neurodegeneration within the hippocampus are underexplored. In this study, we cultured hippocampal neurons from E17 CD-1/ICR mice and assessed the effects of Tat (100 nM), morphine (500 nM), and $GABA_A$ agonist muscimol (100 nM) *in vitro*. 72 h of exposure to recombinant Tat significantly reduced overall neuron survival from 94.5 ± 0.4% to 85.9 ± 3.3%, while morphine and Tat co-exposure improved survival to 92.3 ± 1.8% (two-way interaction, $p<0.001$, repeated measures ANOVA). To discern inhibitory from excitatory populations *in vitro*, we co-labeled neurons for GABAergic marker GAD67 and pan-neuronal marker MAP2 via immunocytochemistry. After 72 h, Tat exposure reduced the GAD67+ neuronal population from 10.5 ± 0.4% to 8.6 ± 0.6% of the neuronal population ($p<0.001$, three-way ANOVA). Acute Tat exposure increased intracellular calcium concentration

by 193.9±53.9% in hippocampal neurons, an effect which was further exacerbated by morphine pretreatment (312.0±31.5%). Muscimol prevented the Tat-induced calcium increase in both morphine- and vehicle-treated cells, reducing intracellular calcium to 87.3±20.0% of control levels in neurons that received muscimol, morphine, and Tat (three-way interaction, $p<0.001$, repeated measures ANOVA). Overall, we found that HIV-Tat treatment reduced survival of GAD67+ GABAergic neurons *in vitro*, while $GABA_A$ agonist muscimol reversed the combined effects of morphine and HIV-Tat on intracellular calcium levels in hippocampal neurons. The impact of HIV-Tat and morphine on GABAergic neurons likely contributes to excitotoxicity and synaptodendritic damage in hippocampal pyramidal cells, thereby increasing hippocampal circuit dysfunction and further contributing to the development of HIV-associated neurocognitive disorders.

Disclosures: V.D. McLane: None. **P.E. Knapp:** None. **K.F. Hauser:** None.

Nanosymposium

014. Neuroinflammation: Virus and Infections

Location: 147B

**Time: ***Saturday, November 11, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***014.02

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant AI097299

Title: Neurotrophic factors and stress hormones selectively regulate herpes simplex virus 1 and 2 (HSV1 and HSV2) infections in peripheral sensory and autonomic neurons

Authors: *A. S. BERTKE, A. M. IVES, A. A. YANEZ
Virginia Tech., Blacksburg, VA

Abstract: Herpes simplex viruses (HSV1 and HSV2) infect and establish latency in peripheral neurons after ocular or genital infection, and can reactivate in response to various environmental triggers to produce different patterns and frequencies of recurrent disease throughout the life of the host. Previous studies have shown that the viruses preferentially replicate and establish latency in different types of sensory neurons, as well as in neurons of the autonomic nervous system. To determine which types of neurons support HSV1 and HSV2 reactivation in response to triggers commonly associated with recurrent disease, we infected primary adult murine sensory and autonomic neuronal cultures, and either treated them with stress hormones or deprived them of target-derived neurotrophic factors to simulate epithelial injury. Deprivation of neurotrophic factors neurturin and glial cell derived neurotrophic factor (GDNF) induced reactivation of HSV1 and HSV2 in sensory neurons expressing glial family receptors, while

NGF deprivation was only able to reactivate HSV1 in sympathetic neurons. Treatment with stress hormones epinephrine (EPI) and corticosterone (CORT) selectively induced HSV1 or HSV2 reactivation; HSV1 only reactivated in sympathetic neurons in response to EPI or CORT, while HSV2 reactivated in both sensory and autonomic neurons but only in response to CORT. Thus, sensory and autonomic neurons respond to different exogenous factors to selectively induce HSV1 and HSV2 reactivation, demonstrating that different types of peripheral neurons have alternative mechanisms to control neurotropic virus infection. These results may also explain divergent patterns and frequencies of recurrent HSV-related disease.

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Nanosymposium

014. Neuroinflammation: Virus and Infections

Location: 147B

**Time: ***Saturday, November 11, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***014.03

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: 1F32MH105288
MH104147
MH64570
P30 AI078494

Title: Complement dependent synapse loss in a mouse model of HIV-associated neurocognitive disorders

Authors: *J. W. HAMMOND[1], W. Q. QIU[2], D. F. MARKER[2], M. J. BELLIZZI[2], S.-M. LU[2], H. A. GELBARD[2]
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Abstract: Microglia activation, enhanced cytokine production, and a reduction in synaptic density are key pathological features of HIV-associated neurocognitive disorders (HAND). Even in the presence of combination antiretroviral therapy (cART), more than 50% of HIV-positive individuals experience cognitive impairment. Although viral replication is inhibited by cART, HIV proteins such as TAT and gp120 are still produced within the nervous system which are neurotoxic and stimulate neuroinflammation. Excessive brain production of complement proteins has been reported to be aberrantly high in the CSF of HIV+ individuals with cognitive impairment. As complement deposition on synapses followed by microglial engulfment has been shown during development and in disease as a mechanism for pruning synapses we have tested

whether complement is required for the synapse loss in a cortical TAT injection mouse model of HAND. In TAT-injected animals, we see elevated levels of early complement pathway components, C1q and C3, even 28 days after injection which is associated with a loss of synaptic terminals and dendritic spines as well as microgliosis. Furthermore, synaptic debris can be colocalized inside microglia suggesting phagocytosis of synapses. C1qA knockout mice were protected from a portion of this TAT-induced synapse loss. We conclude that pathologic activation of the early classical complement pathway mediates synapse elimination and thus likely contributes to the cognitive impairments connected with HAND.

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Nanosymposium

014. Neuroinflammation: Virus and Infections

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**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

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NIH Grant DA027374
NIH Grant DA033200
NIH Grant DA034231
NIH Grant DA037096
NIH Grant DA007027

Title: The effects of HIV-1 Tat and morphine on hippocampal function

Authors: *W. MARKS[1,2], V. D. MCLANE[2], A. R. MCQUISTON[3], P. E. KNAPP[3], K. F. HAUSER[2]
[2]Pharmacol. and Toxicology, [3]Anat. and Neurobio., [1]Virginia Commonwealth Univ., Richmond, VA

Abstract: Neuro-acquired immunodeficiency syndrome (neuroAIDS) affects 30-50% of HIV infected individuals, and is marked by a suite of neurocognitive disorders including hippocampally mediated spatial memory deficits. NeuroAIDS pathogenesis can be compounded by comorbid opioid abuse, which presents a unique public health challenge in light of the current opioid abuse epidemic. We performed studies to examine the comorbid interaction of HIV-1 Tat and morphine on hippocampal function utilizing inducible HIV-1 tat transgenic mice in which the Tat transgene had been induced for a total of ten days administered implanted with a pellet

containing a placebo, or morphine sulfate (time release, ~5mg/day) on day 5 of Tat induction. In the Barnes maze spatial memory task, while no changes were seen in escape latency measures, a significant interaction between HIV-1 Tat expression and morphine exposure was observed in the percent of time animals spent in the goal quadrant, with control animals spending a greater percent of time in the correct quadrant than any other group. Interestingly, morphine appeared to improve the performance of the Tat+ mice compared to Tat+ placebo controls rather worsen it. To identify potential drivers of this effect, electrophysiological studies were also performed to assess the circuit stability of the CA1 subfield of the hippocampus following Tat and/or sustained morphine exposure via time-release (~5 mg/day) subcutaneous implants with a focus on withdrawal-like effects induced by using bath solutions either containing or lacking morphine in slices from mice receiving the morphine implants. Baseline recordings from hippocampal slice preparations showed no difference in basic physiological properties or firing frequency in CA1 pyramidal cells. However, inhibiting AMPA, NMDA, and GABA receptors simultaneously, but not separately, revealed a reduced firing frequency with high current stimulus in Tat+ animals compared to Tat− animals regardless of morphine withdrawal status. These studies suggest that in the hippocampus, the expected comorbid relationship between Tat and opiates might be more complicated than expected.

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Nanosymposium

014. Neuroinflammation: Virus and Infections

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**Presentation Number: ***014.05

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH DA026306
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NIH MH087332

Title: Chronic, low dosage methamphetamine modifies memory performance compromised by exposure to HIV-1 Tat protein

Authors: *M. KAUL[1,2], R. MAUNG[1], D. OJEDA-JUAREZ[1], P. SANCHEZ-PAVON[1], A. B. SANCHEZ[1], A. J. ROBERTS[3], .-. TMARC GROUP[2]
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Abstract: Use of methamphetamine (METH) is associated with an increased risk of contracting an infection with human immunodeficiency virus type-1 (HIV-1). The combination of viral infection and METH appears to exacerbate HIV-associated neurocognitive disorders (HAND). METH abuse is a serious public health concern in its own right because it can lead to irreversible damage in the brain and behavioral changes. However, the combined effects of HIV-1 and METH on the brain are incompletely understood at the mechanistic level.
In order to model a chronic, low-dose METH regimen in the context of HIV infection of the brain, we subjected transgenic mice that express a tetracycline-inducible viral regulatory protein Tat in the brain (iTat mice) at 4 months of age to the following 12-week METH regimen: Week 1, starting at 0.5 mg/kg s.c., 1 x day, step-wise increase by 0.5 mg/kg with each injection over 5 days (Mon-Fri), followed by 11 weeks 1 x 2.5 mg/kg/day (Mon-Fri = 20+ days per month) In addition to METH the mice received i.p. Dox (100 mg/kg) for induction of Tat expression during week four of the regimen. The mouse cohort included rtTA-positive TRE-Tat-negative control animals, which cannot express Tat upon Dox injection, and comprised each about 50 % females and males. The body weights of the animals were recorded daily during the first week of the injections and afterwards on Monday and Friday of each week. Following a four months abstinence period and thus at 11-12 months of age, treated iTat-tg mice underwent behavioral assessment. The behavioral tests included optomotor test of vision (OPT), locomotor activity (LM), novel object recognition (NO) and Barnes maze test (BM; 4 day acquisition + probe trial). The NO and BM paradigms revealed that expression of Tat and exposure to METH each compromised behavioral performance. However, the combination of METH and Tat resulted in a gradual amelioration of the Tat effect in the NO paradigm and a virtually normal performance in the probe trial of the BM. The findings that METH can improve performance in memory tasks otherwise compromised by HIV infection may provide a potential explanation of why some HIV patients continue to use the psychostimulant despite an overall increased risk of neurocognitive deterioration.

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Nanosymposium

014. Neuroinflammation: Virus and Infections

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NIH Grant K02DA027374 (KFH)
NIH Grant R01DA018633 (KFH)

Title: HIV-1 Tat effects to influence morphine-tolerance, -dependence, and -conditioned place preference involve C-C chemokine receptor type 5

Authors: *J. J. PARIS[1], M. GONEK[2], V. D. MCLANE[2], K. M. LIPPOLD[2], P. E. KNAPP[3], W. L. DEWEY[2], K. F. HAUSER[2]
[2]Pharmacol. and Toxicology, [3]Anat. and Neurobio., [1]Virginia Commonwealth Univ., Richmond, VA

Abstract: Human immunodeficiency virus (HIV) and opioid dependence are comorbid epidemics. Within the U.S. alone, over 3,500 new infections involved intravenous drug use in 2015; a year in which overall drug overdose deaths rose another 11%, the majority (63%) of which involved opioids. Opioid dependence, caused by either licit or illicit usage, increases HIV progression and is associated with poorer long-term prognoses. The HIV-1 regulatory protein, trans-activator of transcription (Tat) has been shown to potentiate the rewarding effects of cocaine or alcohol in mice, but its behavioral interactions with opioids are only beginning to be examined. As such, we investigated the effects of morphine-tolerance, -dependence, and -abuse liability in a male, transgenic, murine model that conditionally expressed HIV-1 $Tat_{1\text{-}86}$ in a GFAP-driven manner. Mice were pretreated with vehicle or maraviroc, an antiretroviral drug and C-C chemokine receptor 5 (CCR5) antagonist, prior to morphine exposure. Consistent with recent findings, inducing Tat expression via administration of doxycycline, attenuated the antinociceptive potency of morphine in opioid-naïve mice (1.5-fold rightward ED_{50} shift). These effects were not observed in morphine-tolerant mice. Maraviroc by itself did not affect morphine tolerance (either in C57BL/6J or Tat-transgenic control mice), but significantly blocked Tat's effects to shift the morphine ED_{50} in opioid-naïve mice. In naloxone-precipitated withdrawal, Tat expression attenuated the proportion of mice that jumped from an elevated platform; whereas, maraviroc pretreatment increased jumping behavior in Tat-exposed mice. Moreover, Tat expression enhanced morphine reward in a conditioned place preference assay when mice were assessed in acute withdrawal and maraviroc further exaggerated these effects. Cytokine Bio-Plex™ assay revealed that Tat expression significantly elevated 16 out of 23 cytokines/chemokines assessed in the striatum of mice in acute morphine withdrawal, half of which could be attenuated by maraviroc pretreatment (particularly IL-12, G-CSF, GM-CSF, and MIP-1α). These data support the notion that HIV-1 Tat expression can attenuate morphine-mediated antinociception, an effect that can be blocked by maraviroc. However, maraviroc exacerbates Tat-withdrawal effects suggesting that CCR5 antagonism can increase morphine abuse liability in the withdrawn state. Studies are underway to further assess the CCR5-mediated mechanisms that may shift opiate/Tat interactions in withdrawal.

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Nanosymposium

014. Neuroinflammation: Virus and Infections

Location: 147B

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**Presentation Number: ***014.07

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

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Title: Exposure to neuroinflammatory HIV-1 Tat protein activates brain microglia, potentiates voluntary consumption and conditioned place preference responses to morphine, and reinstates extinguished reward-seeking behavior

Authors: *J. P. MCLAUGHLIN[1], T. J. CIRINO[2], S. O. EANS[2], J. M. MEDINA[2], H. M. STACY[2], K. A. HYMEL[2], M. J. KAUFMAN[3]
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Abstract: Exposure to the HIV-1 transactivator of transcription (Tat) protein in the CNS is sufficient to induce many of the changes associated with HIV infection such as neuroinflammation, and is known to modulate dopaminergic signaling. We hypothesized that HIV-1 Tat expression in brain would modulate the rewarding effects of the opioid painkiller, morphine. Using the GT-tg bigenic (iTat) mouse model, where brain-selective Tat expression is controlled by activation of a doxycycline (Dox) promotor, we tested the effects of Tat protein on morphine-conditioned place preference (CPP) and voluntary morphine consumption in a two-bottle choice (TBC) assay. Western blot analysis confirmed the expression of Tat protein in iTat mouse brain in a manner dependent on the dose and duration of Dox treatment over 14 days. Immunohistochemical labeling of Iba1 showed a concordant increase in brain microglial activation in Dox, but not saline-treated iTat mice, consistent with Tat-induced neuroinflammation. In behavioral testing, saline-treated GT-tg bigenic mice or Dox-treated G-tg mice (lacking the Tat gene) all demonstrated morphine-CPP responses similar to that of saline- or Dox-treated C57BL/6J mice. In contrast, Tat expression significantly increased morphine-CPP 3-fold in iTat mice. The magnitude of potentiation depended on the duration of Tat exposure. iTat, but not G-tg, mice treated 7d with Dox demonstrated significant increases in voluntary consumption of morphine in the TBC, effects that lasted up to a week after Tat induction. Expression of Tat protein also produced an exposure-dependent reinstatement of an extinguished morphine place preference response in previously uninduced mice. Daily pretreatment with the anti-inflammatory indomethacin, or an inhibitor of Tat protein, didehydro-Cortistatin A, during induction of Tat protein was without effect on morphine-CPP in saline-treated GT-tg mice, but prevented the potentiation of morphine-CPP in iTat mice, confirming a role for both Tat protein

and neuroinflammation in the Tat-induced increase in morphine reward. Overall, these data suggest that expression of HIV-1 Tat protein in mouse brain potentiated the rewarding effects of morphine in an exposure-dependent manner involving neuroinflammation, and suggests a biological means by which HIV infection may increase the vulnerability to opioid abuse and relapse in abstinent subjects.

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Nanosymposium

015. Touch, Itch, and Pain

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**Time: ***Saturday, November 11, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***015.01

**Topic: ***D.04. Somatosensation: Touch

Support: Max Delbruck Centrum

Title: The role of USH2A in cutaneous mechanosensation

Authors: *F. SCHWALLER, V. BEGAY-MULLER, B. MCDONALD, G. R. LEWIN
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Abstract: Our tactile environment is as varied as it is complex. Perception of the subtle differences of tactile stimuli relies upon high fidelity coding by mechanosensitive cutaneous sensory neurons. However, the mechanisms by which cutaneous sensory neurons transduce different felt textures into a neural code is poorly understood. Mechanotransduction is a feature common to both hair cells in the cochlea and sensory neurons in the skin, suggesting that the genetic determinants and molecular machinery of mechanotransduction may be partly shared between these two sensory systems. We have previously shown that mutations in the Ush2A that cause hearing loss are also associated with impaired tactile acuity in patients with Usher Syndrome type II. Ush2A encodes a protein with a large extracellular domain and known roles in cochlea hair cell stereocilia function. The aim of this study was to investigate the role of Ush2A in cutaneous mechanotransduction. Using the ex vivo skin nerve preparation, we show here that in Ush2A-/- mice, low-threshold mechanoreceptive Aβ-fibres in the glabrous and hairy hind paw skin exhibit deficits in their ability to code vibration and moving stimuli. Specifically, 42% of rapidly adapting mechanoreceptors (RAMs) recorded in Ush2A-/- mice were vibration insensitive, whilst vibration sensitivity in the remaining vibration-sensitive RAMs was impaired in the 5-50Hz range. Coding of high threshold mechanical stimuli by nociceptors was not impaired in Ush2A-/- mice. We next aim to investigate the ability of behaving Ush2A-/- mice to

perceive tactile and vibration stimuli. These findings indicate that Ush2A, a putative protein involved in extracellular tethering in cochlea hair cells, is also involved in vibration and gentle touch in the skin.

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015. Touch, Itch, and Pain

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**Presentation Number: ***015.02

**Topic: ***D.04. Somatosensation: Touch

Support: NS040538
NS070711

Title: Keratinocytes mediate innocuous touch and pain sensation

Authors: *F. MOEHRING[1], A. M. REYNOLDS[2], A. WEYER[2], A. MENZEL[2], T. ARZUA[3], M. GRZYBOWSKI[3], A. GEURTS[3], O. PALYGIN[3], C. L. STUCKY[2]
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Abstract: The conventional view in somatosensation is that peripheral sensory nerve endings are the initial and sole responders to environmental stimuli such as mechanical force and thermal stimuli. However, there is now clear evidence that sensory neurons are not acting alone, and that Merkel cell-neurite complexes are directly responsive to mechanical stimuli. Logically, external stimuli first come in contact with the epidermis, which is made up of 95% keratinocytes. While the primary function of keratinocytes has long been assumed to be barrier formation and protection, keratinocytes are in an ideal location to contribute to somatosensory functions since they are positioned closest to the external stimulus and lie closely apposed to sensory nerve terminals that innervate the epidermis. Here we sought to determine the roles keratinocytes play in sensing acute tactile and noxious stimuli *in vivo* and *ex vivo* in intact skin with the use of novel ATP biosensors and “cell sniffer” assays, as well as optogenetic and genetic deletion approaches. We demonstrate that ATP is released from the skin upon mechanical stimulation. Furthermore, degradation of ATP in skin *in vivo* resulted in decreased baseline mechanical as well as decreased noxious behavioral sensitivity. Degradation of ATP in *ex vivo* skin nerve recordings decreases responsiveness of afferent fibers. Optogenetic inhibition of keratinocyte function via selective Archaerhodopsin expression under a Keratin 14 Cre driver elevates the mechanical

thresholds and decreases noxious responses of naïve mice, thereby reflecting decreased tactile and nociceptive sensitivity. Conversely, optogenetic activation of keratinocytes via Channelrhodopsin elicits attending behavior responses to stimulated skin *in vivo*. Pharmacological inhibition of P2X receptors reduces normal behavioral mechanical and noxious sensitivity. This suggests that ATP released from keratinocytes acts via P2X receptors in non-injured skin. This study was designed to shed light on the roles that keratinocytes play in sensing baseline touch mechanisms. This will lay the foundation for understanding dysfunctional signaling processes during cutaneous inflammatory pain and disease and potentially reveal novel drug targets for topical therapeutics.

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**Topic: ***D.04. Somatosensation: Touch

Support: NIH Grant K12 GM081295
Burroughs Wellcome Fund PDEP

Title: High resolution mapping of sub-second behavior features of mouse paw withdrawal

Authors: *I. ABDUS-SABOOR, N. FRIED, P. DONG, J. BURDGE, M. LU, L. DING, W. LUO
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Abstract: Rodent models for the study of sensory transmission in the nervous system, including touch, pain, and itch, are critical in our efforts to understand how neural circuits encode behavior. For animal models to serve maximum benefits for uncovering neural circuit mechanisms for somatosensation, the measurement of behavior needs to be consistent and objective. Currently, most animal behavior scoring for nociception is heavily biased based on an experimenter's assumptions about a given stimulus, as opposed to being informed by an animal's kinematic movement features following stimulus application. To overcome these limitations with a more unbiased approach, here we use high-speed recording of mouse body movements with a focus on paw withdrawal, which is the most common output measurement used in both noxious and innocuous behavior assays. Using this analysis, we uncovered a combination of behavioral

syllables in two commonly used mouse strains that reliably discriminate between noxious mechanical and thermal pain responses versus non-noxious mechanical and thermal responses. Importantly, when these measures were analyzed in isolation, as is common in the field, the predictive power to distinguish a painful versus non-painful response in a given animal was quite low. Critically, the use of this combinatorial approach provides greater predictive power than the previously used binary output of paw withdrawal, allowing for a more refined understanding of the sensory experience. For example, for the first time we have been able to quantitatively determine what selective von frey hairs are actually measuring. Lastly, we validate our scoring paradigm using molecular optogenetics to drive the blue-light sensitive ion channel channelrhodopsin in mechanical pain sensing neurons. In summary, an unbiased and quantitative approach using high-speed recording of mouse behavior towards both natural stimuli and optogenetics, has given us an unprecedented description of the paw withdrawal response that should serve as a valuable reference for the field.

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**Topic: ***D.04. Somatosensation: Touch

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R21AR067399

Title: Neural recruitment and Mrgpr activity are required for the development of a mouse model of atopic dermatitis

Authors: *E. A. LERNER[1], T. LUO[1], E. AZIMI[1], S. B. ELMARIAH[2]
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Abstract: Atopic dermatitis is a common allergic skin disorder characterized by chronic inflammation and severe itch. In addition to defective barrier function and immune dysregulation, altered neural innervation and neurogenic inflammation play less well-characterized but important roles in disease pathogenesis. Performing serial *in vivo* imaging of fluorescently-labeled peripheral sensory neurons in mice during the evolution of an allergic eczema, we show that cutaneous nerves function as precursors to the allergic process. Within

hours of antigen exposure, neuropeptidergic fibers begin to pathfind and expand their arbors, while vascular and immune changes follow weeks later. Neural activity was required for the maintenance of nascent fibers and development of allergic skin inflammation. We identify Mas-related G protein coupled receptor signaling as an essential regulator of early neural responses to allergens, priming cellular feedback loops that drive allergic eczema and scratching. Our data provide critical insights regarding the temporal sequence of key cellular events in atopy pathogenesis and prompt a shift in the therapeutic paradigm for its management.

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**Topic: ***D.04. Somatosensation: Touch

Support: NIH Grant NS077224
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Howard Hughes Medical Institute

Title: S1PR3 governs inflammatory pain and mechanonociception

Authors: *R. Z. HILL[1], T. MORITA[3], R. B. BREM[4,2], D. M. B. BAUTISTA, 94720[1]
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Abstract: The bioactive lipid sphingosine 1-phosphate (S1P) has emerged as a mediator of a variety of inflammatory diseases. Here we identify S1P Receptor 3 (S1PR3) as a new modulator and transducer of pain and itch. S1P triggered acute itch and pain behaviors and thermal hypersensitivity, which were completely dependent on S1PR3. S1PR3 knockout animals were significantly impaired in the detection of noxious mechanical stimuli, but displayed normal responses to thermal and innocuous tactile stimuli. In the setting of inflammation, S1PR3 knockout mice also displayed a dramatic loss of thermal hypersensitivity. S1PR3 antagonists increase mechanical pain thresholds under both normal and inflammatory conditions. Our findings establish an essential role for S1PR3 as a selective modulator of mechanical pain and for tissue injury-induced thermal hyperalgesia.

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015. Touch, Itch, and Pain

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Support: NIH Grant NS040538
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Title: Optogenetic silencing of CGRPα-expressing sensory neurons alleviates neuropathic pain

Authors: *A. M. REYNOLDS[1], F. MOEHRING[2], H. ZHANG[1], C. O'HARA[1], C. L. STUCKY[3]
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Abstract: Calcitonin gene-related peptide (CGRP) α-expressing sensory neurons modulate thermal sensation in both the naïve and injured state. Previously, it was demonstrated that chemical ablation of this cell population decreased the heat hypersensitivity that develops following both neuropathic and inflammatory injuries. To determine if transient silencing of these neurons resulted in the same behavioral effects as chemical ablation, and to further investigate the involvement of this cell population in spared nerve injury (SNI), postoperative pain and complete Freud's Adjuvant (CFA) inflammation, we mated CGRPα$^{Cre/ERT2}$ mice with Ai35D$^{fl/fl}$ mice to produce homozygous CGRP-Arch mice that express Archaerhodopsin-3 (Arch) in all CGRPα-positive cells. In naïve CGRP-Arch mice, activation of Arch with 590 nm light increased the heat withdrawal latency two-fold, and decreased the cold withdrawal latency two-fold, as compared to controls. Mechanical thresholds were unchanged. After SNI, mechanical and cold hypersensitivities were reversed in Arch-expressing mice while treated with 590 nm light. In a novel two-choice place preference floor assay where animals chose between 590 nm or 490 nm lit flooring, Arch-expressing SNI mice preferred the 590 nm side over the 490 nm side. After incision or CFA inflammation, inhibition of CGRPα-expressing neurons had no effect on mechanical or heat hypersensitivities. To determine effects of SNI on sensory neurons, CGRP-Arch-positive neurons were isolated from SNI animals at peak mechanical behavioral hypersensitivity, underwent patch clamp recordings, and were focally mechanically stimulated. Neurons from SNI animals (no light treatment) had significantly (2-3 fold) larger mechanically-induced currents than sham neurons. Exposure to 590 nm for 2 min decreased the current density in response to mechanical stimuli in SNI neurons, back to amplitudes of sham neurons; 590 nm light had no effect on sham neurons. We demonstrate here that transient peripheral silencing of CGRPα-expressing neurons evades compensatory mechanisms or circuitry changes that can occur with permanent deletion of neurons during or after development. Our study provides insight into the specific function of CGRPα-expressing neurons *in vivo* both in the naïve state

and after injury and inflammation. Additionally, our study shows that transient inhibition of intact neurons is the best method to study injury models because transient inhibition allows us to decipher modality specific circuits that are altered after injury without potential artificial compensatory changes from ablation and cell death.

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Support: Taiwan Ministry of Scientific and Technology MOST 105-2314-B-214-002-MY3
E-Da Hospital Grants EDPJ 104068, EDAHP 104028

Title: Intrathecal microRNA-124 attenuates complete adjuvant-induced inflammatory pain through inhibiting expression of interleukin-6 receptor and STAT3

Authors: *P.-H. TAN, C.-C. LIU
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Abstract: Background and aims MicroRNAs (miRs) are involved in the regulations of proteins in pain processing pathway. Inhibition of interleukin 6 receptor (IL-6R) was demonstrated to be able to suppress hyperalgesia and allodynia. Signal transducer and activator of transcription (STAT) is a downstream target of IL-6R. In our pilot study, the downregulation of miR-124 that target IL-6R was noted in rat spinal cord in microarray miR profiling under inflammatory pain. Thus, we examined the effect of miR-124 in expression of IL-6R and STAT and on inflammatory pain in this study. **Methods** Intradermal injection of complete Freund's adjuvant (CFA) was performed to induce inflammatory pain. Rats received injection of CFA only and naive rats were assigned to be control groups. In treatment group, 4 nmoles mir-124 mimic were injected intrathecally 3 days after injection of CFA (n=5 each group). Four nmoles miR-124 inhibitor was injected intrathecally in naïve rat (n=5 each group). Behavioral tests were performed after injection of miR-124 inhibitor or miR-124 mimic. The spinal cord was dissected for analysis of miR-124, IL-6R, and STAT after behavioral test. **Results** Significant decrease of miR-124 and increase of IL-6R were noted on 1, 3 and 5 days after injection of CFA in spinal cord of rats. Intrathecal injection of 4 nmole miR-124 mimic could attenuate CFA-induced allodynia and thermal hyperalgesia and significantly decrease the expression of IL-6R and

pSTAT3. In contrast, intrathecal injection of miR-124 inhibitor inhibited the expression of miR-124 in spinal cord and induced mechanical allodynia in naïve rats. **Conclusions** Intrathecal injection miR-124 attenuates inflammatory pain through inhibiting the expression of IL-6R and pSTAT3 in the spinal cord.

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**Topic: ***D.04. Somatosensation: Touch

Support: AR051219/R/NIAMS
GM007367

Title: Mechanisms of neurotransmitter release in slowly adapting touch receptors

Authors: *B. U. HOFFMAN[1,2], Y. BABA[3], E. V. MOSHAROV[4], D. SULZER[4], E. A. LUMPKIN[3]
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Abstract: Of the five cardinal senses, touch is the least understood. The sense of touch allows us to detect tactile features of objects in our environment, enabling us to react with appropriate behaviors. In mammals, the perception of touch involves the integration of inputs from functionally distinct mechanosensory neurons, termed low-threshold mechanoreceptors (LTMRs). An unanswered question is: how do different LTMRs selectively encode distinct aspects of touch, such as edge detection and pressure? Recent studies indicate that signaling between epidermal cells and peripheral LTMR terminals is critical for conferring mechanical response properties. Merkel cell-neurite complexes are LTMRs found in body sites specialized for high tactile acuity. These touch receptors are composed of mechanosensitive, epidermal Merkel cells that form synaptic-like contacts with slowly adapting type I (SAI) LTMRs. The Merkel cell-neurite complex detects pressure, represents shapes and edges, and guides dexterous hand movements. We hypothesized that Merkel cells release synaptic vesicles at VAMP2-dependent synapses to excite firing in tactile afferents. To test this hypothesis, we selectively expressed tetanus toxin light chain (TeNT) in epidermal cells *in vivo* in order to disrupt SNARE-mediated synaptic vesicle release. Using *ex vivo* skin-nerve recordings, we have shown that Merkel cells require functional SNARE proteins to mediate canonical SAI responses. Indeed,

TeNT expressing Merkel cells are unable to mediate sustained firing in the sensory afferents. Moreover, to show that Merkel cells package and release small-molecule neurotransmitters, we employed a fluorescent neurotransmitter analogue (FNA), to label Merkel cells in semi-intact epidermal preparations. Merkel cells load FNA into acidic vesicles in a VMAT-dependent manner, and release FNA in response to mechanical stimulation. These experiments reveal that Merkel cells employ SNARE dependent, regulated vesicular release of neurotransmitters to signal to tactile afferents, and set the stage to study the neuronal pathways through which this information is transduced to the central nervous system.

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Title: Effect of environmental enrichment on somatosensory plasticity in the neocortex following early blindness

Authors: *D. L. RAMAMURTHY[1], L. A. KRUBITZER[2]
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Abstract: Sensory systems do not develop and function independently of one another, yet they are typically studied in isolation. Interactions between sensory systems can be revealed when the ratios of incoming sensory inputs are altered. We examined patterns of behavior and neural activity in short-tailed opossums following the elimination of visual input through bilateral enucleation very early in development. Animals were reared either in standard housing or in a tactilely environment. Although the cage size was substantially larger and more complex than standard housing, early blind animals did not exhibit deficits in exploratory activity, compared to sighted littermates, suggesting that spared sensory systems compensated in these animals to allow them to navigate this environment. We compared neuronal responses in the primary somatosensory cortex (S1) whisker representation of early blind animals to those in sighted controls using extracellular single-unit recording techniques under anesthesia. Relative to sighted

animals, early blind animals reared in standard housing exhibited an overall reduction in the magnitude of neural responses to whisker stimuli in S1, coupled with the spatial sharpening of receptive fields of single neurons. This resulted in a trade-off in sensory processing in S1 - neural discrimination between neighboring whiskers is enhanced at the expense of detectability of single whisker stimuli. For the population of S1 neurons, this resulted in an improved performance for decoding of the position of whisker stimuli on individual trials, particularly along the rostrocaudal axis of the animal, in alignment with the primary component of natural whisker motion. Our results provide evidence that under standard rearing conditions, cross-modal plasticity following sensory loss is not necessarily universally adaptive, but could instead involve a compromise between certain functions within brain areas associated with the remaining senses. We hypothesize that rearing in a more complex and dynamic environment following early blindness will increase reliance on the spared senses, and amplify the compensatory effects observed in sensory coding in the spared modalities.

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Support: NIH Grant R21AR07055401

Title: IL-33/ST2 signaling excites sensory neurons and mediates itch responses in a mouse model of poison ivy contact allergy

Authors: *S. E. JORDT[1], B. LIU[1,2], Y. TAI[1,2], S. ACHANTA[1], M. M. KAELBERER[1], A. I. CACERES[1]
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Abstract: Poison ivy-induced allergic contact dermatitis (ACD) is the most common environmental allergic condition in the U.S. . Severe and treatment-resistant itch is the major complaint of affected patients. Due to limited clinical data and models, the pruritic mechanisms in poison ivy ACD remain unknown. Using transcriptome microarray analysis, we identified IL-33 as a key cytokine upregulated in the inflamed skin of mice challenged with the poison ivy allergen, urushiol. Expression of the IL-33 receptor, ST2, was detected in small to medium-sized dorsal root ganglion (DRG) neurons, including neurons that innervate the skin. IL-33 induced

Ca^{2+}-influx into a subset of DRG neurons through neuronal ST2. Neutralizing antibodies against IL-33 or ST2 reduced scratching behavior and skin inflammation in urushiol-challenged mice. Injection of IL-33 into urushiol-challenged skin rapidly exacerbated itch-related scratching via ST2, in a histamine-independent manner. Targeted silencing of neuronal ST2 expression by intrathecal ST2 siRNA delivery significantly attenuated pruritic responses caused by urushiol-induced ACD. These results indicate that IL-33/ST2 signaling is functionally present in primary sensory neurons and contributes to pruritus in poison ivy ACD. Blocking IL-33/ST2 signaling may represent a novel therapeutic approach to ameliorate itch and skin inflammation related to poison ivy ACD.

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**Topic: ***D.02. Somatosensation

Support: Whitehall Foundation
Terman Fellowship
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Title: The coding of cutaneous temperature in the spinal cord and its modality-specific modulation after injury: an *In vivo* calcium imaging study

Authors: *C. RAN[1], G. N. A. KAMALANI[2], M. A. HOON[3], X. CHEN[2]
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Abstract: The thermosensory system enables animals to maintain the homeostasis of body temperature and to avoid noxious temperatures that cause tissue damage, and changes of this system lead to altered thermal sensitivity under pathological conditions. Compared to our understandings of the molecular and cellular mechanisms of temperature detection in the primary sensory neurons, little is known about how temperature is encoded in the central nervous system. Here, we developed an *in vivo* calcium imaging system to investigate the coding of cutaneous temperature in the spinal cord. In contrast to the primary sensory neurons in the DRG that encode temperature in a modality-specific manner, the spinal cord uses a population intensity code to encode temperature intensity. Once spinal neurons reach their thresholds, responses to

heat faithfully reflect the absolute temperature whereas responses to cold selectively signal the change of temperature. Heat-responsive spinal neurons receive major inputs from $TRPV1^+$ DRG neurons, while cold-responsive neurons receive $TRPM8^+$ DRG inputs as well as novel $TRPV1^+$ DRG inputs that were selectively activated by strong cold. Combining *in vivo* calcium imaging and mouse genetics, we show that formalin- or prostaglandin E2-induced inflammation dramatically increases spinal responses to heating while decreasing responses to cooling. The reduction of cold response is largely eliminated upon ablation of TRPV1-expressing primary sensory neurons, indicating a crossover inhibition of cold response from heat inputs in the spinal cord. Interestingly, the increase in sensitivity to heat and decrease in sensitivity to cold largely occur in a group of dually tuned neurons that respond to both cold and heat, providing a neural substrate that mediate the altered sensitivity in inflammatory pain. By contrast, oxaliplatin, a chemotherapy medication, increases spinal responses to cooling and suppresses responses to heating. Together, our results provide the first comprehensive examination of the neural coding of heat and cold in the spinal cord and its plasticity under pathological conditions.

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**Topic: ***D.03. Somatosensation: Pain

Support: NIH Grant NS065926
NIH grant NS098826

Title: Discovery of protease-activated receptor type 3 (PAR3) ligands and a novel role for PAR3 in pain

Authors: *T. J. PRICE[1], S. N. HASSLER[2], P. R. RAY, 75080[3], A. CHAMESSIAN[4], M. NEIMAN[6], T. VAN DE VEN[5], R.-R. JI[7], G. O. DUSSOR[8], S. BOITANO[9], J. VAGNER[9]
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Abstract: Protease activated receptors (PARs) are well-known pain mediators but research in this area has focused largely on one member of this 4-gene family of G-protein coupled receptors

(GPCRs): PAR2. While conducting RNA sequencing experiments on mouse and human dorsal root ganglion (DRG) we noted conspicuous expression of PAR3 in this tissue in both species. Interestingly, PAR3 expression (F2RL2 gene) was much stronger than PAR2 (F2RL1 gene) in mouse and human DRG and single cell RNA sequencing experiments from mouse suggested that PAR3 is primarily expressed in nociceptors. To verify the RNA sequencing data we performed in situ hybridization (ISH) on mouse DRG and found substantial neuronal expression of PAR3 which overlapped extensively with TRPV1 mRNA expression. We next used a peptidomimetic drug discovery approach we have previously employed for PAR2 to develop PAR3 ligands. We discovered several peptidomimetic ligands, derived from the PAR3 N-terminal sequence in humans, that stimulate Ca^{2+} signaling in mouse DRG and trigeminal ganglion (TG) neurons. From this we identified a lead, putative PAR3 agonist, which we named C660 (structure to be disclosed on the poster), that was tested further *in vitro* and *in vivo*. When injected directly into the mouse hindpaw, C660 produced mechanical hypersensitivity, in a dose-dependent fashion, that was completely absent in PAR3/PAR4 double knockout (DKO) mice. Moreover, C660 failed to evoke Ca^{2+} transients in TG neurons taken from PAR3/PAR4 DKO mice. While PAR3 has traditionally been viewed as a co-receptor with other PARs, these findings suggest that PAR3 plays a novel role in promoting pain that occurs independently of PAR2 and/or PAR1. We are currently testing the hypothesis that PAR3 signals independently of other PARs in sensory neurons to promote sensitization of nociceptors.

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Nanosymposium

016. Spatial and Feature-Based Attention

Location: 156

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***016.01

**Topic: ***D.07. Vision

Support: NSF IRFP 0965110
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GT Neural Engineering Center 1241384

Title: Cortical state fluctuations predict the accuracy of visual spatial perception in mice

Authors: A. M. SPEED[1], J. P. DEL ROSARIO[1], C. P. BURGESS[2], M. CARANDINI[2], *B. HAIDER[1,2]

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Abstract: Global behavioral factors such as locomotion, movement, and arousal change the state of activity in sensory cortex. These cortical state changes modulate neural sensory responses; it remains debated if they also modulate sensory perception. Studies from the mouse auditory system show clear effects of cortical state on responses and behavior, but studies in the mouse somatosensory system show little effect of cortical state. These differences may be due to sensory modality, task difficulty, or limitations in assessing effects of cortical state on isolated single neurons. What are the effects of cortical state fluctuations on visual perception? Do cortical states shape visual perception by modulating excitatory and inhibitory neuron populations?

We designed a behavioral assay of visual spatial perception in head-fixed mice. Stationary visual stimuli (gratings) appear in a fixed spatial location on a monitor, while an infrared beam records licks for water reward. Mice must withhold licks for a random duration (0.5 - 6 s) on every single trial for stimuli to appear. Mice only obtain reward by licking during stimulus presentation. Stimuli appear in a given spatial location for many consecutive trials; stimuli then appear in a new spatial location for a new block of trials. Mice (n = 13) learned this task using vision: the contrast and spatial location of stimuli significantly affected reaction times and detection accuracy.

We performed multi-site silicon probe recordings in primary visual cortex (V1) during this behavior. We recorded local field potentials (LFP) and firing of putative excitatory regular spiking (RS, n = 173) and inhibitory fast spiking (FS, n = 63) neurons. On correct versus incorrect trials, we observed strong differences in pupil dilation, narrowband gamma LFP power, firing rates, and pairwise correlations up to 3 seconds before stimulus onset. During this time period, the best predictor for trial outcome was correlated firing between pairs of RS-FS neurons (71 ± 4% accuracy); trial outcomes were less predictable from RS-RS correlations, RS or FS firing rates, pupil dilation, or LFP. These preliminary findings indicate that trial-by-trial fluctuations of cortical excitation and inhibition can play a major role in visual perception.

Disclosures: A.M. Speed: None. **J.P. Del Rosario:** None. **C.P. Burgess:** None. **M. Carandini:** None. **B. Haider:** None.

Nanosymposium

016. Spatial and Feature-Based Attention

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Title: Spatial attention modulates information processing in mouse primary visual cortex

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Abstract: Attention is a process by which the brain prioritizes a subset of the vast amount of available sensory information in the environment, enhancing perception of attended locations or features and increasing signal-to-noise ratios of neural responses. To directly investigate neural circuitry that produces and supports these changes, we developed a visual selective spatial attention task for the mouse that allows measurement and manipulation of neural circuit activity. Head-fixed mice are presented with drifting grating stimuli on left and right screens, and must detect a contrast change that is more likely to occur in one location than the other and lick within a short time window to receive a reward. Mice perform well on likely change trials and poorly on unlikely change trials, suggesting they selectively attend to or prioritize the likely change side. Since this difference could be due to a failure to learn the task in one hemifield, we trained mice with equal change probabilities. Symmetrically-trained mice perform above chance on left and right change trials, but are less sensitive to contrast changes, suggesting a trade-off between perceptual accuracy and the size of the area being monitored, consistent with divided attention. We performed electrophysiological recordings in both hemispheres of V1 in asymmetrically-trained mice and found that noise correlations are selectively reduced in the attending hemisphere of V1 on correct trials just prior to the contrast change, when the mouse must have been attending - consistent with several attention studies. On miss trials, when the mouse did not respond, there was no difference in noise correlations between hemispheres, demonstrating this is not simply a plasticity change in a single side of the brain. In addition, we find that neurons with increased firing rate on correct trials are more prevalent in the attending hemisphere, though the majority of neurons in both hemispheres decrease in firing rate just prior to the contrast change, perhaps reflecting a suppression of irrelevant information. Just after the contrast change, but before the animals respond, more than half of neurons in the attending hemisphere are significantly more active on correct versus miss trials, perhaps representing a detection signal. Moving forward, we will take advantage of genetic tools to optogenetically manipulate cell types and investigate their role in how the local cortical circuit produces and supports an attentional brain state.

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Nanosymposium

016. Spatial and Feature-Based Attention

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Title: Prefrontal functional inputs in visual cortex during processing of redundant and novel stimuli

Authors: *J. P. HAMM, Y. SHYMKIV, R. YUSTE
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Abstract: Sensory stimuli are naturally perceived within a spatiotemporal and behavioral context, wherein novel events are processed and repetitive elements ignored. Such context-driven processing involves ongoing adaptations within sensory cortex. For instance, neurons in mouse V1 show reduced responses to redundant stimuli (e.g. repeated visual gratings of a fixed orientation) and enhanced responses to deviant stimuli (e.g. rare stimuli of novel orientations). This effect depends on local inhibitory circuitry, and on somatostatin-containing interneurons (Hamm and Yuste, 2016). Yet because such adaptions integrate information about past and contextual regularities, larger brain networks involving prefrontal cortex (PFC) may be implicated as well. Axons from mouse PFC are known to project directly to V1, targeting both local pyramidal neurons and interneurons but the influence of these long range inputs on contextual adaptations in V1 circuits is currently unknown. Moreover, understanding PFC-V1 interactions could prove quite important since coactivation of both regions is affected in schizophrenia patients, a population with fundamentally deficient context processing (as marked by the classic “mismatch negativity” [MMN] biomarker). We sought to examine the functional dynamics of these top-down inputs in awake mice (n=8). We expressed GCaMP6s in mouse PFC and, with fast two-photon calcium imaging (30 Hz), we recorded the dynamic activity of individual PFC axons projecting to primary visual cortex. These long-range axons were mostly restricted to layer I (<150 um from surface). Mice viewed full-field oriented square-wave stimuli in a typical “oddball” paradigm (88% redundant stimuli; 12% deviant or “oddball” stimuli). Robust stimulus-specific adaptation (i.e. reduced responses to redundant) and genuine deviance

detection (i.e. enhanced responses to deviants) were measured in individual PFC axons with the same robustness as in the underlying local V1 neurons, albeit showing slightly later activation, suggesting a feedback role. Further, a subset of axonal segments showed *tonic* activity during this paradigm, which gradually increased over trials and was reset whenever a "deviant" stimulus was presented. These results suggest that the PFC signals the expected redundant stimulus and show that both local and global circuitry may contribute to context processing in sensory cortex. Further, using basic "oddball" paradigms in awake mice could provide a model for understanding the ubiquitous systems level deficits seen in people with schizophrenia and for integrating these deficits with fundamental abnormalities in sensory-cognitive processing.

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Nanosymposium

016. Spatial and Feature-Based Attention

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Topic: *****D.07. Vision

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Title: Modeling the effects of perturbing superior colliculus activity on covert perceptual choices

Authors: ***J. P. HERMAN**[1], R. J. KRAUZLIS[2]
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Abstract: Perturbing neuronal activity in the primate superior colliculus (SC) changes perceptual judgments during covert attention tasks. Here, we tested whether these effects can be explained by a decision-making model that predicts task choices from SC neuronal recordings. We recorded intermediate layer SC neuronal activity (n = 139) from 2 monkeys trained to detect threshold-level saturation changes in a cued visual stimulus by releasing a joystick (yes/no task), and to ignore changes in a distracting foil stimulus, during maintained fixation. Nearly all SC neurons (96%) exhibited phasic bursts shortly after stimulus changes that were predictive of response choice. We applied a linear pooling model to the SC neuronal data, with a decision boundary that required activity in one SC to be higher than that in the other to elicit a "yes" response, and found that this simple model could explain the hit rates (HRs) and false alarm rates (FARs) (monkey HRs: 79 ± 2%, 81 ± 2%; model HRs: 78 ± 2%, 79 ± 2%; monkey FARs: 6.3 ± 2%, 6 ± 2%; model FARs: 7.1 ± 2%, 2.1 ± 2%). The model also offered a novel interpretation of the role of cue-related modulation in SC: to influence choice by shifting SC output nearer to or

farther away from a decision boundary.
To test the causal role of SC activity, we applied unilateral electrical microstimulation or muscimol inactivation at the former recording sites and found spatially specific changes in hit and false alarm rates. Applying the linear model again with the same decision boundaries, but with activity from one SC multiplicatively scaled up or down to simulate the effects of stimulation or inactivation, we were able to reproduce the changes in performance found experimentally, including idiosyncratic differences between monkeys. Inactivation caused a reduction in hit rate inside and a rise in false alarm rate outside the affected area of the visual field (monkey ΔHRs: -37 ± 2%, -35 ± 1%; model ΔHRs: -36% ± 1%, -35 ± 1%; monkey ΔFARs: +12 ± 1%, +2 ± 1%; model ΔFARs: +14 ± 2%, +1 ± 1%; scaling values: 0.92, 0.82). Microstimulation had the opposite effect: a rise in hit rate inside and a small drop in false alarm rate outside the affected area (monkey ΔHRs: +22 ± 2%, +18 ± 2%; model ΔHRs: +24 ± 1%, +20 ± 4%; monkey ΔFARs: -6 ± 2%, -0.5 ± 0.5%; model ΔFARs: -3 ± 1%, 0 ± 0%; scaling values: 1.09, 1.10).
Our findings demonstrate that an SC-based choice model accounts for detection performance in intact animals as well as the changes observed when SC activity is suppressed or facilitated. These results show that SC activity is sufficient to explain performance in a covert detection task, and illustrate how its role in supporting perceptual judgments can explain its importance for spatial attention.

Disclosures: **J.P. Herman:** None. **R.J. Krauzlis:** None.

Nanosymposium

016. Spatial and Feature-Based Attention

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Presentation Number: *016.05

Topic: *D.07. Vision

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NCS

Title: A diverse neural code gives rise to attentional preparation

Authors: *A. C. SNYDER[1,2], B. M. YU[2], M. A. SMITH[1]
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Abstract: Commonly, neurophysiological investigations of attention have focused on trial averaged responses over a fixed window where the modulation due to the task is the greatest. This period of maximal modulation in neuronal firing rate tends to be relatively late with respect to stimulus onset -often later than an animal's reaction time in response to the stimulus. Attentional modulation in the baseline activity, and in the transient response to the stimulus, is less consistent or absent. Understanding the causal cascade of attention requires that neuronal modulation due to attention precedes behavior. One possible means to understand how the attentional state is prepared draws on inspiration from motor preparation. In the saccadic and skeletomotor systems, fixed thresholds cannot explain the transition from planning to action, because activity during the planning period resembles that near motor execution. At the population level, however, diversity of responses across neurons can help explain the difference between planning and execution. Using multielectrode arrays to record population activity in visual area V4 of macaque monkeys performing a spatial selective attention task, we found that a similar approach in the visual cortex reveals a surprising diversity of responses, and can help to explain how the earliest spiking responses of a neuron are altered by selective attention. These results suggest that the preparation of attention states and the effects of those states on stimulus processing could be two fundamentally different processes.

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Nanosymposium

016. Spatial and Feature-Based Attention

Location: 156

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**Presentation Number: ***016.06

**Topic: ***D.07. Vision

Title: Attention alters neural population representations for stimulus shape and location in macaque monkeys

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Abstract: We examined how attention causes neural population representations of shape and location to change, as opposed to studying attentional effects on the signal- to-noise ratio or

salience of a particular representation at the single-cell level. We measured attentional effects on representations for stimulus shape and location in anterior inferotemporal cortex (AIT, ventral stream) and lateral intraparietal cortex (LIP, dorsal stream). Monkeys performed two delayed-match-to-sample tasks. Stimuli were identical in both, but in one the monkey attended to sample shape and in the other to sample location. In AIT, different shapes were more distinctive or discriminable when attention was directed to shape rather than location, as measured by an increase in mean distance between population response vectors. In LIP, on the other hand, attending to location rather than shape did not increase the discriminability of different stimulus locations. Even when the overall change in mean vector response distance was factored out, multidimensional scaling still showed a significant task difference in AIT, but not LIP. This indicates that in addition to magnifying the representational space, attention also causes a global, nonlinear warping of the space in AIT. Despite single-cell attentional modulations in both brain areas, our data showed that attentional modulations of population representations of shape and location were weaker in the dorsal stream. We suggest that this may be because the dorsal stream must maintain more veridical representations for visuomotor control. These findings show that attention can change the organization of high- dimensional neural representation spaces in a manner that changes the relationship between different stimuli, rather than just their salience.

Disclosures: **A.B. Sereno:** None. **S.R. Lehky:** None.

Nanosymposium

016. Spatial and Feature-Based Attention

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Topic: *D.07. Vision

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Title: Rhythmic environmental sampling during selective attention reflects a theta-dependent, push-pull relationship between frontal and parietal cortex

Authors: ***I. C. FIEBELKORN**, M. A. PINSK, S. KASTNER
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Abstract: To filter our complex visual environment, the brain uses various mechanisms, broadly referred to as selective attention. One such mechanism, spatial selection, boosts processing at behaviorally relevant locations, relative to other, less relevant locations. Recent evidence has demonstrated that the boost in processing attributable to spatial selection includes a rhythmic

component (from 3-8 Hz), characterized by alternating periods of either greater or lesser perceptual sensitivity. That is, the metaphorical spotlight of spatial selection appears to be blinking. Despite a growing body of evidence from human behavioral and EEG/MEG studies that such rhythmic sampling is a fundamental property of spatial selection, its neural basis remains largely unknown. Here, we hypothesized that rhythmic sampling observed at the behavioral level is related to oscillatory neural activity within the frontoparietal attention network. We therefore simultaneously recorded from two hubs of this network in macaques—the frontal eye fields (FEF) and the lateral intraparietal area (LIP). If FEF and LIP are linked to rhythmic sampling during spatial selection, as hypothesized, then neural oscillations in these two cortical regions should be correlated with behavioral performance. Our findings confirm such correlations between the phase and power of frontoparietal neural oscillations and behavioral performance (i.e., hit rates) during sustained, covert spatial selection. These ties to behavioral performance occur across multiple frequency bands, but show a general dependence on the phase of theta-band activity (3-8 Hz). Neural oscillations in the theta band modulate higher-frequency oscillations (both within and between regions) through phase-amplitude coupling (PAC). Our data provide evidence that PAC in frontoparietal cortex (i.e., FEF and LIP) creates alternating windows of (i) FEF-driven, beta-band activity, associated with better behavioral performance at the attended location and (ii) LIP-driven, gamma-band activity, associated with worse behavioral performance at the attended location. Thus, sustained, covert spatial selection seems to be characterized by a push-pull relationship between FEF and LIP, leading to theta-band rhythms in environmental sampling and thus alternating windows of either greater or lesser perceptual sensitivity (as measured in behavioral performance). Cell-type specific coupling (among neurons associated with saccade-related activity) suggests that this push-pull relationship might reflect a pulsed suppression of eye movements and attentional shifts.

Disclosures: I.C. Fiebelkorn: None. **M.A. Pinsk:** None. **S. Kastner:** None.

Nanosymposium

016. Spatial and Feature-Based Attention

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Title: Temporal ensemble code of visuospatial attention in primate lateral prefrontal cortex

Authors: *J. C. MARTINEZ-TRUJILLO[1], L. DUONG[3], M. ABBASS[2], A. J. SACHS[4]
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Abstract: Top-down visual attention allows primates to filter behaviourally relevant information from a constant bombardment of incoming information from the environment. Classical single-electrode studies have shown that neurons and local field potentials (LFPs) in primate lateral prefrontal cortex (lPFC) encode spatial attention (Squire et al. 2013). At a population scale, we have previously shown that simultaneously-recorded ensembles of macaque neurons, and certain LFP bands in this area can be used to robustly decode the location of attention on a trial-by-trial basis (Tremblay et al. 2015, 2016). However, little is known about how ensemble composition and temporal precision of information in this area affect the encoding of spatial attention.
We chronically implanted multielectrode arrays in the left lPFC of two male Macaca fascicularis, and simultaneously recorded from ensembles of single- and multi-units, and LFPs while the animals performed a visuospatial attention task. In each trial, monkeys were presented with an initial stimulus cue in one of four possible visual quadrants on a computer screen. Subsequently, monkeys needed to covertly attend to the initially cued stimulus while ignoring identical distractor stimuli that populated the remaining quadrants of the screen (for more details please see Tremblay et al. 2015).
We used softmax regression with elastic net regularization (Friedman et al. 2010) to assess the impact of composition, and temporal coding on information content in ensembles of neurons or LFPs. We did this by constructing three types of classifiers (akin to Nandy et al, 2016) to decode the location of the initial stimulus, and location of covert attention. First was a rate classifier which used time-averaged spike counts/LFP power in a large bin encompassing the entire stimulus or sustained attention epoch; second was a snapshot classifier which used 10ms bins stepped through time; and third was a temporal classifier which segmented the entire epoch into 10ms bins, and used all bins as inputs into the classifier.
Using the rate classifier, we found that relatively few units and LFP channels (10-20) were needed to maximize classification accuracy during the stimulus and sustained attention epochs of our task. Furthermore, although the temporal classifier allowed for a complex temporally-encoded solution to decode the location of the stimulus or location of covert attention, the rate classifier yielded max decoding performance using neural as well as LFP ensembles. Taken together, our findings show that visual and sustained attention responses in PFC are sufficiently described by a rate-code consisting of time-averaged spikes or LFP power.

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Nanosymposium

016. Spatial and Feature-Based Attention

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Title: Natural visual search for categories alters interregional correlations in the human brain

Authors: S. U. H. DAR[1,2,3], *T. CUKUR[3,2,4]
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Abstract: Humans can effortlessly search for thousands of visual objects in cluttered real-world scenes. Attention is central to this ability as it enhances responses to target objects, proposedly through interactions between separate stages of visual processing (Al-Aidroos et al., PNAS 2012; Córdova et al., Neurobiol Learn Mem 2016). In a recent study, we have shown that attention to a category of visual object warps semantic representations of behaviorally-relevant categories broadly across neocortex (Çukur et al., Nat Neuro 2013). Thus, it is likely that category-based attention dynamically alters information flow among a distributed array of temporal, parietal and frontal areas to mediate these changes in representation. To test this hypothesis, here we assessed correlation of BOLD responses across neocortex during natural visual search for object categories frequently encountered in daily life.
Human subjects viewed 30 min of natural movies and searched for either humans or vehicles in distinct runs. Whole-brain BOLD responses were recorded. Interregional correlations were assessed via coherence analysis (Sun et al., Neuroimage 2004). This analysis was performed on the 1st eigenvariate response of voxels in each region after removing stimulus-driven activity from single-voxel responses. To capture responses evoked by low and high-level stimulus features, voxel-wise models were fit based on a set of 3300 regressors pooled across a motion energy and a category model (Çukur et al., J Neurosci 2013). Voxel-wise background response was obtained by projecting out the model-predicted response from the measured response. Interregional correlations were measured on background responses, and then compared across search tasks to examine attentional modulations.
We find that category-based attention causes widely distributed changes in interregional correlations across neocortex. During human search, correlations are increased (Bootstrap test,

P<0.05) between areas selective to the target during passive viewing (FFA and EBA) and parietal/frontal areas implicated in attentional control (IPS, FEF, SEF, FO). During vehicle search, correlations are instead increased (P<0.05) between PPA, RSC, OPA and attentional-control areas. These effects are valid even after removing responses evoked by movie clips in which target categories were present. Our results suggest that category-based attention strengthens information flow among task-relevant areas, and that feedback from attentional control areas onto high-level visual cortex mediates warps in semantic representation during natural visual search.

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Nanosymposium

016. Spatial and Feature-Based Attention

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Title: Uniqueness drives visual salience independently of local contrast

Authors: *D. JECK[1], H. EGETH[2], M. QIN[3], E. NIEBUR[1]
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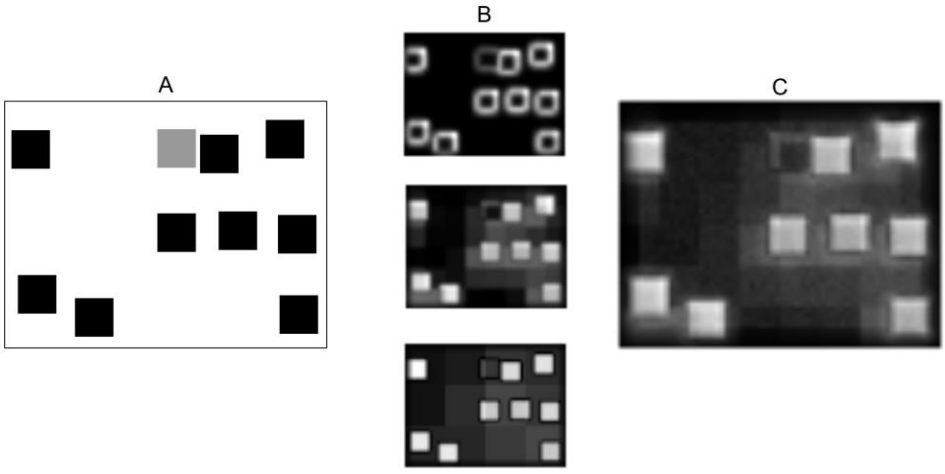
Abstract: Many computational models of visual salience predict that regions of high center-surround (CS) contrast are salient. This leads to an interesting and counterintuitive prediction, which we test in this contribution. Consider the image in Figure 1A, consisting of a number of black squares and one gray square on a white background. As long as the unique gray square is easily discriminated from both the background and the black squares, our intuition suggests that its uniqueness makes it the most salient stimulus. However, because the gray square is closer to the background intensity than the black squares, models of salience predict otherwise. Figure 1B shows a set of the CS responses to the intensity channel of the image in Figure 1A using different spatial scales for the center and surround (other submodalities, like color, orientation, or motion, do not differentiate between the squares). For each of these CS computations, the gray square produces a weaker response than the black squares. Because of the lowered CS responses, the resulting saliency map (Figure 1C computed from Itti et al., IEEE-PAMI 20:1254-9, 1998) also

associates a lower saliency level to the unique gray square than to the black squares.
To verify our intuition about the unique gray square, we gather attentional data by asking participants to tap the first place they look at when presented with an image on a touch sensitive screen (Jeck et al. Vis. Res., in press). This novel paradigm, which can be applied to a large class of questions, allows assessment of attentional selection while minimizing top-down influences. We show that without any instructions about the nature of the upcoming image, and even on their first image presentation, participants preferentially select the unique gray square. We found no published model of visual salience that operates on natural images and is able to correctly predict this outcome, and we modify an existing model to be able to do so without decreasing its effectiveness on natural scenes. Our model generalizes the concept of center-surround to include inter-object comparisons.
Figure 1



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Nanosymposium

017. Cellular Adaptations Produced By Cocaine

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Title: Engineering CRISPR/Cas9 constructs to model the epigenetic and transcriptional phenomena underlying pathogenic mechanisms of cocaine abuse

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Abstract: Drug addiction is a chronic, debilitating syndrome with a substantial body of evidence indicating that epigenetic and transcriptional mechanisms are associated with disease progression. However, a major obstacle in efforts to understand and devise treatments for addiction stem from an inability to determine causality between enrichment of an epigenetic modification or transcription factor binding at a specific gene and the pathogenesis of addiction. Only relatively recently has it become possible to target a given type of epigenetic remodeling to a single gene of interest, in order to probe the causal relationship between such regulation and neuropsychiatric disease (Heller et al., *Nat Neurosci*, 2014; Heller, Hamilton, et al., *J Neurosci*, 2016). Our group has successfully utilized synthetic zinc-finger proteins (ZFPs) fused to epigenetic editing moieties to determine the neural and behavioral effects of targeted in vivo epigenetic reprogramming in a locus-specific and cell-type specific manner. Given the success of our ZFP approaches, we have broadened our technical repertoire to include the more flexible CRISPR/Cas9 technology. We have designed a fusion construct linking the nuclease-dead Cas9 (dCas9) moiety to a pseudo-phosphorylated isoform of the transcription factor CREB (dCas9-CREB(S133D)) and designed guide RNAs (gRNAs) to target the *Fosb* gene locus, a locus heavily implicated in the pathogenesis of drug abuse. CREB binding to the promoter of *Fosb* gene has been demonstrated to underlie the cocaine-mediated induction of ΔFosB. We observe that viral delivery and targeting of dCas9-CREB(S133D) to the *Fosb* promoter is sufficient to up-regulate ΔFosB mRNA and protein levels in the nucleus accumbens (NAc) of mice as well as potentiate cocaine conditioned place preference, indicating a causal role for CREB binding to *Fosb* in the progression of cocaine responses. Having utilized these tools at the well-understood *Fosb* locus, we are now able to design gRNAs targeting CREB to novel loci to understand their causal relevance in the pathogenesis of addiction and other syndromes. The CREB-regulated gene *Zfp189* is a promising novel candidate in that it is induced in NAc by cocaine self-administration. The targeted recruitment of CREB to the *Zfp189* locus will allow us to identify the causal transcriptional and behavioral consequences of this interaction within the brain's reward regions. Supported by NIDA

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Nanosymposium

017. Cellular Adaptations Produced By Cocaine

Location: 144A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***017.02

**Topic: ***G.08. Drugs of Abuse and Addiction

Support: DA033684

Title: RNA-Seq analysis of cocaine abuse identifies genes associated with adult striatal neurogenesis

Authors: D. C. MASH[1], *S. P. GARAMSZEGI[1], C. WU[2], R. T. VONTELL[1], C.-T. LEE[1], Z. JIANG[3], N. TSINOREMAS[3], K. ARDLIE[4], T. SULLIVAN[4], E. GELFAND[4], G. TURECKI[5]
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Abstract: Chronic cocaine administration induces neuroplastic changes in rodent models within corticostriatal systems regulating emotions and cognitive control. Adult striatal neurogenesis only occurs in humans and may derive from local cells within the parenchyma of the caudate, in addition to those deriving from the neurogenic niche of the subventricular zone. We report RNA-Seq data mining and network analysis of the human caudate from cocaine abusers. RNA-Seq analysis was done to quantify transcript changes and global gene expression to identify candidate gene markers that are regulated by cocaine abuse in striatal dopamine pathways. The dorsal caudate was sampled postmortem from individuals who were chronic cocaine abusers (N=25) and from age-matched unaffected control subjects who died suddenly without a history of drug or alcohol abuse (N= 25). The RNA-Seq reads were aligned on human genome (GRCH37) using TopHat. HTSeq-DESeq2 and Cufflinks-SAMr pipelines were used to identify differentially expressed genes and transcripts, respectively. In the caudate, cocaine-mediated changes in DE genes and transcripts were associated with neurophysiological processes, including axon transport and glutamate regulation of dopamine D1 receptor signaling, Wnt signaling in development and degradation of beta-catenin, protein folding and maturation, cadherin-mediated cell adhesion, and cell cycle regulation of G1/S transition. We validated 10 DE genes from the caudate using qPCR and NanoString Technologies nCounter Analysis System. Wnt signaling molecules (Sox11, NeuroD1 and MSX1) and the regulator of dopamine neuron morphology (IRS2) were selected for qPCR validation. We identified dysregulated genes in the Wnt pathway in dorsal caudate, but not in the human NAc. Since Wnt flips a dual switch to activate adult neurogenesis *in vivo* and *in vitro*, we tested the hypothesis that cocaine increases striatal neurogenesis using striatal neurons generated from hPSCs. These results demonstrated that cocaine induced premature striatal neuronal differentiation and increased the number of BrdU labeled neurons. Preliminary immunohistochemical studies in human caudate from cocaine

abusers were done using pan-neuronal (HuC/HuD) and neuronal migration markers (Drebrin, DCX and PSA-NCAM). These results demonstrate cocaine abuse increases neuronal production in the dorsal caudate from chronic cocaine abusers that came to autopsy. Striatal neurogenesis may be one of the long-lasting neuroadaptations that drives the intractable cycle of cocaine addiction. Funded by NIDA (DA033684).

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Nanosymposium

017. Cellular Adaptations Produced By Cocaine

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**Presentation Number: ***017.03

**Topic: ***G.08. Drugs of Abuse and Addiction

Support: NIDA

Title: Long-noncoding RNA Gas5 is associated with cocaine action

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Abstract: Long non-coding RNAs (lncRNAs) are a class of transcribed RNA molecules greater than 200 nucleotides long that do not encode proteins. Recently, many lncRNAs have been recognized to be functionally important, particularly with respect to the regulation of gene expression. Though lncRNAs are abundant in the brain, their neural functions are largely unknown. Here we show that the lncRNA growth arrest-specific 5 (Gas5) is downregulated in the mouse nucleus accumbens (NAc) both 1 and 24 hours after 7 daily cocaine intraperitoneal injections. Furthermore, Gas5 downregulation is maintained 10 days after 28 days of cocaine administration. Gas5 is known to negatively regulate cell survival and is aberrantly expressed in several cancers. However, its role in neural functions is unclear. Accumulating evidence suggests that Gas5 may prevent the glucocorticoid receptor from interacting with the glucocorticoid response element, and thereby suppresses glucocorticoid downstream nuclear signaling. In order to elucidate the role of Gas5 in cocaine action, we incorporated Gas5 into a herpes simplex viral vector and overexpressed it in the mouse nucleus accumbens through steretotaxic surgery injection. Our preliminary data demonstrate that Gas5 overexpression significantly decreases

cocaine preference during conditioned place preference (CPP). As the glucocorticoid receptor is implicated in drug addiction, further study of Gas5 may provide a novel molecular underpinning of drug addiction linked to the glucocorticoid receptor signaling pathway.

Disclosures: A.N. Brown: None. **H. Xu:** None. **G.J. Kaplan:** None. **R. Adams:** None. **E.J. Nestler:** None.

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017. Cellular Adaptations Produced By Cocaine

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**Topic: ***G.08. Drugs of Abuse and Addiction

Support: NIMH 096816
NINDS 076708

Title: Translational control by eIF2A regulates acute and persistent effects of cocaine

Authors: *S. KHATIWADA[1], A. PLACZEK[2], W. HUANG[1], G. VIANA DI PRISCO[1], M. COSTA-MATTIOLI[1]
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Abstract: Drug abuse and addiction is a major global mental health problem; however, the underlying neurobiological mechanisms remain elusive. While the effects of drugs of abuse require *de novo* protein synthesis, the translational control mechanism(s) targeted by drugs of abuse are not known. Our long-term goal is to understand: a) how acute exposure to drugs of abuse usurp specific translational control mechanism(s), and b) how it leads to persistent changes in the reward circuits in the brain to cause maladaptive reward learning and reinforce compulsive drug-seeking behavior.
We recently discovered that translational control by phosphorylation of the α-subunit of eukaryotic translation initiation factor 2 (p-eIF2α) regulates the vulnerability to the effects of cocaine—the model drug for our studies. We found that cocaine reduces p-eIF2α levels in the ventral tegmental area (VTA)—a key reward center in the brain—more readily in adolescent mice compared to adult mice. Specifically, in adolescent mice but not in adults, a sub-threshold dose of cocaine reduced p-eIF2α levels and potentiated synaptic inputs onto dopaminergic neurons in the VTA, and elicited drug-reinforced behavior (place preference).
Strikingly, in a series of gain- and loss-of-function experiments, we found that genetically or pharmacologically increasing or decreasing p-eIF2α levels render mice more resistant and more vulnerable, respectively, to the acute effects of cocaine. Consistent with these findings,

metabotropic glutamate receptor-mediated long-term depression—whose disruption is postulated to increase vulnerability to drug addiction—was impaired in the VTA of both adolescent mice as well as in adult mice with reduced p-eIF2α-mediated translation.
Moreover, we also found that genetically or pharmacologically reducing p-eIF2α-mediated translation facilitates the progression of the transient effects of acute cocaine exposure to a more persistent one. Taken together, our data suggest that a) cocaine hijacks p-eIF2α-mediated translational program to elicit synaptic potentiation in VTA dopaminergic neurons that contributes to addiction-related behavior, and b) p-eIF2α-mediated translation could be a key mechanism gating the progression from transient to persistent effects of cocaine. Thus, modulating p-eIF2α mediated translation could be a therapeutic approach to prevent the persistent effects of drugs of abuse and may hold promise for new treatments for addiction.

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Topic: * G.08. Drugs of Abuse and Addiction

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JSPS

Title: Cocaine inhibits pathway specific GABA transmission in the VP through a non-dopaminergic mechanism

Authors: *A. MATSUI, V. A. ALVAREZ
NIAAA/NIH, Rockville, MD

Abstract: Cocaine disinhibits direct medium spiny neurons (dMSN) by diminishing inhibitory GABA input from indirect medium spiny neurons (iMSN) in the nucleus accumbens (NAc). This cocaine suppression of lateral inhibition between striatal neurons is mediated through D2 dopamine receptors (D2R) on iMSNs, and these D2Rs play a role in the stimulant effect of cocaine on locomotion. iMSNs also send axon terminals in the ventral pallidum (VP). Yet, D2R agonist quinpirole weakly modulates GABA input onto VP neurons. This study examines cocaine modulation of GABA transmission from MSNs in the NAc to the VP. Channelrhodopsin-2 (ChR2) was expressed selectively in iMSNs or dMSNs using Adora2a-Cre and Drd1-Cre transgenic mice, respectively. Whole-cell voltage clamp recordings were made in

VP neurons from acute brain slices of ChR2-injected mice. As previously reported, both iMSNs and dMSNs make synaptic connections to VP neurons, and opto-stimulation evokes GABA inhibitory postsynaptic current (IPSCs) in VP neurons. However, cocaine suppresses GABA IPSCs in VP neurons only from iMSNs, but not from dMSNs. In the presence of a D2R antagonist or using iMSN-D2R knockout mice, cocaine is still able to inhibit GABA IPSCs. Cocaine is a non-selective monoamine transporter blocker, thus it inhibits not only dopamine transporter (DAT), but also serotonin (SERT) and norepinephrine transporters (NET). Using pharmacological characterization, the SERT blocker citalopram mimicked cocaine effects. DAT and NET blockers failed to alter GABA IPSCs. Additionally, serotonin and serotonin 1B/D agonist sumatriptan potently inhibited GABA transmission only from iMSN to VP. There was no effect of serotonin agonists on dMSN to VP input. When serotonin 1B knockout mice were used, cocaine and serotonin inhibition of GABA IPSCs were eliminated. Thus, unlike the findings in the NAc, cocaine acts on SERT to elevate serotonin level in the VP and suppress GABA transmission from iMSN.

Disclosures: A. Matsui: None. **V.A. Alvarez:** None.

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017. Cellular Adaptations Produced By Cocaine

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**Topic: ***G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA031900
Drexel University Dean's Fellowship for Excellence in Collaborative or Themed Research

Title: Cocaine potency at the dopamine transporter is determined by dopamine neuron activation

Authors: *Z. D. BRODNIK[1], R. A. ESPAÑA[2]
[1]Drexel Univ., Philadelphia, PA; [2]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: The reinforcing efficacy of cocaine is largely driven though inhibition of the dopamine transporter, and cocaine potency at the dopamine transporter has been tied to several symptoms of cocaine use disorder. Specifically, high cocaine potency has been tied to excessive motivation to obtain cocaine, and escalation of cocaine taking corresponds with progressive decreases in cocaine potency. While the relationship between cocaine's potency and reinforcing efficacy has become increasingly clear, the physiological determinants of cocaine potency at the

dopamine transporter remain unresolved. In these studies we combine chemogenetics with ex vivo fast scan cyclic voltammetry to measure the effects of increases or decreases dopamine neuron activation on cocaine potency. We discovered that changing dopamine neuron activation produced rapid, bidirectional modulation of cocaine potency with increases in dopamine neuron activation driving increases in terminal cocaine potency, and decreases in dopamine neuron activation driving decreases in terminal cocaine potency.

Disclosures: Z.D. Brodnik: None. **R.A. España:** None.

Nanosymposium

017. Cellular Adaptations Produced By Cocaine

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**Topic: ***G.08. Drugs of Abuse and Addiction

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NIGMS GM09545902

Title: Activin A signaling in the dorsal hippocampus mediates incubated cocaine seeking

Authors: C. T. WERNER[1], Z.-J. WANG[2], J. A. MARTIN[2], A. F. STEWART[2], R. VISWANATHAN[2], A. CACCAMISE[2], R. L. NEVE[3], *D. M. DIETZ[2]
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Abstract: Relapse susceptibility in cocaine addiction is attributed to drug seeking provoked by exposure to drug-associated cues. Drug-dependent plasticity in the reward circuitry of the brain, including the nucleus accumbens and hippocampus (HPC), underlies drug-seeking behavior. The transforming growth factor (TGF)-β superfamily contains multifunctional proteins that regulate a wide variety of cellular responses, including synaptic and epigenetic plasticity. Recent studies from our lab have shown that TGF-β signaling regulates spine morphology and gene expression in the nucleus accumbens to mediate relapse behaviors following cocaine exposure in animal models of addiction. In the HPC, the role of TGF-β signaling in addiction-related behaviors has yet to be examined. Here, we show that following extended-access cocaine self-administration, activin A concentration is decreased in the HPC on withdrawal day (WD)30 in cocaine-treated rats compared to saline controls. However, cue-induced cocaine seeking on WD30, but not on WD1, increases activin A concentrations. Therefore, we asked if activin A signaling mediates

incubated cue-induced cocaine seeking. We found that blocking activin signaling in the dorsal HPC attenuates, while enhancing activin signaling increases, incubated cocaine seeking on WD30. Blockade of activin signaling did not affect cocaine seeking on WD1. Furthermore, evidence suggests activin A may signal through the non-canonical pathway to mediate incubated cocaine seeking via the phosphorylation of NR2B, an NMDA receptor subunit. Together, these data demonstrate that activin A in the dorsal HPC regulates incubated cue-induced cocaine seeking during prolonged withdrawal following extended-access self-administration.

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017. Cellular Adaptations Produced By Cocaine

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**Presentation Number: ***017.08

**Topic: ***G.08. Drugs of Abuse and Addiction

Support: ANR-SERFEED
NIMES UNIVERSITY

Title: Neural underpinnings of excessive intake of cocaine and food can be different

Authors: *V. COMPAN[1], L. LAURENT[1], O. ARIBO[1], G. CONDUCTIER[1], R. MALDONADO[2]
[1]SCIENCES, Nimes Univ., Nimes, France; [2]UNIVERSITY, BARCELONA, Spain

Abstract: In neurons of the nucleus accumbens, activation of the cAMP signaling is a means of transforming an immediate reduction of drugs' rewarding effect into a durable dependence. After recruiting CREB-binding protein, the resultant phosphorylated cAMP-response element binding protein (pCREB) favors the expression of genes (FosB, delta FosB) to the detriment of others (methyltransferase G9a of histone), from where come changes in neuron morphology. Serotonin (5-HT, 5-hydroxytryptamine) volume transmission through many receptors act on cAMP signaling and thus modulate the activity of the reward neural pathways. Here, we examine how the absence of one of the 5-HT receptor subtypes, the Gs-coupled 5-HT4 receptors (5-HT4Rs), impacts on morpho-functional effects of cocaine. Cocaine failed to increase the levels of both cAMP and pCREB in the 5-HT4R knock-out (KO) mice. The resultant expression of FosB and delta FosB was attenuated. In the basal conditions, the mRNA levels of the G9a in the accumbens were higher in mutants than wild-type animals. It was associated with a reduced number of dendritic spines in the accumbens of the mutants. The 5-HT4R KO mice are less

motivated to self-administer cocaine but more motivated to consume food following chronic restriction. Collectively, these findings show differences in the neural basis of addiction to drugs and overconsumption of food.

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Nanosymposium

017. Cellular Adaptations Produced By Cocaine

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NIDA F32DA033088
NIDA 1U01DA041174-01
NIDA 1R01DA041528-01

Title: Recent use of cocaine is associated with functional connectivity changes supporting enhanced alerting, but not executive, attention in individuals with cocaine addiction

Authors: *A. ZILVERSTAND, M. A. PARVAZ, R. Z. GOLDSTEIN
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Abstract: Previous studies in individuals with cocaine use disorder (iCUD) have paradoxically shown both impairing effects, as well as enhancement of cognitive performance, with more recent drug use, depending on the cognitive function involved. Other stimulants such as nicotine and modafinil have also been shown to enhance certain attentional processes (e.g., alerting attention), while impairing others (e.g., executive attention). However, the modulation of attentional performance by recency of drug use and the association with resting-state brain networks, a measure of baseline brain function, have yet to be investigated in iCUD. Here, we investigated the effect of recency of cocaine use (urine status) on the Attentional Network Task (ANT) performance, a task that assesses three functions: 1) alerting, 2) shifting and 3) executive attention. We further studied the impact of both recency of use and performance on the ANT on resting-state functional connectivity of the attentional networks (Xuan et al., 2016). The ANT was performed outside the MR scanner. Ten minute resting-state fMRI scans were acquired in iCUD+ (urine positive, N=26, age 47±8 yrs), iCUD- (urine negative, N=17, age 47±8 yrs) and race- and gender-matched controls (N=32; age 40±8 yrs; covarying for age). Imaging data were preprocessed following standard procedures and analyzed with CONN (MIT, Cambridge). More

recent drug use was associated with enhanced alerting (faster response: iCUD+ < iCUD- < Controls, $p < 0.05$), but worse executive attention (slower response: iCUD+ = iCUD- > Controls, $p < 0.05$). More recent drug use was also associated with linearly decreased functional connectivity within the attention network (e.g., frontal-parietal and inferior-superior parietal connectivity) (iCUD+ < iCUD- < Controls, $p<0.05$, corr). Further, decreased functional connectivity within this network was associated with increased alerting attention across all subjects ($p<0.05$, corr). Results demonstrate a differential modulation of various aspects of attention by recency of cocaine use (enhanced alerting but worse executive attention with more recent use), underlying the importance of parsing out these effects. Parallel linear changes in functional connectivity during rest within the attentional network indicate decreased connectivity as a function of recency of use and faster alerting responses. These results suggest that the cognitive performance in iCUD is coupled to their baseline brain state, highlighting the potential for developing interventions that target these brain states directly (e.g., with neurofeedback).

Disclosures: A. Zilverstand: None. **M.A. Parvaz:** None. **R.Z. Goldstein:** None.

Nanosymposium

018. Perceptual and Spatial Human Learning

Location: 143A

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**Presentation Number: ***018.01

**Topic: ***H.02. Human Cognition and Behavior

Support: ERC Starting Grant 678286, "Contextvision"

Title: Probabilistic forward replay of stimulus sequences in human visual cortex

Authors: *M. EKMAN[1], G. GENNARI[1], F. P. DE LANGE[2]
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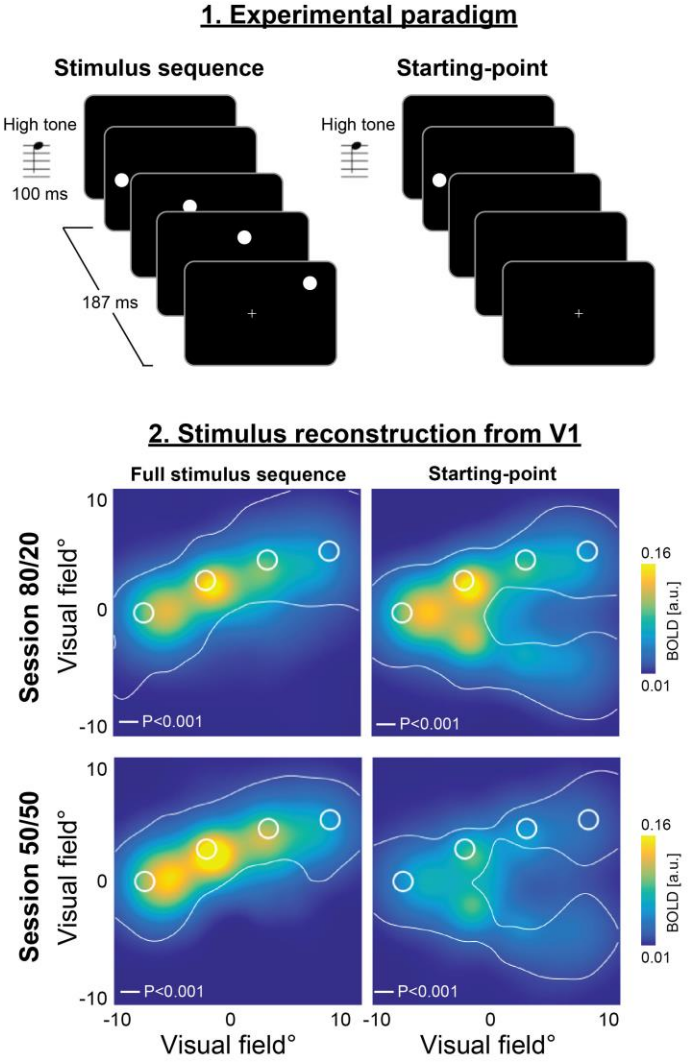
Abstract: Cue-triggered forward replay of upcoming stimulus sequences provides an important mechanism for experience-guided decision-making (Carr et al. 2011; Buckner 2010). However, it is currently unclear how this mechanism operates when multiple, probabilistic cue-stimulus associations are present. It has been proposed that replay preferentially represents the most likely sequence (Karlsson & Frank 2009), while other studies find a preference for less likely (Gupta et al. 2010), or even novel sequences (Chen & Frank 2008). Here we examined replay of visual events in primary visual cortex (V1), using fMRI and a population receptive field-based reconstruction technique. Participants were exposed to two distinct spatio-temporal dot sequences (A and B) that shared the same starting point. Each sequence was paired with either a

high- or low tone that predicted the stimulus sequence with 80% validity. We found that after repeated exposure to the regular sequences, merely presenting the auditory cue together with the starting point resulted in simultaneous forward replay of both, the likely (A) and the less likely (B) stimulus sequence. Crucially, forward replay preserved the probabilistic relationship in a way that the likely sequence was associated with greater BOLD activity compared to the less likely stimulus sequence. Simultaneous forward replay was also found when both stimulus sequences were equally likely (50% cue validity). These observations show that the capacity for cue-triggered recall extends beyond single stimulus sequences (Ekman et al. 2017) and that the probabilistic properties of competing trajectories are represented in the amplitude of the anticipated activity waves.



Disclosures: **M. Ekman:** None. **G. Gennari:** None. **F.P. de Lange:** None.

Nanosymposium

018. Perceptual and Spatial Human Learning

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**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:15 PM

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**Topic: ***H.02. Human Cognition and Behavior

Support: Alexander von Humboldt Foundation to PUT and SMF
DFG GR988 22-1 to MWG

Title: Long time no see: Enduring behavioral and neuronal changes in perceptual learning of motion trajectories three years after training

Authors: *P. U. TSE[1], *P. U. TSE[1], S. M. FRANK[1], M. W. GREENLEE[2]
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Abstract: We report on long-term changes in behavior and brain activity following perceptual learning of visual feature conjunctions. Participants were trained for three weeks on a visual search task involving the detection of a dot moving in a "v"-shaped target trajectory among inverted "v"-shaped distractor trajectories. The first and last training sessions were carried out during fMRI. Learning stability was again examined behaviorally and using fMRI three years after the end of training. Behavioral improvements were remarkably stable over time and these changes were specific to trained target and distractor trajectories. A similar pattern was observed at the neuronal level. When the representation of target and distractor stimuli was examined in retinotopic visual cortex (V1-V3), training enhanced activity for the target relative to the surrounding distractors in the search array and this enhancement persisted after three years. However, exchanging target and distractor trajectories abolished both neuronal and behavioral effects, suggesting that training-induced changes in stimulus representation are specific to trained stimulus identities.

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**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***018.03

**Topic: ***H.02. Human Cognition and Behavior

Title: Probing the mechanism of perceptual learning

Authors: *C. W. TYLER[1,2], J. A. SOLOMON[2]
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Abstract: Rationale. With practice, forced-choice (unbiased) detection of local targets improves over time, a process known as 'perceptual learning'. One possible mechanism for such improvement is that neural firing thresholds adjust to the prevailing noise level to maintain a low average firing level without stimulation, but that under the task demands this sensory threshold resets to the optimal signal-detection criterion, improving performance but increasing the average firing level. Other possibilities are a reduction in internal noise, a reduction in uncertainty about the nature of the target, and an improved match of the operative detection mechanism to the target. Methods. To asses these possibilities, we asked 9 psychophysically inexperienced observers detect a briefly flashed peripheral Gabor patterns in a 4-alternative forced-choice configuration over 5 days of repeated 1-hour sessions. To control for threshold changes and internal noise effects, stimuli were presented in the presence and in the absence of full-field, dynamic noise that elevated detection contrasts by about a factor of 2, well above the level of a putative sensory threshold. Results. Over the course of the 5 days' testing, detection performance improved by about 10% per day (significant perceptual learning for all observers), both with and without the masking noise. The measured psychometric functions were accelerating (log d' slopes of about 3) and were unaffected by either noise or practice. Conclusions. The parallel improvement under external noise masking is incompatible with a sensory threshold account. The steep psychometric functions implied that observers were harboring some "intrinsic" uncertainty regarding which visual signals are actually elicited by the targets. Since the slopes were unaffected by practice, so the reduction in detection thresholds cannot be ascribed to uncertainty reduction. Instead, our measurements are consistent with a process of pruning members from initial pools of local outputs with similar receptive fields at each target location, both reducing the internal noise for detection and narrowing the filtering of external noise when present.

Disclosures: C.W. Tyler: None. **J.A. Solomon:** None.

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**Topic: ***H.02. Human Cognition and Behavior

Support: Seton Research Grant

Title: Context-dependent grid cell activity in the human entorhinal cortex

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Abstract: The spatially periodic activity of grid cells in the mammalian entorhinal cortex (EC) is an expression of an internal coordinate system mammals may use for spatial navigation. The defining features of this grid-like activity, such as scale invariance, orientation relative to distant cues, and a 60-degree rotational symmetry, suggest a robust context independence confirmed by extensive research on rodents. Recent primate and human data validated the prevalence of spatial periodicity in the EC, yet the environmental-dependency of grid-like pattern recorded from human- and subhuman primates remained elusive. Patients diagnosed with non-tractable epilepsy and implanted with electrodes in the EC performing virtual navigation tasks to memorized locations in different virtual environments enabled us to investigate the relationship between grid geometry and environmental features. We argue, based on direct single cell electrophysiology from more than 200 neurons that, in contrast data from rodents, the spatially periodic activity of human EC is context-dependent. Grids appear to linearly scale with the size of environments, orient to the corners and display a broad range of rotational symmetries, including Cartesian symmetries. The combined results suggest that human EC neurons are endowed with an adaptive flexibility, which enables them to quickly rescale their position dependency relative to the actual environment. Whether this enhanced context-dependency of the human EC activity is specific to our species or a result of the continuous evolution driven by the increasing role of visual cortical input to EC, require further studies. To consolidate the variety of grid-like activity from the human EC with the concept of canonical grid cells observed in rodents, we suggest defining the general concept of "spatially periodic" activity, characteristic also to other cortical structures.

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Nanosymposium

018. Perceptual and Spatial Human Learning

Location: 143A

Time: *Saturday, November 11, 2017, 1:00 PM - 3:15 PM

Presentation Number: *018.05

Topic: *H.02. Human Cognition and Behavior

Title: Functional connectivity of regions that preferentially respond to coherent optic flow during an egocentric spatial orientation task are related to self-reported spatial navigation ability

Authors: L. E. ZAJAC[1], *R. J. KILLIANY[2]
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Abstract: The ability to navigate large-scale environments is an essential and complex cognitive skill that relies upon interactions between many brain regions. One important aspect of spatial navigation is the extraction of self-motion information from optic flow. We examined the task-related functional connectivity (trFC) of brain regions that preferentially respond to coherent radial motion during an egocentric spatial orientation (ESO) task in 9 young adults using functional magnetic resonance imaging. We also examined whether trFC or activity measured during task performance were related to self-reported spatial navigation ability measured with the Santa Barbara Sense of Direction (SBSoD) scale. Subjects performed the ESO task with an average accuracy of 94.1% (sd = 0.11). Average SBSoD score was 4.57 (sd = 1.08). During accurate trials of the ESO task, activity was present in regions known to be important to spatial navigation such as the bilateral precuneus, posterior parahippocampal gyrus, posterior hippocampus, thalamus, retrosplenial cortex (RSC), and left caudate. ESO task activity and SBSoD score were negatively correlated in the left central operculum/posterior insula and anterior middle temporal gyrus. We used an optic flow paradigm to define regions that respond preferentially to coherent radial motion at the group level. Fourteen regions of interest (ROIs) located in the occipital, temporal, and parietal lobes were defined. A psychophysiological interactions analysis was used to examine the trFC of these ROIs. Thirteen ROIs showed trFC increases to the precuneus, 5 to the RSC, 3 to the caudate, and 2 to the hippocampus, among other regions. The trFC of 10 ROIs was positively correlated with SBSoD score. Five of these showed a positive correlation between SBSoD score and trFC to the right insula, 6 to a region in the left frontal pole, 6 to a region in the right lateral temporal lobe, and 8 to other frontal areas. No correlations were found between trFC and SBSoD score in the hippocampus or medial

temporal lobe, and only two showed a correlation between trFC and SBSoD score in the precuneus. Overall, these results show (1) the interactions between regions that preferentially respond to coherent radial optic flow and the precuneus are important to egocentric spatial orienting and (2) the interactions between these regions and the frontal lobe, right insula, and right lateral temporal lobe (but not the medial temporal lobe) during egocentric spatial orienting are positively associated with spatial navigation ability.

Disclosures: L.E. Zajac: None. **R.J. Killiany:** None.

Nanosymposium

018. Perceptual and Spatial Human Learning

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**Presentation Number: ***018.06

**Topic: ***H.02. Human Cognition and Behavior

Support: ERC Starting Grant awarded to T. Wolbers 335090 (AGESPACE)

Title: Changes in connectivity profiles as a mechanism for age-related decline in navigational learning?

Authors: *N. DIERSCH[1], J. P. VALDES-HERRERA[1], C. TEMPELMANN[2], T. WOLBERS[1,3]
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Abstract: Spatial navigation, the ability to find our way between specific places in the environment, is known to deteriorate substantially with advancing age. When encountering novel environments, for example, older adults require considerably more time in learning its spatial layout, and they have difficulties in retrieving this newly learnt information later. With respect to the underlying neural mechanisms, previous research indicates that interactions between the retrosplenial cortex and the hippocampus predict navigational performance in younger adults. Here, we characterize for the first time age-related changes in functional connectivity between relevant brain regions during the acquisition of navigational knowledge in a novel, real-world virtual environment (VE). During fMRI scanning, healthy younger and older adults were repeatedly transported around the VE consisting of four interconnected 4-way intersections. Each encoding phase was followed by a retrieval phase during which participants were asked to point in the direction of one of two target landmarks from one of the intersections that were encountered during encoding. Navigational performance was measured by means of the angular deviation of their response from the respective target landmark. A color discrimination task

within the same VE that did not require retrieval of the spatial layout served as control condition. Behaviorally, both age groups performed around chance level at the beginning of testing but diverged considerably over time, with lower accuracy and slower learning in the older group. Importantly, individual rates of learning differed widely, which was well captured by a Bayesian implementation of a state-space model. Including these learning estimates in the analysis of the fMRI data showed that older adults differentially activated key regions of the navigation network, which was modulated by the individuals' degree of learning. Moreover, functional connectivity between these regions was altered in the older age group, indicative of a functional reorganization in the aging brain. Together, these data suggest that older adults' difficulties in encoding the spatial layout of a novel environment are related to age-related deficits in the brain's capability to generate internal spatial representations due to changes in the dynamics of activity in relevant regions.

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Nanosymposium

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Presentation Number: *018.07

Topic: *H.02. Human Cognition and Behavior

Support: project PACE H2020-MSCA-ITN-2014 Ref. 642961

Title: Variability in speed can predict temporal adaptation

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Abstract: To be successful at intercepting moving objects we need to predict the spatiotemporal features of the motion of the object and of our hand. The errors we make can result in updates of these predictions for future interceptions. Although variability in task performance is often seen as an unwanted consequence of noise, recent studies claim that variability in baseline performance can help adapt to a perturbation task. This finding suggests that initial variability in performance can help explore the spatial demands of the task. To see if this relationship can also be found in interception, we studied the link between the variability of movement velocity during baseline trials, and the adaptation to a temporal perturbation. 20 subjects performed an interception task on a graphic tablet with a stylus pen. A target moved from left to right or right to left, with varying speed across trials. Participants were instructed to intercept this target with a

straight shooting movement. Their movements were represented by a cursor on a screen above the tablet, which blocked the view of their hand. The first part of the cursor's trajectory was also blocked from view to prevent online corrections. After a baseline phase of 80 trials, a temporal delay of 100 ms was introduced to the cursor representing the hand (adaptation phase: 80 trials). This delay initially caused the participants to produce temporal errors in the performance (missing the target), but they quickly adapted to the delay of the cursor to account for these errors. We found that variability in baseline movement velocity is a good predictor of adaptation (rate + asymptote). Participants with higher variability in movement speed during the baseline phase show a better adaptation to a temporal delay in the adaptation phase. This finding suggests that high variability in movement velocity can provide people with tools to learn from temporal errors in interception. Further research is required to identify if this advantage is due to an increased ability to either identify the error or adapt to the error.

Disclosures: E. Knelange: None. **J. Lopez-Móliner:** None.

Nanosymposium

018. Perceptual and Spatial Human Learning

Location: 143A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***018.08

**Topic: ***H.02. Human Cognition and Behavior

Title: Converging evidence for learning-dependent changes in perceptual representation and decision-making: Combining response frequencies, response latencies, and the timing of the lateralized readiness potential

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Abstract: The effects of perceptual practice include reductions inthresholds and reaction times, qualitative changes in aspects of perceptual encoding and processing, including shifts in processing architecture and capacity, and changes in cortical correlates. Typically, such changes have been documented in paradigms that either require different trial types in order to obtain more than one dependent variable (e.g., staircase vs. categorization trials), or that make use of only one dependent variable (e.g., reaction times [RTs], response accuracy). Here we report on an investigation of changes in perceptual representation using a meta-theoretical framework (general recognition theory, GRT, Ashby & Townsend, 1986) that has recently (Townsend, Houpt, & Silbert, 2012) been extended to allow for simultaneous predictions for response frequencies and RTs. We take the additional step in this study of extending the predictions for RTs to the onset time of the lateralized readiness potential (LRP). The LRP is a negative-going

waveform in stimulus-locked electroencephelographic (EEG) data, measured in central electrodes contralateral to the motor response that it precedes. We previously (SfN 2016) demonstrated that start times of the LRP provided converging evidence for the inferences supported by the analyses of the RTs. Participants in the present study began by performing a complete identification task (CID), in which stimuli contained 0, 1 (top or bottom feature), or 2 (top and bottom feature) of the components of the target image, presented at either 50% or 10% contrast. They then practiced with all possible stimuli for approximately 20 sessions, using an adaptive staircase procedure to track detection thresholds. Finally, they again performed the CID, with stimuli presented at 50%, 10% and threshold contrast levels. EEG data were collected during both pre- and post-practice performance of the CID task. Analyses of the response frequencies indicate a transition from perceptual independence and separability to dependencies. These inferences were supported first by analyses of the associated RTs, and second by analyses of the start times for the LRPs. The results provide additional evidence that the timings on the LRPs can be used as a source of converging evidence in tests of hypotheses derived from behavioral meta-theories.

Disclosures: M.J. Wenger: None. **S.E. Rhoten:** None.

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**Topic: ***H.02. Human Cognition and Behavior

Support: Sloan Research Fellowship awarded to CJH

Title: A hierarchical model of sequence perception and sequence learning

Authors: *H.-Y. CHIEN, C. J. HONEY
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Abstract: *Background:* Prior information continuously influences the perception and processing of information arriving in the present. This ongoing temporal integration occurs over multiple timescales. For example, in language, phonemes achieve their meaning in a word, and words in the context of a sentence. In the human brain, there appears to be a hierarchical architecture for processing sequential information: as one moves from sensory to higher order regions of cortex, neural dynamics become slower and neural responses become more sensitive to information farther in the past (Hasson et al., 2015). Here, we aimed to answer: (i) what kind of computational architecture could give rise to the temporal processing hierarchy in the brain. and

(ii) how does a temporal processing hierarchy affect learning. *Model Description*: We modeled the temporal processing hierarchy as a stack of temporal auto-encoders. The auto-encoders were based on the architecture of the TRACX sequence learning model (French et al. 2011). In our hierarchical model, HTRACX, each auto-encoder learns the temporal correlation structure of its input, and each auto-encoder continually transmits its hidden states to higher levels of the network. Two features of our model are: (i) increasing time constants for the hidden states in each level of the circuit, so that higher levels preserve more memory; (ii) modulation of surprise on information transmission from lower to higher levels. *Results of Modeling Sequence Learning*: We tested whether HTRACX could capture the data of Giroux and Rey (2009) regarding the learning of embedded sequences. HTRACX successfully captured the empirical observation that, with greater exposure to a super-sequence ("ABC"), the embedded elements of that sequence ("AB", "BC") are less well recognized. *Results of Modeling the Neural Hierarchy*: We tested whether HTRACX could account for dynamical and functional properties of the brain's temporal processing hierarchy. We trained and tested our model on variants of the experimental designs employed by Lerner et al. (2011) and Baldassano et al. (2016). After training, the hidden states of HTRACX exhibited both functional and dynamical properties of temporal processing hierarchy. When the model was trained on random sequences, its detection of sequence boundaries was impaired and it no longer exhibited a hierarchical sensitivity to temporal context. *Conclusion*: We propose HTRACX, a hierarchical auto-encoder in time, as a model for behavioral and neural data in the perception and learning of sequential information. Future work will explore more biologically plausible learning rules and implications for the learning of nested chunks.

Disclosures: H. Chien: None. **C.J. Honey:** None.

Nanosymposium

019. Learning and Memory in Aging

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**Presentation Number: ***019.01

**Topic: ***H.02. Human Cognition and Behavior

Support: NSERC grant awarded to R.S.R., 2014-06704
NSERC grant awarded to M.M., 08347

Title: Discrimination of highly similar sounds does not differ between young and older adults

Authors: *N. V. HOANG[1,2,3], S. BAKER[2], J. DAOU[2], M. MOSCOVITCH[1,3], R. S. ROSENBAUM[2,1]

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Abstract: Pattern separation is a neural mechanism that allows for the behavioural discrimination of overlapping information. It is believed to support the encoding and retrieval of detailed and distinct mnemonic representations in the hippocampus. Insofar as pattern separation has been shown to implicate the hippocampus in visual memory tests involving discrimination between similar targets and lures (Bakker, Kirwan, Miller, & Stark, 2008), little is known of its effects on human auditory memory. Evidence suggests that learned acoustic patterns could also implicate the hippocampus (Kumar et al., 2014, 2016). Therefore, the goal of this research was to investigate how healthy humans behaviorally "pattern separate" or discriminate new from old events, in this case auditory experiences. A novel task, the Mnemonic Auditory Similarity Task (MAST), was developed to detect the recognition memory for auditory stimuli of 53 young adults (17-30 years old) and 31 older adults (60-89 years old). At test, participants were asked to distinguish among auditory stimuli that were previously heard (20 targets), new (20 foils), or similar (20 lures). Regardless of age, participants recognized lures at a significantly lower accuracy rate than targets and foils. This lure discrimination difficulty paralleled similar results found in the visual modality (Bakker et al., 2008). In contrast to previous visual studies (Yassa et al., 2011), there was the absence of an age-related decline in performance accuracy for lure discrimination. This unexpected finding suggests that the hippocampus may play a different role in pattern separation of highly similar sounds than of highly similar visual images.

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Nanosymposium

019. Learning and Memory in Aging

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**Presentation Number: ***019.02

**Topic: ***H.02. Human Cognition and Behavior

Support: Darrell K Royal Fund

Title: Effects of task complexity and age on functional connectivity of attentional networks

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Abstract: Studies investigating the strength and membership of regions within multiple functional networks primarily focus on either resting state or single cognitive tasks. The goal of the current study was to investigate whether task-related functional connectivity changes as a function of task complexity, and whether this connectivity-complexity relationship is exacerbated by age. We assessed seed-to-voxel functional connectivity for the default mode network (DMN) and two attentional networks [fronto-executive (FE), fronto-parietal (FP)] in three cognitive control tasks (Single task, Dual task, and Memory Updating), across both younger and older adults (N=53; N_{Young}=24; N_{Old}=29). Connectivity for the attentional networks, irrespective of age, increased with greater task complexity, indexed by cognitive control demands. DMN seed connectivity, both within- and between-network, was significant only for the Memory Updating task; furthermore, this connectivity was associated with better Memory Updating performance. Age-related differences in connectivity-complexity relationships indicated that the tasks requiring greater cognitive control elicited more within- and between-network connectivity for the seeds of the attentional networks in younger adults, compared to older adults. In contrast, older adults showed greater between-network FP-DMN connectivity during the simplest task, suggesting greater coupling of the DMN with a attentional network in older adults needed to achieve the same accuracy as that of younger adults in Single task. This novel finding expands our understanding on how age-differences influence functional connectivity during cognitively demanding tasks. Task-related connectivity can be a useful way to investigate functional brain networks, specifically when the network theoretically matches the cognitive components of the task.

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Nanosymposium

019. Learning and Memory in Aging

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**Topic: ***H.02. Human Cognition and Behavior

Support: Strategic Innovation fund of the Max Planck Society (67–11HIPPOC)

Title: Hippocampal subfields and limbic white matter are associated with verbal learning in older adults

Authors: *A. R. BENDER[1], A. M. BRANDMAIER[1,2], S. DÜZEL[1], A. KERESZTES[1], O. PASTERNAK[3], U. LINDENBERGER[1,2,4], S. KÜHN[1,5]
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Abstract: The high prevalence of age-associated verbal learning decrements underscores the importance of understanding their structural brain correlates. Numerous reports have revealed associations between age-related memory impairments and concomitant decrements in both cerebral white matter (WM) microstructure and hippocampal (HC) volume. However, the combined roles of specific HC subregions and limbic WM fiber tracts on verbal learning in older adults remain poorly understood. Thus, we sought to model the mutual contributions of limbic WM diffusivity and HC subfield volumes on verbal learning in a population-based sample of older adults 60 to 80 years of age, drawn from the Berlin Aging Study-II. A total of 337 participants (mean age = 69.66, SD = 3.92 years; 38.3% women) completed a verbal learning and memory task of freely recalling 15 words over five trials, and also underwent magnetic resonance imaging (MRI) scans for structural and diffusion MRI. We applied a semi-automated method to segment high-resolution (in plane resolution = 0.4 × 0.4 mm), T_2-weighted MRI data into entorhinal cortex, subiculum, cornu ammonis (CA) areas one and two (CA1/2), and CA3/dentate gyrus (DG). We used constrained spherical deconvolution-based deterministic fiber tractography to produce streamlines corresponding to four bilateral limbic WM tracts connecting medial temporal with prefrontal cortical regions: dorsal and HC cingulum bundles (CBD, CBH), posterior fornix, and uncinate fasciculus. From these four limbic WM tracts, we sampled diffusion tensor imaging (DTI) indices (i.e., fractional anisotropy [FA], axial diffusivity, and radial diffusivity [RD]), corrected for free water contamination. Using a structural equation modeling framework, we fitted a latent growth model to the verbal learning data to estimate rate of change over learning trials, constructed latent factors for each WM tract and each HC subfield, and evaluated associations between WM and HC subfield factors and the intercept, linear and quadratic slopes of verbal learning. Separate models for each DTI index revealed that the rates of verbal learning were associated with WM microstructure in the fornix and CBH, with positive associations for FA and negative associations for RD. In addition, the linear slope of verbal learning was positively associated with CA1/2 and CA3/DG volumes in all models. The present findings demonstrate specific multimodal structural brain correlates of verbal learning in older adults.

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Nanosymposium

019. Learning and Memory in Aging

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**Topic: ***H.02. Human Cognition and Behavior

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AG049583

Title: Neural differentiation during encoding predicts subsequent memory independent of age

Authors: *J. D. KOEN[1], N. HAUCK[2], M. D. RUGG[3]
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Abstract: It is well established that episodic memory - memory for unique events - declines during the course of healthy aging. This decline is thought largely to be a result of inefficient encoding processes. Healthy aging is also associated with reductions in neural differentiation - a decrease in the fidelity with which information is represented in 'feature-selective' cortical regions. Importantly, functional neuroimaging studies in young adults have provided substantial evidence that greater engagement of regions involved in the on-line processing of the features of an event, such as the parahippocampal place area (PPA) when viewing scenes, correlates with successful memory encoding. Here, we tested the prediction that age-related reductions in neural differentiation in the ventral visual cortex are associated with age differences in episodic memory. Young (N =24) and older (N = 24) adults underwent fMRI scanning while studying images of objects and scenes prior to a subsequent recognition memory test. A neural differentiation index was computed in two regions of interest (ROIs) that typically show selective responses to scenes and objects, respectively: (1) PPA, and (2) lateral occipital cortex (LOC). The neural differentiation index was computed as a scaled mean difference in the BOLD response between an ROI's preferred (e.g., scenes for PPA) and non-preferred (e.g., objects in PPA) visual categories. Our findings replicate prior work in showing lower levels of neural differentiation in older adults relative to their young counterparts. In addition, the neural differentiation index was significantly correlated with recognition memory performance. Importantly, age did not moderate the correlation between neural differentiation and recognition memory. These findings are consistent with prior research showing that engagement of feature selective cortical regions is related to successful encoding, and further suggest that while increasing age is associated with reduced neural differentiation, the relationship between differentiation and memory encoding is age-invariant.

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Support: NIH Grant R01AG050523

Title: Age-related declines in neural distinctiveness and GABA concentrations in auditory cortex

Authors: *P. S. LALWANI[1], H. C. GAGNON[1], K. CASSADY[1], J. CHAMBERLAIN[1], M. SIMMONITE[1], B. FOERSTER[2], M. PETROU[2], R. SEIDLER[1], S. F. TAYLOR[3], D. WEISSMAN[1], T. A. POLK[1]
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Abstract: Activation patterns in ventral visual cortex in response to different stimulus categories are more distinctive in young than older adults (*PNAS* 101:13091) and greater neural distinctiveness is associated with better fluid processing ability in older adults (*Jnl Neurosci* 30:9253). Administration of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) improves neural selectivity in older macaques (*Science* 300:812), suggesting that age-related declines in GABA levels might contribute to reduced neural distinctiveness and associated cognitive declines. The aim of the present study was to investigate whether neural distinctiveness declines with age in auditory cortex, whether GABA levels in auditory cortex decline with age, and whether GABA levels predict neural distinctiveness in individuals. Healthy young (ages 18-29) and older adults (over 65) participants completed a 6 mins functional Magnetic Resonance Imaging (fMRI) auditory listening task. The task consisted of six 20-second blocks of music and six 20-second blocks of unfamiliar foreign speech (in pseudorandom order) with 10-second fixation blocks between all the experimental blocks. Subject-specific functional regions of interest (ROIs) were created based on Freesurfer vertices activated by either condition, restricted within the bilateral transverse temporal gyrus, superior temporal gyrus, and bank of the superior temporal sulcus. We computed the average correlation of activation patterns in these ROIs within the same condition (music with music, speech with speech) and between conditions (music vs. speech), and used the within - between difference as a measure of distinctiveness for each subject (Neuroimage 56.2). Participants also underwent Magnetic Resonance Spectroscopy (MRS) scans in a separate session. Individual's fMRI activations were used to determine placement of two 3cm x 3cm x 2.5cm voxels in the left and right auditory cortex for MRS data collection. We used a MEGA-PRESS sequence with frequency selective editing pulses to isolate the GABA signal. Data collection is ongoing, however preliminary results in 10 young and 8 older adults suggests that neural distinctiveness declines with age in auditory cortex, that GABA levels in auditory

cortex also decline with age, and that GABA levels are positively correlated with neural distinctiveness in older adults. These findings suggest that age-related declines in neural distinctiveness extend beyond visual cortex and may be related to age-related declines in GABA levels.

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Title: Reinforcement learning in heathy aging: Similar behavior to Parkinson's disease, opposite mechanisms?

Authors: *I. LERNER[1], R. B. SOJITRA[2], J. R. PETOK[3], M. A. GLUCK[4]
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Abstract: Probabilistic reinforcement learning declines in healthy cognitive aging. Some evidence suggests that impairments are especially conspicuous in learning from positive feedback, resembling deficits in Parkinson’s disease. Others, however, have shown impairments in learning from negative feedback. Here, we tested 252 adults from three age groups (18-25, 53-69, 70-89) on a probabilistic reinforcement-learning task that separated learning from positive and negative feedback. We analyzed trial-by-trial performance with a Q-reinforcement learning model, and correlated both derived model parameters and behavioral measures to polymorphisms in four dopamine-related genes.
Our analyses revealed that for all age groups, learning was markedly different between the two feedback conditions: Whereas with negative feedback performance scores across subjects had a skewed unipolar distribution indicating varying degrees of learning, with positive feedback performance scores had a bipolar distribution with almost all subjects either perfectly learning an optimal solution, or perfectly learning a non-optimal one. Importantly, performance declined with age for both feedback conditions, but in a different manner. For the negative feedback condition, older participants simply learned to a lesser degree than younger participants. In the

positive feedback condition, older participants were more inclined to learn the non-optimal solution. Model-based analysis revealed that each of these two effects stemmed from a different mechanism: The negative feedback result arose because of a noisier decision-making process, whereas settling for a non-optimal solution in the positive feedback condition resulted from unbalanced positive/negative prediction error learning rates. This imbalance was highly correlated with variations in the striatum-specific DARPP-32 gene, thus suggesting an additional link to Parkinson's disease, which is also striatal-related. However, the imbalanced learning rates characterizing the older population were largely due to reward-seeking strategies—the opposite of what is often attributed to Parkinson's patients. Finally, we show that our results can account for previous findings on age and reinforcement learning using the Probabilistic Selection Task. These findings were previously used to draw equivalence between deficits in Parkinson's disease and healthy aging and, with our results, should be re-evaluated.

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Nanosymposium

019. Learning and Memory in Aging

Location: 152A

**Time: ***Saturday, November 11, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***019.07

**Topic: ***H.02. Human Cognition and Behavior

Support: NIA P50 AG05146
NIA R21 AG049220
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NSF GRF DGE-1232825
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UCI Chancellor's Club
ARCS & Roche Foundation

Title: Age-related deficits in mnemonic discrimination of objects associated with dysfunction of anterolateral entorhinal cortex

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Abstract: Cross-species studies have established a functional dissociation between the medial and lateral entorhinal cortex (MEC; LEC). In rodents, the MEC features highly spatially-selective cell populations, whereas cells in the LEC are more tuned to objects or items. Additionally, there is evidence to suggest that the LEC is among the earliest brain regions vulnerable to age-related pathology. However, it remains unknown whether LEC dysfunction exists in the aging human brain. A prior study in our lab used an object vs. spatial mnemonic discrimination paradigm – taxing pattern separation across domains – to functionally dissociate LEC and MEC in young adult humans (note that in humans, this division is more accurately described as anterolateral vs. posteromedial EC). In a separate behavioral study, we demonstrated that nondemented older adults show greater object than spatial discrimination deficits. Here, we coupled this approach with high-resolution fMRI to test the hypothesis that age-related object discrimination deficits are associated with LEC dysfunction. Consistent with our hypothesis, older adults showed striking object discrimination deficits and LEC hypoactivity compared to young adults. Conversely, spatial discrimination was relatively spared, and MEC activity did not differ across age groups. Finally, representational similarity analysis (RSA) of these data revealed that whereas activity patterns for young adults differs significantly between studied target objects and similar lures, older adults did not show this difference, suggesting a failure to orthogonalize representations of similar objects. Together, these findings suggest that even "healthy" aging is associated with dysfunction in the LEC.

Disclosures: Z. Reagh: None. **J.A. Noche:** None. **D. Delisle:** None. **E.A. Murray:** None. **M.A. Yassa:** None.

Nanosymposium

019. Learning and Memory in Aging

Location: 152A

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**Presentation Number: ***019.08

**Topic: ***H.02. Human Cognition and Behavior

Support: BBSRC BB/H008217/1
UK MRC MC_A060_5PR10

Title: Age-related delay in visual and auditory evoked responses is mediated by white and gray matter differences

Authors: *D. PRICE[1], L. K. TYLER[3], R. NETO HENRIQUES[2], K. L. CAMPBELL[4], N. WILLIAMS[5], M. S. TREDER[6], J. TAYLOR[7], R. HENSON[1]
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MA; [5]Neurosci. Ctr., Univ. of Helsinki, Cambridge, United Kingdom; [6]Sch. of Psychology, Univ. of Birmingham, Birmingham, United Kingdom; [7]Sch. of Psychological Sci., Univ. of Manchester, Manchester, United Kingdom

Abstract: Age-related slowing of information processing is widely cited as a primary causal factor in cognitive ageing. Age-related atrophy of white matter (WM) (Peters 2002) and grey matter (GM) (Wang et al. 2005) has been linked to slowing of neuronal responses in animals, but there is no direct evidence for this in humans. We investigated age-related delay of event related fields (ERFs) to auditory tones and visual checkerboards, as measured by magnetoencephalography (MEG), and the mediating effects of structural decline, as measured by T1- and diffusion-weighted (DWI) magnetic resonance imaging (MRI).
Participants from the Cambridge Centre for Ageing and Neuroscience (CamCAN; www.cam-can.org) (Shafto et al. 2014) (N = 617, age-range: 18-88y) were passively presented (no response required) binaural auditory tones (N=60, 300-1200Hz, SOA=1s, dur=300ms) or bilateral visual checkerboards (N=60, SOA=1s, dur=33ms). MEG and structural MRI (T1 and DWI) were collected. Mean ERFs from each participant were fit to a template (the group average ERF) in order to obtain separate relative estimates of 1) constant delay (time shift) and 2) cumulative delay (temporal dispersion). GM volume was calculated for each voxel of the T1 anatomical image. Mean diffusion kurtosis tensor was estimated from the DWI data to estimate the non-gaussianity of axonal water diffusion (an indicator of WM integrity) (Jensen et al. 2005). To test for the mediating effect of age-related structural decline on ERF delay, GM and WM maps were entered into whole brain robust mediation analyses (X=age, M=structure, Y=delay) using the M3 mediation toolbox (Davidson et al. 2008).
Age was related to different types of delay for the two sensory modalities: a constant delay for visual stimuli (R^2 = .11, p<.001) but no cumulative delay (R^2 = .00, p=.996), and a cumulative delay for auditory stimuli (R^2 = .15, p<.001) but no constant delay (R^2 = .00, p=.159). WM decline in the optic radiation partially mediated age-related visual constant delay (mediation effect size = 12%), while GM decline in middle temporal gyrus mediated auditory cumulative delay (mediation effect size = 12%).
Visual and auditory ERFs exhibited different types of age-related delay (constant and cumulative, respectively). Each had distinct underlying anatomical correlates: visual constant delay appears to reflect a delayed arrival time of information to the visual cortex owing to age-related decline in WM tracts from thalamus, while the auditory cumulative delay appears to reflect slowing of local processing due to GM decline in auditory cortex. These results have important implications for the neurobiological and cognitive ageing literature.

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019. Learning and Memory in Aging

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**Topic: ***H.02. Human Cognition and Behavior

Support: NIH Grant AG024102
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NIH Grant R00 AG036848
NIH Grant RC4NS073008

Title: Six-year longitudinal change in association white matter tract integrity: Progression from cognitively healthy to dementia

Authors: *S. L. WILLIS[1], K. M. KENNEDY[2], P. R. ROBINSON[1], K. M. RODRIGUE[2], P. RAST[3], E. ULZIBAATAR[1], T. J. GRABOWSKI[1]
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Abstract: Understanding the transition from cognitively normal status to a diagnosis of dementia and the risk factors predicting this transition is a major public health goal. This requires longitudinal studies, following individuals over time. This study examined 6-year longitudinal change in association white matter tract integrity in the progression from cognitively healthy to dementia diagnosis. At baseline, all old-age participants in the Seattle Longitudinal Study were nondemented (N = 124; mean age = 76; mean education = 16; 61% female, 26% APOEe4, and 57% hypertensive). Over 4 measurement occasions (6 years), N = 15 participants progressed to dementia (12% conversion rate). These participants were older, had a higher proportion APOEe4 (40%) and hypertension (73%) and lower proportion female (47%), but did not differ in education. Multivariate multilevel modeling was used to examine cross-sectional differences and longitudinal change (linear and curvilinear) in fractional anisotropy (FA), axial and radial diffusivity (AD, RD) in 5 association tracts (bilaterally and averaged across hemisphere): Superior and Inferior longitudinal fasciculus (SLF,ILF), Uncinate fasciculus (UNC), Cingulum (CING), and fornix (FX), and the modifying effects of APOE and hypertension. Results: Significant age differences (cross sectional) were found in FA (ILF, UNC, CING), AD (ILF, SLF,UNC, FX) and RD (ILF,UNC,CING,FX). Dementing participants had poorer white matter integrity at baseline in AD (ILF, CING) & FA (SLF,CING). Significant curvilinear longitudinal loss of integrity occurred for AD (ILF,SLF,UNC), RD (ILF,UNC) and FA (UNC,CING), indicating a decrease in rate of loss of integrity across time. Of note, demented participants showed an acceleration of nonlinear loss of integrity in the Cingulum for AD (AD x Time^2,$p<.01$). No interactions of dementia status with hypertension or APOE were found. These

longitudinal findings extend prior cross-sectional reports of association between loss of white matter integrity and progression to dementia in older adults with MCI, frontotemporal, and Alzheimer dementia. Specifically, white matter integrity decline in tracts that connect grey matter structures associated with memory decline are particularly implicated (e.g cingulum).

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019. Learning and Memory in Aging

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**Topic: ***H.02. Human Cognition and Behavior

Support: NIA R00 AG-036848
NIA R00 AG-036818

Title: Effect of DRD2 C957T polymorphism on modulation of activation to working memory load across the adult lifespan

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Abstract: Dopamine (DA) availability has been shown to influence cognitive processes such as working memory (WM). Moreover, both DA availability and WM decline with age. The DRD2 C957T single nucleotide polymorphism in D2 receptor gene influences DA availability differentially throughout the brain, where C homozygotes express the lowest and T homozygotes the highest striatal synaptic DA; but cortically, C carriers have higher extrastriatal D2 receptor density than T carriers. Here we examine DRD2 influence on age-related BOLD modulation to WM load, and its association with cognitive performance. Participants included 158 healthy adults aged 20-94, (mean 53±19; 93 women) who completed fMRI *n*-back scanning and DRD2 genotyping (*n*'s = 47 C/C; 44 T/C; 67 T/T). Participants completed three runs of a digit *n*-back paradigm with four levels of WM load: 0-, 2-, 3-, and 4-digits back. Using SPM8 we conducted multiple regression with age (continuous) and DRD2 genotype (3-level categorical) as predictors of a linear contrast across the four levels of WM load, testing main effect of DRD2 as well as DRD2 x Age interaction. We found no DRD2 x Age interaction, rather a main effect of DRD2 on modulation of activation to increasing WM load, suggesting that DRD2 influence is equivalent across the lifespan but differs by risk allele: C/C individuals displayed greater up-

modulation of bilateral MFG, superior/inferior parietal, and left superior frontal gyrus than both T/T and T/C groups, and additionally in right superior frontal gyrus than T/T individuals. Further, C/C individuals showed greater down-modulation to WM load than T/T individuals in bilateral vmPFC. Importantly, both greater up-modulation and down-modulation were associated with higher accuracy during the task, regardless of genotype. Further, for C/C individuals only, greater up-modulation predicted faster processing speed outside the scanner task. DRD2 C/C individuals show greater modulation in key fronto-parietal cognitive control regions, as well as greater down-modulation of vmPFC, suggesting that greater availability of extrastriatal DA is associated with increased modulatory capacity to increasing cognitive demand that tracks performance both during the task and in processing speed measures tested outside the scanner.
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**Topic: ***H.02. Human Cognition and Behavior

Support: NIH Grant R01AG050523

Title: Aging in the somatosensory system: Neural distinctiveness, GABA concentration and tactile function

Authors: *K. E. CASSADY[1], H. GAGNON[2], J. CHAMBERLAIN[2], P. LALWANI[2], M. SIMMONITE[3], B. FOERSTER[2], M. PETROU[2], R. D. SEIDLER[2], S. F. TAYLOR[4], D. WEISSMAN[2], T. A. POLK[5]
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Abstract: Aging is associated with extensive declines in sensorimotor function. According to the dedifferentiation hypothesis of aging, such age-related impairments stem at least partially from reductions in the distinctiveness of neural representations. Consistent with this hypothesis, recent functional magnetic resonance imaging (fMRI) studies using multi- voxel pattern analysis (MVPA) have reported that (1) neural activation patterns evoked by different visual stimuli or motor actions are significantly less distinctive in older relative to younger adults and (2) reduced

neural distinctiveness in older adults predicts worse performance on a range of behavioral tasks. Animal studies corroborate these age- related declines in neural distinctiveness and further suggest that reductions of the neurotransmitter gamma-aminobutyric acid (GABA) play an important role. In the present study, we employed MVPA to measure age differences in the distinctiveness of somatosensory neural representations during vibrotactile stimulation in healthy young (ages 18-69) and older (over age 65) adults. We also used magnetic resonance spectroscopy of GABA levels and collected measures of vibrotactile detection thresholds to investigate whether individual variability in somatosensory processing is correlated with GABA concentration in sensorimotor cortex. Based on preliminary results from the first 16 participants (8 young adults and 8 older adults), we found that neural activation patterns within somatosensory cortex were less distinctive among older adults than younger adults. Furthermore, GABA levels in sensorimotor cortex were reduced in older adults, and across all participants lower levels were associated with increased tactile thresholds. These findings link, for the first time, age-related declines in somatosensory neural distinctiveness to age-related reductions of GABA and impaired tactile function and thereby suggest a neurochemical substrate of age-related dedifferentiation.

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Nanosymposium

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**Topic: ***H.02. Human Cognition and Behavior

Support: Darrell K Royal grant for Alzheimer's Disease

Title: Age related differences in brain activation during continuous memory updating

Authors: *S. QIN[1], M. O'CONNELL[3], K. NASHIRO[4], C. BASAK[2]
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Abstract: The current functional magnetic resonance imaging (fMRI) study was designed to investigate not only the neurocognitive differences in working memory updating between younger and older adults, but also to further elucidate these differences within an elderly cohort. In the current study, younger adults (M_{age}= 22) and two groups of older adults (younger-old: age

M_{age}= 60; older-old: age M_{age}= 71) were scanned during a mixed block/event-related unpredictable 2-Match task (Basak & O'Connell, 2016), where context-relevant digits needed to be continually recognized and updated in working memory. Older adults showed greater activation in Default Mode Network (DMN) regions, compared to younger adults, for task>fixation contrast (corrected for multiple comparisons at p<.01 and z>2.33), with younger-old showing greater activation in posterior cingulate cortex (PCC). PCC is considered to be a DMN hub supporting complex behavior. In contrast, older-old, compared to younger adults, showed greater activation in additional DMN regions, including ventral PFC and visual cortex. These results suggest that age-related increases in the DMN regions during a cognitive task is limited to a hub in the younger-old, but broadens to other DMN regions in older-old. For updating cost (Update > Non-update), younger adults showed greater activation in left post-central gyrus and left DLPFC, compared to the younger-old. In contrast, the older-old group showed greater activation compared to younger adults in the contralateral, right precentral gyrus for updating cost. These results suggest with increased age, not only performance in working memory updating decreases, but left fronto-parietal activations associated with the updating cost also decrease. Importantly, contra-lateral recruitment of additional fronto-parietal regions during task – a typical finding in aging literature -- was observed only in the older-old. We conclude that there are differences in patterns of task-related brain activations within the older adults cohort, and that age-related changes in neural mechanisms are continuous throughout the adult lifespan.

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Title: Decoding selective attention during context memory encoding: An aging study

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Abstract: Several studies of associative memory in older adults suggest associative memory declines are due to a tendency to bind too much contextual information (hyper-binding), and as a result may rely on episodic reconstruction processes to support successful retrieval of contextual information. However, the degree to which older adults are able to selectively attend to relevant contextual information is less clearly understood To better understand the neural dynamics associated with selective attention to contextual information, the current study used multivariate pattern analysis (MVPA) to explore whether patterns of oscillatory power could predict the degree to which participants selectively attended to relevant contextual information. Participants were 18 young adults, ages 18-35 and 17 older adults, ages 60-80. Participants studied pictures of objects in the presence of two contextual features: a color and a scene, and their attention was directed to the object's relationship with one of those contexts. EEG was recorded as participants made context memory decisions for both attended and unattended features. Using the Princeton MVPA Toolbox, pattern classification analyses decoded selective attention conditions (color vs. scene) based on patterns of oscillatory power during encoding. To examine the relation between classification performance and evidence of hyper-binding we calculated the probability that correctly endorsing one contextual feature (attended or unattended) would result in correct endorsement of the other. Results showed that patterns of oscillatory power successfully predicted whether selective attended was directed to a scene or color, and overall classification performance did not differ between age groups. Further examination of the relationship between classification performance and hyper-binding revealed a stronger negative relationship in older compared to younger adults, suggesting that better classification performance (i.e., better selective attention to the relevant contextual information), was associated with a lower probability of recalling the irrelevant/unattended contextual feature. To the best of our knowledge, the current study is the first use of MVPA to explore whether patterns of oscillatory power in younger and older adults can be used to successfully decode selective attention to contextual information. Furthermore, evidence of a negative relationship between classification performance and our index of hyper-binding supports previous suggestions that hyper-binding in older adults is a consequence of poorer selective attention and inhibitory control.

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**Presentation Number: ***019.14

**Topic: ***H.02. Human Cognition and Behavior

Title: Independent components of neural activation before and after 100 days of cognitive training

Authors: *M. SIMMONITE[1], M. LÖVDÉN[2], P. S. LALWANI[1], J. D. CHAMBERLAIN[1], T. A. POLK[1]
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Abstract: Some cognitive training studies have reported benefits that transfer to other tasks, while other studies have not. What neural changes are associated with general training effects, rather than task specific training effects? We investigated this question in the COGITO study dataset. COGITO is a large longitudinal project consisting of a variety of behavioral assessments before, during, and after 100 days of cognitive training in 101 younger (age: 20-31 years) and 103 older (age: 65-80 years) adults. Pre and post assessments included verbal, numerical, and spatial measures of episodic memory, perceptual speed and working memory. It was therefore possible to assess training effects at a general latent ability level, rather than at the level of individual tasks. Previous analyses of these data found training-related improvements on a latent ability factor reflecting working memory, in both the young and old participants. Functional MRI data was collected from a subsample of the cohort (39 participants: 24 young/15 old) during pre- and post-training sessions. We used Independent Components Analysis (ICA) to identify the networks involved in a perceptual decision making task across both old and young subjects, before and after training. We identified five task-positive components which were task related: two perceptual networks, a motor network and two executive networks. Structural equation modeling (SEM) was then used to determine relationships between latent working memory ability and activity in the five identified networks. Pre-training activity of the motor and striate networks predicted latent working memory performance before training. Additionally, training-related changes in the motor network predicted training-related change in working memory ability. These findings suggest that training-related changes in the motor network may play a role in task-independent working memory improvements.

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Nanosymposium

020. Genetic and Genomic Studies of Schizophrenia

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**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***020.01

**Topic: ***H.03. Schizophrenia

Support: BBRF grant FP00000839

Title: Dysregulated in psychiatric disorders circular RNAs interact with RNA-binding proteins and influence synaptic plasticity

Authors: *N. MELLIOS[1], J. P. WEICK[2], B. RODRIGUEZ[3], S. K. AMOAH[5], M. DELL'ORCO[6], A. HAFEZ[4], J. LALONDE[7], B. J. HARTLEY[8], K. BRENNAND[9], S. J. HAGGARTY[10], N. PERRONE-BIZZOZERO[6]
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Abstract: Schizophrenia (SCZ) and Bipolar disorder (BD) are heterogeneous psychiatric disorders with severe socioeconomic impact and unknown pathogenesis, despite the plethora of genomics and genetic studies focused on protein-coding genes. However, the emerging consensus is that protein-coding genes are only the tip of the iceberg of the mammalian transcriptome, given the plethora of actively transcribed non-coding RNAs (ncRNAs). Circular RNAs (circRNAs) are a novel category of ncRNAs that are derived from the back-splicing and covalent joining of exons, yet with very few exceptions lack the capacity to become translated into protein. Recent studies have suggested that circRNAs are enriched in the brain, are preferentially generated from brain plasticity-associated genes, and are abundant in dendrites and synapses. However, very little is known about the function of circRNAs in the human brain and their potential involvement in neuropsychiatric disease. Here we carried out the systematic profiling of circRNA expression in a large cohort of human postmortem brain samples from the orbitofrontal cortex of subjects with SCZ and BD disorder and uncovered a subset of differentially expressed circRNAs produced from genes with known links to synaptic plasticity and neuronal excitability. We validated the expression of a subset of psychiatric disease-altered circRNAs in human postmortem brain with circRNA-specific qRT-PCR and identified a subset of circRNAs that were also dysregulated in induced pluripotent stem cell (iPSC)-derived neuronal cultures from patients with SCZ ad BD. Analysis of RNA-binding proteins (RBPs) that could bind to psychiatric disease-associated circRNAs revealed interactions with RBPs that affect alternative splicing and synaptic localization. Using circRNA shRNA knockdown in stem cell-derived neuronal cultures we discovered that one of the altered circRNAs regulated the expression of different isoforms of its linear mRNA counterpart and could influence neuronal excitability. Ongoing experiments are attempting to further elucidate the function of SCZ- and BD-associated circRNAs in human neuronal development and maturation and their interplay with RBPs and disease-related molecular pathways. Collectively, our experiments shed light into the unexplored role of circRNAs in brain function and disease.

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Nanosymposium

020. Genetic and Genomic Studies of Schizophrenia

Location: 146C

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Presentation Number: *020.02

Topic: *H.03. Schizophrenia

Support: EU-FP7 MC-ITN IN-SENS (#607616)

Title: Functional analysis of schizophrenia risk genes using high-content screening

Authors: ***M. ROSATO**[1], S. STRINGER[2], T. GEBUIS[3], M. SASSEN[3], D. POSTHUMA[2], A. B. SMIT[4], R. VAN KESTEREN[3]
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Abstract: Schizophrenia (SCZ) is a complex disorder in which brain developmental and maturational abnormalities during adolescence eventually lead to overt symptomatology. This abnormal development requires the contribution over time of both environmental and genetic factors. A well-known rare mutation associated with SCZ is a chromosomal translocation (1;11)(q42.1;q14.3) that affects the *DISC1* gene, whose product is a scaffolding protein that interacts with many other proteins. In addition, a large Genome Wide Association Study found genetic association with SCZ for 108 loci in the human genome. Together, these findings point to the complex molecular and genetic nature of SCZ, and raise the important challenge of identifying how individual genes and proteins contribute to brain developmental impairments and ultimately cause SCZ. We addressed this issue using RNA interference in combination with high-content screening (HCS) on cultured mouse primary hippocampal neurons.
HCS is a powerful tool to collect in-depth data on changes in neuronal morphology during development in vitro. The large number of individual observations and its multiparametric nature, though, urge for rigorous statistical analyses. We used HCS to functionally characterize more than 70 SCZ genes using five independent shRNAs per gene. Multiple neurite growth and synapse formation parameters were collected at different developmental stages. We then developed a data exploration and analysis pipeline to maximize the extraction of reproducible cellular phenotypes. Using this approach we were able to detect reliable and reproducible

statistically significant effects on multiple parameters of neuronal differentiation for approximately 10 genes.
In conclusion, HCS combined with robust statistical analysis provides a powerful procedure to understand gene function in relation to neuronal development and gives an opportunity to identify potential disease pathways for complex neurodevelopmental disorders such as SCZ.

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020. Genetic and Genomic Studies of Schizophrenia

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Presentation Number: *020.03

Topic: *H.03. Schizophrenia

Title: Effects of the knockdown of schizophrenia susceptibility gene NT5C2 (CG32549) in *Drosophila melanogaster*

Authors: ***N. D. BACHTEL**[1], R. R. R. DUARTE[2], T. R. POWELL[2], D. F. NIXON[1], D. P. SRIVASTAVA[2], I. ELEFTHERIANOS[1]
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Abstract: Genome-wide association studies (GWAS) have provided an unparalleled starting point for the characterization of etiological risk mechanisms for complex traits. In humans, *NT5C2* is encoded on chromosome 10q24, the third top association signal to emerge from the latest GWAS. Risk genotype for schizophrenia at this locus has been associated with decreased levels of *NT5C2* in multiple human brain tissues, but downstream biological mechanisms associated with altered expression of this gene remain unclear. In *D. melanogaster, NT5C2 (CG32549)* is encoded in the X chromosome and, according to modENCODE, this gene is moderately/highly expressed ubiquitously at all developmental stages. We therefore aimed to knock down the expression of this gene in *D. melanogaster* at the larval stage by using (1) a ubiquitous Gal4-driven siRNA system, and (2) a Gal4-driven siRNA system specific to the central nervous system. We assessed the effect of these knockdown conditions in male flies by performing a climbing assay at 1-3 days post-emergence and a mortality analysis at day 17-20 post-emergence. These two assays would indicate a role for *NT5C2* in locomotion and survival, respectively. Our hypothesis is that we can recreate a biological risk mechanism for schizophrenia in *D. melanogaster,* potentially revealing clues to the biological effects associated with reduced expression of *NT5C2* in the body and more specifically in the brain.

Disclosures: **N.D. Bachtel:** None. **R.R.R. Duarte:** None. **T.R. Powell:** None. **D.F. Nixon:** None. **D.P. Srivastava:** None. **I. Eleftherianos:** None.

Nanosymposium

020. Genetic and Genomic Studies of Schizophrenia

Location: 146C

Time: *Saturday, November 11, 2017, 1:00 PM - 3:30 PM

Presentation Number: *020.04

Topic: *H.03. Schizophrenia

Support: IIT
2015 NARSAD Indipendent Investigator Grant
SAN PAOLO

Title: Dysbindin-1 genetics through cortical D2 trafficking differentiate subjects with better cognitive responses to antipsychotic drugs

Authors: ***F. PAPALEO**[1], D. SCHEGGIA[2], R. MASTROGIACOMO[2], M. MEREU[3], S. SANNINO[2], R. E. STRAUB[4], M. ARMANDO[5], F. MANAGÒ[2], F. PIRAS[6], J. E. KLEINMAN[4], T. M. HYDE[4], M. A. DE LUCA[7], D. R. WEINBERGER[4], G. SPALLETTA[6]
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Abstract: Antipsychotics are the first-line and most widely used medications for the treatment of schizophrenia spectrum disorders. These drugs generally ameliorate positive symptoms, whereas clinical responses for negative symptoms and cognitive impairments are not optimal and highly variable. Predictors of individual responses to antipsychotic treatments have been elusive. Here we report a pharmacogenetics interaction related to core cognitive dysfunctions in patients with schizophrenia. In particular, in humans and mice, genetic variations reducing dysbindin-1 expression differentiate individuals with better executive functions responses to antipsychotic drugs. Such antipsychotics-by-dysbindin-1 interaction relies on a peculiar enhanced presynaptic dopamine D2 functioning within the medial PFC. These findings provide a genetic indicator for the implementation of personalized treatments for cognitive disabilities in schizophrenia based on a concrete biological mechanism.

Disclosures: **F. Papaleo:** None. **D. Scheggia:** None. **R. Mastrogiacomo:** None. **M. Mereu:** None. **S. Sannino:** None. **R.E. Straub:** None. **M. Armando:** None. **F. Managò:** None. **F.**

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Nanosymposium

020. Genetic and Genomic Studies of Schizophrenia

Location: 146C

Time: *Saturday, November 11, 2017, 1:00 PM - 3:30 PM

Presentation Number: *020.05

Topic: *H.03. Schizophrenia

Title: Differential effect of estrogen receptor alpha haplotypes on gene expression and memory in men and women with schizophrenia

Authors: ***C. MURPHY**[1,2], C. S. WEICKERT[1,2], R. LENROOT[1,2], T. W. WEICKERT[1,2]
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Abstract: Background: Aberrant estrogen signalling has been proposed as a contributing factor to the pathophysiology of schizophrenia. Estrogen is neuroprotective and implicated in many of the cognitive processes impaired in schizophrenia. Estrogen receptor alpha (ERα) is encoded by ESR1 on 6q25.1 and intron 1 single nucleotide polymorphisms (SNPs) have been associated with ESR1 gene expression in the brain. We hypothesised that carrying one or more risk alleles at these intronic sites would be associated with less ERα mRNA in the dorsolateral prefrontal cortex (DLPFC), and that people with schizophrenia would be more likely to have a 'risk haplotype' than healthy controls. We also hypothesised that carrying one or more risk alleles would be associated with worse cognitive performance in living patients.
Methods: Post-mortem DLPFC tissue from 37 schizophrenia cases and 37 healthy control cases was provided by the New South Wales Brain Tissue Resource Centre (TRC). Genomic DNA was isolated from the blood samples of 78 healthy adult controls and 91 adult patients. ESR1 SNPs were assayed in both males and females in the TRC cohort and in the living cohort using qPCR. mRNA expression was then measured in DLPFC tissue using qPCR gene expression assays. Cognitive capacity in living patients was assessed based on current and pre-morbid IQ estimates, and performance in domain-specific psychometric tests of immediate and delayed verbal memory, verbal fluency, working memory, and attention and perceptual-motor speed.
Results: There was no significant difference in ERα mRNA expression in the DLPFC of controls and patients. In patients, there was a significant effect of ESR1 haplotype on ERα mRNA ($t = 1.86$, $df = 30$, $p = 0.04$) such that risk-carriers expressed less ERα mRNA than non-risk carriers. This effect was not found in controls. There was no significant difference in the distribution of ESR1 haplotypes between patients and controls. In patients, there was a

significant effect of ESR1 haplotype on both immediate (t = 1.61, df = 88 p = 0.05) and delayed (t = 1.62, df = 88, p = 0.05) verbal memory, such that risk carriers performed significantly worse than non-risk carriers. This effect was not found in controls.
Conclusion: Patients with the 'risk haplotype' may have deficiencies in estrogen sensitivity, signalling and subsequent estrogen-dependent gene transcription that contribute to cognitive impairment. Estrogenic drugs that do not increase the risk of breast or uterine cancers, such as selective estrogen receptor modulators (SERMs), may be of therapeutic value to a subset of patients with schizophrenia.

Disclosures: C. Murphy: None. **C.S. Weickert:** None. **R. Lenroot:** None. **T.W. Weickert:** None.

Nanosymposium

020. Genetic and Genomic Studies of Schizophrenia

Location: 146C

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***020.06

**Topic: ***H.03. Schizophrenia

Support: NIH grant MH110185

Title: Mitochondrial defects in stem cell derived neurons from people with 22q11.2 deletion syndrome and schizophrenia

Authors: *J. LI[1], S. RYAN[2], E. DEBOER[1], E. PEDROSA[3], H. LACHMAN[3], D. WALLACE[1,2], S. ANDERSON[1,2]
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Abstract: Schizophrenia (SZ) is a highly heterogeneous disorder with undetermined etiologies and a multitude of risk factors. The strongest of the genetic risk factors for SZ is the hemizygous deletion of chromosome 22q11.2 (22q11DS), that confers a nearly 25-fold increased risk. While there has been considerable study regarding etiologies of SZ in the 22q11DS context, a definitive mechanism is unknown. One of the many pathological correlates to SZ is dysfunction of mitochondria and altered metabolism. Interestingly, 6 of the roughly 40 genes directly disrupted in 22q11DS encode for mitochondrial localizing proteins. One of these is *mrpl40*, a component of the mitochondrial ribosome involved in regulating translation of the 13 mitochondrial-encoded proteins, all of which function in oxidative phosphorylation. We thus hypothesize that SZ in the 22q11DS context is associated with the disruption of mitochondrial function. To begin to test this hypothesis, we studied 5 Induced Pluripotent Stem Cell (iPSC) lines from patients

with 22q11DS and schizophrenia, and 5 lines from grossly age and sex-matched healthy individuals. In forebrain excitatory neuron-like cells derived from these lines, we find that, as expected, MRPL40 RNA and protein levels are reduced. Remarkably, we find that the protein products of several mitochondrial DNA-encoded genes are significantly reduced in patient IPSC derived neurons. In addition, the patient-derived neurons show significantly decreased complex I/III/IV activity, and decreased ATP levels. Preliminary analyses suggest that this reduction in ATP is also associated with alterations of neuronal firing properties. Critical future directions of this work are to determine whether iPSC-derived neurons from 22q11DS+SZ have more impaired mitochondrial function than 22q11DS without SZ, and whether patients with 22q11DS+SZ are more likely to harbor mutations in mitochondrial-functioning genes than patients with 22q11DS without SZ. Such a finding could lead to novel approaches for premorbid identification and preventative intervention in individuals at risk for developing schizophrenia in the 22q11DS context and quite possibly beyond.

Disclosures: J. Li: None. **S. Ryan:** None. **E. Deboer:** None. **E. Pedrosa:** None. **H. Lachman:** None. **D. Wallace:** None. **S. Anderson:** None.

Nanosymposium

020. Genetic and Genomic Studies of Schizophrenia

Location: 146C

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***020.07

**Topic: ***H.03. Schizophrenia

Support: Stanley Medical Research Institute

Title: Splicing between repetitive elements and annotated exons is enriched near genomic regions associated with schizophrenia

Authors: *S. SABUNCIYAN, R. H. YOLKEN
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Abstract: Our recent work revealed that repetitive element loci (RE) are extensively spliced into coding regions of gene transcripts yielding thousands of novel mRNA variants with altered coding potential. The same pattern of RE splicing was detected in the brain tissue of all seven species we examined, ranging from humans to the fruit fly. RE splicing with exons occurs largely at the canonical GT-AG splice junctions and is not restricted to a particular RE class. This type of splicing usually gives rise to a minor splice variant and in silico analysis suggests that in certain cases RE splicing may introduce a novel open reading frame. Reanalysis of sequencing data performed on polysome associated RNAs in the mouse cerebellum revealed that

many RE splice variants might be translated into proteins. These findings raise the possibility that RE splicing may give rise to functional protein isoforms. Given these findings and the potential association between schizophrenia and neural somatic mosaicism induced by the LINE-1 RE element, we decided to investigate whether RE expression or splicing is associated with psychiatric disease. We find that 69 of the 108 schizophrenia associated genomic regions contain at least one intronic or intergenic RE that forms a splice junction with an annotated exon in the orbitofrontal cortex (OFC). When we compare RE splice junctions within the schizophrenia associated regions to those that are elsewhere in the genome, we find intronic (1.6 fold enrichment;p<6.7E-28) and intergenic (5.6 fold enrichment;p<1.2E-38) RE splicing in the OFC is significantly enriched in genomic regions associated with schizophrenia. We were able to replicate this finding in RNAseq data from an unrelated cohort of 102 hippocampus samples (69 out of 108 regions has RE splicing; intronic 1.6 fold enrichment & p<3.2E-30;intergenic 5.7 fold enrichment & p<4.6E-53). The enrichment of RE splicing in genomic loci associated with schizophrenia might be indicative of defects in the splicing or the non-sense mediated decay machinery in disease. Alternatively, inappropriate expression of RE transcripts or expression of particular RE alleles may cause an inflammatory response.

Disclosures: S. Sabunciyan: None. **R.H. Yolken:** None.

Nanosymposium

020. Genetic and Genomic Studies of Schizophrenia

Location: 146C

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**Topic: ***H.03. Schizophrenia

Support: Stratified Medicine Centre Grant
Western Health and Social Care Trust Funding

Title: Interactions between genetic polymorphisms in the COMT gene and psychiatric disorders

Authors: C. R. LAPSLEY[1], C. DEVINE[1], S. DOWNES[2], J. BRADY[3], A. J. BJOURSON[1], *E. K. MURRAY[4]
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Abstract: Schizophrenia is a chronic, severe mental health condition affecting approximately 1% of the population. Despite its prevalence, the biological basis of schizophrenia remains poorly understood. Single nucleotide polymorphisms have been identified in genes relating to

neurotransmitter signalling including the dopamine, serotonin and adrenaline signaling but the role of this genetic variation in risk for, pathophysiology and response to treatment in schizophrenia remains elusive. The COMT gene encodes catechol-o-methyl-transferase, a key enzyme in the breakdown of dopamine, adrenaline and noradrenaline. The rs4680 polymorphism in COMT affects coding at Val158Met, but the role of COMT Val158Met in psychiatric disorders has not been clearly defined. The genetics of COMT are complicated by two other synonymous exonic SNPs, rs4633 and rs4818 that affect mRNA stability. These 3 SNPs lead to an eighteen-fold difference in COMT activity between the most and least favourable haplotypes. Genetic variability in the COMT gene in patients diagnosed with schizophrenia and healthy matched controls with no personal or family history of psychiatric disorders were recruited. DNA was extracted from whole blood samples, followed by PCR amplification using suitable COMT primers, and SNP genotyping via pyrosequencing. Prevalence of genotype between schizophrenia, depression and healthy control groups was compared using Chi squared test. Significant differences in the COMT 4818 genotypes were observed between schizophrenia, depression and healthy groups. Depression and schizophrenia cohorts were combined and compared against the healthy cohort, again the COMT 4818 genotypes were significantly different. Individuals with depression and schizophrenia had higher prevalence of the COMT 4818 GG genotype and COMT 4680 AA genotype when compared matched controls. No differences were observed in prevalence of the COMT 4633 genotypes between groups. These results suggest that the COMT 4818 and COMT 4680 SNPs could be potential biomarkers for schizophrenia. Future work will determine whether these markers are indicative of treatment response to establish which genotypes offer higher prospects of response to particular treatments within our cohort.

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Nanosymposium

020. Genetic and Genomic Studies of Schizophrenia

Location: 146C

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***020.09

**Topic: ***H.03. Schizophrenia

Support: Thesis Project

Title: Ancestry and population structure in genetic association studies. IL1B gene and schizophrenia in Peruvian population

Authors: *C. APARICIO[1], D. HUERTA[2], W. LEYVA[4], E. BRAVO[3], J. SANDOVAL[5], R. FUJITA[5], M. GUEVARA[5], O. ACOSTA[1,5]
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Abstract: Aim: To evaluate the importance of ancestry and population structure in a genetic association study of IL1β gene (511 C/T polymorphism) with schizophrenia in Peruvian Population.
Design: Observational, case- control study based-population.
Institutions: Facultad de Farmacia y Bioquímica-UNMSM, facultad de Medicina-UNMSM; Centro de Genética y Biología Molecular-USMP, Hospital Hermilio Valdizán. Lima, Perú.
Subjects: 50 schizophrenics and control individuals divided in 2 sets: G1=168 from various subpopulations and G2=118, without considering 50 samples from Puno-Taquile and Puno-Uros (native ancestry determined by Y-chromosome and mtDNA markers).
Methods: Prior informed consent, DNA extraction (blood/oral epithelium). Analysis of 511 C/T polymorphism by RFLP-PCR (enzyme digestion with AvaI, 2% agarose gel electrophoresis) and automatic sequencing. Statistical analysis (association-risk) in cases-G1 and cases-G2 pairs.
Results: Genotype frequencies were on Hardy-Weinberg equilibrium both in control G1 and G2. There was no difference on allele frequencies. Genotype frequencies (TT/ vs CT+CC) in cases-G1 pair showed an association between genotypes with C allele and schizophrenia (p=0.036; OR=1.967, IC 95%: 1.040-3.725). However, cases-G2 pair lacked of that association (p=0.417; OR=1.317, IC 95%: 0.677-2.560). That means, under the proposed study design, that it could exist an ancestry and population structure influence in this genetic association study.
Conclusion: Preliminary evidence of the importance of ancestry and population structure in the assessment of IL1β gene with schizophrenia is provided. It is recommended to use ancestry-informative markers (AIMs) in order to avoid bias in genetic association studies of Peruvian population.
Keywords: Ancestry, population structure, IL1β gene, schizophrenia, Peru.

Disclosures: C. Aparicio: None. **D. Huerta:** None. **W. Leyva:** None. **E. Bravo:** None. **J. Sandoval:** None. **R. Fujita:** None. **M. Guevara:** None. **O. Acosta:** None.

Nanosymposium

020. Genetic and Genomic Studies of Schizophrenia

Location: 146C

**Time: ***Saturday, November 11, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***020.10

**Topic: ***H.03. Schizophrenia

Title: Polygenic risk profile score increases schizophrenia liability mostly through cognition pathways: Mathematical causation models with latent cognition and polygenic risk

Authors: *T. TOULOPOULOU[1], X. ZHANG[2], P. SHAM[2], D. R. WEINBERGER[3]
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Abstract: Background: Cognition shares substantial genetic variance with schizophrenia, with recent evidence from statistical modelling of twin data indicating direct causality from the former to schizophrenia. However, it is not clear how much of the genetic component of schizophrenia is mediated by cognition. Thus, we included direct measurements of genetic risk (e.g. polygenic risk profile scores) in trivariate causation models to quantify the genetic component of schizophrenia that is 1) mediated by latent cognition and captured by the polygenic risk profile score; 2) mediated by covariation pathways that include latent cognition; 3) mediated by latent cognition and not captured by the polygenic risk profile score; 4) captured directly by polygenic risk profile score; and 5) not captured by the polygenic risk profile score and not mediated by latent cognition.
Methods: Data were from 1,313 members of 1,078 families, and included 416 schizophrenia patients, 290 siblings, and 607 controls (NIMH sibling study). Polygenic risk profile score was based on the latest data from the Schizophrenia Working Group of the Psychiatric Genomics Consortium after excluding the current sample and represented the sum of genotypic scores for all common genetic variants associated with schizophrenia risk at P value threshold of 0.05 (i.e. RPS). Latent cognition captured the variance common across all measurements in six cognitive domains: processing speed, verbal memory, visual memory, span, working memory, and executive function.
Results: Eight percent of the variance in schizophrenia liability was contributed by the polygenic risk profile score. Of this, 2.71% was mediated by latent cognition, 3.93% by covariation pathways that included latent cognition, and 1.43% by direct contribution (e.g. variance in genetic schizophrenia liability captured by polygenic risk profile score) and not through latent cognition. Of the genetic component of schizophrenia, 26.87% was mediated by latent cognition pathways not captured by the RPS. The remaining 65.06% was mediated through pathways other than latent cognition and polygenic risk profile score.
Conclusion: A significant part of the genetic component of schizophrenia is mediated by cognition pathways captured by the polygenic risk profile score. Because the polygenic risk profile score is an impressive measure, an even bigger part is mediated by other latent cognition pathways not captured by polygenic profile risk score. Understanding the molecular and cellular basis of cognition could provide critical new insights in the etiology and pathophysiology of schizophrenia.

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Nanosymposium

103. iPSCs: Disease Models I

Location: 152A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***103.01

**Topic: ***A.03. Stem Cells and Reprogramming

Support: JSPS KAKENHI JP16K15240
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JST

Title: The chromatin remodeler CHD7 in human cell fate regulation: A default mechanism for neuroepithelial fate

Authors: *M. CHAI[1], T. SANOSAKA[1], H. OKUNO[1], Z. ZHOU[2], I. KOYA[1], S. BANNO[1], T. ANDOH-NODA[1], Y. TABATA[2], R. SHIMAMURA[1], H. OKANO[1], J. KOHYAMA[1]
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Abstract: Abstract:
Stem cell lineage identity, commitment and terminal differentiation are dictated by a series of chromatin modifications that either support or repress the activity of transcription factors, thereby facilitating the establishment of customized transcription programs in different cellular contexts. Mutations in chromatin remodeling genes are causally associated with multiple human neurodevelopmental disorders, such as CHARGE syndrome, Alpha thalassemia X-linked intellectual disability (ATRX) syndrome, Kabuki syndrome, autism and Rett syndrome. These multiple congenital disorders often present complex phenotypes, but the means by which the mutation of individual genetic factors can lead to multiple defects remains poorly understood. In the present study, we used induced pluripotent stem cell-derived neuroepithelial cells (iPSC-NE cells) from healthy donors and CHARGE syndrome patients as an *in vitro* model system to identify the function of CHD7, whose mutation is frequently observed in CHARGE syndrome. We found that CHD7 controls neuroepithelial–neural crest bifurcation, such that dysregulation of CHD7 led to the transdifferentiation of NE to neural crest (NC)-like cells. We further found that CHD7, through its interactions with super-enhancer elements, acts as a regulatory hub in the orchestration of the spatiotemporal dynamics of CNS-specific transcription factors to regulate NE and CNS lineage identities. These findings thus suggest a hitherto unknown etiological link between the central nervous system (CNS) and craniofacial anomalies observed in multiple anomaly disorders. Taken together, our study suggests that CHD7-mediated epigenetic mechanism is crucial in modulating cell and lineage identities during neuroectodermal development, with implications for the pathogenesis of CHARGE syndrome.

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Nanosymposium

103. iPSCs: Disease Models I

Location: 152A

Time: *Sunday, November 12, 2017, 8:00 AM - 10:45 AM

Presentation Number: *103.02

Topic: *A.03. Stem Cells and Reprogramming

Support: Funding from the Project for the Realization of Regenerative Medicine (MEXT)
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Title: *In vitro* and *In vivo* cell dynamics analysis of iPSC-derived neural crest cells harboring CHD7 mutations reveals defective migration of CHARGE syndrome

Authors: ***H. OKUNO**[1], F. M. RENAULT[1], S. OHTA[1], K. FUKUDA[2], K. KUROSAWA[3], W. AKAMATSU[4], T. SANOSAKA[1], J. KOHYAMA[1], T. TAKAHASHI[1], J. WYSOCKA[5], K. KOSAKI[1], H. OKANO[1]
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Abstract: ABSTRACT:
CHARGE syndrome is caused by heterozygous mutations in the chromatin remodeler, CHD7, and is characterized by a set of malformations that, on clinical grounds, were historically postulated to arise from defects in neural crest formation during embryogenesis. A recent study on knockdown of CHD7 in human ES cells revealed disruption of migratory neural crest cells. Knockdown of Chd7 in Xenopus or zebrafish embryos also led to abnormalities in neural crest specification and migration. However it remains unclear whether neural crest cells are actually dysfunctional in CHARGE syndrome patients. To better delineate neural crest defects in CHARGE syndrome, we generated induced pluripotent stem cells (iPSCs) from two patients with truncating mutations in CHD7 and typical syndrome manifestations, and characterized

neural crest cells differentiated in vitro from these iPSCs (iPSC-NCCs). We found that expression of genes associated with cell migration was altered in CHARGE iPSC-NCCs compared to control iPSC-NCCs. Consistently, CHARGE iPSC-NCCs showed defective delamination, migration and motility in vitro, and their transplantation *in ovo* revealed overall defective migratory activity in the chick embryo. These results support the historical inference that CHARGE syndrome patients exhibit defects in neural crest migration, and provide the first successful application of patient-derived iPSCs in modeling craniofacial disorders.

Disclosures: **H. Okuno:** None. **F.M. Renault:** None. **S. Ohta:** None. **K. Fukuda:** None. **K. Kurosawa:** None. **W. Akamatsu:** None. **T. Sanosaka:** None. **J. Kohyama:** None. **T. Takahashi:** None. **J. Wysocka:** None. **K. Kosaki:** None. **H. Okano:** Other; SanBio Co.,Ltd., K-Pharma Inc..

Nanosymposium

103. iPSCs: Disease Models I

Location: 152A

Time: *****Sunday, November 12, 2017, 8:00 AM - 10:45 AM

Presentation Number: *****103.03

Topic: *****A.03. Stem Cells and Reprogramming

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Bob and Mary Jane Engman
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Title: Differentiation of inflammation-responsive astrocytes from human induced pluripotent stem ell-derived glial progenitors

Authors: ***K. C. VADODARIA**[1], R. SANTOS[2], B. JAEGER[4], A. MEI[5], S. LEFCOCHILOS-FOGELQUIST[5], A. MENDES[5], G. ERIKSON[5], M. MAXIM SHOKHIREV[5], L. MOORE[5], C. FREDLENDER[5], S. DAVE[5], C. FITZPATRICK[5], B. KERMAN[6], P. CHARNAY[3], J. KELSOE[7], C. MARCHETTO[8], F. H. GAGE[9]
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Abstract: Astrocyte dysfunction and neuroinflammation are detrimental features in multiple CNS pathologies and may play roles in the pathology of neuropsychiatric disorders such as major depression and bipolar disorder. The development of methods that produce functional and inflammation-responsive human astrocytes represent represent a valuable advance in the study of neuroinflammation related disorder. We report an efficient method for generating astrocytes from human induced pluripotent stem cells (iPS) via an intermediate glial progenitor stage. The generated astrocytes showed levels of glutamate uptake and calcium transients comparable to those observed for human primary astrocytes. Notably, astrocytes derived by this method are inflammation responsive, as stimulation of iPS-derived astrocytes with IL-1beta or TNF-alpha elicits a strong and rapid pro-inflammatory response. RNA-sequencing analysis of stimulated iPS-derived astrocytes revealed a transcriptomic signature with several inflammation-related genes upregulated. Further, IL-6 and IL-8 cytokines were detected in a large proportion of iPS-derived astrocytes following stimulation. iPS-derived inflammation responsive astrocytes provide a novel tool for studying components of neuroinflammation in the context of disease modeling in vitro.

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Nanosymposium

103. iPSCs: Disease Models I

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**Presentation Number: ***103.04

**Topic: ***A.03. Stem Cells and Reprogramming

Support: Governor's Council for Medical Research and Treatment of Autism CAUT13APS010
Nancy Lurie Marks Family Foundation

Title: Identifying common as well as personalized developmental and molecular phenotypes in idiopathic autism neural precursor cells (NPCs)

Authors: *S. PREM[1], M. WILLIAMS[2], P. MATTESON[2], J. MILLONIG[2], E. M. DICICCO-BLOOM[3]
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Abstract: Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impaired social communication and presence of repetitive restrictive behaviors. While defects in developmental processes such as proliferation and migration are implicated in ASD, the inability to directly study human neurons, limitations of animal models, and disorder heterogeneity have thwarted discovery of cellular and molecular mechanisms. Now induced pluripotent stem cells allow for generation and study of live human neural precursor cells (NPCs) from affected individuals to identify common and personalized phenotypes in idiopathic ASD. We are studying neurite outgrowth, migration, and signaling pathways in NPCs from 8 severely affected males and their unaffected brothers (Sib). Our strategy employs extracellular factors (EFs) that challenge NPCs to reveal deficits absent in control conditions and identify dysfunctional signaling. To quantify neurite outgrowth, NPCs were plated at low density and % of cells with neurites was analyzed at 48h. To examine migration, neurospheres generated from NPCs are plated for 48h on Matrigel. Migration = total neurosphere area-inner mass area. Our studies show common deficits in neurite outgrowth and cell migration in 2 ASD individuals from our cohort. Specifically, while Sib NPCs from 2 families exhibited increased neurite outgrowth in response to PACAP (3nM), NGF (30 ng/mL), and 5HT (100ug/mL), both sets of ASD NPCs failed to increase neurites in response to these EFs. Similarly, Sib neurospheres had increased migration with PACAP while ASD neurospheres were unresponsive. Mechanistically, PACAP acts via the PKA-cAMP-P-CREB pathway. ASD NPCs in Family-1, which did not respond to PACAP, exhibited 4x-lower PACAP induced P-CREB levels compared to Sib NPCs. Conversely increasing ASD P-CREB levels using db-cAMP restored neurite outgrowth and migration to levels of PACAP-treated Sib NPCs. Moreover, as Family-1 ASD NPCs also had reduced PI3K signaling (5x-lower P-AKT and P-S6) P-AKT stimulation with SC-79 similarly restored neurite outgrowth and migration. In sum, we detect common phenotypes in our idiopathic ASD NPCs. ASD NPCs from one family showed impaired neurite outgrowth and migration associated with abnormal PKA and PI3K signaling. In the 2nd family NPCs also displayed neurite and migration phenotypes though preliminary data suggest distinct, personalized signaling defects. While heterogeneity of idiopathic ASD reduces the chances of identical phenotypes in all our patients, our studies indicate the value of using EFs to uncover impaired and patient-specific pathways that may lead to personalized ASD therapies.

Disclosures: S. Prem: None. **M. Williams:** None. **P. Matteson:** None. **J. Millonig:** None. **E.M. DiCicco-Bloom:** None.

Nanosymposium

103. iPSCs: Disease Models I

Location: 152A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***103.05

**Topic: ***A.03. Stem Cells and Reprogramming

Support: CIHR
Ontario Brain Institute

Title: Elucidating the pathophysiology of the 15q13.3 micro deletion syndrome

Authors: *K. K. SINGH[1], B. K. UNDA[2], M. UDDIN[4], V. KWAN[3], L. CHALIL[3], S. H. WHITE[3], N. HOLZAPFEL[3], M. WOODBURY-SMITH[1], K. HO[5], N. MURTAZA[3], E. HARWARD[5], G. PELLECCHIA[4], L. D'ABATE[4], T. NALPATHAMKALAM[4], S. LAMOUREUX[4], J. WEI[4], M. SPEEVAK[6], J. STAVROPOULOS[6], K. HOPE[1], B. DOBLE[1], J. NIELSON[7], S. SCHERER[4]
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Abstract: Copy number variations (CNVs) are chromosomal deletions or duplications that confer high risk for many neuropsychiatric conditions. The 15q13.3 CNV microdeletion is associated with high risk for epilepsy, intellectual disability, schizophrenia and autism spectrum disorder (ASD). However, the neurodevelopmental abnormalities underlying the clinical phenotypes and the gene(s) driving these phenotypes are unknown. To study this CNV, we are utilizing a heterozygous 15q13.3 microdeletion mouse model and patient-derived IPS cells. RNA-sequencing and gene set enrichment analysis (GSEA) of cortical brain tissue from WT and heterozygous mice revealed that differentially expressed genes are highly enriched in forebrain development. We analyzed neuronal morphology, which revealed alterations in dendritic arborization and dendritic spine morphology in excitatory cortical neurons. This is accompanied by alterations in neural activity using patch-clamp electrophysiology. To understand the pathophysiology of 15q13.3 microdeletion syndrome, we dissected candidate driver genes using whole-genome sequencing (WGS) and brain-critical exon analysis of human transcriptome data. WGS of ASD quartet families identified *De Novo* variants in one of the genes within the deletion, OTUD7A. OTUD7A is also the only gene within the deletion containing a brain-critical exon and is brain-enriched. GSEA of human protein expression data revealed that genes that are highly co-expressed with OTUD7A are highly enriched in pathways involved in synaptic connectivity. Additionally, preliminary experiments showed that OTUD7A is localized to the post-synaptic density of neurons supporting a role for OTUD7A in synaptic connectivity. Current approaches include examining the role of OTUD7A in patient-derived IPSC-neurons, as well as WT IPSC-neurons lacking OTUD7A using CRISPR/Cas9 gene editing. Together, our data suggest OTUD7A is a novel driver gene of the 15q13.3 microdeletion syndrome.

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Nanosymposium

103. iPSCs: Disease Models I

Location: 152A

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**Presentation Number: ***103.06

**Topic: ***A.03. Stem Cells and Reprogramming

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Title: Identifying critical components of Zika virus that disrupt mammalian cortical neurogenesis in mouse models and human cerebral organoids

Authors: *K.-J. YOON[1], G. SONG[2], X. QIAN[2], J. PAN[3], D. XU[4], H.-S. RHO[5], F. ZHANG[6], E. LEE[8], Q.-F. WU[4], K. M. CHRISTIAN[10], H. TANG[9], P. JIN[7], Z. XU[4], J. QIAN[11], H. ZHU[12], H. SONG[10,13], G.-L. MING[14,13]
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Abstract: Zika virus (ZIKV) directly infects neural progenitors and causes proliferation deficits. However, the way in which ZIKV interacts with the host machinery to impact neurogenesis in the developing mammalian brain is not well understood. To reveal the critical components that induce the ZIKV pathogenesis linked with microcephaly, we cloned 10 open reading frames from the ZIKV genome into an expression vector, which we used to introduce individual proteins into radial glial neural stem cells in the embryonic mouse cortex by in utero electroporation. As a result, we identified two ZIKV-encoded proteins that affect the proliferation and maintenance of radial glial cells. To investigate how ZIKV proteins directly interact with the host machinery to impact neural stem cell behavior, we performed a protein microarray assay to screen for human proteins that can bind to ZIKV proteins in vitro in an unbiased manner. We identified host interacting protein candidates that are essential for neural

progenitor functions and validated the binding in cultured mouse neural stem cells using a co-immunoprecipitation assay. Next, we observed that expression of a candidate ZIKV coding component in human forebrain organoids led to reduced radial glial cell proliferation and deficits in radial glia fiber scaffolding, resembling postmortem forebrain tissue of the first reported ZIKV-infected microcephalic fetus from an infected mother. Together, our results reveal novel pathogenic mechanisms underlying ZIKV infection in the developing mammalian brain.

Disclosures: **K. Yoon:** None. **G. Song:** None. **X. Qian:** None. **J. Pan:** None. **D. Xu:** None. **H. Rho:** None. **F. Zhang:** None. **E. Lee:** None. **Q. Wu:** None. **K.M. Christian:** None. **H. Tang:** None. **P. Jin:** None. **Z. Xu:** None. **J. Qian:** None. **H. Zhu:** None. **H. Song:** None. **G. Ming:** None.

Nanosymposium

103. iPSCs: Disease Models I

Location: 152A

Time: *Sunday, November 12, 2017, 8:00 AM - 10:45 AM

Presentation Number: *103.07

Topic: *A.03. Stem Cells and Reprogramming

Support: CDMRP Autism Research Program

Title: Modeling idiopathic autism using pluripotent stem cells

Authors: ***C. MARCHETTO**[1], Y. KIM[2], S. LINKER[1], D. N. AMATYA[1], A. P. D. MENDES[1], R. SANTOS[3], F. H. GAGE[1]
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Abstract: Autism spectrum disorders (ASD) are complex neurodevelopmental diseases that affect about 1% of children in the United States. Individuals with ASD are characterized by deficits in verbal communication, impaired social interaction and present limited and repetitive interests and behavior. The major impediment to testing hypotheses and potential therapeutic interventions for autism is the lack of relevant animal and cell models. Reprogramming of human somatic cells to induced pluripotent stem cells (iPSC) provided an exciting opportunity to produce a relevant human cellular model for complex neurogenetic disorders such as ASD. We use Multielectrode Array (MEA) technology to perform functional field potential analysis of iPSC-derived neuronal populations from ASD individuals and controls during development and after treatment with a drug that is currently in clinical trials for ASD (Insulin-like growth factor 1, IGF1). Our preliminary results indicate that ASD neurons respond to drug treatment by increasing neuronal spiking and neuronal bursts. Additionally, we performed expression profile

analysis on developing ASD neurons and neurotypical controls after drug treatment to uncover pathways that are potentially involved in the recovery of the neuronal activity. Our data indicates that IGF1 has a specific molecular effect on ASD neurons. Studying biological basis of ASD and cellular drug responsiveness would potentially lead to the development of clinically useful biomarkers of risk for this disorder, which may lead to the development of novel therapies.

Disclosures: C. Marchetto: None. **Y. Kim:** None. **S. Linker:** None. **D.N. Amatya:** None. **A.P.D. Mendes:** None. **R. Santos:** None. **F.H. Gage:** None.

Nanosymposium

103. iPSCs: Disease Models I

Location: 152A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***103.08

**Topic: ***A.03. Stem Cells and Reprogramming

Support: Slifka/Ritvo Innovation in Autism Award and Whitehall Foundation
Brain Research Foundation
Utah Neuroscience Initiative Seed Grant

Title: Single rosette-derived cortical organoids for studying human cortical development, synapses, and synaptopathies

Authors: *C. RUSSELL[1], Y. WANG[2], Y. WU[2], J. SPAMPANATO[3], L. BELL[2], P. TARBOTON[1], S. GREBENYUK[2], A. SHCHEGLOVITOV[2]
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Abstract: Human cerebral cortex is a complex brain structure associated with many human-specific behaviors and disorders. Remarkably, this structure evolves from a single population of neuroepithelial cells organized into a tube-like structure early in development, called the neural tube. We have developed a new method enabling generation of three-dimensional induced pluripotent stem cell (iPSC)-derived cortical organoids from single neural rosettes - neural tube-like structures - in vitro. We demonstrate that single rosette-derived cortical organoids grow large in suspension culture, reaching 4-5 mm in diameter by 4 months while maintaining a single internal lumen, and consist of different types of neuronal cells, including cortical neural progenitors, deep and superficial layer cortical excitatory neurons, inhibitory neurons, and astrocytes, organized around the lumen. Using patch-clamp electrophysiology, we also show that many neurons in slices from single-rosette-derived cortical organoids fire repetitive action potentials, receive excitatory and inhibitory synaptic inputs, exhibit typical pyramidal-like morphologies, and develop dendritic spines. Our results indicate that cortical organoids

generated from single iPSC-derived neural rosettes could be useful for studying and modeling the organization and functions of human neurons in developing cortical networks in health and disease.

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Nanosymposium

103. iPSCs: Disease Models I

Location: 152A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***103.09

**Topic: ***A.03. Stem Cells and Reprogramming

Support: RGC of Hong Kong (664113, 16103614, AoE-M09-12, and T13-607/12R)
973 program grant from the Minister of Science and Technology of China (2014CB910204 to M.Z.)
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Title: Disruption of ATF4-DISC1 interaction leads to transcriptional dysregulation in an iPSC model of mental disorders

Authors: *X. WANG[1,2], F. YE[3,4], Y. CHUAN[3,4], Z. WEN[5], Z. GUO[6], F. R. RINGELING[5], W.-K. HUANG[5], C. ZHANG[5], M. ZHANG[3,4], H. SONG[6], G.-L. MING[6]
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Abstract: Genetic risk, aberrant neurodevelopment, and synaptic dysfunction have been considered as three major contributors to the etiology of neuropsychiatric disorders. Although data from our previous study have suggested that a psychiatric disorder-relevant 4 base-pair deletion DISC1 mutation affects synaptic function via transcriptional dysregulation in human iPSCs derived neurons, the mechanism of how the DISC1 mutation affect gene expression is unknown. ATF4, an important transcription factor, is one of the binding partners of DISC1 protein. However, the details of ATF4-DISC1 interaction, as well as the resulting functions are

unclear. Here, through structural and biochemical analysis, we identified minimal sequence of DISC1 protein required for complete ATF4 binding, which is disrupted by the 4 base-pair DISC1 mutation found in patients. LOF of ATF4 in DISC1 mutant neurons or GOF of ATF4 in wild-type cells rescue or recapture transcriptional dysregulations and synaptic deficits in mutant DISC1 neurons, respectively. Our study thus reveals the underlying molecular mechanisms of how DISC1 regulate gene expression and shed light on how DISC1 contribute to mental disorders.

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Nanosymposium

103. iPSCs: Disease Models I

Location: 152A

Time: *Sunday, November 12, 2017, 8:00 AM - 10:45 AM

Presentation Number: *103.10

Topic: *A.03. Stem Cells and Reprogramming

Support: FAPESP/ 2011/20683-0
FAPESP/ 2013/08844-3
FAPESP/2016/02978-6

Title: Modeling the interplay between neurons and astrocytes in autism using iPSC

Authors: ***P. BELTRÃO-BRAGA**[1], F. B. RUSSO[2], B. C. G. FREITAS[3]
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Abstract: Autism Spectrum Disorders (ASD) comprises a complex neurodevelopmental disorder characterized by communication and social interaction impairment, with restricted and repetitive patterns of behavior. ASD has unclear etiology and imprecise genetic causes affecting approximately 1% of worldwide population. Induced pluripotent stem cells (iPSC) have been successfully generated modeling human neurological disorders. However, studies involving complex neurological disorders, such as idiopathic ASD, remain a major challenge in this field. The main goal of this work was to investigate neuronal connectivity and the interplay between neurons and astrocytes from ASD individuals using iPSC. Our iPSC were derived from a clinically well-characterized cohort of three idiopathic ASD individuals, sharing common behaviors, and three controls, two clones each. We have obtained our cohort from the Tooth Fairy Project, in Brazil, in which donated teeth were used to isolate dental pulp stem cells for cellular reprogramming. We generated mixed neural cultures and analyzed synaptogenesis and

neuronal activity using a multi-electrode array (MEA) platform. Furthermore, using an enriched astrocytes population, we investigated their role in neuronal maintenance. Our results revealed that ASD-derived neurons had a significant decrease in synaptic gene and protein expression levels, glutamate neurotransmitter release and, consequently, reduced spontaneous firing rate. Based on co-culture experiments, we observed that ASD-derived astrocytes interfered with proper neuronal development. In contrast, control-derived astrocytes rescued the morphological neuronal phenotype and synaptogenesis defects from ASD neurons. We also investigated IL-6 levels, since this interleukin has been previously associated with autism and its severity. Furthermore, after identifying IL-6 secretion from astrocytes in our ASD individuals as a possible culprit for neural defects, we were able to increase synaptogenesis by blocking IL-6 levels in our cultures. Our findings reveal that astrocytes can unequivocally contribute to neuronal morphology and synaptogenesis and confirm previous studies linking IL-6 and autism, suggesting potential novel therapeutic pathways for a subtype of ASD individuals. This work highlights the influence of glial cells on neurons in ASD. In addition, our results reinforce the benefit of iPSC technology for model idiopathic autism, generating novel insights on autism pathophysiology and providing a platform to test drugs for future potential therapies.

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Nanosymposium

103. iPSCs: Disease Models I

Location: 152A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***103.11

**Topic: ***A.03. Stem Cells and Reprogramming

Title: Modeling molecular changes and network response to Risperidone during neuronal differentiation in iPSC derived from Autism patients

Authors: *Y. KIM[1], *Y. KIM[1,2], C. MARCHETTO[2], R. SANTOS[2], D. AMATYA[2], S. LINKER[2], A. P. D. MENDES[2], F. H. GAGE[2]
[1]Child Adolescent Psychiatry, Natl. Ctr. For Mental Hlth., Seoul, Korea, Republic of; [2]Salk Inst., La Jolla, CA

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that manifests significant social communication deficits and restricted patterns of interests and behaviors. The current treatment options for the core symptoms of autism are limited to psychosocial therapies. Medications are utilized to control mostly behavioral symptoms such as irritability, aggression, self-injurious behaviors, anxiety, hyperactivity, impulsivity, inattention, and insomnia. Risperidone is one of the only two drugs approved by the Food and Drug Administration (FDA)

for the treatment of irritability in children with ASD. Trials have shown that risperidone is not only effective in improvement of irritability, aggressiveness, and hyperactivity associated with ASD, but also in some of the core autism symptoms, especially the repetitive behaviors. In order to understand the therapeutic mechanism of risperidone in ASD, the molecular changes and network response caused by risperidone during neuronal differentiation and initial phases of network formation, the process was modeled by differentiating neurons from neural stem cells derived from induced pleuripotent cells of ASD patients. The electrical activity of neurons during neuronal network formation was analyzed using various parameters acquired through multielectrode array (MEA) platform in the presence and the absence of risperidone. Expression profile analysis was performed in parallel system to uncover the molecular basis for the therapeutic mechanisms of risperidone. In our analysis, we observed differential expression profiles in genes pivotal to neurodevelopment according to the individual-based network sensitivity to risperidone. These findings suggest that electrical properties of neuronal networks modeled from patient iPSCs may provide new markers for drug development targets and also molecular candidates for disease markers.

Disclosures: Y. Kim: None. **C. Marchetto:** None. **R. Santos:** None. **D. Amatya:** None. **S. Linker:** None. **A.P.D. Mendes:** None. **F.H. Gage:** None.

Nanosymposium

104. iPSCs: Disease Models II

Location: 140A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***104.01

**Topic: ***A.03. Stem Cells and Reprogramming

Title: Ectopic development of neuronal organoids via direct tissue reprogramming

Authors: *D. GALLEGO-PEREZ[1,2], S. GHATAK[2], N. HIGUITA-CASTRO[2], A. SUNYECZ[2], J. MOORE[2], R. STEWART[2], T. ZIEBRO[2], R. NORTHCUTT[2], V. SUNDARESAN[2], J. OTERO[2], K. SINGH[2], S. ROY[2], C. RINK[2], S. KHANNA[2], L. LEE[2], C. K. SEN[2]
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Abstract: Direct cellular reprogramming has the potential to enable safer and more effective therapeutic approaches, and/or personalized disease/tissue models for drug discovery and development. Current approaches to cell reprogramming, however, are fraught with caveats, including heavy reliance on viral transfection. We implemented a novel non-viral approach to controllably reprogram stromal tissue into brain-like parenchyma, *in* vivo, via nanoscale electroporation of specific modulators of endogenous transcription factors (*e.g.*, *Ascl1*, *Brn2*, and *Myt1l*) and/or RNA-binding proteins (*e.g.*, PTB siRNA). Experiments in C57BL6 mice

demonstrated skin stroma gradually converted into neuronal parenchyma following delivery of such modulators. Direct reprogramming of skin fibroblasts and keratinocytes was detected as early as day 7, as evidenced by lineage tracing experiments and increased expression of a wide variety of neuronal markers including Tuj1, Synapsin, and Neurofilament. Hair follicle-like structures, in particular, showed enhanced immunoreactivity for these markers. Skin-derived neuronal tissue also exhibited positive electrophysiological activity as determined through a polypyrrole (PPy)-based sensing platform. Whole transcriptome array analyses revealed a cluster of >3,000 probe-sets that showed expression pattern homology between skin-derived neuronal tissue and neurons reprogrammed *in vitro*. Ingenuity Pathway Analysis revealed the induction of genes implicated in brain development, including a large cluster of genes associated with the olfactory bulb. Further analysis of the reprogrammed skin niche suggested a gradual increase in the expression of neurotrophic factors concomitant with tissue reprogramming. Our findings suggest that non-viral direct cellular reprogramming could be a viable approach for the induction brain-like neuronal organoids *in vivo*, which could potentially be used in the development of novel therapeutic approaches for neurodegenerative disorders, and/or as disease/tissue models to support drug discovery efforts.

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Nanosymposium

104. iPSCs: Disease Models II

Location: 140A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***104.02

**Topic: ***A.03. Stem Cells and Reprogramming

Title: Generation of organoids from human neural stem cells and from patient-derived glioblastoma cells

Authors: *M. E. BARISH[1], A. VELAZQUEZ OJEDA[1], B. BREWSTER[1], C. E. BROWN[2], K. S. ABOODY[1], M. GUTOVA[1]
[1]Neurosciences, Beckman Res. Inst. City of Hope, Duarte, CA; [2]Hematology/HCT, Med. Ctr. City of Hope, Duarte, CA

Abstract: Three dimensional cultures that form self-assembling structures termed organoids that are reminiscent of their source tissue have emerged as a valuable technique in fundamental/translational medical science. We are interested in using this preparation to study

cellular process of brain and brain tumor development and progression. Here we describe using L-myc immortalized human neural stem cells (NSCs; LM-NSC008) and characterized patient-derived glioblastoma (GBM) cells (PBT017) to initiate organoid cultures in Matrigel. Grown in appropriate media with gentle circular mixing, neural and brain tumor organoids survive without signs of necrosis for over two months. We explored temporal and spatial expression of markers of neural lineage, and of tumor progression, in organoids initiated with LM-NSC008 neural progenitor cells, and PBT017 GBM cells. Over time, LM-NSC008 organoids expand and increasingly expressed markers of neural differentiation while maintaining neural progenitor cell populations. In older organoids, we observed regions of circumferential and radial orientation. PBT017 organoids became highly heterogeneous, with expression of neural differentiation markers and large hypoxic regions evident. Together, these data suggest that three-dimensional organoids are capable of emulating neural tissue development and of recapitulating behaviors of gliolastoma cells. We also suggest that GBM organoids may provide a physiologically-relevant platform for preclinical in vitro evaluation of nascent therapies for patients with GBM.

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Nanosymposium

104. iPSCs: Disease Models II

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Presentation Number: *104.03

Topic: *A.03. Stem Cells and Reprogramming

Support: NIH Grant R01 NS086890
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NIH Grant P30 NS076411

Title: Accelerated derivation of functional microglia from hiPSCs for modeling neurological disorders

Authors: D. TRUDLER[1], A. SULTAN[1], K. LOPEZ[1], J. PARKER[1], S. A. LIPTON[1,2,3], *R. AMBASUDHAN[1]
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Abstract: Microglia, the resident immune cells of the CNS, are phagocytic cells that contribute to neurogenesis and neuronal survival, as well as neuronal loss and synaptic pruning. Microglia-related inflammation and microglial dysfunction have been described in various neurodevelopmental, neurological and neurodegenerative diseases, including Autism spectrum disorder (ASD), stroke, Alzheimer's disease (AD), and Parkinson's disease (PD). While there is emerging research on the involvement of inflammation in neurological pathologies in mice, human investigations are mostly correlative, and there is a real need for improved and rapid human model systems. Recently, a few methods have been developed to convert human induced pluripotent stem cells (hiPSCs) into microglia-like cells. Although these manipulations specify defined microglia-like cells, the protocols have limitations. They either do not follow the developmental ontogeny of microgliogenesis, as it occurs from the yolk sac, or involve lengthy differentiation procedures and cumbersome culturing methods. Therefore, there is a need for a robust and rapid method for deriving microglia from hiPSCs that would rectify these shortcomings. Here, we describe a simple and effective method for step-wise differentiation of human pluripotent cells to microglia-like cells in an accelerated fashion, modeled on the yolk-sac and erythro-myeloid developmental program. The differentiating cells reveal gene expression profiles that agree with progressive stages of embryonic development. Our easily adaptable method involves 3 weeks of hiPSC differentiation to produce a highly homogenous population of functional microglia-like cells without the need for cell sorting. These cells share an overlapping global gene expression pattern and functional capabilities with human brain derived-microglia. Moreover, they respond to complex inflammatory cues, release proinflammatory cytokines, perform phagocytosis, and appear activated in the disease models tested. Furthermore, these cells can be co-cultured with hiPSC-derived neurons and astrocytes and produce disease relevant phenotypes that can be used for drug screening. These functionally appropriate human microglia-like cells can serve as a platform for modeling human neurological diseases, both for studying cell-autonomous and non-cell-autonomous mechanisms, and will facilitate drug development for novel targets.

Disclosures: D. Trudler: None. **A. Sultan:** None. **K. Lopez:** None. **J. Parker:** None. **S.A. Lipton:** None. **R. Ambasudhan:** None.

Nanosymposium

104. iPSCs: Disease Models II

Location: 140A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***104.04

**Topic: ***A.03. Stem Cells and Reprogramming

Support: Stanley Center

Title: Modeling human brain development and disease at single-cell resolution with human brain organoids

Authors: *G. QUADRATO[1,2], T. NGUYEN[2,1], E. MACOSKO[2], J. SHERWOOD[1,2], D. BERGER[1], S. YANG[1], E. BOYDEN[3], J. LICHTMAN[1], Z. WILLIAMS[4], S. MCCARROLL[2,5], P. ARLOTTA[2,1]
[1]Harvard Univ., Cambridge, MA; [2]Broad Inst. of MIT and Harvard, Cambridge, MA; [3]MIT, Cambridge, MA; [4]MGH, Boston, MA; [5]Harvard Med. Sch., Boston, MA

Abstract: In vitro models of the developing human brain such as 3D brain organoids offer an unprecedented opportunity to study aspects of human brain development and neurodevelopmental disorders in a format amenable to large-scale production and genetic engineering. However, it remains undefined what cell populations are generated within organoids and to what extent brain organoids recapitulate the regional complexity, cellular diversity, and circuit functionality of the human brain. Here, we analyzed gene expression in over 80,000 individual cells isolated from 31 human whole-brain organoids that developed for 3-6 months. We find that organoids can generate a broad diversity of cells, which we show are related to known endogenous classes, including subpopulations of neurons and progenitors of the cerebral cortex and of the retina. Organoids could be developed over extended periods (up to 1 year) enabling unprecedented levels of maturity including the formation of dendritic spines and of spontaneously-active networks. Neuronal activity within organoids could be controlled using light-stimulation of photosensitive cells, which may offer a way to probe the functionality of human neuronal circuits using physiological sensory stimuli. All together, these data provide insight into the range of cellular diversity that results when generating brain organoids and further validate their use to model human brain development and cell-type specific changes in neuropsychiatric diseases.

Disclosures: G. Quadrato: None. **T. Nguyen:** None. **E. Macosko:** None. **J. Sherwood:** None. **D. Berger:** None. **S. Yang:** None. **E. Boyden:** None. **J. Lichtman:** None. **Z. Williams:** None. **S. McCarroll:** None. **P. Arlotta:** None.

Nanosymposium

104. iPSCs: Disease Models II

Location: 140A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***104.05

**Topic: ***A.03. Stem Cells and Reprogramming

Title: iPSC-derived neural progenitors for phenotypic compound screenings of mitochondrial neurological disorders due to MT-ATP6 mutations

Authors: *C. LORENZ[1,2,3], S. STAEGE[2], A. ZINK[2,4], G. INAK[2], B. MLODY[2], E. WANKER[2], M. SCHUELKE[4], A. PRIGIONE[2]
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Abstract: Mutations in mitochondrial DNA (mtDNA) are strongly linked to diseases affecting the nervous system and for which no effective treatment exists. It has been difficult to develop animal models, due to challenges inherent in engineering mtDNA. Existing cellular models often lack the metabolic features of neural cells and do not provide the patient-specific match between mitochondrial and nuclear genomes. But this is crucial in the study of mtDNA disorders, since specific characteristics of an individual patient's nuclear DNA have been shown to influence the course of these diseases. The development of appropriate model systems is therefore critical. We recently showed that neural progenitor cells (NPCs) differentiated from patient-derived iPSCs are an effective modeling tool for neurological diseases associated with mtDNA mutations (Lorenz et al, *Cell Stem Cell* 2017). We found that patient-derived NPCs carrying a mutation in the mitochondrial gene *MT-ATP6* (m.9185T>C) showed defects in ATP production and abnormal increase in mitochondrial membrane potential (MMP). Patient NPCs also exhibited altered calcium homeostasis, which might represent a potential cause of neural impairment. We then used patient NPCs to carry out a high-content screening based on the MMP phenotype using FDA-approved drugs. The screening highlighted the compound avanafil, which we found capable of partially rescuing the calcium defect in patient-derived NPCs and neurons. Following this study, we have generated additional patient NPC lines carrying other *MT-ATP6* mutations (m.8993T>C and m.8993T>G) and confirmed the presence of altered MMP and altered calcium homeostasis. We have therefore developed a high-throughput compound screening approach based on the patient-specific calcium defect. We now aim to apply this approach for a large automated screening using patient NPCs. The employment of FDA-approved libraries in such phenotype-based screenings may allow a fast translation to clinical application through drug repositioning. Overall, our data suggest that patient-derived NPCs represent an effective model system to allow the discovery of treatment strategies for debilitating mtDNA encephalopathies.

Disclosures: C. Lorenz: None. **S. Staege:** None. **A. Zink:** None. **G. Inak:** None. **B. Mlody:** None. **E. Wanker:** None. **M. Schuelke:** None. **A. Prigione:** None.

Nanosymposium

104. iPSCs: Disease Models II

Location: 140A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***104.06

Topic: *A.03. Stem Cells and Reprogramming

Support: KAKENHI JP15H01568
KAKENHI JP17H05707
AMED 16ek0109025h0003
AMED 16ek0109165h0102
AMED 17ek0109243h0001

Title: Pathophysiological analysis of spinal-bulbar muscular atrophy using disease specific iPSCs

Authors: *Y. OKADA[1], K. ONODERA[1,2], T. ITO[1], D. SHIMOJO[1,5], Y. ISHIHARA[5], S. TANAKA[1,3], M. KATSUNO[2], M. DOYU[1], G. SOBUE[4], H. OKANO[5]
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Abstract: Spinal-bulbar muscular atrophy (SBMA) is an adult onset, slowly progressive lower motor neuron disease caused by a CAG repeat expansion in androgen receptor (AR) gene. Previous analyses of SBMA model mice have revealed that mutant AR with expanded polyglutamine tract form aggregation in testosterone-dependent manner and cause motor neuron degeneration. However, the phenotypes of model mice are different from those of patients in several aspects, and the clinical trial of anti-androgen treatment by LH-RH analogue, leuprorelin acetate, has shown its effectiveness only in patients of early-disease, suggesting the necessity of more appropriate human disease models, elucidation of early pathogenesis of SBMA, and early diagnosis. Moreover, recent analysis has shown the involvements of skeletal muscles in neurodegeneration in SBMA. Here, we generated induced pluripotent stem cells (iPSCs) from SBMA patients to establish more accurate disease models, and investigated the pathogenesis of SBMA from the aspect of pre-aggregation early pathology, disease accelerating signals, and neuromuscular interactions. We established iPSCs from 4 SBMA patients and 3 age- and sex-matched controls. Reprograming did not affect the number of CAG repeats. For the analysis of motor neuron degeneration, iPSC-derived motor neurons (MNs) were cultured with dihydrotestosterone (DHT), a ligand for AR, for 4 weeks, and were evaluated for mutant AR aggregation, neuronal cell death, gene expressions, and alteration of intracellular signals. As for differentiation ratio into MNs and neuronal cell death, significant difference was not observed between SBMA patients' and control MNs. Mutant AR aggregations were not detected in SBMA-MNs by immunocytochemistry or western blot analysis, while these SBMA-MNs showed alteration of the expressions of several genes associated with early pathology of SBMA, such as *CALCA* (CGRP-1) and *TβR2*. For the analysis of disease accelerating signals, we screened several compounds which cause cellular stresses, and found that ER stress inducers, tunicamycin and thapsigargin, significantly suppressed neurite outgrowth of SBMA-MNs, suggesting that ER stress promoted disease progression and could be a novel therapeutic target for SBMA. Finally, we co-cultured control-MNs with skeletal muscles expressing mutant AR, and found that significant decrease in the number of neuromuscular junctions and significant increase in neuronal cell death, suggesting non-cell autonomous neurodegeneration by skeletal

muscles. These iPSC-derived disease models provide powerful tools for the analysis of pathogenesis of SBMA and for drug screening.

Disclosures: **Y. Okada:** 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.; AMED 17ek0109243h0001. **K. Onodera:** None. **T. Ito:** None. **D. Shimojo:** None. **Y. Ishihara:** None. **S. Tanaka:** None. **M. Katsuno:** None. **M. Doyu:** None. **G. Sobue:** None. **H. Okano:** None.

Nanosymposium

104. iPSCs: Disease Models II

Location: 140A

Time: *Sunday, November 12, 2017, 8:00 AM - 10:15 AM

Presentation Number: *104.07

Topic: *A.03. Stem Cells and Reprogramming

Support: Ministerio de Economía y Competitividad, Spain
ISCIII-Subdirección General de Evaluación and European Regional Development Fund (ERDF) [RETICS and CIBERNED]
Catalonia Trade and Investment, Generalitat de Catalunya and ERDF [ADVANCE(CAT)], Spain
CHDI Foundation Inc., USA

Title: Human iPSC-mouse chimeras to study Huntington's disease phenotypes

Authors: ***A. MIGUEZ**[1,2,3,4,5], P. SANDERS[1,2,3,4,5], G. BOMBAU[1,2,3,4,5], C. VILA[1,2,3,4,5], J. M. CANALS[1,2,3,4,5]
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Abstract: Huntington's disease (HD) is a hereditary neurodegenerative disorder mainly characterized by striatal atrophy and degeneration of medium spiny neurons (MSNs). Although mouse models have provided a substantial amount of information about HD, they show important limitations for understanding the pathogenesis in humans. Generation of human induced pluripotent stem cells (iPSCs) is one of the most promising technologies for the study of HD. Current *in vitro* HD iPSC models can recapitulate some disease phenotypes, but they are not

useful for studying long-term differentiation, aging and the establishment of brain connections. Interestingly, new *in vivo* models using HD patient-derived iPSCs transplanted into mice could avoid these shortcomings, by allowing cell differentiation and aging within a physiologically relevant environment.
Previous transplantation studies in the HD field have been hampered by the poor survival and functional integration of differentiated grafted human cells in murine models. To circumvent these drawbacks, we have transplanted iPSC-derived telencephalic progenitors from healthy subjects and HD patients transduced with a GFP lentivirus into the forebrain of neonatal mice. At this early age, patterning cues present in the host developing brain act to instruct specific cell fates and play a key role in determining the migration, connectivity and functional integration of engrafted cells.
Our data show that the vast majority of transplanted cells express Ctip2, including a subpopulation co-expressing DARPP-32, indicative of MSN identity. Furthermore, human iPSC-derived differentiated neurons sent axons towards MSN targets and were able to establish synapses, suggesting functional integration within the basal ganglia circuitry. Remarkably, transplanted cells survived up to 5 months and recapitulated HD human pathology, as evidenced by altered autophagy, mutant huntingtin aggregation and striatal degeneration.

Disclosures: **A. Miguez:** None. **P. Sanders:** None. **G. Bombau:** None. **C. Vila:** None. **J.M. Canals:** None.

Nanosymposium

104. iPSCs: Disease Models II

Location: 140A

Time: *****Sunday, November 12, 2017, 8:00 AM - 10:15 AM

Presentation Number: *****104.08

Topic: *****A.03. Stem Cells and Reprogramming

Support: NIH (Grants MH095741 and MH092758)
G. Harold & Leila Y. Mathers Charitable Foundation
The Engman Foundation
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Helmsley Charitable Trust
The German Research Foundation (DFG)

Title: Early pathological priming of time-critical gene networks causes neurodevelopmental acceleration in autism

Authors: *S. T. SCHAFER, A. PAQUOLA, S. STERN, M. C. MARCHETTO, J. MERTENS, F. H. GAGE
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Abstract: Autism spectrum disorder (ASD) is a disorder of early brain development. One of the current challenges in understanding ASD pathophysiology is to determine critical neurodevelopmental periods and cellular states that might provide the ground for disease propensity. To comprehensively profile early neurodevelopmental alterations in individuals with ASD, we harnessed a time series approach to monitor patient-derived induced pluripotent stem cells (iPSCs) throughout the recapitulation of cortical development. Our analysis revealed ASD-associated changes in the maturational sequence of cortical neuron development, involving temporal dysregulation of specific neurodevelopmental gene networks and morphological growth acceleration. The observed changes tracked back to an insufficient suppression of network genes at the neural stem cell (NSC) stage. Concerted overrepresentation of network factors in control NSCs was sufficient to trigger ASD-like features, and circumventing the pathologically primed NSC stage by direct conversion of ASD iPSCs into induced neurons (iPSC-iNs) abolished ASD-associated phenotypes. Our findings identify accelerated dynamics of a gene network that, while primed earlier in development, causes neurodevelopmental aberrations in ASD.

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Nanosymposium

104. iPSCs: Disease Models II

Location: 140A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***104.09

**Topic: ***A.03. Stem Cells and Reprogramming

Title: Establishment of a human induced pluripotent stem cell derived neuromuscular co-culture platform for disease modeling

Authors: *E. SWARTZ[1], G. SHINTANI[2], J. WAN[2], S. WANG[2], M. PRIBADI[2], Z. YANG[2], L. HAVTON[2], G. COPPOLA[2]
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Abstract: Abstract
Human neuromuscular disorders (NMDs) are a group of rare, monogenic disorders that collectively exceed an incidence of 1 in 3000. Our understanding of the disease pathogenesis

leading to the collapse of the neuromuscular junction (NMJ) in NMDs is poor, owing to difficult in access to affected tissues and lack of a sufficient *in vitro* model. Here, we present the establishment of an entirely human induced pluripotent stem cell- (iPSC-) derived co-culture system comprised of skeletal myotubes and spinal motor neurons. We validated NMJ formation morphologically through immunocytochemistry, confocal imaging, and electron microscopy, and functionally via patch clamp electrophysiology. Additionally, we utilized isogenic iPSC lines from patients harboring a G_4C_2 repeat expansion in *C9orf72*, the most common genetic cause of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD). We use this co-culture strategy to investigate NMJ-related phenotypes in diseased and isogenic control cells in two ways. First, by co-culturing cells on multi-electrode arrays (MEAs) to observe potential electrophysiological phenotypes. And second, by creating iPSC-derived motor neurons under optogenetic control and recording skeletal muscle calcium transients following light-induced stimulation. We aim to further utilize this platform as a novel approach for interrogating pathogenic mechanisms of ALS and other NMDs.

Disclosures: **E. Swartz:** F. Consulting Fees (e.g., advisory boards); Verge Genomics. **G. Shintani:** None. **J. Wan:** None. **S. Wang:** None. **M. Pribadi:** None. **Z. Yang:** None. **L. Havton:** None. **G. Coppola:** None.

Nanosymposium

105. Alzheimer's Disease and Neuroinflammation

Location: 152B

Time: *Sunday, November 12, 2017, 8:00 AM - 10:30 AM

Presentation Number: *105.01

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

Support: NS37853

Title: The cerebrovascular and cognitive dysfunction induced by Aβ requires the innate immunity receptor CD36 in perivascular macrophages

Authors: ***K. UEKAWA**, L. PARK, Y. HATTORI, P. ZHOU, M. MURPHY, J. ANRATHER, C. IADECOLA
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Abstract: Amyloid-β (Aβ) exerts deleterious effects on the cerebrovascular microcirculation, which may contribute to cognitive impairment in Alzheimer’s disease and mixed dementias. The neurovascular effects of Aβ are mediated by the innate immunity receptor CD36, which induces production of reactive oxygen species (ROS) through a Nox2-containing NADPH oxidase (Park et al., PNAS, 108:5063, 2011). However, the cell type(s) expressing CD36 and responsible for

the harmful vascular effects of Aβ remain unknown. Perivascular macrophages (PVM) are exposed to Aβ in the perivascular space, express CD36 and have the potential to produce large amounts of ROS. We tested the hypothesis that the neurovascular and cognitive dysfunction induced by Aβ requires CD36 in PVM. To this end, we transplanted $CD36^{-/-}$ bone marrow (BM) to irradiated male tg2576 mice (age 12 months) to repopulate their perivascular space with $CD36^{-/-}$ PVM. Three months later, cerebral blood flow (CBF) was measured by laser-Doppler flowmetry in the somatosensory cortex of urethane-chloralose anesthetized mice with monitoring of blood pressure and blood gases (n=5/group). In 15-month-old WT mice transplanted with WT BM (wt→wt), CBF response induced by whisker stimulation (WS) or by neocortical superfusion of the endothelium-dependent vasodilator acetylcholine (ACh) was attenuated compared to 3-month-old wt→wt chimeras (WS: -29±2%; ACh: -27±3%; $p<0.05$). The increase in CBF induced by the smooth muscle relaxant adenosine was not attenuated ($p>0.05$). In 15-month-old tg2576 mice transplanted with WT BM (wt→tg), CBF responses evoked by WS or ACh were attenuated further compared to aged wt→wt (WS, -35%; ACh, -36%; $p<0.05$). However, transplantation of $CD36^{-/-}$ BM prevented the attenuation in cerebrovascular responses in tg2576 mice (CD36→tg) (WS: wt→tg, 21±2%; ACh: wt→tg, 9±1% vs CD36→tg, 17±2%; $p<0.05$ from wt→tg). The protective effect in aged tg2576 mice receiving $CD36^{-/-}$ BM was associated with reduced cerebrovascular deposition of Aβ (vascular amyloid load: -58%; $p<0.05$ from wt→tg). Aged tg2576 mice receiving WT BM exhibited impairment in spatial memory, assessed by the time (sec) spent to find the escape hole in a Barnes maze, a deficit rescued in aged tg2576 receiving $CD36^{-/-}$ BM (wt→wt, 104±9 sec; wt→tg, 172±5 sec; CD36→wt, 111±20 sec; $p<0.05$). We conclude that PVM are the CD36-expressing cells necessary for the cerebrovascular and cognitive dysfunctions induced by Aβ. CD36 in PVM may be therapeutic targets to counteract the detrimental neurovascular and cognitive effects of Aβ.

Disclosures: **K. Uekawa:** None. **L. Park:** None. **Y. Hattori:** None. **P. Zhou:** None. **M. Murphy:** None. **J. Anrather:** None. **C. Iadecola:** None.

Nanosymposium

105. Alzheimer's Disease and Neuroinflammation

Location: 152B

Time: *Sunday, November 12, 2017, 8:00 AM - 10:30 AM

Presentation Number: *105.02

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

Support: National Natural Science Foundation of China, 81571039

Title: Neuroinflammation & Alzheimer's disease

Authors: *X. LIU, Q. TAN
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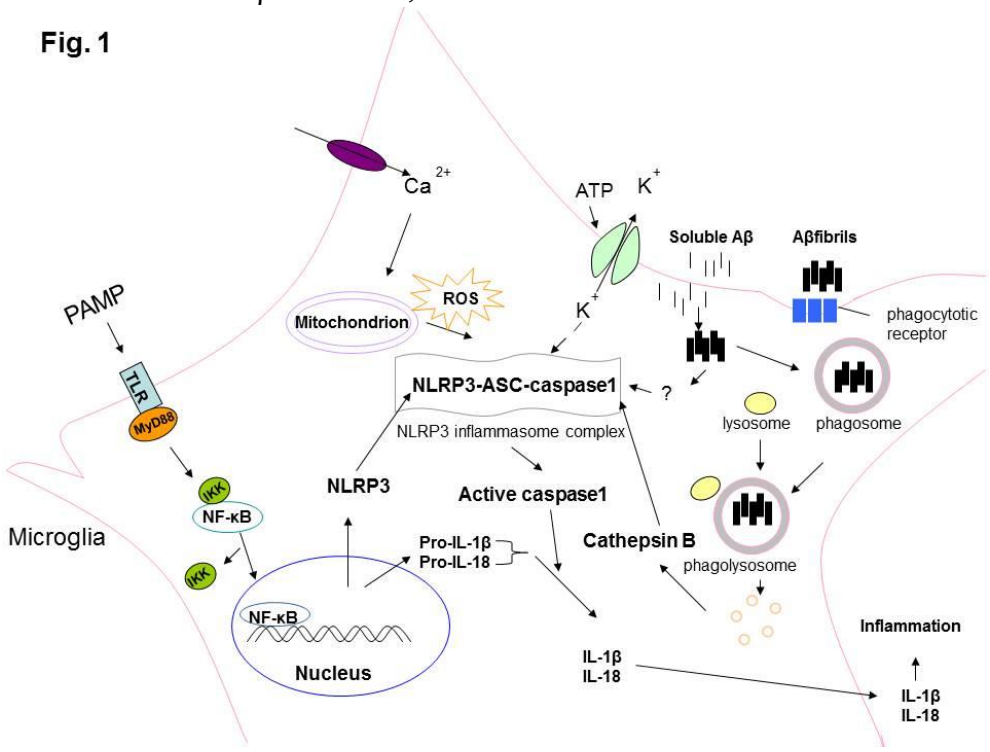
Abstract: The study of the pathogenesis of Alzheimer's disease (AD) over the past few decades is based on the amyloid hypothesis. However, the neuroinflammatory response associated with AD is only considered as pathophysiological events. Several attempts have been made to treat AD using anti-amyloid strategies with disappointing results. It is clear that the “amyloid cascade hypothesis” alone can not completely explain the pathological changes in AD. Increasing data have confirmed that neuroinflammation plays an important role in the process of AD neurodegeneration and involved in the malignant cycle of amyloid deposition, neuronal damage, NFTs formation, and neuronal death. Recent data clearly show that immune activation can promote AD pathophysiological changes. Thus the immune system may be able to provide a new pathways for diagnosis and treatment of AD.These insights have suggested that neuroinflammation has now become a major field of AD research today and inhibiting it may be of novel potential therapeutic targets for AD.

Fig.1 Activation of the NLRP3 inflammasome in microglial cell. Aβ not only cause the expression of NLRP3 and pro-IL-1β by TLR-mediated activation of NF-κB, but also can activate NLPR3 inflammasome complex by phagocytosis. Active caspase-1 cleaves pro-IL-1β and pro-IL-18 to active IL-1β and IL-18, which is released into the extracellular fluid.



Disclosures: **X. Liu:** None. **Q. Tan:** None.

Nanosymposium

105. Alzheimer's Disease and Neuroinflammation

Location: 152B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***105.03

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

Support: NHMRC Career Development Fellowship APP1123564
ARC discovery project grant DP150104321

Title: Lim kinase 1 regulates amyloid beta load in alzheimer's mice

Authors: *Y. D. KE[1], L. M. ITTNER[2]
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Abstract: LIM Kinase 1 (LIMK1) is a serine/threonine kinase that plays a central role in the regulation of actin cytoskeletal dynamics and consequently, is important in the maintenance of synaptic integrity, and essential for cognitive function. It was previously published that LIMK1 knockout (KO) mice have synaptic and cognitive deficits, similar to those observed in Alzheimer's disease (AD) models. Synaptic loss and subsequent neuronal degeneration are key events in AD that occur concomitantly with the two histopathological hallmarks of AD, namely amyloid β (Aβ) plaques and tau-containing neurofibrillary tangles.
Here, we investigated the role of LIMK1 in the pathogenesis of disease in the Aβ-forming, APP23 AD mouse model. APP23 mice express the Swedish K670D/M671L double mutation in the amyloid precursor protein APP under a neuronal murine Thy1.2 promoter. These mice were previously published to develop Aβ plaques at approximately 6 months of age with deposits localized to various brain regions including the cortex and hippocampus.
We crossed these APP23 mice with the LIMK1 KO mice and found that depletion of LIMK1 in APP23 mice resulted in an accelerated late-onset lethality (>20 months) not previously reported. Moreover, there was a marked increase in Aβ plaque burden when comparing aged APP23/LIMK1$^{-/-}$ mice with APP23 mice alone. Quantitative analysis revealed this higher plaque burden occurs in both the cortices and hippocampi of APP23/LIMK1$^{-/-}$ as compared to APP23/LIMK$^{+/+}$ mice. This increase in plaque load occurred independently of plaque size, with plaque sizes presenting comparable between both genotypes. No differences were observed in the production of $A\beta_{1-42}$ and $A\beta_{1-40}$.
Interestingly, this increased Aβ plaque deposition occurs in the presence of a marked reduction in the recruitment of activated astrocytes needed for limiting Aβ plaque formation and its clearance. This reduction in GFAP-positive, activated astrocytes around Thioflavin S-positive plaques occur with no change to the recruitment of IBA1-positive microglial cells.
In summary, the above novel finding indicates that LIMK1 has an important role in either

limiting Aβ plaques formation or has a crucial role in orchestrating its clearance. Either way, our findings have implications for future treatment strategies aimed at reducing the deposition of Aβ plaques.

Disclosures: Y.D. Ke: None. **L.M. Ittner:** None.

Nanosymposium

105. Alzheimer's Disease and Neuroinflammation

Location: 152B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***105.04

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

Support: Massachusetts Center for Alzheimer's Therapeutic Sciences (MassCATS)

Title: Microglia contain, release, and process bioactive tau seeds

Authors: *S. C. HOPP[1], Y. LIN[3], S. DEVOS[2], R. E. BENNETT[4], A. D. SHERMAN-ROE[1], B. T. HYMAN, MD,PhD[2]
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Abstract: Misfolding of microtubule-associated protein tau (MAPT) within neurons into neurofibrillary tangles is an important pathological feature of Alzheimer's disease (AD). Tau pathology correlates with cognitive decline in AD and follows a stereotypical anatomical course; several recent studies indicate that tau pathology spreads interneuronally via misfolded tau "seeds." Tau seeding activity can be conveniently measured with an in vitro fluorescence resonance energy transfer (FRET) based biosensor cell line that detects tau aggregation. Previous research has focused on neurons as the source of these tau seeds. However, recent studies, as well as the data contained herein, suggest that microglia, the resident immune cells of the central nervous system, play a direct role in the spread of tau pathology. Here, we show that microglia isolated from both human AD cases and the rTg4510 tauopathy mouse model contain tau seeds and that microglia release these tau seeds in vitro into their conditioned media (CM). This suggests that microglia have taken up tau but are incapable of neutralizing its seeding activity. Indeed, when in vitro microglia are plated with media containing tau seeds, they reduce resultant seeding activity from conditioned media in the FRET seeding assay but do not eliminate seeding. Overall, these data suggesting that microglia are capable of breaking down tau, but not efficiently enough to entirely prevent the spread of tau pathology.

Disclosures: **S.C. Hopp:** None. **Y. Lin:** None. **S. DeVos:** None. **R.E. Bennett:** None. **A.D. Sherman-Roe:** None. **B.T. Hyman:** None.

Nanosymposium

105. Alzheimer's Disease and Neuroinflammation

Location: 152B

Time: *Sunday, November 12, 2017, 8:00 AM - 10:30 AM

Presentation Number: *105.05

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

Title: Normal brain APOE4 structure and functions are altered by ibuprofen

Authors: ***G. W. REBECK**, S. FLOWERS
Neurosci., Georgetown Univer, Washington, DC

Abstract: APOE is the strongest genetic risk factor for Alzheimer's disease. The APOE protein acts as an anti-inflammatory agent in vitro and in vivo, and drugs based on its structure have been used in preclinical models of neurodisorders. We have examined APOE3 and APOE4 knock-in mice for evidence of impairment of brain function in the absence of overt damage from Alzheimer's disease or other age-related disorders. APOE4 mice showed reduced neuronal complexity (as measured by Golgi staining) and delayed ability to achieve a spatial learning task, the Barnes maze. The APOE protein in APOE4 mouse brain showed a different pattern of isolation compared to APOE3 mouse brain, with more APOE readily soluble from APOE4 brains; we made similar findings in samples of human brains. We found that readily soluble APOE was characterized by post-translational modifications as determined by one-dimensional and two-dimensional gel electrophoresis. We characterized the glycosites and the attached glycans of the APOE protein, using samples of human cerebrospinal fluid and plasma. Using a novel mass spectrometry method, we found glycosylation of APOE Thr-194, as previously reported, but also substantial modification of APOE at other sites. We treated APOE4 animals with 375 ppm ibuprofen in chow for two months, and measured its effects on behavior and neuron structure. Ibuprofen-treated APOE4 mice showed significantly higher levels of neuron complexity, as measured by dendritic spine density, and significantly improved spatial learning, as measured by the Barnes maze. We found similar effects on neuronal complexity with a one-week treatment of APOE4 mice, and we are currently examining the effects of lower doses of ibuprofen. These data suggest that the contribution of APOE genotype to Alzheimer's disease risk may be related to an effect on predisposition of the brain to inflammation.

Disclosures: **G.W. Rebeck:** None. **S. Flowers:** None.

Nanosymposium

105. Alzheimer's Disease and Neuroinflammation

Location: 152B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***105.06

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

Support: NIH-NIA R01 AG044404-04

Title: Effects of substrate stiffness on NOX-mediated superoxide production in Aβ-stimulated microglia

Authors: *X. GENG[1], T. TENG[1], G. Y. SUN[2], J. W. SHIN[1], M. J. LADU[1], O. LAZAROV[1], J. C. LEE[1]
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Abstract: Magnetic Resonance Electrography (MRE) studies have provided evidence that brain tissue becomes softer during normal aging, and that these mechanical changes in brain tissue are more pronounced in Alzheimer's disease (AD) patients. Since cells in the brain can be stimulated by both chemical and mechanical signaling, alterations in brain tissue stiffness may result in aberrant neuronal and glial function. Although AD brain tissue was found softer as compared with those in normal healthy subjects, the impact of tissue softening in AD brain on AD-related cell function has not been studied in detail. Microglial cells play an important role in mediating multiple oxidative and inflammatory responses in the brain. NADPH oxidase (NOX), an enzyme complex comprising of different cytosolic and membrane bound subunits, is important in mediating production of reactive oxygen species (ROS) in these cells. Here, we study the effects of substrate elasticity on p47phox and gp91phox, the respective cytosolic and membrane subunits of NOX, and its ability to mediate superoxide production in Aβ-stimulated microglia. We found that increase in p47phox, but not in gp91phox was observed in BV2 cells cultured with softer substrates. When cells grown on substrates of different stiffness were exposed to oligomeric Aβ for 2 h, increases in superoxide were observed and these increases were further enhanced in cells grown on softer substrates, suggesting that cells on soft substrates are more vulnerable to oxidative effects of Aβ. These results suggest that softer brain tissue typical of AD pathology may increase oxidative stress in microglia, which might contribute to the development of AD.

Disclosures: X. Geng: None. **T. Teng:** None. **G.Y. Sun:** None. **J.W. Shin:** None. **M.J. Ladu:** None. **O. Lazarov:** None. **J.C. Lee:** None.

Nanosymposium

105. Alzheimer's Disease and Neuroinflammation

Location: 152B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***105.07

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

Support: NIH Grant RF1AG05148501
NIH Grant 5T32CA009547-30
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Israel Science Foundation (ISF)-Legacy-Bio-Med program
Minerva Foundation
ISF-Neurology

Title: Single cell RNA-seq identifies a unique microglia type associated with Alzheimer's disease

Authors: *O. MATCOVITCH-NATAN[1], H. KEREN-SHAUL[2], A. SPINRAD[1], A. WEINER[2], R. DVIR SZTERNFELD[3], T. K. ULLAND[5], E. DAVID[2], K. BARUCH[3], D. LARA-ASTAISO[2], B. TOTH[4], S. ITZKOVITZ[4], M. COLONNA[5], M. SCHWARTZ[3], I. AMIT[2]
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Abstract: Alzheimer's disease (AD) is a detrimental neurodegenerative disease with currently no effective treatments. Due to cellular heterogeneity, the roles of immune cell subsets in AD onset and progression are poorly understood. Using transcriptional single cell sorting, we comprehensively map all immune populations in wild type and AD-transgenic (Tg-AD) mouse brains. We describe a novel microglia type associated with neurodegenerative diseases (DAM) and identify the markers, spatial-location, and pathways associated with these cells. Immunohistochemical staining of mice and human brain slices showed DAM with intracellular/phagocytic Aβ particles. Single cell analysis of DAM in Tg-AD and $Trem2^{-/-}$ Tg-AD revealed that the DAM program is activated in a two-step process. Activation is initiated in a Trem2 independent step which includes down-regulation of microglia signature genes, followed by activation of a Trem2-dependent program. These data identify a unique microglia-type, which may have important implications for future treatment of AD and other neurodegenerative diseases.

Disclosures: O. Matcovitch-Natan: None. **H. Keren-Shaul:** None. **A. Spinrad:** None. **A. Weiner:** None. **R. Dvir Szternfeld:** None. **T.K. Ulland:** None. **E. David:** None. **K. Baruch:**

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Nanosymposium

105. Alzheimer's Disease and Neuroinflammation

Location: 152B

Time: *Sunday, November 12, 2017, 8:00 AM - 10:30 AM

Presentation Number: *105.08

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

Support: NIH F31 AG053976
Donors Cure Award CCAD201703
The JPB Foundation
NIH P30 NS057105

Title: Trem2 knockout attenuates neuroinflammation and protects against neurodegeneration in a mouse model of tauopathy

Authors: *C. E. LEYNS, J. D. ULRICH, M. B. FINN, F. R. STEWART, L. J. KOSCAL, J. REMOLINA SERRANO, G. O. ROBINSON, E. ANDERSON, D. M. HOLTZMAN
Neurol., Washington University-St. Louis, Saint Louis, MO

Abstract: Alzheimer's disease (AD) is the most common cause of dementia, yet the definitive molecular mechanisms underlining disease initiation and progression remain elusive. Recently, whole exome sequencing studies identified variants in the gene encoding triggering receptor expressed on myeloid cells 2 (Trem2) that increased the risk for developing AD 2-4 fold. Trem2 is predominately expressed on microglia in the brain and its association with AD adds to increasing evidence implicating a role for the innate immune system in AD initiation and progression. AD pathology is characterized first by the appearance of amyloid beta (Aβ) plaques followed by neurofibrillary tau tangles. Thus far, several studies have investigated the effects of Trem2 on Aβ plaques and associated pathology. One consistent observation has been that Trem2 knockdown or loss of Trem2 function reduces the number of plaque-associated microglia. Trem2 is hypothesized to be important for microglial survival and proliferation that sustains a microglial barrier around plaques that may help to contain toxic Aβ species and protect neurites. Therefore, Trem2 is currently thought to be protective in the response to amyloid pathology while variants leading to a loss of Trem2 function impair microglia signaling and are deleterious. However, the potential role of Trem2 in the context of tau pathology has not yet been characterized. To investigate whether Trem2 affected tau pathology, the microglial response to tau pathology, or neurodegeneration, we crossed $Trem2^{+/+}$ and $Trem2^{-/-}$ mice to the P301S tau transgenic line, which expresses a mutant form of human tau that is causative for a familial form of

frontotemporal dementia. Strikingly, Trem2$^{-/-}$P301S mice exhibited significantly less neurodegeneration as quantified by ventricular enlargement and preserved cortical volume in the entorhinal and piriform regions compared to Trem2$^{+/+}$P301S mice. However, no Trem2-dependent differences were observed for phosphorylated tau staining or insoluble tau levels. Trem2$^{-/-}$P301S mice exhibited significantly reduced microgliosis in the hippocampus and piriform cortex compared to Trem2$^{+/+}$P301S mice. Gene expression analyses show that complement signaling is significantly attenuated in Trem2$^{-/-}$P301S mice and there Trem2 lower levels of inflammatory cytokines. These results suggest that impairing microglial Trem2 signaling lowers neuroinflammation and is protective against neurodegeneration in the context of pure tauopathy. Future experiments aim to elucidate possible mechanisms by which Trem2 signaling may enhance tau-mediated neurodegeneration.

Disclosures: **C.E. Leyns:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent: Anti-tau constructs. **J.D. Ulrich:** None. **M.B. Finn:** None. **F.R. Stewart:** None. **L.J. Koscal:** None. **J. Remolina Serrano:** None. **G.O. Robinson:** None. **E. Anderson:** None. **D.M. Holtzman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent: Anti-tau constructs, Patent: Antibodies to tau. F. Consulting Fees (e.g., advisory boards); Co-founder and Advisor: C2N Diagnostics, Advisor: Proclara Biosciences, Consult: Genentech, Consult: Eli Lilly, Consult: AbbVie, Consult: AstraZeneca.

Nanosymposium

105. Alzheimer's Disease and Neuroinflammation

Location: 152B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***105.09

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

Support: BrightFocus Foundation (PI: Ikezu)

Title: Triggering receptor expressed on myeloid cells 2: Functional characteristics and therapeutic implications of a novel immune receptor in microglia for the treatment of Alzheimer's disease

Authors: *K. CLAYTON[1], M. M. VARNUM[1], A. YOSHII-KITAHARA[1], G. YONEMOTO[1], L. KORO[1], S. IKEZU[1], T. IKEZU[2]
[2]Pharmacol. and Neurol., [1]Boston Univ. Sch. of Med., Boston, MA

Abstract: Alzheimer's disease (AD), the most common form of dementia, is a crippling neurodegenerative disease that is growing quickly in prevalence. Currently, there are no FDA approved medications that serve to prevent or reduce AD pathology; all drugs are merely cognitive enhancers used to offset the deficits of dementia. Genome-wide association studies (GWAS) identified Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) as a genetic node in the risk of developing AD. The main function of TREM2 significant to AD is stimulation of macrophage and neutrophil-mediated inflammatory responses, suggesting the exacerbation or alleviation of TREM2 to AD pathology is heavily based on chronic, injurious neuroinflammation and amyloid-β clearance. Conveniently, amyloid-β oligomers themselves are known ligands of the TREM2 receptor. Several studies published within the last five years produced mixed results as to whether decreasing the activity of TREM2 with antibody antagonism and gene knockout mitigates or provokes the pathology of AD. Therefore, further validation of these findings is warranted, particularly pertaining to modulation of TREM2 signaling through tyrosine kinase-binding protein (TYROBP), its adaptor protein, to assess the effect of increasing phagocytosis of amyloid-β oligomers and fibrils. In order to pursue this topic, an in-house luciferase assay was developed and validated as a robust method for assessing TREM2-TYROBP signaling in Human Embryonic Kidney cells (HEK293) that were transfected with a construct of both genes. Using this model, an agonistic TREM2 antibody was found to increase TREM2-TYROBP signaling as well as enhance phagocytosis in murine microglia. Investigations into TREM2 mutations associated with Nasu-Hakola disease and multiple neurodegenerative disorders later revealed that the T66M mutation likely leads to reduced cell surface localization of TREM2 while simultaneously increasing coupling to TYROBP. Following these studies, the HEK293 luciferase model was used to screen for both agonistic and antagonistic small molecules with the potential to modulate TREM2-TYROBP signaling *in vitro*, which lead to the discovery of several hits. Following these efforts, approximately 100 derivatives of antagonistic compounds were generated and observed to reduce TREM2-TYROBP signaling in HEK293 cells. Eventually, compounds with the highest potential to modulate TREM2-TYROBP coupling will be evaluated for therapeutic benefit *in vivo* using transgenic mouse models of AD. These studies aim to 1) contribute to the understanding of TREM2 and its role in AD pathology and 2) produce viable drug candidates for clinical development.

Disclosures: K. Clayton: None. **M.M. Varnum:** None. **A. Yoshii-Kitahara:** None. **G. Yonemoto:** None. **L. Koro:** None. **S. Ikezu:** None. **T. Ikezu:** None.

Nanosymposium

105. Alzheimer's Disease and Neuroinflammation

Location: 152B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***105.10

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

Support: NEI EY006311
NIA AG18031
AG038834

Title: Bacteroidetes fragilis of the human GI tract microbiome secretes a noxious mixture of lipopolysaccharides (BF-LPSs), amyloids, endotoxins and small non-coding (microRNA-like) RNAs, that drives inflammatory signaling in sporadic Alzheimer's disease (AD) tissues

Authors: *W. J. LUKIW[1,2], V. JABER[3], L. CONG[3], Y. ZHAO[4]
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Abstract: Background: While the contribution of the human gastrointestinal (GI) tract microbiome to human health, aging and disease is becoming increasingly recognized, the molecular mechanics, epigenetics and biophysics of just how this is accomplished is not well understood. Major bacterial species of the human GI tract such as the Gram-negative bacillus *Bacteroides fragilis* (*B. fragilis)* secrete a remarkably complex array of highly pro-inflammatory neurotoxins *which*, when released from the confines of the healthy GI tract, are highly toxic to neurons of the CNS. One important aspect of this process is the transfer of these *B. fragilis* toxins through GI tract and blood brain barriers, dynamic structures which are known to become more 'leaky' with aging and disease. **Methods:** bacteria cell culture, bioinformatics, DNA sequencing, immunohistochemistry, microbiome extraction, Northern and Western analysis, 16S RNA sequencing, RT-PCR **Results:** For the first time this paper will show the presence of a GI tract microbiome-derived *B. fragilis* lipopolysaccharide (BF-LPS) in the neocortex and hippocampus of Alzheimer's disease (AD) affected brain. This paper **(i)** will also report recent findings and provide new data on GI tract microbiome abundance, speciation, complexity and stoichiometry in sporadic AD; **(ii)** will evaluate microbial signaling products with emphasis on potentially neurotoxic exudates including endotoxins and exotoxins, fragilysin, select lipoglycans, lipooligosaccahrides (LOSs) and LPSs, amyloids and small non-coding RNAs (sncRNA); and **(iii)** will assess the pathogenic potential of these products to drive the AD process. **Conclusions:** The potential contribution of neurotoxic components of the human GI tract microbiome to the sporadic AD process may be significant. For example, BF-LPS **(i)** represents an internally generated GI tract microbiome-derived neurotoxin capable of driving

AD-type change and **(ii)** has enormous potential to initiate and/or propagate inflammatory neurodegeneration along the gut-brain axis.

Disclosures: **W.J. Lukiw:** None. **V. Jaber:** None. **L. Cong:** None. **Y. Zhao:** None.

Nanosymposium

106. Stroke Rehab and Imaging: Novel Approaches

Location: 147A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***106.01

**Topic: ***C.08.Stroke

Support: NIH K24HD074722
NIH T32AR047752

Title: Application of neuroimaging in early stroke for motor recovery prediction

Authors: *J. M. CASSIDY[1], S. C. CRAMER[1,2,3,4]
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Abstract: OBJECTIVE: Neuroimaging studies have provided insights into stroke recovery, but clinical decision-making remains reliant on behavioral assessments. The primary aim of this project was to determine whether incorporating neuroimaging measurements in early stroke rehabilitation improved prediction of motor recovery. We hypothesized that functional sensorimotor network connectivity measurements would outperform behavioral measures for predicting motor recovery and, further, combining connectivity measurements with structural imaging would enhance prediction and complement behavioral assessment.
MATERIALS AND METHODS: In this ongoing study, 16 adults (12 males, 56.3±12.6 years, 11.8±6.3 days post-stroke, median NIH Stroke Scale [interquartile range]=3.5 [3-6]) admitted to an inpatient rehabilitation facility completed structural, diffusion-weighted, and resting-state functional imaging and a behavioral battery. Motor recovery was defined as Functional Independence Measurement motor (FIM-motor) score change from admission to discharge. Correlation coefficients were computed to identify the strongest bivariate relationships between FIM-motor and injury (corticospinal tract (CST) integrity, stroke volume, lesion overlap with CST) and behavior (baseline arm Fugl-Meyer (FM), grip and pinch strength). Simple and multivariate linear regression analyses were employed to determine the optimal combination of neuroimaging and behavior measurements for motor recovery prediction.
RESULTS: Connectivity between contralesional primary motor and sensory cortices explained 33% ($r=0.57$, $p=0.02$) of the variance in FIM-motor change. Results did not vary according to

age, baseline motor impairment (arm FM score), and time post-stroke. Behavior and injury measurements did not significantly predict variance in FIM-motor change in bivariate analyses; furthermore, adding these measurements to connectivity in multivariate analyses did not significantly ($p>0.05$) enhance prediction.
CONCLUSIONS: A functional connectivity measurement outperformed injury and behavioral measurements in the context of motor recovery prediction in early stroke. These findings support the incorporation of neuroimaging-based measures in a stroke rehabilitation environment to potentially improve clinical decision-making. Results also show that intrahemispheric connectivity involving contralesional sensorimotor regions play a valuable role in early motor recovery. These areas may serve as viable therapeutic targets in early stages of post-stroke recovery.

Disclosures: J.M. Cassidy: None. **S.C. Cramer:** F. Consulting Fees (e.g., advisory boards); Dart Neuroscience, Toyama, MicroTransponder.

Nanosymposium

106. Stroke Rehab and Imaging: Novel Approaches

Location: 147A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***106.02

**Topic: ***C.08.Stroke

Support: Medical Research Council: MR/K0336/1

Title: How does iReadMore therapy change the reading network of patients with central alexia?

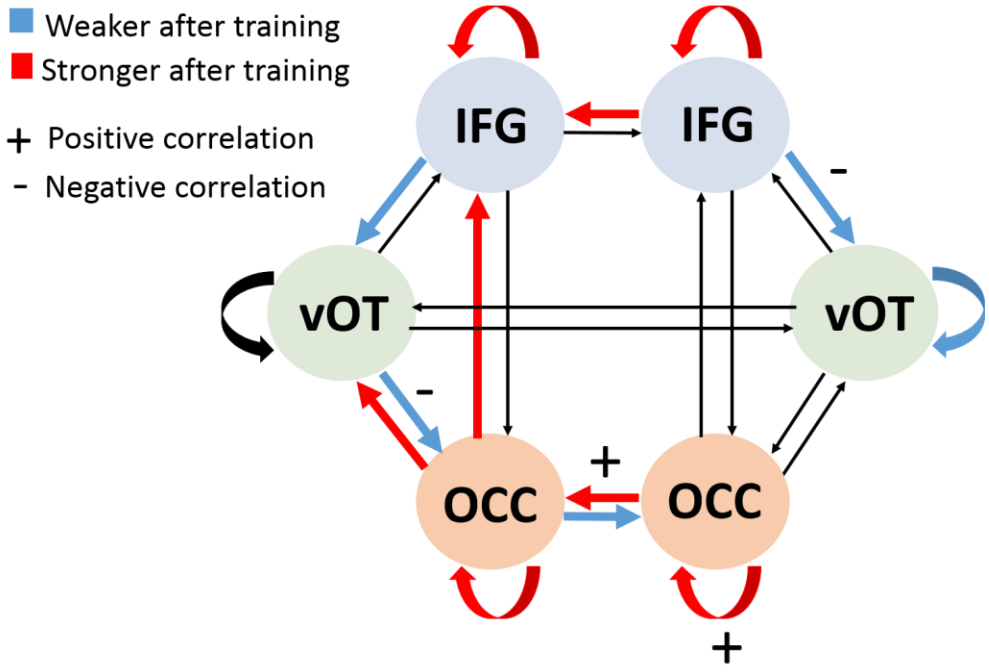
Authors: *S. KERRY[1], Z. V. J. WOODHEAD[2], O. M. AGUILAR[3], J. CRINION[4], W. PENNY[2], Y.-O. HOON[2], A. P. LEFF[1]
[2]Wellcome Trust Ctr. for Neuroimaging, [3]Dept. of Brain Repair and Rehabil., [1]Univ. Col. London, London, United Kingdom; [4]UCL, London, United Kingdom

Abstract: Introduction:
Central alexia is an acquired reading disorder co-occurring with a generalised language deficit (aphasia). We investigated the effects of iReadMore, a reading training App, on the reading network of patients with Central Alexia.
Methods:
23 patients with central alexia in the chronic post-stroke phase participated in the study. Participants completed a four week therapy block. They attended three 40 minute face-to-face sessions per week and completed a total of 35 hours of training at home. Before and after therapy, word reading accuracy for trained words and a matched list of untrained words was

assessed and an MEG scan was conducted where trained and untrained words were presented. Variational Bayes Equivalent Current Dipole source localisation identified subject specific dipoles in the following locations: left and right occipital regions (OCC), ventral occipitotemporal regions (vOT) and inferior frontal gyrus (IFG). Dynamic causal modelling estimated the modulation in effective connectivity for reading trained words after therapy compared to before therapy. A random effects Bayesian Model Averaging analysis was conducted to identify significantly modulated connection strengths.
The relationship between reading network modulation and percentage change in word reading accuracy was investigated using Automatic Linear Modelling.

Results and Discussion

Participants reading accuracy improved by on average 9.2%, Cohen's d =1.29 (large). Fig.1 displays significantly modulated connections for trained words after therapy. Connections with significant positive correlations ($p<0.05$) to reading accuracy improvement are marked with '+' and negative correlations are marked with '-'. Larger therapy gains were associated with greater strengthening of the right OCC self-connection and the lateral connection from right OCC to left OCC, suggesting that patients who processed the left-side (prefix) of words well and integrated this information across hemispheres did better than those who did not.



Disclosures: **S. Kerry:** None. **Z.V.J. Woodhead:** None. **O.M. Aguilar:** None. **J. Crinion:** None. **W. Penny:** None. **Y. Hoon:** None. **A.P. Leff:** None.

Nanosymposium

106. Stroke Rehab and Imaging: Novel Approaches

Location: 147A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***106.03

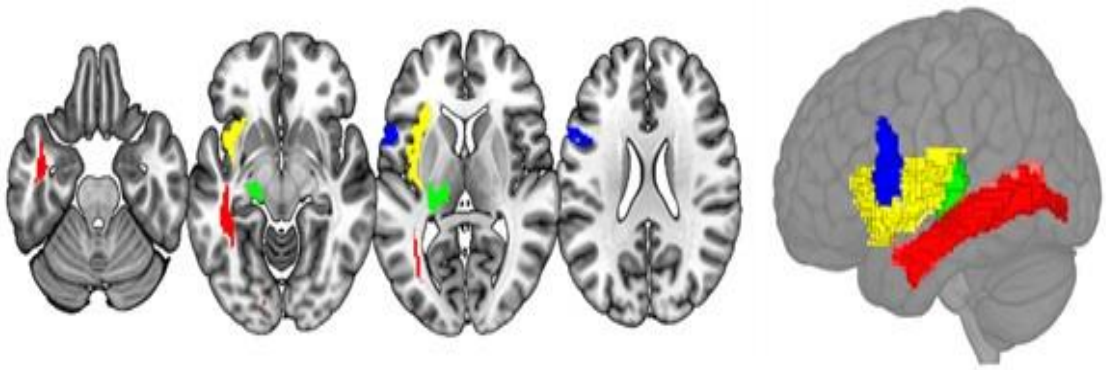
**Topic: ***C.08.Stroke

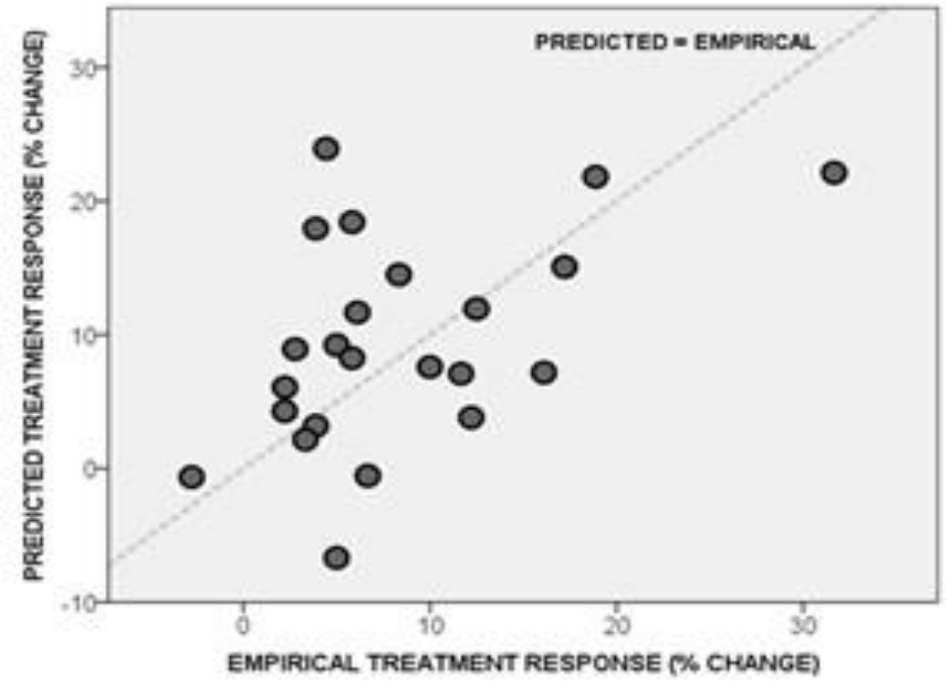
Support: Medical Reserach Council: MR/K022563/1

Title: Lesion site dependent treatment responses to speech and language therapy in stroke patients

Authors: T. HOPE[1], O. AGUILAR[1], S. KERRY[1], Y.-H. ONG[1], M. CALLAGHAN[1], J. CRINION[1], Z. WOODHEAD[3], *A. P. LEFF[2]
[1]Inst. of Neurol., [2]Univ. Col. London, London, United Kingdom; [3]Dept. of Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom

Abstract: Objective
Stroke survivors with aphasia are famously variable, encouraging the view that their recovery is too variable to be predicted. Here, we ask whether individual treatment responses might depend on the details of the brain damage that patients have suffered, and whether we can use that dependence to predict patients' responses to therapy.
Methods
We use pre-treatment patient data to explain and predict 23 stroke survivors' responses to a computerised therapeutic intervention for reading deficits (iReadMore). Our explanatory analysis distinguishes models driven by: (i) behavioural and demographic data; (ii) lesion location data (extracted from structural MRI); or (iii) all of the data together. Our predictive analysis uses nested cross-validation to assess whether we can predict new patients' responses to the treatment.
Results
Using the Akaike Information Criterion, we show that lesion location (Fig.1) explains more of the variance in patients' treatment responses than demographic and behavioural data, but that the best model includes all three data types. Pre-treatment data can also be used to predict new patients' treatment responses (Fig.2).
Interpretation
This is the first demonstration that responses to any therapeutic intervention for post-stroke aphasia are lesion-site-dependent, and that those treatment responses can in principle be predicted from pre-treatment data alone. We hope that results like this will drive personalised medicine for stroke survivors with aphasia.





Disclosures: **T. Hope:** None. **O. Aguilar:** None. **S. Kerry:** None. **Y. Ong:** None. **M. Callaghan:** None. **J. Crinion:** None. **Z. Woodhead:** None. **A.P. Leff:** None.

Nanosymposium

106. Stroke Rehab and Imaging: Novel Approaches

Location: 147A

Time: *Sunday, November 12, 2017, 8:00 AM - 11:00 AM

Presentation Number: *106.04

**Topic: ***C.08.Stroke

Support: NIDCD R0105375
NIDCD P50 014664

Title: Predicting recovery of acute post-stroke aphasia

Authors: *A. E. HILLIS[1], R. SEBASTIAN[1], B. BREINING[1], A. WRIGHT[1], S. SAXENA[2]
[1]Dept Neurol, Johns Hopkins Univ. Sch. Med., Baltimore, MD; [2]Dept Neurol, Sadhvi Saxena, Baltimore, MD

Abstract: Most studies of language recovery after stroke have evaluated people at different times post-stroke and identified variables associated with good versus poor recovery. There have been some longitudinal studies of aphasia recovery, but few have used advanced brain imaging, and no longitudinal studies have evaluated the influence of medications.

Methods:

We studied 31 patients from the first 48 hours after stroke, 1 month, and 6 months on picture descriptions (quantitatively analyzed for Content Units (CU; mentioned by normal controls in describing the picture) and the Boston Naming Test (BNT). Patients had structural and functional MRI at each time point. We evaluated associations between improvement (measured by BNT and CU) and imaging variables and selective serotonin reuptake inhibitors (SSRIs). We then tested predictions from this set of patients in a separate set of 42 patients with chronic stroke, with logistic regression and t-tests.

Results

The only regions where damage was associated with the degree of naming recovery were left superior longitudinal fasciculus (SLF) and posterior superior temporal gyrus (pSTG), after controlling for lesion volume. Changes in activation patterns associated with naming differed across patients, even with similar lesions. Good recovery was associated with increased balance of activity across pSTG, inferior frontal gyrus, and angular gyrus bilaterally in patients without damage to these key areas.

SSRI use during the first 3 months after stroke was associated with greater naming improvement ($X^2 = 6.30$; $p=0.012$) and greater improvement in picture description content ($X^2 = 6.92$; $p= 0.009$) (after correcting for initial severity for both), even though patients taking SSRIs were nonsignificantly *more* depressed.

In the independent group of patients with chronic stroke, we confirmed that damage to pSTG and/or SLF was associated with failure to recover naming ($X^2=24.2$; $p<0.0001$). Damage to pSTG/SLF was associated with lower odds of achieving highest quartile of object naming, after controlling for lesion volume and months since onset (OR:0.034; CI 0.0033-0.35; $p=0.005$). We also confirmed that among those with pSTG/SLF lesions, SSRIs users showed better recovery in object naming than non-users (45.5 vs. 83.5% correct; $t=2.0$; $p=0.029$). Those without pSTG/SLF lesions showed excellent naming recovery with or without SSRIs (99.7 vs 99.3% correct).

Conclusions

Preliminary data indicate that language recovery is influenced by lesion location and SSRI use.

Larger studies are needed to determine the extent to which they prospectively predict recovery by a particular time point.

Disclosures: A.E. Hillis: None. **R. Sebastian:** None. **B. Breining:** None. **A. Wright:** None. **S. Saxena:** None.

Nanosymposium

106. Stroke Rehab and Imaging: Novel Approaches

Location: 147A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***106.05

**Topic: ***C.08.Stroke

Support: Guarantors of Brain
NIHR Professorship

Title: Targeted treatment for cognitive impairments following traumatic brain injury with methylphenidate

Authors: *P. O. JENKINS, N. BOURKE, S. DE SIMONI, J. H. COLE, D. J. SHARP
Computational, Cognitive and Clin. Neuroimaging Lab., Imperial Col., London, United Kingdom

Abstract: *Background.* Cognitive problems following traumatic brain injury (TBI) are common. The heterogeneous nature of TBI means that the basis of these cognitive deficits is likely to be multi-factorial. Previous studies show dopaminergic dysfunction following TBI. Drugs that increase dopamine in the brain, such as methylphenidate, are sometimes used to enhance cognition after TBI. The response to treatment, however, can be highly variable between patients. Therefore, what is needed is a way to target the use of these drugs to patients who are likely to respond.
Objective. To investigate whether: 1) treatment with methylphenidate improves cognition following traumatic brain injury; 2) brain dopamine levels predict the magnitude of any improvement in symptoms.
Methods. 40 moderate-severe TBI patients with persistent cognitive impairments were randomized into a double-blind, placebo controlled, crossover design study. They received a baseline ^{123}I ioflupane SPECT scan (DaTscan), detailed magnetic resonance imaging (MRI) assessment and neuropsychological testing. Patients received 0.3mg/kg of methylphenidate twice a day and placebo in two two-week blocks. Subjects completed daily cognitive testing during the treatment trial and had an MRI and neuropsychological assessment at the end of each two-week block. The primary outcome measure was the change in reaction time on the choice reaction time

task produced by methylphenidate treatment and its relationship to specific binding ratio of the dopamine transporter in the striatum.
Results. Dopaminergic abnormalities were common after TBI. Abnormalities were most consistently seen in the caudate and related to damage in the nigrostriatal system. Methylphenidate did not improve reaction times compared to placebo across the whole patient group, although patients did report subjective improvements in fatigue and apathy. However, patients with low ^{123}I ioflupane SPECT binding showed a significant improvement in their reaction times on methylphenidate in contrast to patients with normal scans (~5% improvement vs. ~0.5% deterioration).
Conclusions. In patients who have suffered a moderate-severe traumatic injury and have persistent cognitive problems, ^{123}I ioflupane SPECT scanning predicts response to treatment with methylphenidate.

Disclosures: P.O. Jenkins: None. **N. Bourke:** None. **S. De Simoni:** None. **J.H. Cole:** None. **D.J. Sharp:** None.

Nanosymposium

106. Stroke Rehab and Imaging: Novel Approaches

Location: 147A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***106.06

**Topic: ***C.08.Stroke

Support: Canadian Institutes of Health Research MOP 133460
Canadian Institutes of Health Research, Strategic Training Program in Vascular Research

Title: Sox9 knockout mice have improved recovery and increased reparative sprouting following stroke

Authors: *A. BROWN, X. XU, B. BASS, W. M. MCKILLOP, J. MAILLOUX, T. LIU, N. M. GEREMIA, T. HRYCIW
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Abstract: The partial recovery that can occur after a stroke has been attributed to structural and functional plasticity that compensate for damage and lost functions. This plasticity is thought to be limited in part by the presence of growth inhibitors in the central nervous system. Blocking or reducing signals from inhibitors of axonal sprouting such as Nogo and chondroitin sulfate proteoglycans (CSPGs) increases post-stroke axonal sprouting and improves recovery. We previously identified the transcription factor SOX9 as a key up-regulator of CSPG production

and demonstrated that conditional *Sox9* ablation leads to increased axonal sprouting and improved recovery after spinal cord injury. In the present study we evaluate the effect of conditional *Sox9* ablation in a transient middle cerebral artery occlusion (MCAO) model of stroke. We demonstrate that conditional *Sox9* ablation leads to reduced CSPG levels and improved post-stroke neurological recovery. Anterograde tract tracing studies demonstrate that in the *Sox9* conditional knockout mice corticorubral and corticospinal projections from the contralateral, uninjured cortex increase projections to targets in the midbrain and spinal cord denervated by the injury. These results suggest that targeting SOX9 is a viable strategy to promote reparative axonal sprouting and neurological recovery after stroke.

Disclosures: A. Brown: None. **X. Xu:** None. **B. Bass:** None. **W.M. McKillop:** None. **J. Mailloux:** None. **T. Liu:** None. **N.M. Geremia:** None. **T. Hryciw:** None.

Nanosymposium

106. Stroke Rehab and Imaging: Novel Approaches

Location: 147A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***106.07

**Topic: ***C.08.Stroke

Title: Glial enriched progenitors : A novel cell-based therapeutic for white matter stroke

Authors: *I. L. LLORENTE[1], W. E. LOWRY[2], S. T. CARMICHAEL[3]
[1]Neurol., Univ. of California , Los Angeles, Los Angeles, CA; [2]Dept. of Molecular, Cell and Developmental Biol., [3]Neurol., UCLA, Los Angeles, CA

Abstract: White matter stroke (WMS) occurs in deep penetrating blood vessels in the brain and includes a spectrum of diseases from small infarcts to more diffuse areas of damage. Subcortical WMS constitutes up to 30% of all stroke subtypes. There have been no studies of specific cell transplant in neural repair in WMS. Because of the different cellular constituents of white matter, WMS, unlike large artery stroke, damages primarily astrocytes, axons, oligodendrocytes, and myelin we hypothesized that a more astrocyte-based therapy is ideally suited for brain repair after WMS.
Brief changes in oxygen tension permanently alter the fate commitment of induced pluripotent stem (iPS) cells. This effect is mediated by hypoxia-inducible factor 1, and can be mimicked by prolyl hydroxylase inhibition, such as with deferoxamine (DFX). Brief treatment of iPS-neural progenitor cells (iPS-NPCs) with DFX permanently biases differentiation so that a substantial percentage of cells differentiate into astrocytes. This process allows rapid and efficient production of a new astrocyte-based line of iPS glial enriched progenitors (iPS-GEPs), ideally suited for brain repair after WMS that allows scaling of this process for a clinical application.

In this study, IPS-GEPs were tested in a model of subcortical white matter stroke that mimics aspects of vascular dementia. These cells were transplanted at a late or subacute stage after the infarct. iPS-GEPs migrate widely in the injured brain and stimulate OPC proliferation and differentiation, myelination of damaged brain tissue and the formation of cortical connections after stroke. iPS-GEPs promote recovery of neurological deficits in white matter stroke. Importantly, this recovery is more substantial and complete compared to other iPS cells types, including the parent line for iPS-GEPs.

Disclosures: I.L. Llorente: None. **W.E. Lowry:** None. **S.T. Carmichael:** None.

Nanosymposium

106. Stroke Rehab and Imaging: Novel Approaches

Location: 147A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***106.08

**Topic: ***C.08.Stroke

Support: R01NS08226

Title: ECM hydrogel injection for the treatment of stroke

Authors: *M. M. MODO[1], H. GHUMAN[2], M. GERWIG[2], F. NICHOLLS[2], J. LIU[2], J. DONNELLI[2], B. WAHLBERG[2], S. BADYLAK[2]
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Abstract: Stroke is the leading cause of adult disability and a significant effort is underway to develop therapies to repair the damaged tissue. A key challenge in treating chronic stroke is the dramatic loss of brain tissue, and the formation of a cavity filled with extracellular fluid (ECF). Biomaterials composed of mammalian ECM promote constructive tissue remodeling with minimal scar formation in peripheral tissue and organs. However, the biodegradation and functional effect of injecting a large volume of ECM hydrogel into the brain are unknown. The current study therefore aimed to determine if biodegradation occurs and if ECM remodeling will affect the behavioral deficits of animals with stroke damage. At an 8 mg/mL concentration, ECM hydrogel has rheological properties similar to brain tissue. It can be formulated in a fluid phase at room temperature, while forming hydrogels at body temperature. Two weeks post-stroke, Magnetic Resonance Imaging-defined lesion volume equivalents of ECM was injected into the lesion cavity of stroke rats. A battery of behavioral tests including Grip Strength, Bilateral Asymmetry Test (BAT), Footfault, and Rotameter were performed at pre-treatment, 1, 4, and 12 weeks post-treatment for control (n=14), untreated (n=11) and ECM-treated (n=11) groups. Retention, gelation, and biodegradation of the ECM, as well as host cell invasion and phenotype

were analyzed at 12 weeks post-injection using immunohistochemistry. Behavioral tests indicated a functional impairment that was not affected by the injection of a large volume of ECM into the cavity. ECM showed a robust gelation and retention in the lesion cavity with a 30% decrease in volume over 12 weeks. A significant host cell invasion into the ECM hydrogel was seen, with an average of 72,000 cells present within the hydrogel. This characterization demonstrates that an ECM hydrogel can be readily injected and retained within the lesion cavity, while promoting an acute endogenous repair response, without deleterious effects. A time course study with varying ECM concentrations is necessary to determine the optimal rate of in vivo biodegradation to further improve the endogenous repair processes.

Disclosures: **M.M. Modo:** None. **H. Ghuman:** None. **M. Gerwig:** None. **F. Nicholls:** None. **J. Liu:** None. **J. Donnelli:** None. **B. Wahlberg:** None. **S. Badylak:** None.

Nanosymposium

106. Stroke Rehab and Imaging: Novel Approaches

Location: 147A

Time: *Sunday, November 12, 2017, 8:00 AM - 11:00 AM

Presentation Number: *106.09

Topic: *C.08.Stroke

Support: PS15/01318
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Title: Emerging potential of exosomes for treatment of neurological diseases

Authors: ***M. GUTIERREZ FERNANDEZ**, L. OTERO ORTEGA, F. LASO GARCÍA, M. GOMEZ DE FRUTOS, A. MARTINEZ ARROYO, E. DIEZ TEJEDOR
LA PAZ UNIVERSITY HOSPITAL, Madrid, Spain

Abstract: Mesenchymal stem cells have previously been shown to mediate brain repair after stroke; they secrete 50-100 nm complexes called exosomes that store within themselves multivesicular bodies (DNA, RNA, proteins and lipids) and information on their various biological functions and their cell type-specific molecular composition. They are widely distributed in serum, urine, saliva and other biological fluids. As important transfer vectors for intercellular communication and genetic material, exosomes can stimulate target exerting their biological functions and might be responsible for the long-distance effects of stem cell therapy. In particular, exosomes induce long-term brain protection, promote gray matter repair and neurological recovery, and modulate peripheral post-stroke immune response. Previous studies

from our group have demonstrated that exosomes derived from mesenchymal stem cells are a therapeutic strategy to repair white matter damage after neurological disorders. After intravenous infusion, exosomes were found in the brain and in the peripheral organs (liver, lung and spleen). After exosomes treatment, the animals showed improved functional recovery and increased axonal sprouting, oligodendrocyte-associated marker expression and myelin formation, white matter thickness (width, breadth, depth) and restoration of tract connectivity. Proteomics analysis of the exosomes identified 2416 proteins that are implicated in brain repair function. Although several studies show that exosomes are effective as a treatment for experimental animal models central nervous system diseases, any study has currently tested dose escalation. Thus, in our laboratory, we have studied the minimum effective dose of exosomes that does not cause adverse effects for the treatment of stroke in animal experimental models. Preclinical studies suggest a therapeutic role of exosomes administration which appear to be as effective as cell therapy.

Disclosures: M. Gutierrez Fernandez: None. **L. Otero ortega:** None. **F. Laso garcía:** None. **M. Gomez de frutos:** None. **A. Martinez arroyo:** None. **E. Diez tejedor:** None.

Nanosymposium

106. Stroke Rehab and Imaging: Novel Approaches

Location: 147A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***106.10

**Topic: ***C.08.Stroke

Support: CIRM Grant SP3A-07552

Title: ESC-derived oligodendrocyte progenitor cells (AST-OPC1): Clinical update and preclinical progress in cervical spinal cord injury

Authors: *N. C. MANLEY[1], C. C. CASE[1], E. D. WIRTH, III[2], J. S. LEBKOWSKI[1]
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Abstract: AST-OPC1 is a population of early-stage oligodendrocyte progenitor cells (OPCs) that is differentiated from human embryonic stem cells (hESCs) using the H1 cell line. The AST-OPC1 differentiation process is commercially scalable, compatible with current Good Manufacturing Practices (cGMP), and the resulting OPC population has been approved by the U.S. FDA for early Phase clinical testing in spinal cord injury (SCI).
Studies of AST-OPC1 in rodent models of SCI provide evidence of its therapeutic benefit when transplanted directly into the injured spinal cord approximately 1 week after injury and have indicated that AST-OPC1 can act via multiple therapeutic mechanisms to promote CNS repair and augment functional recovery. In this presentation, we will discuss recent preclinical studies

that explore AST-OPC1's cellular composition, potency, and multi-faceted mechanisms of action. An update on the ongoing cervical SCI clinical trial will be provided, and future directions of this candidate cell therapy will be discussed.

Disclosures: N.C. Manley: A. Employment/Salary (full or part-time):; Asterias Biotherapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asterias Biotherapeutics. **C.C. Case:** A. Employment/Salary (full or part-time):; Asterias Biotherapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asterias Biotherapeutics. **E.D. Wirth:** A. Employment/Salary (full or part-time):; Asterias Biotherapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asterias Biotherapeutics. **J.S. Lebkowski:** A. Employment/Salary (full or part-time):; Asterias Biotherapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asterias Biotherapeutics.

Nanosymposium

106. Stroke Rehab and Imaging: Novel Approaches

Location: 147A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***106.11

**Topic: ***C.08.Stroke

Title: Human iPS-derived interneurons enhance functional recovery after cortical stroke

Authors: *J. A. MAZZITELLI[1], I. L. LLORENTE[1], E. SIDERIS[2], T. SEGURA[2], W. E. LOWRY[3], S. T. CARMICHAEL[1]
[1]Neurol., [2]Chem. and Biomolecular Engin., [3]Molecular, Cell, and Developmental Biol., UCLA, Los Angeles, CA

Abstract: Stroke is the leading cause of adult disability. There are no therapies that promote recovery in the disease. Cell transplantation in cortical stroke has utilized neural progenitors in early differentiation stages; however, these have often shown poor survival, migration, and differentiation after transplant. The present studies develop a different paradigm of cell transplantation in cortical stroke by using iPS-interneurons. Interneuron transplantation in diseases other than stroke shows that these cells survive in hostile brain environments, migrate widely within the adult CNS, and integrate into the adult brain circuitry. iPS-interneurons were produced using small molecule inhibitors of Wnt, TGF-beta, and BMP, and are therefore termed iPS-3i. The iPS-3i cells progress through a molecular expression pattern resembling median

ganglionic eminence (MGE) cells. iPS-interneurons were transplanted into the stroke cavity with a hyaluronan (HA) hydrogel containing clustered vascular endothelial growth factor (VEGF) immobilized on heparin nanocapsules to reduce transplant stress from the direct transplantation into the stroke cavity. Transplants were done at either the subacute or chronic stage after cortical stroke (7 days vs 1 month after stroke). In order to assess motor deficit and recovery after stroke, gridwalking and pasta handling tasks were performed. We report significant behavioral recovery in mice suffering from motor cortex stroke when the HA-hydrogel+ VEGF nanoparticles, and iPS-3i are injected simultaneously into the stroke core. Confocal images of ipsilateral tissue show concurrent structural changes while electrophysiological recordings demonstrate integration of iPS-3i into pre-existing circuitry. Notably, these results are seen when treatment is administered in either the sub-acute or chronic stage of stroke. Overall findings provide promising evidence of a stem cell treatment for stroke unique to the subtype iPS-3i. Supported by CIRM DISC1-08723.

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Nanosymposium

106. Stroke Rehab and Imaging: Novel Approaches

Location: 147A

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Presentation Number: *106.12

Topic: *C.08.Stroke

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NYSTEM
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Junior 1 Career Award

Title: Human embryonic stem cell-derived oligodendrocyte progenitors remyelinate the brain and rescue behavioral deficits following radiation

Authors: ***J. PIAO**[1], T. MAJOR[1], G. AUYEUNG[1], E. POLICARPIO[1], J. MENON[1], L. DROMS[1], P. GUTIN[1], K. URYU[2], J. TCHIEU[3], D. SOULET[4], V. TABAR[1]
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Abstract: Radiation therapy to the brain and chemotherapy are powerful tools in the management of many cancers, but they are both associated with significant and irreversible cognitive decline, and other neurological manifestations. There are currently no therapies available to either reverse or reduce these symptoms. Data from our group and others demonstrate that the oligodendrocyte progenitor population (OPC) in the brain is vulnerable to radiation injury. At therapeutic doses, the OPCs are depleted over several months, followed by a progressive and diffuse demyelination, associated with behavioral changes. We have also developed a protocol to differentiate human ES or iPS cells into OPCs. The human OPCs were fully characterized by morphology, immunohistochemistry and transcriptomal profile. We then performed a series of experiments to determine the capacity of the OPCs to migrate, differentiate and remyelinate injured areas within the brain as well as ameliorate behavior. Four-week old rats received whole brain radiation at 50 Gy in 10 fractions. Tissue analysis showed depletion of OPCs ($O4^+$, $Olig2^+$) followed by diffuse demyelination along the major white matter pathways including the corpus callosum and the cerebellum. We then subjected human ESCs to our neural induction protocol, based on dual Smad inhibition and exposure to sonic hedgehog. From day 40, the cells were exposed to PDGFα, IGF-1, cAMP, T3 to promote OPC differentiation. Early OPCs (characterized by NKx2.2/Olig2/PDGFRα/Sox10 expression) emerged by day 45. Late OPCs ($O4^+$) appeared on day 50 and increased to ~35% on day 100. $O4^+$ cells (enriched by FACS) were capable of maturation and myelination of axons of human neurons in vitro. Upon transplantation into the irradiated rat brain, the human OPCs migrated widely throughout the brain and achieved remyelination of axons, as well as restoring of the total number of $Olig2^+$ cells in the corpus callosum. Behavioral testing also showed complete recovery of cognitive function while additional recovery from motor deficits required concomitant transplantation in the corpus callosum and the cerebellum. There were no teratomas, tumors, or overgrowth in any of the animals tested. In conclusion, human OPCs could be efficiently differentiated and enriched from hESCs, resulting in both structural and functional repair in vivo. The ability to repair radiation-induced damage to the brain could dramatically improve the outlook for cancer survivors and enable more effective use of radiation therapy, especially in young patients. The development of a cell therapy strategy to restore chemotherapy injury to the brain is currently under investigation in our lab.

Disclosures: **J. Piao:** None. **T. Major:** None. **G. Auyeung:** None. **E. Policarpio:** None. **J. Menon:** None. **L. Droms:** None. **P. Gutin:** None. **K. Uryu:** None. **J. Tchieu:** None. **D. Soulet:** None. **V. Tabar:** None.

Nanosymposium

107. Brain Injury: Cellular and Molecular Mechanisms

Location: 156

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***107.01

**Topic: ***C.09. Brain Injury and Trauma

Support: R37HD059288
T32HL007713-23

Title: Hippocampal network changes during spatial object recognition task performance after mild traumatic brain injury

Authors: *A. S. COHEN[1], B. JOHNSON[1], H. METHENY[1], J. F. BURKE[2], G. XIONG[1], R. PATERNO[3]
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Abstract: Traumatic brain injury (TBI) is the primary cause of death and disability in children and young adults. TBI causes substantial cognitive impairments such as learning and memory alteration and sleep disorder in humans. Memory is a dynamic neural and cognitive progression characterized by three separate processes: encoding, maintenance and retrieval. These processes are theoretically independent and have different electrophysiological signatures. Previous research has demonstrated that TBI preferentially leads to hippocampal damage in both the human condition and rodent models of TBI leading to an established overall deficit in certain types of memory. However, it is not known which memory component (encoding, maintenance or retrieval) is affected after mild TBI. Here we used an established animal model of TBI - lateral fluid percussion injury (LFPI) to establish which phase of spatial episodic memory is affected with a circuit-level physiological approach. Male C57BL/6J were used to assess spatial memory performance at 7 and 16 post-injury days. Mild TBI mice exhibit impaired spatial performance as expected. In this study, we additionally investigated electrophysiological alterations in hippocampal activity *in vivo*, using tetrodes located in area CA1 and CA3. In a separate cohort of sham and TBI animals we used 32-channel silicone probes with recording electrodes distributed across different regions of the hippocampus (area CA1, CA3 and DG) while the animals perform the spatial memory task. Specifically, we recorded local field potential across the entire hippocampus while the animals were in the home cage (often resting or sleeping) and while performing hippocampal-dependent memory task interspersed with rest sessions in the home cage. In this study, we found a multitude of spectral changes especially in the theta and gamma band that occurs after TBI. Furthermore, we found differential activity in CA1 versus CA3 in a

complex interaction depending on behavior performance between TBI animal versus Sham control group. Our approach highlights the potential to identify the network activity liking TBI, hippocampus and memory.

Disclosures: A.S. Cohen: None. **B. Johnson:** None. **H. Metheny:** None. **J.F. Burke:** None. **G. Xiong:** None. **R. Paterno:** None.

Nanosymposium

107. Brain Injury: Cellular and Molecular Mechanisms

Location: 156

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***107.02

**Topic: ***C.09. Brain Injury and Trauma

Support: R37 HD059288

Title: Electrophysiological properties of parvalbumin-expressing interneurons in the dentate gyrus after mild traumatic brain injury

Authors: *K. A. FOLWEILER[1,2], H. E. METHENY[2], A. S. COHEN[3,2]
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Abstract: Inhibitory interneurons and their functional integration into the network are thought to play a key role in regulation of cortical excitatory input to the dentate gyrus (DG). After traumatic brain injury, GABAergic inhibition is reduced onto dentate granule cells, and is associated with DG network hyperexcitability. Within the DG, parvalbumin-positive (PV+) interneurons (i.e., fast-spiking basket cells and axo-axonic cells) exert strong perisomatic inhibition onto dentate granule cells. While it is known that PV+ interneuron loss occurs after injury, it is unknown how the intrinsic and synaptic properties of the surviving DG PV+ population is affected. In this study, we examined both the intrinsic properties and excitatory synaptic input onto DG PV+ interneurons one week after lateral fluid percussion injury (LFPI) or sham surgery in transgenic mice expressing the fluorescent marker tdTomato in PV+ interneurons. Preliminary data from whole-cell patch clamp recordings reveal no change in the intrinsic membrane properties—including resting membrane potential, action potential threshold and input resistance—of PV+ interneurons after LFPI. However, voltage clamp recordings demonstrate a reduction in spontaneous and miniature EPSC frequency and amplitude in PV+ neurons from LFPI mice compared to sham controls. These findings suggest that while membrane excitability of PV+ interneurons is left intact after LFPI, excitatory drive onto this

inhibitory population may be diminished. Less excitatory activation of PV+ interneurons could provide a mechanism of reduced inhibition onto granule cells, and contribute to shifts in DG network excitability after injury.

Disclosures: K.A. Folweiler: None. **H.E. Metheny:** None. **A.S. Cohen:** None.

Nanosymposium

107. Brain Injury: Cellular and Molecular Mechanisms

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**Topic: ***C.09. Brain Injury and Trauma

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Title: The dynamics of structural changes after repeated mild TBI

Authors: A. KAMNAKSH[1], A. BADEA[2], R. J. ANDERSON[3], E. CALABRESE[4], J. LONG[5], *D. V. AGOSTON[6]
[1]Anatomy, Physiol. and Genet., The Uniformed Services Univ., Bethesda, MD; [2]Radiology, Duke Univ. Hosp., Durham, NC; [3]Radiology, Duke Univ. Med. Ctr., Durham, NC; [4]Duke Univ., Durham, NC; [5]WRAIR, Silver Spring, MD; [6]USUHS, B2036, Bethesda, MD

Abstract: A history of mild traumatic brain injury (mTBI), particularly repeated mTBI (rmTBI), has been identified as a risk factor for late-onset neurodegenerative conditions. Although civilian and military populations are equally affected, blast-induced rmTBI (rmbTBI) in young service members can have significant implications for force readiness and the military health care system. While the transient and mild nature of early neurobehavioral and cognitive symptoms impede the timely diagnosis in young soldiers exposed to blast, age-associated neurocognitive changes can confound the diagnosis of injury-induced neurodegeneration and its symptomatology in veterans. Therefore, we used DTI to quantify the extent and nature of rmbTBI-related pathology at 7 and 90 days post-injury, and its evolution between the two time points in young male rats. Animals were exposed to repeated mild blast overpressure (3 total; peak total pressure = 15.5-19.4 psi) or anesthetized as shams, and perfused and their brains imaged and analyzed. We found that total brain volumes were similar in injured and sham rats at 7 and 90 days. However, we detected local volume reductions 7 days post-injury, and more extensive changes at 90 days, in white matter tracts including the internal capsule (medial

longitudinal fasciculus) as well as in gray matter volumes of the olfactory, striatal, septal, thalamic and cerebellar areas. Among areas showing increased volume, the amygdala, an important substrate for anxiogenic behavior, was significantly enlarged at 90 days. DTI also detected changes in white matter microstructure, most notably a widespread increase in radial diffusivity 7 days post-injury, which largely subsided by 90 days. Conversely, differences in white matter integrity detected at 7 days persisted in injured rats as decreased fractional anisotropy at 90 days. Importantly, we found significant age by injury interactions on regional volumes and diffusion tensor parameters, indicating an altered ageing/developmental trajectory as result of injury. Our findings suggest that in addition to its direct short- and long-term effects on the brain, rmbTBI can adversely alter the course of late stage neurodevelopment at microstructural levels. If proven clinically, these findings can have short-term implications for force readiness and have long-term effects for the military health care system.

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Nanosymposium

107. Brain Injury: Cellular and Molecular Mechanisms

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**Topic: ***C.09. Brain Injury and Trauma

Support: Grant NS056202

Title: Mechanisms of recovery after targeted injury in neuronal islands

Authors: *M. F. ADEGOKE[1], D. F. MEANEY[2]
[1]Bioengineering, Univ. of Pennsylvania, Philadelphia, PA; [2]Bioengineering, Univ. Pennsylvania, Philadelphia, PA

Abstract: While allowing for detailed studies of the single-cell pathophysiology of neuronal injury, dissociated neuronal cultures do not accurately represent the modular structure of the brain. This is particularly important since studies of computational neuronal networks have shown differential susceptibility of specific nodes or network architectures to injury. In this study, we characterize network recovery after selective injury to individual nodes in neuronal systems of varying sizes *in vitro*. Multi-neuron isolated clusters of neurons (islands) ranging in size from 750 microns (um) to 1.4 mm (90 - 304 cells) were generated. At 13-15 days *in vitro* (DIV), a micro-injector device was used to selectively injure 10-30% randomly chosen neurons in islands, at a level of injury that does not cause cell death or island-wide activity collapse (Fig

1A). The genetically-encoded calcium indicator GCaMP6f was used to record neural activity at 4 timepoints: baseline, 0, 6 and 20 hours post-injury. We characterized single-cell Ca^{2+} transient rates before and after injury, and estimated functional connectivity among neurons using previously published methods. Neuronal islands ranged in activity pattern from non-synchronous events to full network coordinated bursts (1-5 events/min). On a single-cell basis, two characteristic neuronal populations emerged: (1) neurons with irregular activity in the 0.03-0.05 Hz range; (2) fast-pacing neurons with regular transients with a peak at 0.33 Hz in the frequency domain. At the 6 and 20 hour timepoints, the overall pattern of activity (non-synchronous vs bursting) was preserved and activity rates were not significantly different from baseline ($p > 0.5$) (Fig 1B). The proportion of fast-pacing neurons increased at 6 and 20 hours post-injury in islands with baseline non-synchronous activity, but not in islands that were bursting or in control dishes (Fig 1C). Taken together, these data suggest that activity state plays a role in the recovery after targeted injury, and prompts further investigation of the role of fast-pacing neurons in the process of recovery.

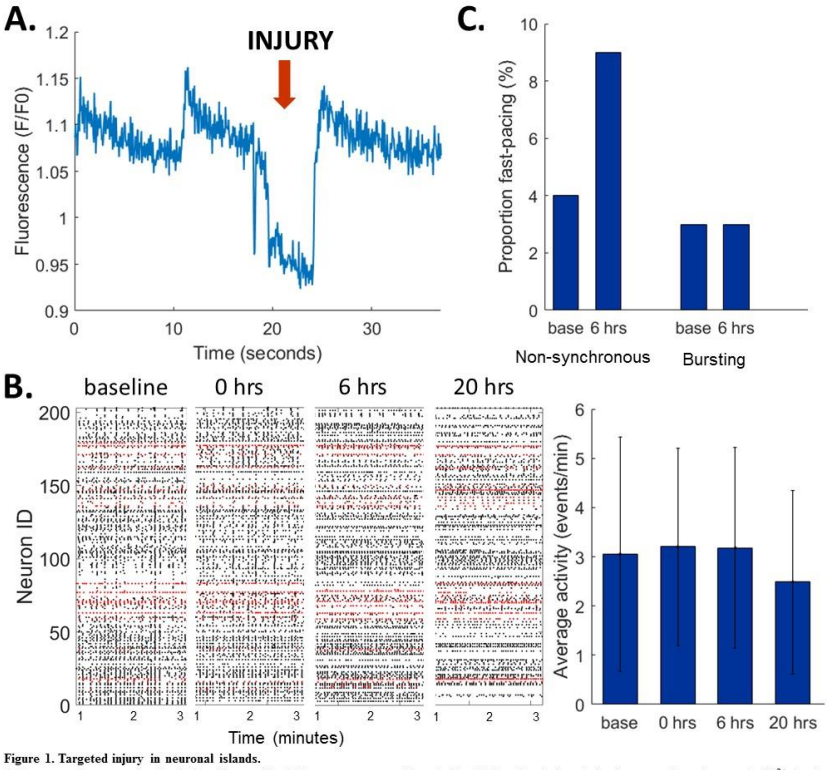

Figure 1. Targeted injury in neuronal islands.
A. Representative example of a single-cell normalized fluorescence trace. Injury is identified at the single-cell level as a transient decrease in Ca^{2+} signal. **B**. Representative raster plots of Ca^{2+} activity recorded for 3 minutes at baseline, immediately after, 6 and 20 hrs post-injury in one island show preservation of the activity pattern. Neurons that were injured are marked in red. Aggregate progression of the average number of events across all islands (n=6) also shows no significant change in the activity level after injury.
C. Aggregate change in the proportion of fast-pacing neurons in islands that had bursting (n=3) or non-synchronous (n=3) activity at baseline shows an increase in the ratio of fast-pacing neurons in injured non-synchronous islands.

Disclosures: M.F. Adegoke: None. **D.F. Meaney:** None.

Nanosymposium

107. Brain Injury: Cellular and Molecular Mechanisms

Location: 156

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***107.05

**Topic: ***C.09. Brain Injury and Trauma

Support: EY025622
R01NS094516

Title: Activation of PERK elicits memory impairment following TBI

Authors: *N. SEN, T. SEN
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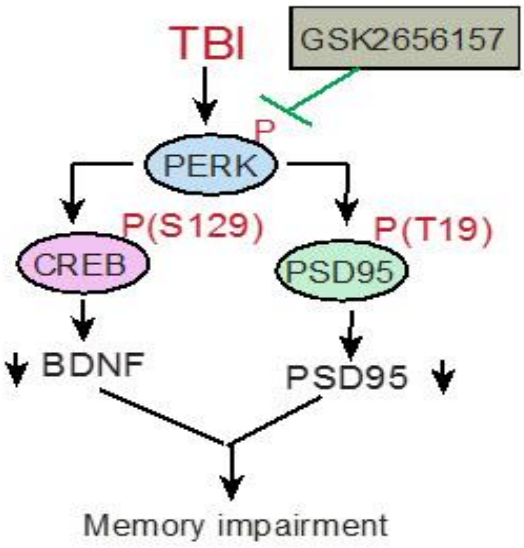
Abstract: The PKR-like ER kinase (PERK) a transmembrane protein resides in the endoplasmic reticulum (ER) and activation of PERK serve as a key sensor of ER-stress which has been implicated in Traumatic Brain Injury (TBI). The loss of memory is one of the most common symptoms following TBI; however, the precise role of PERK activation in memory impairment after TBI has not been well elucidated. Here we have shown that blocking the activation of PERK using GSK2656157 prevents the loss of dendritic spines and rescues memory deficits following TBI. To elucidate the molecular mechanism, we found that activated PERK directly phosphorylates CREB and PSD95 at S129 and T19 residues respectively. Phosphorylation of CREB protein prevents its interaction with a coactivator CBP and subsequently reduces BDNF level following TBI. On the other hand, phosphorylation of PSD95 leads to its downregulation in pericontusional cortex after TBI in male mice. Treatment with either GSK2656157 or overexpression of a kinase-dead mutant of PERK (PERK-K618A) rescues BDNF and PSD95 levels in the pericontusional cortex by reducing phosphorylation of CREB and PSD95 proteins following TBI. Similarly, administration of either GSK2656157 or overexpression of PERK-K618A in primary neurons rescues the loss of dendritic outgrowth and number of synapses after treatment with a PERK activator, tunicamycin. Thus, our study suggests that inhibition of PERK phosphorylation could be a potential therapeutic target to restore memory deficits following TBI.



Disclosures: **N. Sen:** None. **T. Sen:** None.

Nanosymposium

107. Brain Injury: Cellular and Molecular Mechanisms

Location: 156

Time: *Sunday, November 12, 2017, 8:00 AM - 10:45 AM

Presentation Number: *107.06

Topic: *C.09. Brain Injury and Trauma

Title: Glycyrrhizin reduces neuroinflammation acutely after paediatric traumatic brain injury

Authors: K. M. WEBSTER[1], M. SUN[3], T. J. O'BRIEN[5], *S. R. SHULTZ[2], B. D. SEMPLE[4]
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Abstract: Traumatic brain injury (TBI) is a leading cause of mortality and morbidity for children. Recent research suggests that children may be more vulnerable to poor outcomes after paediatric TBI (pTBI) compared to adults. One of the major initiators and recruiters of the inflammatory cascade, high mobility group box protein 1 (HMGB1) is associated with worsened outcomes after TBI in young patients. Glycyrrhizin (Gly) is a natural extract from liquorice root

shown to inhibit HMGB1 after adult TBI but has never been investigated after pTBI, after which the inflammatory response is heightened. This study therefore aims to investigate the acute effects of Gly on the inflammatory cascade after pTBI. Male and female C57Bl/6 mice at postnatal day 21 were subjected to an experimental model of moderate-severe controlled cortical impact injury and randomly assigned to three treatment groups: pre-treated Gly (1 h prior to injury then 1, 6, 24, 48 and 72 h post-injury, 50mg/kg i.p.), post-treated Gly (post-injury treatment only) or vehicle. Focal brain tissue was collected at day 3 for western blot and oedema analysis, and perfused brains were taken for immunofluorescence analysis of inflammatory factors. Gly treatment was found to only reduce HMGB1 expression and oedema when administered prior to injury. This suggests that the mechanism by which HMGB1 can affect the brain after pTBI occurs earlier than 1h post injury. This is in contrast to the anti-inflammatory effect of Gly afforded by treatment starting post-injury in adult experimental TBI models. These findings suggest that the expression, time course or role of HMGB1 may differ after TBI in the paediatric compared to adult brain.

Disclosures: K.M. Webster: None. **M. Sun:** None. **T.J. O'Brien:** None. **S.R. Shultz:** None. **B.D. Semple:** None.

Nanosymposium

107. Brain Injury: Cellular and Molecular Mechanisms

Location: 156

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***107.07

**Topic: ***C.09. Brain Injury and Trauma

Support: EraNet Neuron CNSAflame
TRAIL-ANR

Title: Intracorical blood-vessel and MRI alterations after juvenile closed head injury

Authors: *J. BADAUT[1,2], A. ICHKOVA, Ms[1], G. COUTRAND[1], S. S. BERTRAND[1], B. RODRIGUEZ-GRANDE[1], A. OBENAUS[3,4]
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Abstract: Vascular dysfunction is observed after pediatric traumatic brain injury (TBI) and predicts poor outcome on the long term. In this study we investigated intracortical blood-vessel changes after injury in a new mouse model of pediatric TBI, **CHILD - C**losed-**H**ead **I**njury with **L**ongterm **D**isorders. **CHILD** uses an electromagnetic impactor to induce TBI in post-natal day 17 mice. Blood-brain barrier (BBB) permeability, using immunoglobulin G (IgG) extravasation,

showed increased BBB permeability in **CHILD** mice only at 1 day post-TBI. Moreover tomato-lectin labeling exhibited morphological changes in the blood vessels with smaller diameters at 1 day but larger diameters at 7 days post-TBI compared to shams. BBB changes were associated with increased MRI T2 signals in the ipsi and contralateral cortex at 1 day but resolved by 7 days. Vascular reactivity of the intraparenchymal blood vessels was measured in acute brain slices from the ipsilateral cortex at 1, 3 and 7 days post-TBI by application of the thromboxane A2 receptor (TXA2R) agonist U46619 (vasoconstrictor) and N-Methyl-D-Aspartate, NMDA (vasodilator). At 1 day post-TBI, the intracortical blood vessels in the **CHILD** group are 20% more constricted after a 10 minute application of U46619 and then had reduced vasodilation after NMDA application compared to the shams. However at day 3 post-TBI, the blood vessels in **CHILD** mice showed a decreased of constriction by 22% less than the vessels in the shams after 15 minutes of U46619 application and had greater vasodilation after NMDA. These vascular reactivity changes were not associated with different expression of TXA2Rs or α-smooth muscle actin in the ipsilateral cortex as measured by Western blot. Importantly, **CHILD** mice also exhibited significant increase of anxiety at 1 and 3 days post-TBI using an open field test. Therefore, the vascular alterations in the acute phase after TBI may contribute to post-injury behavioral deficits.

Disclosures: J. Badaut: None. **A. Ichkova:** None. **G. Coutrand:** None. **S.S. Bertrand:** None. **B. Rodriguez-Grande:** None. **A. Obenaus:** None.

Nanosymposium

107. Brain Injury: Cellular and Molecular Mechanisms

Location: 156

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***107.08

**Topic: ***C.09. Brain Injury and Trauma

Title: Traumatic brain injury impairs central metabolic function and increases the vulnerability to ischemic cell death

Authors: *Z. M. WEIL, S. NICHOLSON, N. ZHANG, K. KARELINA, A. C. DEVRIES
Neurosci., Ohio State Univ. Med. Ctr., Columbus, OH

Abstract: Traumatic brain injury (TBI) is an independent risk factor for ischemic and hemorrhagic stroke in both men and women. Furthermore, TBI survivors who subsequently have a stroke have increased likelihood of morbidity and mortality, suggesting that TBI also increases stroke-related brain damage. The physiological mechanisms through which TBI alters stroke vulnerability are unknown, however, understanding the relationship between TBI and stroke is the critical first step in preventing stroke, and in turn promoting the fullest possible recovery

among TBI patients. One critical component of TBI pathophysiology is central metabolic dysfunction. Shortly after a TBI, the brain enters a period of hyperglycolysis, in which glucose utilization increases to meet the metabolic demands associated with recovery from the insult, followed by a prolonged period of metabolic depression. In addition to derangements in glucose metabolism, TBI is associated with impairments in central mitochondrial physiology and resistance to insulin signaling. This period of depressed metabolic physiology is associated with increased vulnerability to the damaging effects of a subsequent brain injury; ergo, even a mild injury, with its associated metabolic costs, if it occurs during the period of metabolic dysfunction, can have severe and long-lasting consequences. In order to test whether TBI-induced metabolic dysfunction would alter stroke outcomes, we performed mild, closed-head, midline TBI on adult male mice (or a non-injury control procedure). One-week later mice underwent 60 min right middle cerebral artery occlusion (MCAO) or the sham procedure; we intentionally chose a short duration MCAO that would produce less than 10% core infarct in otherwise healthy mice. Twenty-four hours later mice were tested in the corner and cylinder tests and then euthanized to assess infarct size. TBI, one week prior to stroke, greatly increased ischemic cell death, edema, and functional deficits Critically, there were no behavioral changes induced by TBI alone, indicating that TBI induces vulnerability to ischemic damage without directly impairing behavioral outcomes. Further, TBI alone produces mild bilateral axonal degeneration and microglial activation. However, when MCAO occurs in mice that had already experienced a TBI there was much greater axonal degeneration and microglial reactivity. These data suggest that TBI significantly increases tissue vulnerability to ischemic damage and indicate that stroke prevention is of paramount importance in the TBI patient population.

Disclosures: Z.M. Weil: None. **S. Nicholson:** None. **N. Zhang:** None. **K. Karelina:** None. **A.C. DeVries:** None.

Nanosymposium

107. Brain Injury: Cellular and Molecular Mechanisms

Location: 156

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***107.09

**Topic: ***C.09. Brain Injury and Trauma

Support: Boston Children's Hospital Translational Research Program
NIH-R01: PI - Alexander Rotenberg

Title: Natural History and rescue of astrocyte glutamate transporter GLT-1 expression after traumatic brain injury

Authors: *M. Q. HAMEED, H. H. LEE, P. A. ROSENBERG, T. K. HENSCH, A. ROTENBERG
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Abstract: Introduction: Excess accumulation of extracellular glutamate after traumatic brain injury (TBI) contributes to excitotoxic cell death and post-traumatic neurologic symptoms such as epilepsy. Glutamate transport, the major mechanism of extracellular glutamate clearance, is mediated in the CNS largely by the astrocyte glutamate transporter GLT-1, expression of which is depressed by TBI. Notably, the duration of post-TBI GLT-1 depression, which identifies a plausible therapeutic window, is not known. Also, whether changes in expression of GLT-1 after TBI are reflected similarly at the mRNA and protein level is not clear. We tested here whether decreased cortical GLT-1 expression post-TBI is detectable by immunohistochemistry (IHC) and PCR. We also studied the natural history of change in GLT-1 mRNA expression in the weeks following TBI, and tested whether GLT-1 expression is durably restored by ceftriaxone (Cef) treatment.
Methods: Anesthetized male SD rats (12-14 w) were exposed to sham or true rapid epidural fluid percussion injury (REFP, 4.45 ± 0.2 atm) via craniotomy over the left parietal region and divided into 3 groups – Sham, TBI/Saline (T/S) and TBI/Cef (250mg/kg Cef IP daily for 1 week after TBI, T/C). 7 days after TBI, cortical tissue was harvested for GLT-1 mRNA quantification and immunohistochemistry (IHC). Tissue was also extracted 2, 4 and 6 weeks after TBI for GLT-1 mRNA quantification.
Results: 7 days after TBI, GLT-1 mRNA expression in lesioned cortex was decreased in T/S rats relative to sham ($p<0.001$, n=6). IHC indicated decreased GLT-1 in perilesional compared to contralesional cortex in T/S rats ($p<0.05$, n=5) 1 week after TBI. The decrease in GLT-1 was selective in perisomatic sites around non-parvalbumin positive cells ($p<0.0001$, n=5). Additionally, GLT-1 mRNA levels remained depressed 2 weeks post-TBI ($p<0.01$, n=5). However, there was no difference between injured and sham rats 4 and 6 weeks post-TBI. 1 week of Cef treatment attenuated GLT-1 loss in perilesional sites in T/C rats as measured by IHC ($p<0.001$, n=5) and PCR ($p<0.01$, n=6) 1 week after TBI, but did not affect cortical GLT-1 mRNA 2, 4 and 6 weeks after TBI.
Conclusion: TBI leads to a transient GLT-1 decrease in the injured cortex which lasts for up to 2 weeks and is detectable at both protein and mRNA transcript level. Cortical GLT-1 levels in untreated injured rats normalize 4 weeks after injury, whereas 1 week of daily Cef administration attenuates the GLT-1 mRNA and protein loss, but only during period of treatment. We thus identify a relatively short therapeutic window to target GLT-1 loss after TBI. We also show that Cef effect on GLT-1 expression does not extend beyond duration of treatment.

Disclosures: M.Q. Hameed: None. **H.H. Lee:** None. **P.A. Rosenberg:** None. **T.K. Hensch:** None. **A. Rotenberg:** None.

Nanosymposium

107. Brain Injury: Cellular and Molecular Mechanisms

Location: 156

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**Presentation Number: ***107.10

**Topic: ***C.09. Brain Injury and Trauma

Support: The Basic Science Research Program through the National Research Foundation of Korea (NRF-2017R1A2B4002922)
The Basic Science Research Program through the National Research Foundation of Korea (NRF-2014R1A2A1A11050246)

Title: Characterization of vessel-associated cells expressing nestin and platelet-derived growth factor receptor-β in response to 3-nitropropionic acid intoxication

Authors: *T. RIEW[1,2,3], J.-H. CHOI[1,2,3], H. KIM[4], X. JIN[1,2,3], M.-Y. LEE[1,2,3]
[1]Dept. of Anatomy, Col. of Medicine, The Catholic Univ. of Korea, Seoul/seocho-Gu, Korea, Republic of; [2]Catholic Neurosci. Inst., Seoul, Korea, Republic of; [3]Cell Death Dis. Res. Ctr., Seoul, Korea, Republic of; [4]Integrative Res. Support Center, Lab. of Electron Microscopy, Col. of Medicine, The Catholic Univ. of Korea, Seoul/seocho-Gu, Korea, Republic of

Abstract: Nestin is a type VI intermediate filament protein and has been reported to be induced in the vasculature-associated cells that undergo dynamic structural changes in the ischemic core in a rat model of ischemic stroke. The current study was designed to investigate the potential role of vessel-associated nestin-positive cells in the fibrotic scar formation, which is characterized by excess deposition of fibrous extracellular matrix, in the striatum of rats treated with the mitochondrial toxin 3-nitropropionic acid (3-NP). Adult male Sprague Dawley rats were injected with 3-NP and sacrificed at 3, 7, 14, and 28 days after the final injection. Immunohistochemistry, immune-electron microscopy, correlative electron microscopy and focused ion beam milling-scanning electron microscopy combined with 3-dimensional reconstruction were used to visualize and characterize nestin and platelet-derived growth factor receptor-β (PDGFR- β) expressing cells. First, nestin expression was exclusively induced within the vasculature in the lesion core, where the blood-brain barrier is broken and astrocytes are virtually absent, while nestin-positive cells in the peri-lesional area were indeed glial fibrillary acidic protein-positive reactive astrocytes. Vasculature-associated nestin was induced by 3 days post-lesion, persisted until 28 days, and was largely co-labeled with PDGFR-β. At 14 days after the injury, nestin and PDGFR-β double-positive cells had long interwined processes and started to form a network within the lesion core. Also, these cells were in close contact with type IV collagen and fibronectin, both of which are markers for fibrotic extracellular matrix, implying their role in formation of the fibrotic scar. They were closely apposed to vessel walls but clearly distinguishable from endothelial cells, pericytes, smooth muscle cells, or perivascular

microglia/macrophages. During the chronic phase (> 14 days post-injury), nestin and PDGFR-β double-positive cells were observed not only in the multilayered vascular sheath, but they were extending extremely long, tenuous processes in the lesion parenchyma which were juxtaposed to collagen fibril bundles. Ultrastructural study revealed that nestin-positive cells had euchromatic nuclei with a prominent nucleolus, and long processes. Taken together, our data suggest an active role for nestin in cellular structural remodeling of vascular adventitial cells that contribute to the fibrotic scar formation in response to brain insults.

Disclosures: **T. Riew:** None. **J. Choi:** None. **H. Kim:** None. **X. Jin:** None. **M. Lee:** None.

Nanosymposium

107. Brain Injury: Cellular and Molecular Mechanisms

Location: 156

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**Presentation Number: ***107.11

**Topic: ***C.09. Brain Injury and Trauma

Support: R21NS099836

Title: Lethal giant larvae 1 (lgl1) promotes asymmetric cell division and differentiation of oligodendrocyte precursor cells

Authors: *M. DAYNAC[1], H. COLLINS[2], I. MEYERS[2], N. MURPHY[3], B. KADHKODAEI[2], N. TRUFFAUX[2], J. NIU[2], S. FANCY[2], C. PETRITSCH[2]
[1]Neurolog. surgery, [2]UCSF, San Francisco, CA; [3]UCSF, San Franciscco, CA

Abstract: Embryonic neural stem cells (Noctor SC *et al.*, Nat Neurosci 2004) and adult oligodendrocyte progenitor cells (OPC) undergo asymmetric cell division (ACD) to self-renew and generate functional cells (Sugiarto S *et al.,* Cancer Cell 2011). ACD is a fundamental process to restrict proliferation and balance it with self-renewal. Loss of ACD at the expense of symmetric, self-renewing divisions is observed when OPC turn into glioma cells (Sugiarto S *et al.,* Cancer Cell 2011). The majority of ACD regulators *in Drosophila* neuroblast are conserved in the mammalian genome (Gomez-Lopez S *et al.,* Cell Mol Life Sci 2014). Lethal giant larvae 1 (Lgl1) has been implicated in the asymmetric localization of cell fate determinants in neural progenitor cells (Klezovitch *et al.,* Genes Dev, 2004). Functional characterization of mammalian ACD homologues is incomplete, especially in OPC. The objective of this project is to provide a better understanding of how ACD is established and regulated and to determine if disruption of ACD is causal to neoplastic transformation. To reach this goal, we determine whether Lgl1, a gene that was initially identified as a tumor suppressor in Drosophila, regulates ACD in corpus callosum progenitor cells. We propose that Lgl1 regulates ACD and thereby restricts

proliferation and promotes differentiation in OPC. Indeed, in murine OPC carrying conditional null alleles of Lgl1, depletion of Lgl1 *in vivo* increases symmetric divisions of proliferative NG2+ OPC and disrupts ACD, leading to a decrease in CC1+ pre-myelinating oligodendrocytes cells. In a murine model of spinal cord demyelination, Lgl1 ablation in NG2+ OPC *in vivo* increases their proliferation during re-myelination but the cells fail to differentiate properly. We confirmed *in vitro* that Lgl1 loss increases proliferation of OPC but disrupts asymmetric divisions and differentiation. Transcriptome analyses of Lgl1 depleted OPC provide cues into the mechanism by which Lgl1 regulates ACD and will be discussed at the presentation. Our data suggest that loss of Lgl1 disrupts ACD, which contributes to phenotypes associated with malignant transformation.

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Nanosymposium

108. Somatosensory Cortex

Location: 144A

Time: *****Sunday, November 12, 2017, 8:00 AM - 10:30 AM

Presentation Number: *****108.01

Topic: *****D.04. Somatosensation: Touch

Title: Molecular changes induced by environmental enrichment in adult rat somatosensory cortex

Authors: ***S. MANCINI**[1], K. M. MURPHY[2]
[1]MiNDS, [2]Dept Psychol Neurosci & Behaviour, McMaster Univ., Hamilton, ON, Canada

Abstract: Environmental enrichment (EE), by adding physical and/or social stimulation, enhances plasticity during both development and adulthood. Importantly, mature sensory systems undergo functional changes when adult animals are exposed to EE. For example, Sale et al. (2007) showed that visual acuity and ocular dominance of adult amblyopic rats was rescued by EE. While the functional effects of EE in adulthood are well documented, the molecular changes induced by EE are less well understood. We investigated the effects of short-term and long-term EE, within rat somatosensory cortex, on a collection of synaptic and non-neuronal proteins implicated in experience-dependent plasticity. Adult rats were placed into one of three conditions: exposure to EE for period of 2 weeks (short-term EE), EE for a duration of 14 months (long-term EE) or standard cage conditions (control). Protein expression was quantified using Western blot analysis. Proteins selected for measurement included: a marker of dendritic spine motility — Drebrin (both isoforms: embryonic Drebrin-E, adult Drebrin-A); a marker of spine dynamics — Ubiquitin-Protein Ligase E3A (UBE3A); an anchoring portion for excitatory

receptors — Post-Synaptic Density Protein 95 (PSD95); an obligatory N-methyl-d-aspartate (NMDA) receptor subunit — GluN1; a myelin marker — Myelin Basic Protein (MBP); and an astrocyte marker — Glial Fibrillary Acidic Protein (GFAP). We found a significant increase in MBP levels after both short- (64.8%, p=0.03) and long-term (37.3%, p=0.02) EE. In addition, both enrichment conditions had reduced GFAP expression: short-term (27.2%, p=0.001); long-term (25.7%, p=0.001). To analyze the effects of EE on dendritic spines, we calculated an index of the embryonic:adult isoforms (Drebrin-E:Drebrin-A) and found that long-term EE led to significantly greater expression of the embryonic isoform of Drebrin. These results provide new insights into the molecular mechanisms underlying EE-induced synaptic plasticity. The lack of change in synaptic proteins across both EE groups suggests that EE does not simply shift expression to a more juvenile state. Hence, EE may manifest as initial dynamic changes that dissipate over the course of several days or months. Surprisingly, MBP levels increased in both the short- and long-term EE groups. We know that MBP increases into adulthood, but declines during aging. These results point toward EE-induced recovery of MBP, shifting expression toward a young adult state. Lastly, the increased ratio of embryonic-to-adult Drebrin supports the well-known finding that EE increases dendritic spine number and/or volume and induces spine motility.

Disclosures: S. Mancini: None. **K.M. Murphy:** None.

Nanosymposium

108. Somatosensory Cortex

Location: 144A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***108.02

**Topic: ***D.04. Somatosensation: Touch

Support: UZH Forschungskredit Candoc

Title: GABAergic postsynaptic compartment regulates neuronal activity in principal cells in mouse barrel cortex

Authors: *Y.-C. TSAI, J. STOBART, K. D. FERRARI, M. BARRETT, B. WEBER, S. K. TYAGARAJAN
Inst. of Pharmacol. and Toxicology, UZH, Zuerich, Switzerland

Abstract: In the cortex, GABAergic inhibition from a diverse pool of interneurons coordinates sensory input specificity onto principal cells. Consequently, the molecular composition of the GABAergic postsynaptic compartment facilitates input-specific regulation of principal neurons. Gephyrin, a multifunctional protein at GABAergic postsynaptic sites, is essential for synapse

formation and maintenance of GABAergic transmission. Gephyrin post-translational modifications influence inhibition via altered interactions with various signaling molecules, thereby adding an additional layer of regulation to the circuit specific effects. Hence, transgenic expression of eGFP-gephyrin mutants can render GABAergic postsynapse insensitive to specific signaling pathways, leading to enhanced or reduced inhibition of principal neurons. In this *in vivo* study, we employed inducible virus for transgenic expression of eGFP-gephyrin mutant variants in a Cre dependent manner in principal neurons in mouse barrel cortex. The co-expression of pyramidal cell-specific calcium indicator RCaMP1.07 allowed us to record both spontaneous and activity-induced Ca^{2+} transients in response to whisker stimulation. We present proof of concept data showing gephyrin scaffold size and density proportionally shapes GABAergic inhibition. This in turn increases or decreases amplitude and frequency of Ca^{2+} transients in principal neurons after whisker stimulation. Moreover, disruption of gephyrin scaffolding in principal cells causes faster Ca^{2+} responses to whisker stimulation. Together, our results highlight a role for signaling pathways in gephyrin scaffold regulation to integrate interneuron specific inputs during sensory information processing.

Disclosures: **Y. Tsai:** None. **J. Stobart:** None. **K.D. Ferrari:** None. **M. Barrett:** None. **B. Weber:** None. **S.K. Tyagarajan:** None.

Nanosymposium

108. Somatosensory Cortex

Location: 144A

Time: *****Sunday, November 12, 2017, 8:00 AM - 10:30 AM

Presentation Number: *****108.03

Topic: *****D.04. Somatosensation: Touch

Support: RNF Grant 16-15-10174

Title: The mechanisms of the intrinsic optical signal in the barrel cortex of the neonatal rats

Authors: ***M. MINLEBAEV**[1,2], M. SINTSOV[2], D. SUCHKOV[2], R. KHAZIPOV[1,2]
[1]INMED INSERM U901, Marseille, France; [2]Kazan Federal Univ., Kazan, Russian Federation

Abstract: Among of the many approaches used in the neuroimaging, the intrinsic optical signal (IOS) takes the special place. This method allows to locate the active site of neuronal tissue, that makes possible to use it for studying the functional maps in the brain. Moreover, the external position of the light source and absence of additional manipulations with living tissue, the intactness of the method, as well as its low cost, create a number of advantages of IOS imaging compared with other imaging approaches (fMRI, PET, CT, MEG etc.). It is accepted that IOS is the functional analogue of BOLD fMRI imaging, meaning that it is largely based on the tracking

the oxy- and hemoglobin changes (ie. hemodynamic changes) in the active cortical spots. However, efficiency of the IOS during early developmental periods, while BOLD fMRI is not effective, put a question about the similarity of the mechanisms, underlying IOS and BOLD fMRI. Here, using the barrel system of the neonatal rat pups in vivo we have characterized the mechanisms and the developmental changes of the IOS. We demonstrated that during the early postnatal period, the IOS is highly sensitive to the frequency of the stimulation and its developmental profile is bell-shaped with the peak at P9-10. The amplitude of the IOS linearly correlated with the power of the evoked early gamma oscillations in the active barrel that indirectly supported the idea of the domination of the tissue component in the generation of the IOS during the early postnatal period. Using in vitro thalamocortical slices of the barrel system we have observed that electrical stimulation of the thalamocortical connections resulted in the IOS in the stimulated barrels, meaning that IOS in the neonatal cortex could be induced in the conditions of the oxy- and hemoglobin absence, that also supported the idea that hemodynamic component is not the key player in the generation of the IOS during the early postnatal stages. Based on the presented evidences and results of the experiments with reflectance/transmittance estimations we propose that in contrast to adult brain, where the dominant mechanism of the IOS is hemodynamic changes, the IOS in the immature cortex directly relates to neuronal activity and thus predominantly has the tissue nature.

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Nanosymposium

108. Somatosensory Cortex

Location: 144A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***108.04

**Topic: ***D.04. Somatosensation: Touch

Support: Simons Foundation SCGB 415569

Title: Multiphoton holographic silencing of neural population codes in behaving animals

Authors: *I. A. OLDENBURG, H. ADESNIK
MCB, Univ. of California Berkeley, Berkeley, CA

Abstract: Sensory perception involves the coordinated effort of thousands of interrelated and often genetically similar neurons. These neurons form physically intermingled networks and subnetworks that act together to amplify and strengthen sensory perceptions. Although, current technologies can manipulate genetically identified neurons in a region, they are incapable of

selectively manipulating intermingled neurons that differ only by their functional properties. Therefore, new techniques are needed to manipulate cells chosen by their activity patterns in order to dissect the functional elements of perception. To address this technical gap, we developed and optimized a new approach to edit neural population codes in the neocortex during behavior using spatiotemporally precise multiphoton optogenetics. We engineered a new optogenetic tool IRES-ST-eGtACR1 that allows rapid and reliable silencing of many neurons simultaneously, or individually with exquisite spatial resolution and temporal precision. We use this tool to alter the firing properties of functionally identified neurons, and observe how these changes affect neighboring neurons involved in sensory perception.

Disclosures: I.A. Oldenburg: None. **H. Adesnik:** None.

Nanosymposium

108. Somatosensory Cortex

Location: 144A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***108.05

**Topic: ***D.04. Somatosensation: Touch

Support: HFSP
SFB 1089

Title: Externally induced arousal state modifies spontaneous and evoked synaptic activities in the somatosensory cortex

Authors: *A. N. RAPPAPORT, I. LAMPL
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Behavioral states, such as arousal and attention are defined by a set of psychological and physiological variables. They have profound effects on sensation, perception, learning, and cognition. In the brain, global states are characterized by distinct cortical and hippocampal EEG patterns. These changes that are clearly observed in the local field potential (LFP) are also evident in network and cellular dynamics. At the population level, the more active states are manifested as asynchronous neuronal firing between neighboring cells. At the cellular level, the membrane potential during active states is characterized by a continuous depolarized state, high synaptic activity, reduced variance and reduced membrane potential correlations between cells. In recent years it has been demonstrated in rodents that pupil size is a robust indicator of a range of neural activity from neuromodulator release to cortical neuronal membrane potential. Our goals in this study were to firstly evaluate if through aversive stimuli we are able to cause a change in brain state in mice as indicated by pupil size. We then wanted to evaluate the effect of

pupil size on the neural dynamics in mice both during ongoing evoked activity. To accomplish this we conducted intracellular recordings in the barrel cortex in conjunction with extracellular LFP recordings in the same area from awake head fixed mice. We recorded the pupil throughout the experiment in order to evaluate brain state via pupil size. There were periods of time without sensory stimuli in order to evaluate ongoing activity as well as whisker deflections in order to evaluate evoked activity. We interleaved those trials with trials in which a strong air puff, an aversive stimulus, was delivered to the back of the animal. We have found that over 80% of the time delivering an aversive stimulus to the animal will lead to an increase in pupil size. We have further found that there is a significant correlation between the mean depolarization of membrane potential of cells in S1 and pupil size. Furthermore, the membrane potential and LFP is decorrelated when the animal is in a state of arousal as indicated by pupil size. Furthermore, during states of arousal the response of S1 neurons to whisker stimulation increased. These results suggest that externally induced arousal state decorrelates neuronal activity and increases the saliency of sensory response.

Disclosures: **A.N. Rappaport:** None. **I. Lampl:** None.

Nanosymposium

108. Somatosensory Cortex

Location: 144A

Time: *Sunday, November 12, 2017, 8:00 AM - 10:30 AM

Presentation Number: *108.06

Topic: *D.04. Somatosensation: Touch

Support: NINDS RO1 NS069679
NINDS F32 NS084768

Title: Transient, but not chronic, manipulations of somatosensory cortex disrupt sensory detection

Authors: ***Y. HONG**, C. O. LACEFIELD, C. C. RODGERS, B. C. PIL, A. KASE, R. M. BRUNO
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Abstract: Rodents rhythmically move their whiskers and actively seek contact with objects as they navigate their environment. Numerous studies have sought to establish whether the primary sensory cortex (S1) is required for sensory detection behaviors, but with conflicting results. The discrepancies have been attributed to numerous factors, such as aversive vs. appetitive conditioning, passive vs. active detection, task complexity or method of inactivation. Recent work in motor cortex suggested that long-term homeostatic regulation of neural activity can

reverse deficits caused by transient inactivation, questioning the validity of concluding necessity of a brain area from transient inactivation. These issues have yet to be addressed in sensory cortex. Here, we examine the effects of transient versus chronic inactivation of S1 in mice trained to actively whisk and respond to object detection. We find that transient S1 inactivation alters whisker movement, resulting in decreased contact force and number. However, the decline in performance cannot be explained by changes in whisker kinematics alone; sensory threshold significantly increases when S1 is inactivated. Lesioning S1 similarly impairs detection on the first session post-lesion. Surprisingly, animals rapidly recover by the following session in an experience-dependent manner. Recovery is not due to a compensatory behavioral strategy, since whisker motion and sensory threshold returned to pre-lesion levels. Together, our results suggest that S1 inactivation initially alters both whisking motor output and sensory threshold, resulting in impaired sensory detection. However, these effects are only temporary, as the circuitry adjusts after a single session of exposure to the task, bypassing any requirement for S1 in sensory detection. We further explore whether S1, while chronically not required for sensory detection, may be required for task acquisition.

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Nanosymposium

108. Somatosensory Cortex

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Presentation Number: *108.07

Topic: *D.04. Somatosensation: Touch

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Sigrid Jusélius Foundation Grant
Instrumentarium Foundation Grant
Finnish Cultural Foundation Grant

Title: Interindividual variability of somatosensory representations - comparison of TMS and fMRI mapping in healthy subjects

Authors: ***J. D. GOGULSKI**[1], R. ZETTER[2], M. NYRHINEN[2], H. LIN[1], A. PERTOVAARA[1], S. CARLSON[1,2,3]
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Abstract: Large interindividual variability has been reported in associative cortical regions but earlier studies show that there is considerable topographical and functional variability between individuals also in the primary cortical areas, such as the primary somatosensory cortex (S1). Here we examined the extent of interindividual variability of the somatosensory cortical representation area of the tip of the index finger as revealed by blocking of the mechanically evoked tactile perception by navigated transcranial magnetic stimulation (nTMS)[1]. We also examined the spatial extent of the nTMS blocking effect within individuals. Next, we investigated how well the cortical representation area that was determined using single-pulse nTMS ($S1_{HS}$) corresponded to the individual fMRI activation evoked by the mechanical tactile stimulus to the right index finger. We also analyzed the fMRI data at the group level.
The variability of the $S1_{HS}$ location *between* the subjects was larger than the spatial extent of the somatotopic blocking effect *within* individuals. Within subjects, the fMRI activation overlapped only partly with the corresponding $S1_{HS}$ area. Between subjects, the locations of the fMRI activations evoked by tactile stimulation showed larger variability than the locations of the $S1_{HS}$. The group-level fMRI analysis showed four activation clusters ($Z > 2.3$, $P < 0.001$; corrected), one of which was in the left hemisphere. This cluster (717 voxels) was located more laterally and posteriorly than the $S1_{HS}$ locations.
In conclusion, the interindividual variability in the somatotopic representation of the tip of the index finger was smaller when determined with nTMS than with fMRI. The somatotopic representation areas determined using nTMS, individual fMRI or group fMRI overlapped only partially with each other. The study implies that choosing the TMS target according to the group-level fMRI activation may result in stimulating somatotopically or functionally unintended areas.
References
1. Hannula, H., *et al. Hum Brain Mapp* **26**, 100-109 (2005).

Disclosures: J.D. Gogulski: None. **R. Zetter:** None. **M. Nyrhinen:** None. **H. Lin:** None. **A. Pertovaara:** None. **S. Carlson:** None.

Nanosymposium

108. Somatosensory Cortex

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Topic: *D.04. Somatosensation: Touch

Support: Juho Vainio Foundation, Helsinki, Finland grant number 201410296

Ministry of Education and Culture, Helsinki, Finland grant number 56/626/2013

Title: Bilateral modulation of insular activity observed after peripheral electrical stimulation in healthy adults

Authors: P. HAUTASAARI[1], H. SALORANTA[1], A. M. SAVIC[2], K. KORNILOFF[1], U. M. KUJALA[1], *I. M. TARKKA[1]
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Abstract: Interhemispheric transfer is necessary for sensory integration and coordination of both body sides. Lesion studies have shown defects in interhemispheric transfer. In order to understand the effects of specific brain damages it is necessary to study, in addition to usual contralateral representation of somatosensory input in primary somatosensory cortex, more context-dependent bilateral integration of somatosensory inputs. Our aim was to investigate which uni- and bilateral brain areas are involved in consecutive stages of automatic sensory processing of non-nociceptive peripheral stimulation in healthy adults.
We recorded 18 healthy individuals (aged 18-41 years) with whole head 306-channel magnetoencephalography. We registered somatosensory evoked fields (SEFs) to electrical stimulation of corresponding intensities in two conditions. In condition I, SEFs were registered following sensory radial nerve (RN) stimulation to the dorsal surface of the right hand and, in condition II, following median nerve (MN) stimulation at the right wrist.
Main cortical activations were located in contralateral postcentral gyrus after MN and RN stimulations and in bilateral posterior insular area after RN stimulation, however corresponding bilateral activation was not present after MN stimulation. First component occurred earlier after MN (20 ± 2.0 ms) than RN (32 ± 4.9 ms) stimulation and showed stronger activation in contralateral postcentral gyrus after MN stimulation. Middle latency components after MN (65 ± 7.0 ms) and after RN (67 ± 4.8 ms) stimulation had similar latencies, but again showed stronger activation in contralateral postcentral gyrus after MN stimulation. Long latency components located in bilateral posterior insular area after RN stimulation showing latency difference between hemispheres, i.e. contralateral activation started and peaked earlier than ipsilateral side (112 ± 11.6 ms, 130 ± 21.7 ms, $p < 0.001$).
Different brain areas were active following slightly diverging hand stimulation areas. Early and middle latency activations located in contralateral postcentral gyrus, however source strengths and peak latencies of first components differed. Interestingly, only RN stimulation showed long latency activation in bilateral posterior insular areas. Insular area, known to participate in pain network, may have been activated owing to possible discomfort experienced from stimulus. We showed that peripheral stimulation activates, in addition to primary sensory areas in contralateral postcentral gyrus, bilateral posterior insular areas with distinct latency difference between contra- and ipsilateral hemispheres.

Disclosures: **P. Hautasaari:** None. **H. Saloranta:** None. **A.M. Savic:** None. **K. Korniloff:** None. **U.M. Kujala:** None. **I.M. Tarkka:** None.

Nanosymposium

108. Somatosensory Cortex

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**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***108.09

**Topic: ***D.04. Somatosensation: Touch

Support: The Dana Foundation

Title: Cortical reorganization following lower limb amputation

Authors: *S. N. TOMSON[1], L. WANG[2], J. M. YAU[3]
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Abstract: Recent evidence suggests that more than 1.7 million Americans are living with limb loss. Among individuals who have had major amputations, the vast majority have experienced *lower* limb loss. Previous characterizations of cortical changes associated with limb loss have focused on region-specific alterations in the upper body. Little is known about the impact of lower limb loss, and even less is known about functional processing at the network level. In this study, we aim to characterize cortical reorganization in transtibial amputees with a particular focus on network-level alterations. Using functional MRI, we first identify the brain regions that represent the missing limb by having amputees perform a simple motor task that is designed to map the somatotopic organization of somatomotor cortex. We refer to these regions as the phantom cortex. Our first analysis will compare phantom cortex to the cortical regions that represent the sound limb. We hypothesize that the phantom cortex will be symmetric to the sound limb representation, but slightly smaller due to the diminished capacity for use. With the phantom cortex defined, we then proceed to study how the phantom cortex associates with classic network neighborhoods during two 15-minute resting state fMRI scans. In accordance with previous studies in upper limb amputees, we hypothesize that the phantom motor cortex will be less associated with traditional somatomotor networks and more associated with resting state networks such as the Default Mode Network. Our preliminary data suggest that the phantom cortex looks nearly identical (if not slightly larger) relative to the sound limb representations, implying that lost limb representations are remarkably robust to time and experience. These preserved limb representations and their distributed cortical connections may underlie the common experience of phantom limbs and pain.

Disclosures: S.N. Tomson: None. **L. Wang:** None. **J.M. Yau:** None.

Nanosymposium

108. Somatosensory Cortex

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**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***108.10

**Topic: ***D.04. Somatosensation: Touch

Support: R01-DA038642
T32-EB019940
MIT Simons Center Seed Grant

Title: Probing the origins of resting state functional connectivity

Authors: *S. J. BRICAULT[1], J. LEE[4], M. DESAI[2], E. DETIENNE[3], A. JASANOFF[2]
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Abstract: Long-range correlations in noninvasive brain imaging data are commonly observed in the absence of specific tasks or stimuli, comprising a phenomenon termed resting state functional connectivity (RSFC). Despite great interest in using RSFC measurements to understand and diagnose human brain disorders, the neural basis of RSFC remains poorly characterized. Given the potency with which structured sensory input evokes correlated activity across the brain, we hypothesize that ambient sensory input might remain a major driving factor of stochastic cortical activity even in the absence of discrete stimuli, and that such input might be a major contributor to RSFC effects. Using functional magnetic resonance imaging (fMRI) and local neuromodulation in awake rats, we find that RSFC in cortical regions can indeed be significantly disrupted by pharmacological inactivation of lower level regions. This effect is pronounced in the vibrissal system, where muscimol injections targeting ventroposterior thalamus reduce both the amplitude and the bilateral cross-correlation strength of resting state fMRI signal fluctuations in barrel cortex. Other cortical and subcortical regions are also altered by perturbation of lower level sensory structures. Our results suggest that intracortical connectivity relationships in the resting state arise at least in part from cortico-thalamic dynamics, and possibly from more peripheral input to these regions. More broadly, the data provide evidence that RSFC phenomena can be influenced by signals from brain regions external to areas that exhibit the most pronounced apparent connectivity, a result with cautionary implications for interpretation of normal and abnormal functional connectivity patterns in human neuroimaging data.

Disclosures: S.J. Bricault: None. **J. Lee:** None. **M. Desai:** None. **E. DeTienne:** None. **A. Jasanoff:** None.

Nanosymposium

109. Cellular Mechanisms Underlying Cerebellum Plasticity

Location: 143A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***109.01

**Topic: ***E.02. Cerebellum

Support: NINDS Grant NS062771
NIH Grant NS045193

Title: Clustered complex spike activity rescues long-term depression in cerebellar slices under near-physiological conditions

Authors: *H. K. TITLEY[1], M. KISLIN[2], D. H. SIMMONS[1], S. S.-H. WANG[2], C. HANSEL[1]
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Abstract: Synaptic plasticity at the parallel fiber (PF) to Purkinje cell synapse has been widely regarded as a correlate for motor learning. In cerebellar slices, long-term potentiation can be induced by PF stimulation, while long-term depression (LTD) is induced by the consistent pairing of a complex spike (CS). In previous slice studies, the time interval required between the PF and climbing fiber (CF) stimulation to obtain LTD has been suggested to match the time intervals needed between conditioned and unconditioned stimuli in associative learning tasks (CF delay: 0-150ms; e.g. Wang et al., *Nat. Neurosci*. 3, 2000). However, recent studies claim that CS-US intervals ≤50ms are inefficient to drive associative learning (Wetmore et al., *J. Neurosci*. 34, 2014), and that LTD time intervals may differ between cerebellar areas (Sruvathan et al., *Neuron* 92, 2016). To assess LTD induction parameters under realistic, near-physiological conditions, we performed whole-cell patch-clamp recordings in mouse slices with GABAergic inhibition intact, at elevated temperatures (32°C) and using physiological Mg^{2+} and Ca^{2+} ASCF concentrations (1 and 1.2mM, respectively). Under these conditions, a CF pulse paired with PF stimulation resulted in potentiation at 0, 70, and 200ms PF-CF timing intervals, and no change at 100ms and 150ms intervals. We found no correlation with the change in EPSC amplitude after plasticity and the number of spikelets evoked in the complex spike. In addition we independently measured Purkinje cell spontaneous responses from Crus I/II in vivo using whole cell (n=7) and extracellular (n=6) recordings in anesthetized rats and awake mice, respectively. In anesthetized rats complex spikes occurred at a mean firing rate of 1.24 ± 0.08Hz and was found to have a clustering pattern, with 12.3% of CSs showing an interspike interval of less than 150ms and 16.5% with an interspike interval of less than 200ms. In awake mice, the frequency of CSs was found to be 1.55 ± 0.10Hz with 9.3% showing clustering within at 150ms interspike interval and 12.7% showing clustering with 200ms. Similarly, using GCamMP6f-based two-photon imaging in awake mice, we observed an absence of periodicity in complex spike firing, but instead found that complex spikes are often clustered. In our LTD experiments, we observed that LTD is

rescued (PF-CF interval =150ms) when two complex spikes are evoked with CS-CS intervals of 50-150ms, but not at intervals of 200ms or 250ms. We suggest that the burst of complex spike activity may serve to facilitate LTD *in vivo*.

Disclosures: H.K. Titley: None. **M. Kislin:** None. **D.H. Simmons:** None. **S.S. Wang:** None. **C. Hansel:** None.

Nanosymposium

109. Cellular Mechanisms Underlying Cerebellum Plasticity

Location: 143A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***109.02

**Topic: ***E.02. Cerebellum

Support: NS086916
NS069229
Whitehead Foundation

Title: Inferior olivary TMEM16B mediates cerebellar motor learning

Authors: *Y. ZHANG[1], Z. ZHANG[1], S. XIAO[3], J. TIEN[3], L. Y. JAN[4], H. YANG[2]
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Abstract: Ca^{2+}-activated ion channels shape membrane excitability and Ca^{2+} dynamics in response to cytoplasmic Ca^{2+} elevation. Compared to the Ca^{2+}-activated K^+ channels known as BK and SK channels, the physiological importance of Ca^{2+}-activated Cl^- channels (CaCCs) in neurons has been largely overlooked. Here we report that CaCCs coexist with BK and SK channels in inferior olivary (IO) neurons that send climbing fibers to innervate cerebellar Purkinje cells for the control of motor learning and timing. Ca^{2+} influx through the dendritic high-threshold voltage-gated Ca^{2+} channels activates CaCCs, which contribute to membrane repolarization of IO neurons. Loss of TMEM16B function resulted in the absence of CaCCs in IO neurons, leading to markedly diminished action potential firing of IO neurons in TMEM16B knockout (KO) mice. Moreover, these mutant mice exhibited severe cerebellar motor learning deficits. Our findings thus unveil a new physiological role of CaCCs in controlling IO neuron excitability and motor learning.

Disclosures: Y. Zhang: None. **Z. Zhang:** None. **S. Xiao:** None. **J. Tien:** None. **L.Y. Jan:** None. **H. Yang:** None.

Nanosymposium

109. Cellular Mechanisms Underlying Cerebellum Plasticity

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**Presentation Number: ***109.03

**Topic: ***E.02. Cerebellum

Support: NIH grant R01 NS18338
NIH grant T32 GM008471
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NSF grant IGERT DGE-1069104

Title: Climbing fibers predict movement kinematics and performance errors

Authors: *M. L. STRENG, L. S. POPA, T. J. EBNER
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Abstract: Requisite for understanding cerebellar function is a complete characterization of the signals provided by complex spike (CS) discharge of Purkinje cells, the output neurons of the cerebellar cortex. Numerous studies have provided insights into CS function, with the most predominant view being that they are evoked by error events. However, several reports suggest that CSs encode other aspects of movements and do not always respond to errors or unexpected perturbations. To address this, we evaluated CS firing during a pseudo-random manual tracking task in the monkey (Macaca mulatta). This task provides extensive coverage of the work space and relative independence of movement parameters, delivering a robust data set to assess the signals that activate climbing fibers. Using reverse correlation, we determined feedforward and feedback CSs firing probability maps with position, velocity and acceleration, as well as position error, a measure of tracking performance. The direction and magnitude of the CS modulation were quantified using linear regression analysis. The major findings are that CSs significantly encode all three kinematic parameters and position error, with acceleration modulation particularly common. The modulation is not related to 'events,' either for position error or kinematics. Instead, CSs are spatially tuned and provide a linear representation of each parameter evaluated. The CS modulation is largely predictive. Similar analyses show the simple spike firing is modulated by the same parameters as the CSs. Therefore, CSs carry a broader array of signals than previously described and argue for climbing fiber input having a prominent role in online motor control.

Disclosures: M.L. Streng: None. **L.S. Popa:** None. **T.J. Ebner:** None.

Nanosymposium

109. Cellular Mechanisms Underlying Cerebellum Plasticity

Location: 143A

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**Presentation Number: ***109.04

**Topic: ***E.02. Cerebellum

Title: Kinetic analysis of constitutive and activity-dependent receptor-trafficking in cerebellar Purkinje cell

Authors: *K. YAMAGUCHI
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Abstract: Insertion of AMPA-type glutamate receptors (AMPA-Rs) into and elimination of them from the synaptic membrane regulates basal density of AMPA-Rs at the parallel fiber (PF)-Purkinje cell (PC) synapse in the cerebellum. Exo/endocytosis and lateral diffusion of the receptor are supposed to play essential roles in this receptor trafficking, and some mathematical models has been published, however, actual kinetic parameters of exo/endocytosis and lateral diffusion of AMPA-Rs at the PF-PC synapse was elusive. Here, I measured a rate of elimination of AMPA-Rs from synaptic membrane by means of photolysis of intracellularly applied caged inhibitory peptide, which blocks exocytic insertion of GluA2 by suppressing interaction between GluA2 and NSF. This caged-inhibitory peptide was applied intracellularly through a whole-cell patch-pipette located on Purkinje cell body in rat cerebellar slice (thickness: 300μm). Caged inhibitory peptide itself had no effect on PF-EPSC amplitude, but on photolytic release of the peptide by irradiation of UV (330-430nm) caused rapid decrease in PF-EPSC amplitude. Decay time-constant was 0.9 ± 0.2 min (n = 4) in control group. This elimination should be composed of lateral diffusion and/or endocytosis of AMPA-Rs. To dissociate lateral diffusion component, caged inhibitory peptide was uncaged during blockade of endocytosis by dynasore. Surprisingly, almost no reduction of PF-EPSC amplitude was detected, suggesting that free lateral diffusion of AMPA-Rs from synaptic to extrasynaptic region is negligible. Next, we examined effects of LTD-inducing conjunctive stimulation (PF and somatic depolarization, 300 stimuli at 1Hz) on time-course of the photolysis-induced decay of EPSC-amplitude. To our surprise, decay time-constant was not altered by LTD-inducing stimulation (0.8 ± 0.2 min, n = 4, $p>0.5$, *t*-test). Because these decay time-constants can be considered to reflect the rate of endocytic elimination of AMPA-Rs from the synaptic membrane, it is concluded that enhancement of endocytic elimination of AMPA-Rs is not a responsible mechanism of LTD.

Disclosures: K. Yamaguchi: None.

Nanosymposium

109. Cellular Mechanisms Underlying Cerebellum Plasticity

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**Presentation Number: ***109.05

**Topic: ***E.02. Cerebellum

Support: ANR-08-SYSC-005
Labex MEMOLIFE
NSF IIS-1430296
ANR-10-LABX-54 MEMOLIFE
ANR-11-IDEX-0001-02

Title: The capacity of perturbation-based cerebellar learning

Authors: *J. ALJADEFF[1], V. HAKIM[3], B. BARBOUR[4], N. BRUNEL[2]
[1]Dept. of Neurobio., [2]Statistics and Neurobio., Univ. of Chicago, Chicago, IL; [3]CNRS & Ecole Normale Superieure, Paris, France; [4]Ecole Normale Supérieure, Paris, France

Abstract: Learning abstract input-output associations is a fundamental problem which is solved by multiple brain regions, including the cerebellum, cortex and hippocampus. The perceptron is a useful model to study this problem, providing a framework within which one can analytically compute the capacity - the maximal number of associations that can be stored - as a function of the properties of the neuronal substrate and the statistics of the associations. Finding a set of synaptic weights which implement a prescribed set of associations is traditionally done using "perceptron learning," a gradient-based rule that is guaranteed to converge if a solution exists.A major hurdle in relating this class of models to neurobiology is that perceptron learning requires that each neuron receives full error information: updates of each synapse are based on the error, or the difference between the output using the current synaptic weights and the desired output. In the cerebellum, climbing fibre input to Purkinje Cells (PC) is thought to convey error information used for learning in Parallel Fibre (PF) to PC synapses. Though this input is correlated with error in some cases, such a relationship does not seem to be universal. Thus, it is still unclear how the cerebellum solves the credit assignment problem, especially during acquisition of fine motor skills where the relationship between the error and the appropriate correction is complex.
It has recently been shown how plasticity rules measured in slice under physiological conditions can be mapped to a Stochastic Gradient Descent (SGD) learning algorithm (Bouvier et al., 2016 bioRxiv). In the proposed algorithm, spontaneous complex spikes (CS) perturb movements, and the existence or absence of a CS following the movement provides an evaluation.
Here we study the capacity of SGD learning and show that under certain conditions the theoretical limit is achieved. Our analysis suggests that plasticity in the Deep Cerebellar Nuclei

(DCN), which allows the system to maintain a running estimate of the errors, and PC inhibition of DCN neurons, play a crucial role in ensuring that different inputs do not interfere with each other during learning.

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Nanosymposium

109. Cellular Mechanisms Underlying Cerebellum Plasticity

Location: 143A

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**Presentation Number: ***109.06

**Topic: ***E.02. Cerebellum

Support: MEXT Grant-in-Aid for Scientific Research (B) 16H02901

Title: Human predictive optokinetic eye movement is correlated with the presence of velocity storage: Demonstration in a virtual reality environment

Authors: Y. MATSUZAWA[1], R. BAKER[2], *Y. HIRATA[1]
[1]Chubu Univ. Col. of Engin., Aichi, Japan; [2]Physiol. and Neurosci., New York Univ. Langone Med. Ctr., New York, NY

Abstract: Optokinetic behaviors have been demonstrated to be under predictive control in goldfish and carp. Namely, after prolonged presentation of a periodic optokinetic visual stimulation eye velocity starts to decrease before a change in direction of the same stimulus. When the visual stimulation period is suddenly elongated, eye velocity starts to decrease around the timing of the change in direction of the training stimulus. When the light is turned off, eye velocity continues to respond in the dark as if the training stimulation is still present. We have previously shown in goldfish that the cerebellum is necessary for acquisition and maintenance of the predictive behaviors. We also demonstrated that goldfish expressing a longer time constant of oculomotor velocity storage as quantified by the duration of optokinetic after nystagmus (OKAN) showed better acquisition of the predictive behaviors. These predictive behaviors were not acquired in medaka and zebrafish whose velocity storage time constants were minimal (Urase et al., SfN, 2016). Here we tested if human subjects could acquire similar predictive optokinetic behaviors and evaluated the relationship with velocity storage time constants. Six subjects (male university students 21-23 yrs.) participated in the experiment. Each wore a head-mount display (HMD; Oculus Rift) and sat comfortably in a chair with chin rested. A 3D random dot stimulation was designed by using a game engine (Unity) and displayed in the HMD so each participant virtually saw a projection on a surrounding transparent cylindrical screen at 1 m. Eye movements were recorded by electro-oculography. To evaluate velocity storage time constants,

the visual stimulus was rotated at a constant speed of 30 deg/s for 1 min in the rightward direction, followed by complete darkness for 1 min. After a break in the training session, the visual stimulation was given at the same speed in the rightward direction for 8 s and stopped for 4 s. This training stimulation was given periodically for 5 min and followed immediately by a test session in which left and rightward constant speed rotation at 30 deg/s was given for 16 s in each direction. Among the 6 participants, four showed little OKAN and did not present a detectable predictive eye velocity component in the post training test session. However, two participants showed a robust OKAN (initial velocity of > 7 deg/s), and each presented a significant predictive eye velocity component in the post training test session. These results strongly support the hypothesis that, in similarity with fish, predictive optokinetic eye movement control in humans is dependent on the presence of velocity storage.

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Nanosymposium

109. Cellular Mechanisms Underlying Cerebellum Plasticity

Location: 143A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***109.07

**Topic: ***E.02. Cerebellum

Support: MH 46904
NS 98308

Title: Optogenetic manipulation of eyelid conditioned responses in rabbits

Authors: *A. KHILKEVICH[1], J. ZAMBRANO[2], M.-M. RICHARDS[2], F. RIUSECH[2], B. V. ZEMELMAN[2], M. D. MAUK[2]
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Abstract: Eyelid conditioning is a cerebellar-dependent behavior that provided numerous insights into cerebellar computation and learning mechanisms. A large portion of eyelid conditioning studies used New Zealand rabbits as subjects, which provided a well-mapped cerebellar circuitry and careful examination of behavioral properties for these species. In addition, compared to mice for example, rabbits are capable of learning more demanding eyelid conditioning tasks and produce more robust and well-timed behavioral responses. A major advantage of mice though was the availability of transgenic lines and well-defined procedures for optogenetic manipulation of cerebellar circuitry. Here we report an implementation of optogenetic manipulation of cerebellar circuitry in New Zealand albino rabbits. We focused on

silencing cerebellar output and downstream structures that mediate expression of eyelid conditioned responses (CRs) to replicate previous studies which used reversible pharmacological lesions. Viral constructs (AAV1-CamKII-ArchT-tdTomato or AAV1-CamKII-GtACR2-GFP) were injected into a) ipsilateral anterior interpositus nucleus (IPN), b) contralateral red nucleus or c) ipsilateral facial nucleus, structures that all were previously shown to be necessary for the expression of CRs. A 400 μm diameter, 0.39 NA optic fiber was chronically implanted 0.2 mm above the target structure in each case. Subjects were initially trained at ISI500 ms using either 1kHz tone or direct electrical stimulation of mossy fibers as CS. Illumination with laser or LED through optic fiber (532 nm wavelength for ArchT, 470 nm wavelength for GtACR2) was able to reliably affect the expression of CR. With a light pulse duration extended through the whole CS, CRs were reliably blocked. Presentation of brief pulses of light (100—200 ms) during a CR suppressed further increase in CR velocity during the laser pulse with a short delay (<=25 ms) from the onset of laser pulse. Single unit recordings using optrode implanted in ipsilateral IPN also showed reliable silencing of IPN neurons. In sum, these studies provide a foundation for more elaborate designs using optogenetics in rabbits in future.

Disclosures: A. Khilkevich: None. **J. Zambrano:** None. **M. Richards:** None. **F. Riusech:** None. **B.V. Zemelman:** None. **M.D. Mauk:** None.

Nanosymposium

110. Animal Models for Depression: Molecular and Genetic Approaches

Location: 146C

**Time: ***Sunday, November 12, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***110.01

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH
HDRF

Title: FACS-RNAseq of nucleus accumbens reveals cell type-enriched mediators of stress susceptibility

Authors: *H. KRONMAN[1], C. PENA[1], E. RIBEIRO[1], B. LABONTÉ[2], E. LOH[1], N. STRAT[1], C. LARDNER[1], D. WALKER[1], E. NESTLER[1]
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Abstract: Stress induces pathological changes in the nucleus accumbens (NAc), a largely GABAergic nucleus receiving dopaminergic input from the ventral tegmental area and glutamatergic inputs from several forebrain regions. The NAc contains distinct neuronal

populations, the most abundant of which are the dopamine-responsive, GABAergic medium spiny neurons (MSNs). MSNs are subdivided by their response to dopamine, with one class expressing predominantly the dopamine receptor type 1 (D1) and the other expressing type 2 (D2). While these MSNs utilize different receptors and G proteins, few other D1- and D2-enriched genes are known. It is important to identify D1-/D2-enriched target genes and functional networks in order to find a molecular basis for the distinct roles that these populations have been shown to play in stress susceptibility. This project aims to characterize the transcriptional identity of D1- and D2-expressing MSNs in stress-susceptible versus stress-resilient mice. We first analyze these cells at baseline in order to generate a list of D1- and D2-enriched genes. Then we investigate changes in D1- and D2-expressing MSNs after stress in the context of these baseline enrichments to examine overarching patterns in their transcriptional responses to stress. Finally, we identify high-value targets, which mediate stress susceptibility or resilience in D1 and D2 MSNs differentially. One promising such target identified to date is the histone lysine methyltransferase, Dot1l, as a D2-enriched mediator of stress susceptibility. We are now exploring its precise role in transcriptional and behavioral control through epigenetic analyses and viral manipulation of Dot1l expression in this cell type.

Disclosures: **H. Kronman:** None. **C. Pena:** None. **E. Ribeiro:** None. **B. Labonté:** None. **E. Loh:** None. **N. Strat:** None. **C. Lardner:** None. **D. Walker:** None. **E. Nestler:** None.

Nanosymposium

110. Animal Models for Depression: Molecular and Genetic Approaches

Location: 146C

Time: *Sunday, November 12, 2017, 8:00 AM - 9:45 AM

Presentation Number: *110.02

Topic: *G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH
HDRF

Title: The role of long non-coding RNAs in depression

Authors: ***O. ISSLER**[1], Z. S. LORSCH[1], P. J. HAMILTON[1], I. PURUSHOTHAMAN[1], Y.-H. E. LOH[1], B. J. HARTLEY[1], E. FLAHERTY[1], Y. VAN DER ZEE[2], D. M. WALKER[1], A. START[1], C. J. PENA[1], H. KRONMAN[1], E. S. CALIPARI[1], B. LABONTÉ[1], K. BRENNAND[1], L. SHEN[1], E. J. NESTLER[1]
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Abstract: Depression is a common, chronic, and debilitating disorder. The molecular mechanisms underlying depression are only partially understood, and there is a great need for

novel antidepressant drugs, particularly directed towards the sizeable proportion of treatment-resistant patients. Long non-coding RNAs (lncRNAs) are a recently discovered large class of regulatory transcripts which represent a substantial portion of the human genome. To date, there is virtually no characterization of the role of brain lncRNAs in depression. To address this, we utilized a unique and comprehensive genome-wide profile of RNAs in 6 brain regions from both male and female post-mortem depressed human subjects. Overall, lncRNAs represent about one-third of the differentially expressed genes in depressed subjects compared to controls and displayed complex region- and sex-specific patterns of regulation. Next, we carried out bioinformatic genome-wide correlation analysis between lncRNAs and protein-coding genes in our dataset. Using this approach, we identified target lncRNAs with potential key roles in depression. To analyze the molecular targets of two key depression-related lncRNAs, we performed loss- and gain-of-function experimentation in human neuron progenitor cells followed by RNAseq. These single gene manipulations recapitulated segments of the transcriptional landscape of depression. Overexpression of one lncRNA regulated levels of mRNAs of genes linked with mitochondrial dysfunction, while knockdown of another lead to transcriptional abnormalities of synaptic genes. Current experiments are examining the effects of these lncRNAs on cellular properties in vitro either on mitochondria activity and structure, or electrophysiological properties and dendritic spine formation. To establish a causal role of these lncRNAs in depression-related phenomena, each lncRNA was expressed in mouse prefrontal cortex. Such viral-mediated expression mimicked the human sex-specific phenotype: expressing an upregulated depression-related lncRNA increased depression- and anxiety-related behaviors in female, but not male mice, while expressing a downregulated lncRNA induced stress resilience in females. These studies provide a fundamentally new view of molecular adaptations in brain that contribute to depression risk and may lead to the identification of novel targets for improved treatment or biomarkers of depression.

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110. Animal Models for Depression: Molecular and Genetic Approaches

Location: 146C

**Time: ***Sunday, November 12, 2017, 8:00 AM - 9:45 AM

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**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIHF30MH110073

NIHP50MH096890
Hope for Depression Research Foundation

Title: CREB-Zfp189 interactions regulate a resilient-specific transcriptional network in mouse models of depression

Authors: *Z. S. LORSCH[1], P. J. HAMILTON[1], Y. LOH[1], I. PURUSHOTHAMAN[1], E. M. PARISE[1], L. F. ALCANTARA[3], O. ISSLER[1], A. MCKENZIE[2], A. LEPACK[1], S. MONTGOMERY[1], M. WANG[2], I. MAZE[1], L. SHEN[1], B. ZHANG[2], R. C. BAGOT[4], E. J. NESTLER[1]
[1]Neurosci. and Friedman Brain Inst., [2]Genet. and Genomic Sci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [3]Psychology, Texas A&M Univ., College Station, TX; [4]Psychology, McGill Univ., Montreal, QC, Canada

Abstract: Major Depressive Disorder (MDD) is associated with abundant transcriptional alterations across brain regions. RNA sequencing studies in animal depression models corroborate these findings, but indicate that quantitatively more changes are required for stress resilience compared to stress susceptibility. Despite this, most studies of resilience have focused on single genes, and the mechanism by which sets of genes interact to induce resilience is currently unknown. To address this, we performed weighted gene co-expression network analysis (WGCNA) on RNA transcripts following 10 days of chronic social defeat stress (CSDS) and identified a network of genes unique to the resilient phenotype. Using key driver analysis, we found that Zfp189, which encodes a previously uncharacterized zinc finger protein, was the most connected gene in this network. In concert, differential expression analysis revealed both network-wide enrichment of upregulated genes and upregulation of Zfp189 in the prefrontal cortex (PFC) of resilient mice, suggesting that Zfp189 modulates other in-network genes to affect network function. Consistent with this hypothesis, Zfp189 overexpression in mouse PFC was both pro-resilient and antidepressant, and RNA sequencing of virally infected tissue showed preferential changes in the network from which Zfp189 originates. Interrogating known binding motifs within this network identified CREB as a predicted upstream regulator. Accordingly, re-analysis of previously published ChIP-chip data found that CSDS decreased CREB binding to Zfp189, a phenomenon that was reversed by the antidepressant imipramine. Consistent with these observations, knockout of CREB in the PFC increased susceptibility to stress, but the deleterious effects of CREB knockout were ablated by Zfp189 overexpression. As a whole, these findings suggest that CREB interacts with Zfp189 to regulate a resilient-specific transcriptional network in PFC that induces behavioral resilience.

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Nanosymposium

110. Animal Models for Depression: Molecular and Genetic Approaches

Location: 146C

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**Presentation Number: ***110.04

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Critical role of miRNAs in mediating neural and behavioral changes in chronic social defeat stress induced mouse model of depression

Authors: *N. KHANDELWAL[1], S. DEY[1], S. CHAKRAVARTY[2], A. KUMAR[1]
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Abstract: Depression, anxiety and related mood disorders are major psychiatric illnesses worldwide, where chronic stress appears to be one of the foremost underlying cause. Apart from the genetic component, research in the past decade has shown the involvement of diverse epigenetic mechanisms in mediating the negative effects of chronic stressful events on neural circuits. However, non-coding RNAs, another layer of epigenetic regulation, have relatively lesser studied in this context. Here, we aimed to uncover the dysregulated non-coding RNAs in the neurogenic dentate gyrus (DG) region of the hippocampus in the mouse model of chronic social defeat stress (CSDS) induced depression. Using high-throughput small RNA sequencing approach, we found dysregulation in numerous small non-coding RNAs, in particular, miRNAs, in DG of the defeated C57BL/6 mice. We selected few of the dysregulated miRNAs and validated their differential expression in individual DG samples. We also performed RNA sequencing on the same samples to identify the probable gene targets through which these altered miRNAs might be involved in stress-induced cellular and molecular changes under the impact of depression. CSDS is a well- established aggressive stress paradigm in animals, which affects several signaling pathways. As expected, we could find upregulation of the genes involved in the neural-immune response, defense response, stress response and inflammatory response in DG of the defeated mice. On the other hand, genes, which are required for the maintenance of homeostasis or neuronal activity and regulation of animal behavior were found to be downregulated. Consequently, using several miRNA target databases and bioinformatic approach, we discovered few probable gene targets of the selected miRNAs and validated their mRNA expression in individual DG samples. Later, using miRNA mimics and inhibitors and by luciferase reporter assay, we ascertained genes, directly targeted by these miRNAs. Our results suggest that the dysregulated miRNAs, identified in the DG of CSDS-induced depressed mice, alter neural functions and animal behavior through regulating transcription factors, epigenetic regulators, and few critical elements involved in cell-signalling events.

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110. Animal Models for Depression: Molecular and Genetic Approaches

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**Presentation Number: ***110.05

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH R01MH104261
ONR N00014-12-1-0366
Hope for Depression Research Foundation
Pritzker Neuropsychiatric Research Center

Title: The effects of restraint stress on reelin mrna expression in glucocorticoid receptor-overexpressing female mice

Authors: *D. M. KROLEWSKI, E. K. HEBDA-BAUER, Q. WEI, M. SHAIKH, R. A. ILLAGAN, M. WASELUS, H. AKIL, S. J. WATSON, Jr.
Univ. of Michigan, Ann Arbor, MI

Abstract: Reelin is a large neuronally secreted excitatory glycoprotein (~450 kDa) whose regulation has been largely studied within cortical and hippocampal interneurons. Alterations in Reelin gene expression amongst these neuronal populations has been linked to psychiatric illness in humans and various stress paradigms utilizing animal models. In order to further examine the effects of stress on Reelin gene activity, we took advantage of a transgenic mouse line that overexpresses glucocorticoid receptors (GRov) in the forebrain and demonstrates increased emotional lability similar to that reported in some psychiatric disorders (Wei et al., 2004). **Methods:** GRov (n=16) and wild-type (WT; n=16) female mice were separated into two groups that underwent either 20 minutes of restraint (RST, n=8) or were maintained in their home- cage (controls; CTRL, n=8). Following a post-restraint recovery period of 2 hours and 40 min that took place post-restraint recovery period in the home-cages, animals were sacrificed, brains removed and stored at -80°C. In situ-hybridization using an S35-labeled Reelin cRNA riboprobe was performed on 10 µM-thick sections, exposed on autoradiographic film, and signal quantified using Image J software. Neuroanatomical regions of interest included the motor, prelimbic, infralimbic, piriform, auditory, and entorhinal cortices as well as the hippocampus, striatum, and nucleus accumbens. **Results:** Quantitative analyses are currently ongoing and thus far, no significant effect of mouse strain or restraint on Reelin mRNA in the motor, prelimbic or infralimbic prefrontal cortices has been observed. However, within the striatum, Reelin expression was elevated in the GRov phenotype compared to WT mice. Moreover, restraint was associated with a significant reduction in Reelin expression specifically in GRov mice, but not WT mice. **Conclusion:** These preliminary findings suggest that stress-mediated activation of glucocorticoid receptors may be connected to dysregulation of Reelin gene expression in

subcortical motor circuits. Moreover, the effects of stress on Reelin mRNA may be more pronounced in the striatum vs. prefrontal cortex of female mice.

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Nanosymposium

110. Animal Models for Depression: Molecular and Genetic Approaches

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**Presentation Number: ***110.06

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant F31AI106357

Title: AOAH as a modulator of corticotrophin releasing factor

Authors: *L. AGUINIGA[1], A. J. SCHAEFFER[2], D. J. KLUMPP[2]
[2]Urology, [1]Northwestern Univ., Chicago, IL

Abstract: Interstitial cystitis (IC) is a disease characterized by chronic pelvic pain and co-morbid depression. Patients that suffer from IC have reported that their symptoms worsen upon stress and have altered cortisol levels compared to control patients, suggesting they suffer from hypothalamic pituitary adrenal (HPA) axis dysregulation. Corticotropin releasing factor (CRF) is the initiator of the HPA axis, the body's central stress response system, and mediates the effect of stress on depression. Our lab identified AOAH as a genetic determinant of pelvic hypersensitivity and has shown AOAH-deficient mice have spontaneous chronic pelvic pain and thus serve as a model of IC. Characterization of AOAH distribution in the brain showed AOAH is widely distributed throughout the mouse brain, including the paraventricular nucleus (PVN). Furthermore, we found elevated arachidonic acid (AA) and PGE2 in the spinal cords of AOAH-deficient mice. Because AA and AA metabolites have been shown to modulate *Crf* expression, we are investigating the role of AOAH in modulating CRF and CRF-mediated depression. We evaluated depression-like behavioral phenotypes in *Aoah*$^{-/-}$ mice relative to wild type (WT) using a novelty suppressed feeding (NSF) assay, and found *Aoah*$^{-/-}$ mice take significantly longer to approach the food pellet and to consume the food pellet, consistent with depression behavioral phenotypes. Further characterization using the sucrose preference test showed *Aoah*$^{-/-}$ mice had decreased preference for sucrose water compared to WT mice, consistent with loss of hedonic activity seen in depression. We quantified *Crf* mRNA expression using qRT-PCR from 1mm brain sections from the paraventricular nucleus of WT and *Aoah*$^{-/-}$ mice. *Aoah*$^{-/-}$ mice had increased *Crf* mRNA levels in the paraventricular nucleus compared to WT mice. Finally, we

found elevated serum corticosterone in AOAH-deficient mice compared to WT mice. These results suggest *Aoah* is a novel genetic modulator of *Crf* and subsequent CRF-mediated depression and HPA axis dysfunction. Therefore AOAH is a novel therapeutic target for the treatment of depression.

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Nanosymposium

110. Animal Models for Depression: Molecular and Genetic Approaches

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**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH grant MH067229
Eating Disorders Research Grants Program from The Klarman Family Foundation
Colorado State University

Title: Food withdrawal-induced depression-like behavior by Kir2.1 upregulation in the nucleus accumbens

Authors: *S. KIM[1], J. SHOU[1], S. ABERA[2], E. B. ZIFF[2]
[1]Biomed. Sci., Colorado State Univ., Fort Collins, CO; [2]New York Univ. Langone Med. Ctr., New York, NY

Abstract: Background: Binge eating disorder (BED) is a major eating disorder and characterized by recurrent episodes of eating large amounts of food. A key psychiatric feature of BED is depression, which is experienced especially after attempts to stop overeating and results in reversion to unhealthy eating habits. However, neurobiological mechanisms that underlie food withdrawal-induced depression have not been fully understood. **Methods:** We used the two-bottle sucrose choice paradigm as a sucrose overeating and withdrawal model. Depression-like behavior was assayed by using the tail-suspension test and the sucrose preference test. We also cultured striatal neurons to identify alteration of the dopamine pathway related to food withdrawal. **Results:** Sucrose overeating was sufficient to induce obesity-like weight gains, and withdrawal elicited depression-like behavior, which was reversed by sucrose reinstatement. In medium spiny neurons expressing D1 receptors (D1-MSNs) of the nucleus accumbens (NAc) of food withdrawal animals, extracellular dopamine levels were significantly reduced and the inwardly rectifying K^+ channel, Kir2.1, was significantly elevated. In cultured MSNs, a D1 receptor antagonist inactivated CREB and increased Kir2.1 expression. Finally, selective overexpression of Kir2.1 in D1 neurons induced depression-like behavior. **Conclusion:**

Withdrawal from sucrose after lengthy sucrose consumption reduces the activity of the dopamine pathway in the NAc, resulting in upregulation of the expression of K^+ channels and depression-like behavior. Given the fact that elevated K^+ channels reduce neuronal activity, decreased neuron activity resulting from an increase in Kir2.1 expression in D1-MSNs of the NAc provides a cellular basis for depression-like behavior in mice following food withdrawal.

Disclosures: S. Kim: None. **J. Shou:** None. **S. Abera:** None. **E.B. Ziff:** None.

Nanosymposium

111. Attention Networks

Location: 150A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***111.01

**Topic: ***H.02. Human Cognition and Behavior

Title: Loneliness is reflected in the intrinsic architecture of attention and executive control networks

Authors: *L. MWILAMBWE-TSHILOBO[1], M. A. FERGUSON[2], R. SPRENG[1]
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Abstract: People are intrinsically motivated to form and maintain meaningful social bonds. Our ability to do so is supported by a range of cognitive processes through the synchronized activity of spatial distributed brain regions. Perceived social isolation, or loneliness, is thought to drive self-preservation mechanisms that orient attentional focus towards social threats. While previous studies have shown that loneliness is associated with altered processing in regions of the brain involved in attention and cognitive control, little is known about how these changes modulate neural activity within large-scale brain networks.
Here, we examine the relational dynamics between individual differences in loneliness and intrinsic network architecture of the brain using data collected as part of the Human Connectome Project (HCP) data. Data from 830 participants (mean age: 28.8; SD= 3.9 years; 465 female) for whom both self-report measure of loneliness and full resting-state fMRI data was available. To perform our analysis, the cerebral cortex was parcellated into functionally-defined regions. We then extracted BOLD activity signal from these regions to obtain a resting-state functional connectivity matrix for each participant. We used spectral decomposition to produce functionally orthogonal principal components, which identified spatially distributed brain regions whose activity co-varied across the duration of the resting-state scan. For each PC, we calculated the magnitude of network synchrony which reflects the magnitude to which the regions comprising each functional network demonstrate persistent synchronous activity across the resting-state time

series. Measures of synchrony were then correlated with individual subjects' loneliness score. Our results indicate that individual differences in loneliness was related to greater functional connectivity within PCs that showed features of canonical brain networks. These included the dorsal attention network, a lateralization of the frontoparietal control network, and functional ensembles of frontoparietal regions. We examined whether these correlations could be explained by personality traits of extroversion and neuroticism, and found persistent synchrony within a functional ensemble of the frontoparietal network and the posterior attention regions. Given that the dorsal attention network supports externally oriented attention and the frontoparietal network is involved in top-down regulation of attention and emotion, these findings provide additional insight into how the state of loneliness shapes the way in which people attend to and perceive their social environment.

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Nanosymposium

111. Attention Networks

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**Presentation Number: ***111.02

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH Grant Y1AA-3009

Title: Conscious and unconscious brain responses to positively and negatively valenced cues

Authors: *C. E. WIERS, J. ZHAO, V. RAMIREZ, C. FREEMAN, A. ZEHRA, S. B. DEMIRAL, P. MANZA, E. SHOKRI-KOJORI, G.-J. WANG, D. TOMASI, N. D. VOLKOW
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Abstract: Studies with functional MRI (fMRI) have shown that the visual presentation of appetitive food cues triggers responses in brain reward areas, such as the striatum, medial prefrontal cortex (mPFC), and visual cortex. These areas are also active when patients with substance use disorders view drug-related cues, and have been positively associated with drug craving and relapse. Although fMRI cue reactivity paradigms vary in presentation times from subliminal or "unconscious" (smaller than 50ms) to "conscious" (1-4s), no study has systematically compared the effect of different presentation times on brain activation to food and drug-related cues.
The first aim of the study was to compare fMRI brain responses to food, cocaine, and neutral cues presented outside and within conscious awareness in healthy individuals. The second aim was to test reactivity to these cues in mornings versus evenings, since preclinical studies suggest

that the dopaminergic reward circuit is more active in evenings. 16 healthy volunteers (mean age=42 years, 6 female) completed 3 fMRI tasks in which 40 food cues, 40 cocaine cues and 40 neutral cues were presented in random order. All cues were presented subliminally for 33ms (task1), and consciously for 750ms (task2) and 3s (task3). Tasks were performed on two separate days; once between 9-11am and once between 5-7pm, in randomized order. To induce mild hunger, participants did not to eat at least 3 hours before fMRI sessions. Participants evaluated food cues as very positive, arousing and "wanted", whereas neutral cues were rated as neutral in these dimensions, and cocaine cues as extremely negative, not arousing or wanted. Food cues were wanted more in evenings than in mornings; yet hunger ratings did not differ between morning and afternoon. In the fMRI experiments, subliminally presented food>neutral cues evoked activations in subcortical brain areas (thalamus and ventral striatum), whereas with longer presentation times brain activations shifted to visual cortex (750 ms), insula and mPFC (3s). For 750ms and 3s, there were stronger food cue-evoked brain activations in dorsal and ventral striatum in the evening compared to morning session; suggesting a more reactive dopaminergic reward system in evenings. Interestingly, cocaine>food cues evoked strong activations in visual areas in the subliminal 33ms task; suggesting that negatively valenced items (cocaine) may be perceived at faster speed than positive items (food). Whether this effect generalizes to general positively and negatively valenced items remains to be investigated.

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Nanosymposium

111. Attention Networks

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**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***111.03

**Topic: ***H.02. Human Cognition and Behavior

Support: Brain & Behavior Research Foundation – NARSAD Young Investigator Award
NIH/ NCATS UL1TR000124
Klingenstein Third Generation Foundation

Title: Inter-hemispheric brain volume asymmetries in adhd

Authors: C. N. LARIOS[1], *P. K. DOUGLAS[2,3]
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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable neurodevelopmental disorder with an estimated childhood prevalence of 5-10%, and an economic burden to society estimated to be in the tens of billions of dollars every year. Diagnosis is typically based on parental reports and behavioral assessment scores. Determining the structural neuroimaging correlates of the disease would potentially enable quantitative benchmarking changes across the lifespan and treatment efficacy. Although studied extensively with MRI, the findings to date have provided mixed results, particularly with respect to the laterality of findings. We hypothesized that these discrepancies may be partly due to differences in hemispheric asymmetries that may occur over the course of development, consistent with the delayed maturation theory of ADHD. Here, we studied structural MRI (sMRI) data from both ADHD and typically developing (TD) participants that had no history of pharmacotherapy treatment. We included data from the publicly shared ADHD200 database as well as an additional database of sMRI data from UCLA. In total, 607 participants (362 typically developing, 245 ADHD-free of medication) between the ages of 6-21 years met our inclusion criteria. We derived volumetric metrics from 34 cortical and 14 non-cortical brain regions for each hemisphere, as well as shape morphology of subcortical nuclei. Calculations for group comparisons were made for each hemisphere (e.g., ADHD right amygdala volume vs. TD-right amygdala volume) as well as inter-hemispheric asymmetry indices (AI) for each cortical and subcortical structure. Eleven cortical regions and two non-cortical volumes were significantly more asymmetric in ADHD individuals compared to typically developing individuals, after comparison for multiple comparisons. Morphometric analyses provided additional information on asymmetry than volumetric analyses, revealing the caudate, hippocampus, thalamus, and amygdala to be more asymmetric ($p<0.0001$) in ADHD than typically developing subjects. Although neuroimaging is not used in ADHD diagnostics, understanding brain asymmetry patterns may improve our understanding of the heterogeneous phenotype observed in ADHD subjects.

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111. Attention Networks

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**Topic: ***H.02. Human Cognition and Behavior

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

Title: Dorsal attention network activation and diminished attention in cerebral visual impairment

Authors: *C. M. BAUER[1], E. S. BAILIN[1], P. J. BEX[2], L. B. MERABET[1]
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Abstract: Visual attention is a complex process, encompassing projections between the thalamus and frontal, parietal, and occipital cortices. Damage to any of the specific brain regions or to the white matter connections between them can cause functional deficits in visual attention. The dorsal attention network (DAN) is responsible for the top-down conscious control of attention and may be particularly affected in children with cortical/cerebral visual impairment (CVI), who demonstrate grey and white matter damage throughout occipital, parietal, and subcortical regions. Visual attention is often limited in children with CVI, but it is not known whether these deficits are due to structural or functional abnormalities within the DAN. To this end, the current study examined functional connectivity of the DAN using resting state functional MRI (rsfMRI) in a cohort of individuals with CVI compared to controls.

Resting state fMRI was run on a cohort of 7 individuals with CVI (Ages 14-24, mean 18.4 years) and normally sighted and developed controls (Ages 15-24, mean 19.75 years). A structural T1W and field map were also acquired on a 3T Philips Achieva System. To correct for motion, ICA-AROMA was performed on each subject's rsfMRI data, which were then processed in FreeSurfer. A 6mm diameter spherical seed was placed in the frontal eye fields (MNI 26, -6, 48). The average time course between the seed and the rest of the cortex was calculated for each subject and a GLM was run to compare between CVI and control groups. Visual attention was assessed using computer-based psychometric tests of functional vision, namely a conjunction search and go-no-go sustained attention paradigm.

Compared to controls, individuals with CVI demonstrated significant increases in functional activation between the frontal eye fields, superior frontal, caudal middle frontal, par orbitalis, inferior parietal, and pericalcarine regions ($p < 0.05$). Clusters of significant decreases in activation were observed between the frontal eye fields and the precuneus/rostral anterior cingulate and inferior parietal areas ($p < 0.05$). The CVI group also demonstrated poor performance on both psychophysical tests of visual attention, as indexed by increased error rates and reaction times ($p < 0.05$).

Our results indicate that functional correlations between the frontal eye fields and portions of the dorsal and ventral attention networks are increased in individuals with CVI compared to controls. These functional changes likely relate to the visual attention difficulties observed in CVI, whereby individuals with poorer performance must recruit more cortical resources in order to complete the task.

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Nanosymposium

111. Attention Networks

Location: 150A

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***111.05

**Topic: ***H.02. Human Cognition and Behavior

Support: Far East Organization

Title: Low trait mind wandering is associated with optimized intrinsic functional connectivity

Authors: *J. Z. LIM[1], S. A. A. MASSAR[2], J. TENG[3], Z. HASSIRIM[3], K. WONG[3], C. WANG[3], M. W. CHEE[3]
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Abstract: Objective
Mind wandering and low meta-awareness are associated with poor cognitive performance and unhappiness in daily life. Furthermore, the tendency to mind wander is trait-like, yet amenable to change through training. Here, we conducted a resting-state fMRI to investigate the individual differences in functional connectivity associated with trait-mind wandering, We hypothesized that lower levels of mind wandering would be associated with greater optimization of the intrinsic functional connectome (i.e. connectivity patterns with higher similarity to that seen during task engagement).
Methods
100 healthy young participants were recruited to perform a breath-counting task, a covert measure of meta-awareness and mind wandering. Participants kept track of their breath over an 18-minute period by pressing a button with every 1st to 8th breath, and a separate button for every 9th breath. From this sample, good (accuracy > 81%; N=15) and poor (accuracy < 63%; N=11) performers were invited for an imaging session, which consisted of a second run of the breath-counting task (behavioral), and an ~8 minute resting state (rs)fMRI scan.
Whole-brain data were segmented based on the Yeo parcellation, and connectivity was computed using the multiplication of temporal derivatives (MTD) method. Static connectivity maps were calculated as a time-series average, and dynamic functional connectivity analysis was performed using k-means clustering after averaging within a 7-TR sliding window across the MTD time series. Connectivity was compared between the good and poor groups.
Results
Inter-session reliability of breath counting accuracy was high (ICC = .57; $p < .001$), and good and poor performers continued to differ significantly in their second test ($p = .01$).
Static rsfMRI connectivity maps showed greater anti-correlation between the dorsal attention network and the default mode network, and greater connectivity strength within the salience

network in good performers. Dynamic functional connectivity analysis revealed two reproducible patterns of connectivity, corresponding to optimized (high arousal) and non-optimized (low arousal) brain states. Good performers had significantly more dwell time in the optimized state compared to poor performers.

Conclusions

Our data demonstrate that breath-counting accuracy is trait-like and reproducible, and indicate that intrinsic functional connectivity is more optimized in individuals with low trait mind wandering. Shifts towards this pattern of optimization may represent a useful biomarker of the gains from training meta-awareness, such as those obtained from mindfulness-based interventions.

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Topic: *H.02. Human Cognition and Behavior

Support: Lockheed Martin Corporation Grant U12001B
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Title: The relationship between cognitive workload and attentional reserve: An empirical investigation

Authors: ***K. JAQUESS**[1], R. J. GENTILI[1], L.-C. LO[1], H. OH[1], J. ZHANG[2], J. C. RIETSCHEL[3], M. W. MILLER[4], Y. Y. TAN[5], B. D. HATFIELD[6]
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Abstract: It has long been considered, on the conceptual level, that cognitive workload and attentional reserve have an inverse relationship. However, to our knowledge, this relationship has never been tested empirically. The purpose of this study was to investigate the relationship between cognitive workload and attentional reserve using objective measures derived from the electroencephalogram (EEG). To assess cognitive workload, we utilized spectral power measures of cortical activation (theta, alpha, beta, and the ratio of theta/alpha). To assess attentional reserve, we utilized components of the event-related potential (ERP) from the presentation of

unattended “novel” sounds (N1, P2, and P3a amplitudes). The relationship between these two families of measures was assessed using a canonical correlation methodology. Twenty-seven participants undergoing flight training performed a flight simulator task under three levels of difficulty. Results revealed a strong, negative relationship between measures of cognitive workload and attentional reserve (all canonical correlation coefficients > 0.9). This finding provides empirical support for the theoretical and intuitive notion that cognitive workload and attentional reserve are inversely related. While cognitive workload and attentional reserve are broad concepts and may consist of many elements, these results inform further work investigating the more specific aspects of these constructs and their relationships.

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111. Attention Networks

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NIH R01 MH049334

Title: Deficits and compensation in visual attention networks in schizophrenia

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Abstract: Background: Selective visual attention is governed by the interactions of low-level visual (striate/extrastriate), high-level visual (lateral/ventral occipital), dorsal attention, ventral attention, and task control networks. Schizophrenia patients (SzP) may be impaired in one or more of these networks, resulting in significant disability.
Methods: We compared these networks in 20 SzP and 20 healthy controls (HC) with functional magnetic resonance imaging (fMRI) of rapid serial visual presentation (RSVP) task-evoked activity and resting state functional connectivity (RSFC). We defined regions of interest (ROIs) in each group by activation/deactivations evoked by the monitoring and detection of targets in

the RSVP stream. These ROIs were used to calculate task-evoked activity magnitude and inter-ROI RSFC strength in each individual.
Results: In the task data, detection rates and activation magnitudes did not differ between groups. However, TPJ deactivation by RSVP stream monitoring strongly correlated with detection rate in SzP ($r=-.60$, $p=.0051$), but not HC ($r=.0091$). In the RSFC data, only connectivity of high-level visual areas was weaker in SzP than HC ($p<.0128$). Detection rate correlated positively with RSFC of high-level visual areas to low-level visual areas and negatively with RSFC of dorsal to ventral attention areas ($p<.05$). TPJ deactivation correlated with RSFC of right prefrontal cortex (PFC) to both high- and low-level visual cortex ($p=.0196$). Two alternative linear models combined these measures to predict detection rate more than TPJ deactivation alone ($p<.05$). Model 1 included TPJ deactivation, high/low-level visual cortex RSFC, and dorsal/ventral attention network RSFC ($r^2=.655$, adjusted $r^2=.581$, $F=8.84$). Model 2 replaced TPJ deactivation with right PFC-visual connectivity ($r^2=.695$, adjusted $r^2=.634$, $F=11.4$).
Conclusion: We found that while performance and task activation of the visual/attention networks were similar in the two groups, SzP had an underlying deficit in the RSFC of visual cortex areas. SzP compensated for these deficits with improved connectivity of visual and attention areas, allowing for efficient use of the TPJ to suppress the processing of distracting stimuli. TPJ deactivation in turn relied on intact connectivity of PFC to visual areas, as predicted by the model by Corbetta *et al*. The results demonstrate how SzP may use the attention network to overcome visual processing deficits.

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Nanosymposium

111. Attention Networks

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**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***111.08

**Topic: ***H.02. Human Cognition and Behavior

Title: The anterior prefrontal cortex represents low-level stimulus characteristics necessary for implicit attentional reallocation

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Abstract: Flexibly reallocating attention between different stimuli and task sets is a cognitive ability crucial for the successful interaction with a constantly changing environment. The most anterior part of the human brain, the frontopolar cortex (FPC), is involved in attentional reallocation, specifically in complex, underspecified situations. While FPC function has mostly been investigated using complex decision-making and exploration paradigms, some studies demonstrate its involvement in attentional reallocation in very basic, implicit tasks. For example, in visual search tasks the FPC was found to be active in trials that require an implicit reallocation from one to another target dimension. Contrary to traditional accounts of anterior prefrontal function, the above finding suggests, that the FPC actually holds a representation of the low-level stimulus characteristics required for this reallocation process. To investigate this, we applied a simple dimension change paradigm. Brain activation of 18 healthy volunteers was measured using functional magnetic resonance imagining (fMRI), while they decided in 1200 trials whether the middle one of three Gabor patches differed from the outer ones. Among the difference trials, there were equally many (1) repeat trials, in which the present middle patch was similar to the one in the previous trial, (2) feature change trials, in which the defining feature changed from the previous one, but was in the same dimension (e.g., red vs. green) and (3) dimension change trials, in which the defining dimension changed from the previous one (e.g., color vs. orientation). As expected, participants took longer to respond to dimension change as compared to feature change or repeat trials. A linear support vector machine achieved significant above-chance classification accuracy of stimulus orientation not only in occipital areas, thalamus and hippocampus, but also, bilaterally, in the medial FPC. Stimulus color could also be decoded from prefrontal areas, albeit the superior frontal and middle frontal gyrus. The latter may be due to an easier detection of color compared to orientation differences as indicated in reaction times. In sum, the present results demonstrate that prefrontal areas, including their most anterior part, the FPC, hold a representation of basic low-level stimulus characteristics needed for flexible attentional adjustment, and therefore urges us to reconsider the commonly held hierarchical view of prefrontal representations being limited to complex and abstract information.

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Topic: *H.02. Human Cognition and Behavior

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Title: Altered connectivity of the dorsal attention network in semantic dementia

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Abstract: Semantic Dementia is a devastating neurodegenerative disease characterized by the progressive loss of semantic memory and focal atrophy in the left anterior temporal lobe. Strikingly, semantic dementia patients also frequently exhibit increased visual interest and repetitive artistic activity. The goal of this study was to investigate whether this heightened visual interest may be due to a reorganization of the functional architecture of the dorsal attention network in these patients.

We used resting state functional connectivity to investigate the intra- and inter-network connectivity of the dorsal attention network and the visual association network in independent samples of 89 young adult controls, 40 older adult controls, and 12 patients with semantic Dementia. Regions of interest in the dorsal attention network included left and right motion-selective cortex (lMT/rMT), frontal eye fields (lFEF/rFEF), and superior parietal lobes (lSPL/rSPL). Left and right fusiform face area (lFFA/rFFA) regions of interest were used to investigate the connectivity of the ventral association network with dorsal attention network nodes.

Relative to the older healthy control group, patients with semantic dementia exhibited significantly increased intra-network functional connectivity between nodes of the dorsal attention network, and demonstrated increased inter-network connectivity between the FFA and dorsal attention network nodes. Significant intra-network connectivity differences between nodes of the dorsal attention network were also observed for the young and older adult control groups, with the network architecture of the dorsal attention network in semantic dementia patients more closely resembling that of the young control group.

Our results indicate that the connectivity of the dorsal attention network in semantic dementia more closely resembles that of young adults as opposed to age-matched older controls. We also show that nodes of the dorsal attention network have increased functional connectivity with a critical ventral association region (the FFA) relative to OCs. This altered functional architecture of the dorsal attention network may contribute to heightened visual interest in semantic dementia.

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Title: Real-time neurofeedback of functional connectivity in large-scale brain networks that predict attention

Authors: *M. D. ROSENBERG[1], D. SCHEINOST[2], W.-T. HSU[3], R. T. CONSTABLE[2], M. M. CHUN[3]
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Abstract: Recent work has demonstrated that real-time neurofeedback based on patterns of fMRI activity may be used to train attention (deBettencourt et al., 2015; Zilverstand et al., 2017). Given evidence that attention relies on coordinated activity across the brain, we explored the feasibility of using connectome-based feedback to train focus. Specifically, we used fMRI neurofeedback to modulate functional connectivity in two networks — a "high-attention" network with 757 connections and a "low-attention" network with 630 connections — that predict individuals' attentional abilities across several independent datasets (Rosenberg et al., 2016a, 2016b). To this end, 10 participants performed the gradual-onset continuous performance task (Esterman et al., 2013) during 3 fMRI runs. Each run included four 3-min task blocks each followed by a 30-s block of feedback, visualized as a gas gauge. Participants were told that a "full" gauge indicated optimal attention whereas an "empty" gauge indicated suboptimal focus, and were instructed to keep the gauge as close to full as possible. For neurofeedback participants (n = 6), the position of the gauge reflected high-attention relative to low-attention network strength during the preceding task block. Stronger high-attention and weaker low-attention networks resulted in better feedback. Sham feedback participants (n = 4) saw a yoked participant's feedback. During neurofeedback sessions, a 268-node brain atlas (Shen et al., 2013) was warped into subject space. Motion correction and nuisance variable regression were performed during data collection (Scheinost et al., 2013). After each task block, timecourses in each pair of nodes were correlated to generate a 268 × 268 connectivity matrix. High- and low-

attention network strength values were calculated as the dot product of the connectivity matrix and the attention network masks defined previously. Demonstrating the feasibility of connectome-based feedback, network strength values calculated in real-time and after data collection using published methods were significantly correlated (mean within-subject *r*-value = .80; range = .58–.94; $p < .05$ in all participants). As expected, the relationship between feedback and network strength calculated off-line was lower in the sham feedback group (mean within-subject *r*-value = .44; $p < .05$ in one participant). Furthermore, mean feedback was more positively correlated with mean task performance (*d'*) in the neurofeedback than the sham feedback group ($r = .48$ vs. $r = –.61$). Thus, these results provide preliminary evidence that whole-brain connectivity-based neurofeedback is feasible and may be useful for attention training.

Disclosures: M.D. Rosenberg: None. **D. Scheinost:** None. **W. Hsu:** None. **R.T. Constable:** None. **M.M. Chun:** None.

Nanosymposium

111. Attention Networks

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**Presentation Number: ***111.11

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH MH 108591

Title: Connectome-based predictive modeling (CPM) of sustained attention: Comparing different methods for feature selection and prediction

Authors: *K. R. YOO[1], ***K. R. YOO**[1], M. D. ROSENBERG[2], W.-T. HSU[1], S. ZHANG[6], C.-S. R. LI[3], D. SCHEINOST[4], R. T. CONSTABLE[5], M. M. CHUN[4]
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Abstract: Connectome-based predictive modeling (CPM; Shen et al., 2017) was recently developed to predict individual differences in traits and behaviors, including fluid intelligence (Finn et al., 2015) and sustained attention (Rosenberg et al., 2016a). CPM is a data-driven approach to construct a model predicting individual behaviors from brain connectome data. Here, we compared the predictive power of three different connectivity features (Pearson's correlation, accordance and discordance) and two different prediction algorithms (linear regression and partial least square regression; PLSR) in CPM for attention function. Accordance and discordance are recently proposed connectivity measures that separately track in-phase

synchronization and out-of-phase anti-correlation, respectively (Meskaldji et al., 2016). We defined models over task or rest fMRI data, and tested 1) whether accordance and discordance are more reliable measures than Pearson's correlation for functional connectivity and 2) whether PLSR or linear regression better relates connectivity features to behavioral traits. We assessed predictive models defined over an internal dataset using leave-one-out-cross-validation, and then externally validated across three independent datasets. Connectome-based predictive models of sustained attention were developed from fMRI data collected while participants performed a sustained attention task (gradCPT), and while at rest (N=25; Rosenberg et al., 2016a). The three other independent fMRI datasets included: 1) data collected during stop-signal task performance and rest (N=83, including 19 participants administered methylphenidate prior to scanning; Rosenberg et al., 2016b), 2) data collected during Attention Network Task performance and rest (N=41), and 3) resting data and ADHD symptom severity from the ADHD-200 Consortium (N=113; Rosenberg et al., 2016a). All models significantly predicted individual performance with correlations between predicted and observed measures of attention as high as 0.9 for internal, and 0.6 for external validation; all p's < 0.05). Models trained on task-data outperformed models based on rest data. Accordance features generally showed a small numerical advantage over correlation features, while PLSR models were usually better than linear regression models. Overall, in addition to correlation features combined with linear models (Rosenberg et al., 2016a), it is useful to consider accordance features and PLSR for CPM.

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Nanosymposium

112. Mapping Language Onto Structure

Location: 147B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***112.01

**Topic: ***H.02. Human Cognition and Behavior

Title: Mirror neurons and language acquisition through deictic, concrete and abstract concepts

Authors: *M. ORKODASHVILI
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Abstract: The present paper analyzes the importance of mirror neurons in tracing the language acquisition process through the stages of a) perceiving deictic referents of location, b) grasping concrete observable actions and objects, and c) deciphering abstract concepts. When an individual observes the action of another, mirror neurons fire. Their operation becomes even more significant in the process of language acquisition and verbal communication. To

understand how mirror neurons are involved in the emergence of language, it should be surmised that mirror neurons are internal representations. In the process of communication or language acquisition, they become coupled with linguistic items, which can take gestural, visual, aural or verbal forms. Mirror neurons are particularly important in acquiring, deciphering and using specific locations, concrete objects, and abstract concepts. They provide substrates both for generalized schemas (i.e. for grasping abstract concepts) and for fine-grained perceptions of individual objects, events and locations (i.e. for understanding concrete locations and concepts). In other words, biological transition can be traced from mirror neurons to the types of cognitive generalizations that are available for lexical items and deictic constructions. Since spatial cognition and language acquisition faculty are linked, mirror neurons help perceive the process of moving from spatial cognition that is realized through identifying concrete locations, to complex linguistic procedure of grasping concrete and abstract concepts. The following lexical items have been analyzed in terms of understanding the significance of firing mirror neurons in the language acquisition process: a) The concrete deictic locations are: *here, there, far, near, on the right, on the left, across, next to, opposite, beside, above, below, beneath, under, over, between, in the front, at the back, in the middle, on the side, around, etc.* These deictic referents cause firing of mirror neurons at the initial stage of language acquisition process. *b)* The next stage is understanding specific objects and actions, such as: *ball, throw, jump, grasp, hand, hit, squeeze, book, etc.* c) The more complex stage is deciphering abstract concepts, such as: *compassion, empathy, uncertainty, forgiveness, friendship, determination, commensurability, envy, grudge, happiness*. However, it should be noted that instance and importance of firing of mirror neurons during the stage of deciphering abstract concepts still needs further observation and understanding.

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Nanosymposium

112. Mapping Language Onto Structure

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**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***112.02

**Topic: ***H.02. Human Cognition and Behavior

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Title: Spatial-temporal dynamics of neural activity in Broca’s area during sentence completion measured with intracranial EEG

Authors: *Y. WANG[1], A. VALENZUELA[2], A. ALHOURANI[3], W. J. LIPSKI[4], M. RICHARDSON[3], N. E. CRONE[5]

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Abstract: While it is widely accepted that Broca's area plays an important role in spoken word production, its exact role remains controversial. Hagoort's memory, unification and control (MUC) model proposes that Broca's area and adjacent cortex is a key language network node that is important for unification of anatomically distributed syntactic, phonological, and lexical-semantic representations during comprehension and production of sentences. Here, unification is the outcome of competition and selection among viable candidates for a contextually determined lexical representation. Previous neuroimaging studies have compared activations in Broca's area for sentences with higher demands on unification compared to less demanding sentences. However, most of these studies do not provide a sufficiently detailed picture of its spatial-temporal dynamics. Direct intracranial cortical recordings such as electrocorticograpy (ECoG) and stereo-EEG (SEEG) offer a unique opportunity to overcome these limitations. Here we recorded high gamma (70-120Hz) activity from two patients undergoing invasive monitoring for seizure localization. Both patients performed a sentence completion task in which they were instructed to covertly read a sentence word by word, and to complete the sentence with one overtly spoken word. The sentences varied in number of words as well as cloze probability, the probability that a participant will choose to end a sentence stem with a specific word, based on previous performance by normal subjects. Our hypothesis was that the process of lexical selection during this task requires unification of contextually determined representations that accumulate during sentence comprehension. With high cloze probability sentences, this unification process is highly determined and easily converges on few lexical targets, whereas with low cloze probability sentences, more targets are possible, making unification and selection more difficult. We found that the high gamma activation in Broca's area accumulated throughout stimulus presentation in a word-by-word manner, and decreased right after the last word, just before response articulation. Most importantly, its activation was higher during low cloze probability sentences than during high cloze probability ones around 200-400ms after stimulus offset. Our findings appear to be consistent with a chief prediction of the MUC model in that it requires more Broca's area activation with higher demands on unification.

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Nanosymposium

112. Mapping Language Onto Structure

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Title: Anterior-posterior gradient within ventro-occipito-temporal reading regions: Functional and structural MRI converging evidence

Authors: *G. LERMA-USABIAGA[1], M. CARREIRAS[1,2], P. M. PAZ-ALONSO[1]
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Abstract: The ventral occipito-temporal (vOT) association cortex significantly contributes to recognize different types of visual patterns. It is widely accepted that a subset of this circuitry becomes trained to perform the task of rapidly identifying word-forms. However, there are still important open questions unanswered: how is the functional contribution of the different cortical regions to the visual word recognition? Does function relate to the structural connectivity of vOT regions with other language areas? There are previous reports of functional dissociations along the vOT. Structurally, while some authors report connections between the vOT and the posterior parietal cortex (pPC) via the vertical occipital fasciculus, others highlight more anterior vOT-pPC connections through the arcuate fasciculus. Characterizing the vOT connectivity pattern can be critical to shed further light on the computational role of the VWFA. Here we present the results of a multimodal (functional, diffusion-weighted and quantitative) study including 100 MRI sessions with young adults aimed at investigating the functional and structural connectivity patterns of the vOT reading regions. To examine how functional contrasts selection influence the location of the VWFA, we used the most relevant contrasts reported in the literature. Furthermore, due to the large intraindividual variability present in previous studies, our analyses were performed at the individual-subject level, and half of the subjects were scanned twice to check for test-retest reliability. Finally, we examined the contribution of the vOT regions to word, pseudo-word and consonant string reading. Our results revealed a functional gradient across different functional contrasts that goes along the anterior-posterior vOT, and that was concurrently associated with the differences in vOT-pPC structural connectivity previously reported. Reading behavior was predicted by functional activation in these vOT regions and by the structural properties of the white matter fiber tracts linking vOT with other regions within the reading network. We propose a new subdivision of the vOT reading regions, and a reproducible procedure of interest for researchers working in this area.

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112. Mapping Language Onto Structure

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**Topic: ***H.02. Human Cognition and Behavior

Support: ERC, facessvep 284025

Title: A comprehensive cartography of selective responses to letters and words in the left ventral temporal cortex with direct recordings of neural activity

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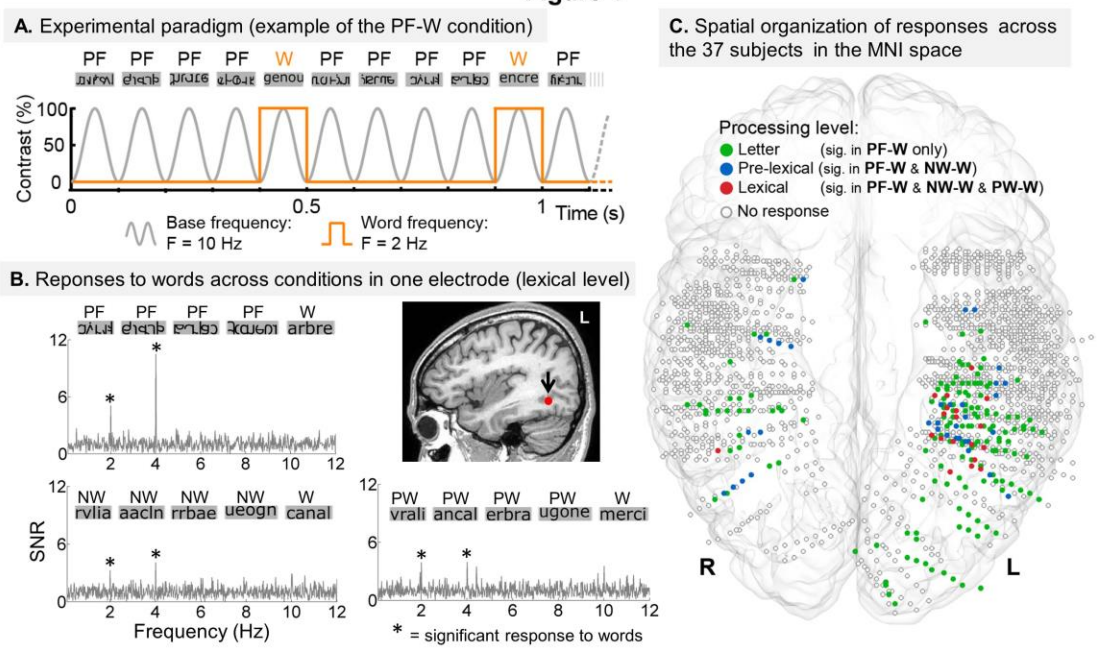
Abstract: The central role of the left ventral occipito-temporal cortex (VOTC) in reading is widely accepted but its precise functional organization and specialization remain largely unknown. Here we report a comprehensive mapping of VOTC selective responses to visual words with intracranial EEG recordings in a large human population (N=37). Using a paradigm validated on the scalp with electroencephalography (Lochy et al., 2015), participants viewed 3 types of sequences of visual stimuli varying in word-likeness (pseudo-fonts: PF, non-words: NW, or pseudo-words: PW), displayed periodically at a fast rate (10 Hz). Various words (W) were inserted every 5 stimuli, i.e. at a 2 Hz frequency (Figure 1A). Selective neural responses to words were objectively identified in the frequency domain at 2 Hz and harmonics (Figure 1B) and were assigned to a hierarchical level of processing according to the combination of significant responses to words across conditions (significant word response only among PF = letter level; word response among PF and NW = prelexical level; word response among PF, NW and PW = lexical level; Figure 1B for a lexical response). We report 2 key findings. First, while letter-selective responses were widely distributed across the left VOTC, higher level responses (prelexical and lexical) were restricted to the left fusiform gyrus (Figure 1C), showing a hierarchical spatial organization between letter and prelexical/lexical representations. Second, we found evidence for pure lexical responses (Figure 1B), providing direct evidence of specific representation for words in the VOTC. Given the brief presentation time of words (100ms SOA) with forward- and backward-masking, we interpret these responses as reflecting whole-word visual representations rather than semantic representations. Overall, these observations clarify the functional organization of reading in the VOTC with objective intracerebral responses during fast periodic visual stimulation.

Figure 1



Disclosures: J. Jonas: None. **A. Lochy:** None. **C. Jacques:** None. **S. Colnat-Coubois:** None. **L. Maillard:** None. **B. Rossion:** None.

Nanosymposium

112. Mapping Language Onto Structure

Location: 147B

Time: *Sunday, November 12, 2017, 8:00 AM - 11:00 AM

Presentation Number: *112.05

Topic: *H.02. Human Cognition and Behavior

Title: Semantic similarity effect for written words in left perirhinal cortex: Influence of type of property retrieved, visual versus nonvisual

Authors: *A. G. LIUZZI[1], P. DUPONT[2], R. PEETERS[3], S. DE DEYNE[4], G. STORMS[4], R. R. VANDENBERGHE[5]
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Abstract: An increasing number of studies have demonstrated that left perirhinal activity patterns code for semantic similarity between concrete written words. Here we examine how

these effects are influenced by the type of property retrieved, visual versus nonvisual, and by the input-modality, picture versus written word.
An event-related fMRI study was run on a Philips Achieva dstream 3T equipped with a 32-channel head coil in 18 subjects. Twelve animate (mammals, birds, insects) and 12 inanimate entities (kitchen tools, clothes, music instruments) (De Deyne et al.,2008) were presented as either a written word or a picture. From the concept-feature matrix 52 properties were evaluated online by 11 healthy volunteers who judged on a 1-7 rating scale the degree to which each property was visual or nonvisual. Four visual and 4 nonvisual properties for each subcategory were selected. From the word association matrix (De Deyne et al.,2016), the pairwise semantic cosine similarity was calculated for each pair of items (semantic matrix). During fMRI, subjects performed a property verification task. fMRI data were modelled using a General Linear Model (GLM). By calculating the pairwise cosine similarity between every pair of trials, 10 fMRI matrices in perirhinal cortex were generated: for written words, pictures, written words and pictures pooled, crossmodal effect, visual properties, nonvisual properties, visual properties for written words, nonvisual properties for written words, visual properties for pictures, nonvisual properties for pictures. A representational similarity analysis between the semantic matrix and each fMRI matrix was conducted by using one-tailed statistical threshold of $P < 0.05$.
A 3-way repeated measures ANOVA with reaction times as outcome showed a main effect of input-modality (written words: 1.7s pictures: 1.63s) ($F(1,15)=31.9$ $p=.000$) and property (non-visual: 1.69s; visual: 1.63s) ($F(1,15)=17.60$ $p=.001$). The accuracy of responses was 70.8%. The correlation between semantic similarity and the similarity of activity patterns in left perirhinal cortex was significant for written words (Pearson correlation (r) = 0.15 p = 0.0086), written words and pictures pooled (r = 0.20 p = 0.001), for crossmodal word-picture pairs (r = 0.20 p = 0.0002) and for the retrieval of visual properties for written words (r = 0.14 p = 0.013) but not for nonvisual properties (r = -0.03 p = 0.7) and neither for visual or nonvisual properties of pictures (r = -0.0058 p = 0.52, r = 0.07 p = 0.13).
The effect of type of property and input-modality leads us to hypothesize that left perirhinal cortex mediates mnemonic retrieval of properties of referents of concrete written words.

Disclosures: A.G. Liuzzi: None. **P. Dupont:** None. **R. Peeters:** None. **S. De Deyne:** None. **G. Storms:** None. **R.R. Vandenberghe:** None.

Nanosymposium

112. Mapping Language Onto Structure

Location: 147B

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**Topic: ***H.02. Human Cognition and Behavior

Support: FWO GOAO9.13
KU Leuven OT/12/097
BelSpo P7/11

Title: Cytoarchitectonic mapping of semantic similarity in the intraparietal sulcus

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Abstract: A recent study (Devereux et al 2013) has revealed effects of semantic similarity in left middle intraparietal sulcus (IPS) during category naming. This is surprising given the fact that patient lesion studies do not provide evidence of a semantic deficit following IPS lesions. Using event-related fMRI in a total of 46 participants, we examined the replicability of this effect under passive viewing conditions and the potential role of visuoperceptual similarity. We examined its anatomical specificity within a cytoarchitectonic reference frame and its relation to object identity and location effects in IPS. Visuoperceptual similarity was modelled based on three models: the HMAX model, a deep convolutional learning model based on AlexNet, and a model based on subjective visuoperceptual similarity ratings. Semantic similarity was calculated from a concept-feature matrix obtained in more than 1000 subjects (De Deyne et al, 2008). Among the IPS regions examined, only left middle IPS showed a semantic similarity effect. The effect was significant in each of the hIP subregions (hIP1, hIP2, hIP3). The semantic similarity effect in left middle IPS was significantly stronger than in the right middle IPS and also stronger than in the left or right posterior IPS. None of the measures of visuoperceptual similarity correlated with similarity of activity patterns in left middle IPS. Object identity effects were widespread across nearly all parietal areas examined. Location effects were relatively specific for posterior IPS and area 7 bilaterally. To conclude, the current findings replicate the semantic similarity effect in left middle IPS under passive viewing conditions, demonstrate its anatomical specificity within a cytoarchitectonic reference frame, and render a visuoperceptual account unlikely as an explanation.

Disclosures: R.R. Vandenberghe: None. **V. Neyens:** None. **R. Bruffaerts:** None. **R. Vogels:** None. **P. Dupont:** None.

Nanosymposium

112. Mapping Language Onto Structure

Location: 147B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***112.07

**Topic: ***H.02. Human Cognition and Behavior

Support: NSF BCS-1533664

Title: Bayesian probabilistic map to localize essential cortical language sites

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Abstract: Population studies of stimulation language mapping have suffered four major problems. First, current is applied to the surface - either by subdural grid electrodes in seizure mapping or by a stimulator in awake mapping. Second, sparse sampling due to integration across small cohorts limits statistical power. Third, registration between patients has traditionally been measured relative to coarse anatomic landmarks like the tip of the frontal or temporal lobes. Fourth, the statistics used to generate population-level probabilistic estimates of language do not consider the strong clinical bias to focus evaluation on canonical language sites. We address these concerns with a study of cortical stimulation mapping involving 4 distinct processes: picture naming, auditory naming to definition, auditory sentence repetition, and motor function. First, we integrate stimulation mapping from 3 sources: awake mappings (n = 36), subdural grid electrodes (n = 66), and stereotactic depth electrodes (n = 31). Second, this large cohort has complete coverage of lateral and ventral temporal regions. Third, we implement a surface-based registration that co-localizes positive and negative stimulation sites between patients based on patterns in cortical topology. Fourth, we analyze this data within a Bayesian statistical framework; specifically, an independent beta-binomial model at each node of the group cortical mesh beginning with a non-informative prior distribution. In these 133 patients (60 male, 73 female, mean 31 years old, mean 97 IQ), 3289 unique sites were evaluated for language and motor function. Picture naming was disrupted at 347 sites, auditory naming to definition at 298 sites, auditory repetition at 235 sites, and motor function at 403 sites. We identify four language sites: inferior frontal gyrus, superior temporal gyrus, ventral temporal cortex, and dorsolateral prefrontal cortex. This analysis constitutes a significance advance in population-level stimulation maps of human language.

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Nanosymposium

112. Mapping Language Onto Structure

Location: 147B

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**Presentation Number: ***112.08

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH RO1DC014589

Title: Chronology of activity in pre-motor articulation sites

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Abstract: People can generate the name for an object and articulate that word with remarkable speed, precision, and fluency. Unfortunately, language is lost in millions of people each year due to trauma, stroke, neuro-degeneration, and neoplasms with devastating impact to social interaction and quality of life. We seek to characterize the temporal dynamics of brain regions involved in speech articulation. Current models of speech production instantiated in neurobiology recruit a lateralized peri-sylvian network, but these neurobiological correlates and their dynamics have not been formalized. We leverage the unique advantages of electrocorticography in a large cohort with both surface and penetrating electrodes (excellent spatiotemporal resolution, direct full spectrum recordings, and complete cortical coverage) to study the cognitive processes leading to articulation in a picture naming paradigm. The cohort consisted of 86 patients (40 Male, 46 Female, mean 27 years old, mean IQ 103) with left hemispheric language dominance. 14095 electrodes were implanted (3516 excluded), accumulating coverage over more than 95% of the cortical surface in both hemispheres. To delineate nodes of the bilateral articulatory network, we implemented a surface-based mixed-effects multilevel analysis of broadband gamma activity (60 - 120 Hz). We identified the dorsal and ventral visual processing streams as well as 9 distinct nodes within the articulatory network (presented by temporal sequence of activation): pre-SMA, SMA-proper, anterior insula, pars triangularis, pars opercularis, anterior and posterior subcentral gyrus, sylvian parietal-temporal junction, and superior temporal gyrus. The relative timing of these regions in both hemispheres is presented.

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Nanosymposium

112. Mapping Language Onto Structure

Location: 147B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***112.09

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH Grant U01 NS098981

Title: Phonological and lexical streams of reading revealed by intracranial recordings

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Abstract: Objective: We investigate the putative phonological and lexical streams of reading by means of intracranial recordings as part of an ongoing Brain Initiative project that aims at creating a unified model of reading.
Methods: Seven patients with epilepsy who had been implanted with depth or subdural electrodes over the left hemisphere were asked to read single words. Word stimuli consisted of regular words (W), exception words (EW) (lexical valid and addressed phonology), pseudohomophones (PH) (lexically valid but requiring phonologic assembly) and pseudowords (PW) (lexically invalid). Data were analyzed by computing averaged spectrograms for each recording location, and averaging spectrograms across contacts located in the same anatomical brain region at the individual level. Further, averaging across brain regions was performed at the group level, and significant gamma band activations (more than 4 SD change from baseline) were compared across conditions. All results are reported for left hemisphere brain structures.
Results: All four conditions showed early activations in the fusiform gyrus at 80ms after stimulus onset. When the neural time series were aligned to articulation onset, the subcentral gyrus activated 100ms earlier for PW and PH than for W and EW. Pars triangularis activated approximatively 50ms earlier for PW and PH and maintained higher activation than W and EW until articulation completed. Pars opercularis also exhibited higher activation for PW and PH, but with almost instant activation for all conditions, suggesting higher effort in processing non-lexical word representations. The parahippocampal gyrus activated 220ms and 40ms before articulation for W and EW, respectively, and 20ms after articulation for PS. PW did not activate parahippocampus. This timeline, and the fact that inferior temporal gyrus followed the same activation pattern as the parahippocampus, suggests involvement in memory retrieval of the word meaning and delay in semantic processing based on phonological representation of the stimuli.
Conclusion: The results show different activation patterns for reading words with various phonological complexity and having distinct lexical representations. A larger cohort with

increased spatial sampling will allow for the derivation of a model of reading based on electrophysiological evidence.

Disclosures: C. Donos: None. **P. Rollo:** None. **N. Tandon:** None.

Nanosymposium

112. Mapping Language Onto Structure

Location: 147B

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**Presentation Number: ***112.10

**Topic: ***E.04. Voluntary Movements

Support: NIH BRAIN Initiative U01 NS098969

Title: Speech encoding in the human subthalamic nucleus

Authors: W. J. LIPSKI[1], A. ALHOURANI[1], T. PIRNIA[1], P. W. JONES[1], C. DASTOLFO[2], L. B. HELOU[3], D. J. CRAMMOND[1], S. SHAIMAN[2], M. W. DICKEY[2], L. L. HOLT[4], R. S. TURNER[3], J. A. FIEZ[5], *M. RICHARDSON[1]
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Abstract: Speech production is disrupted in many neurological diseases that involve the basal ganglia. Notably, hypophonia and hypokinetic dysarthria (characterized by decreased motor gain) are prevalent in patients with Parkinson's disease (PD). Deep brain stimulation (DBS) of the subthalamic nucleus (STN) produces predictable improvements in other motor symptoms of PD but does not result in consistent improvement in speech and can negatively impact language function. However, neurophysiological models of speech production typically do not account for the involvement of basal ganglia nuclei. To examine the role of the STN in speech production, we recorded STN neuron activity, STN local field potentials (LFP), and spoken acoustics while 14 PD subjects performed a speech task during awake, microelectrode recording-guided DBS surgery. On each trial, subjects were asked to read aloud a consonant-vowel-consonant syllable presented on a computer screen. Spike waveforms were sorted into single- and multi-unit recordings. LFP signals were bandpass filtered into canonical bands (delta 2-4Hz, theta 4-8Hz, alpha 8-12 Hz, beta 13-30Hz and gamma 50-90Hz). Power changes were calculated as a z-score relative to baseline, after applying a Hilbert transform to estimate signal amplitude and phase. First, we found evidence for the participation of STN neurons in speech production. Nearly half of the unit recordings (22 of 45; 13 subjects) showed either increases or decreases in firing rate when aligned to speech onset. STN LFP recordings also showed evidence for modulation related

to speech production. Consistent with tracking the motor aspects of speech, we found an increase in gamma power in 13/14 subjects locked to the onset of speech, but not locked to cue presentation. In contrast, theta power increases were locked to cue presentation rather than speech onset (11/14 subjects), and this modulation was associated with an increase in inter-trial phase consistency (ITPC) (7/14 subjects), suggesting a role for theta-encoding in cognitive processing prior to speech onset. Likewise, we observed alpha and beta power decreases locked to cue presentation, but not to speech onset. In a subset of these recordings, we observed differences in both alpha and beta ITPC that were specific to whether the presented stimulus was a real word or a non-word. Lastly, we observed delta power and ITPC increases in relation to both cue presentation and speech onset (11/14 subjects), further suggesting that several types of speech-related information transfer occur within the STN. These results provide a foundation for continued work to develop a detailed model of basal ganglia participation in speech.

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Nanosymposium

112. Mapping Language Onto Structure

Location: 147B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***112.11

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH Grant R01MH107513

Title: The interactive brain model: An emerging theoretical framework for two-person social communication

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Abstract: Although spontaneous and natural human-to-human communication is an essential social behavior, dynamic neural mechanisms for these processes are not well-understood. The current knowledge gap reflects limitations of conventional neuroimaging methods, including solitary confinement in scanners and minimal tolerance of head movement. These limitations are substantially resolved by recent technical developments in functional near-infrared spectroscopy (fNIRS), a non-invasive spectral absorbance technique that detects changes in cortical blood

oxygen levels with surface-mounted optical sensors. Functional NIRS is tolerant of limited head motion and enables simultaneous acquisitions of hemodynamic signals from interacting dyads in natural conditions. The goal of this investigation is to advance an evidence-based theoretical framework for two-person social interaction. We used an 84-channel NIRS system (Shimadzu LABNIRS) with 42 channels covering both hemispheres of each participant to acquire deoxyhemoglobin signals during live two-person interactions. The paradigm was motivated by the Interactive Brain Hypothesis[1], which proposes that interpersonal interaction between individuals evokes unique, specialized, and dynamic neural mechanisms. Interacting dyads (58 participants) alternated between 15 s talking and listening epochs under two conditions: dialogue (interactive) and monologue (non-interactive). Left inferior frontal (Broca's) and temporoparietal (Wernicke's) regions were associated with talking and listening tasks, and served as functionally defined regions-of-interest. We tested two hypotheses: 1) talking and listening language mechanisms are upregulated and extended during interaction; and 2) signal coherence between dyads increases during interaction. Signals acquired during listening epochs increased within Wernicke's regions during dialogue ($p<0.05$); however, speech processes were not similarly modulated, and did not support the hypothesis. Consistent with these findings, cross-brain coherence of signals increased between Wernicke's regions and the subcentral area during dialogue relative to monologue ($p<0.01$). Two fundamental components of an Interactive Brain Model, neural specialization and cross-brain coherence, emerge from these results: 1) left temporoparietal regions include specializations that are responsive to two-brain verbal interactions, and 2) cross-brain signal coherence is a novel indicator of these dynamic mechanisms.

[1] Di Paolo, E., & De Jaegher, H. (2012). The interactive brain hypothesis. *Frontiers in Human Neuroscience, 6*(163). doi: 10.3389/fnhum.2012.00163

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Nanosymposium

112. Mapping Language Onto Structure

Location: 147B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***112.12

**Topic: ***H.02. Human Cognition and Behavior

Title: Motor system contributions to cross-linguistic translation when deaf signers read English

Authors: *L. C. QUANDT[1], E. M. KUBICEK[2]
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Abstract: When a bilingual person reads in one language, words may be automatically translated into another known language, a process known as cross-linguistic translation. While this process is established in bilingual, unimodal people (those who use two spoken languages), there is less known about how deaf bilinguals link meaning between languages that rely on different modalities--written language (e.g., English) and signed language (e.g., American Sign Language, ASL). There is some evidence suggesting that when deaf signers read English, there may be automatic translation into ASL (cross-linguistic, cross-modal translation). Phonological and semantic processes in the canonical language networks have been implicated in this process, but it is unknown to what extent action simulation in the brain's motor system also plays a role in cross-modal, cross-linguistic translation. Since sign language uses motion and space to convey linguistic content, it is possible that motor system of the brain plays an important role in linking meaning between the two languages in addition to those regions traditionally considered part of the language network. We performed an EEG experiment to test whether deaf signers automatically simulate motor production of the ASL-translated signs of English words as they read. We hypothesized that there would be greater mu rhythm suppression (i.e., activity of primary somatosensory and motor cortex) during the reading of English words whose ASL translations use two hands ("2-handed words"), compared to English words whose ASL translations use only one hand ("1-handed words"). The two groups of English words were matched for frequency, length, and other linguistic parameters. Simulation of signs that use two hands would presumably recruit greater activity in sensorimotor cortices due to the increased motor processing required in contrast to signs that use only one hand. We recorded EEG from deaf participants fluent in ASL as they read individual English words, half of which were "2-handed words", and half of which were "1-handed words". Event-related spectral perturbations (ERSPs) in the alpha/mu-range were calculated for the two conditions at central electrode sites, and paired comparisons showed significantly more mu rhythm suppression when participants read "2-handed words" compared to "1-handed words". This finding suggests that motor aspects of ASL translations are activated when English words are read. These results provide the first evidence of involvement of the motor system in the process of cross-linguistic, cross-modal translation, and suggest that action simulation processes may be key to deaf signers' language concepts.

Disclosures: L.C. Quandt: None. **E.M. Kubicek:** None.

Nanosymposium

113. Optical Methods for Connectivity

Location: 150B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***113.01

**Topic: ***I.04. Physiological Methods

Title: Engineering hybrid genetically encoded voltage indicators incorporating Janelia Fluor dyes for *In vivo* voltage imaging

Authors: *A. S. ABDELFATTAH, T. KAWASHIMA, J. GRIMM, A. MUTHUSAMY, M. AHRENS, L. LAVIS, E. SCHREITER
Janelia Res. Campus, Ashburn, VA

Abstract: Voltage imaging using genetically encoded fluorescent voltage indicators (GEVIs) has emerged as a powerful approach for detecting neuronal activity with high spatial and temporal resolution. For a GEVI to successfully report action potentials with high fidelity, it needs to combine sufficient response amplitude, bright fluorescence, and fast kinetics. An inherent problem in voltage imaging is the requisite high frame rate and intense illumination, which can lead to rapid photobleaching of the indicator[1]. There has been tremendous progress in GEVI engineering over the past few years, resulting in designs based on fluorescent proteins and microbial opsins. However, the intrinsic brightness and photostability of their chromophores limits their utility for voltage imaging experiments that demand high excitation power. To address this issue, we engineered GEVIs that utilize the bright and photostable Janelia Fluor dyes[2] together with self-labeling protein tags. In our hybrid design, a self-labeling protein tag (e.g HaloTag[3] or SNAP-tag[4]) is fused to microbial rhodopsins and can be targeted to specific cell types. Dye-tag conjugates are then used to covalently attach the fluorophore selectively in the targeted cell types expressing our voltage constructs. Voltage-dependent fluorescence changes rely on energy transfer (FRET) between the fluorophore emission and opsin retinal absorption. Action potentials are reliably observed in cultured neurons using dyes emitting between 500-650 nm (Fig. 1). In neuron culture, the hybrid indicators are significantly brighter and more photostable than existing GEVIs, extending productive imaging time by more than 10x. Furthermore, we are able to deliver the dye-tags *in vivo*, and we demonstrate the utility of our hybrid voltage indicators to report activity in genetically labeled zebrafish neurons during fictive behavior.

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2Grimm, J. B. *et al*. *Nat. Methods* **12**, 244-250, (2015)
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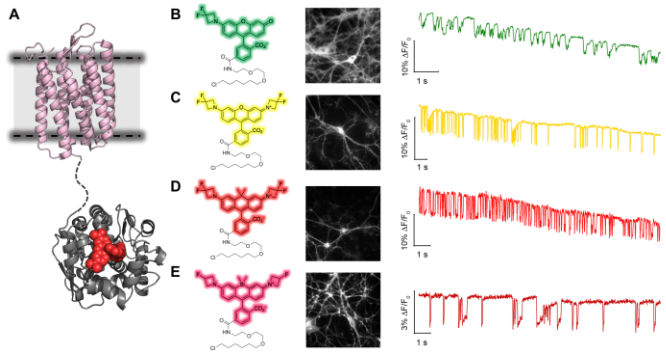

Disclosures: **A.S. Abdelfattah:** None. **T. Kawashima:** None. **J. Grimm:** None. **A. Muthusamy:** None. **M. Ahrens:** None. **L. Lavis:** None. **E. Schreiter:** None.

Nanosymposium

113. Optical Methods for Connectivity

Location: 150B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***113.02

**Topic: ***I.04. Physiological Methods

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The General Program of National Natural Science Foundation of China, project 31671118
The General Program of National Natural Science Foundation of China, project 31371442

Title: Developing a genetically-encoded ACh indicator

Authors: *M. JING[1], P. ZHANG[2], G. WANG[2], H. JIANG[1], L. MESIK[3], J. FENG[1], L. I. ZHANG[3], M. LUO[4], J. ZHU[2], Y. LI[1]
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Abstract: Acetylcholine (ACh) regulates a diverse array of physiological processes throughout the body, yet cholinergic transmission in the majority of tissues/organs remains poorly understood due primarily to the limitations of available ACh-monitoring techniques. We here developed a family of G-protein-coupled receptor activation-based ACh sensors (GACh) with sensitivity, specificity, signal-to-noise ratio, kinetics and photostability suitable for monitoring ACh signals *in vitro* and *in vivo*. The GACh sensors were constructed by inserting circular permutated fluorescent protein (cpFP) into loops of muscarinic acetylcholine receptors, and screened through random mutagenesis focusing on the interface between receptors and fluorescent proteins. The GACh sensors which successfully convert the conformational change to the fluorescence response were further characterized for their performance in cultured cells, acute brain slices and *in vivo* in flies and mice. In all preparations, GACh sensors selectively responded to exogenous and/or endogenous ACh with robust fluorescence signals that were captured by epifluorescent, confocal and/or two-photon microscopy. Moreover, analysis of endogenous ACh release revealed firing pattern-dependent release and presynaptic regulated transmission, which provides critical information for the central cholinergic transmission. Thus, GACh sensors provide a convenient, broadly applicable tool for monitoring cholinergic transmission underlying diverse biological processes.

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Nanosymposium

113. Optical Methods for Connectivity

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**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***113.03

**Topic: ***I.04. Physiological Methods

Title: Ultrasonically sculpted optical patterns for light delivery and beam steering within the brain tissue

Authors: *M. SCOPELLITI[1], E. CONTE[3], A. H. GITTIS[2], M. CHAMANZAR[1]
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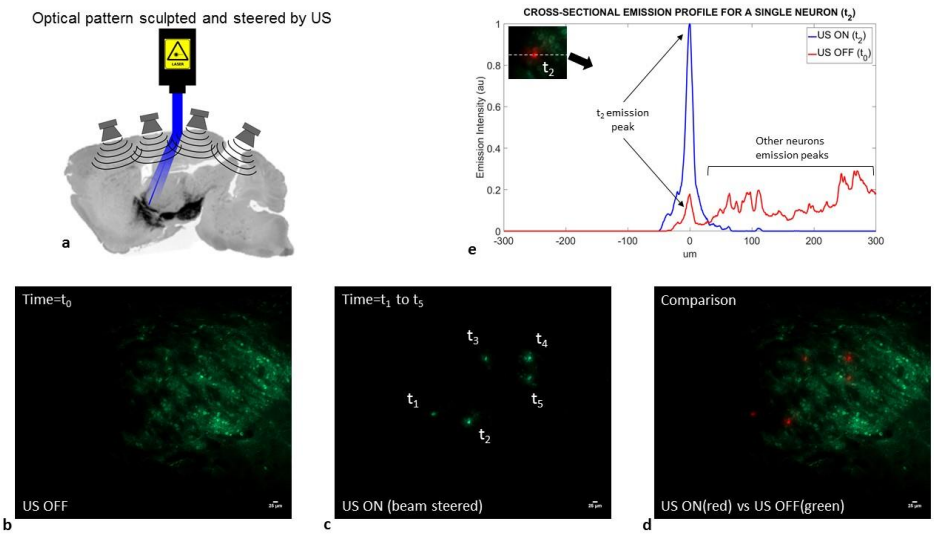
Abstract: We use non-invasive ultrasound to define and steer the trajectory of light within the brain tissue. Ultrasonic waves, launched from outside the brain using an array of piezoelectric transducers can propagate deep into the tissue with minimal scattering and absorption (propagation loss in the range of ~0.3-0.6 dB/(cm·MHz). Such pressure waves compress the tissue locally at the peak positive pressure and rarefy it at the peak negative pressure, thus modulating the refractive index of the medium. Using a pulsed ultrasound that can create a peak pressure of 11 MPa, a refractive index contrast of $\sim\Delta n=1.8\times 10^{-3}$ can be achieved, which is sufficient to confine a guided optical mode within tissue. We demonstrated that these ultrasonically sculpted waveguides can be steered within the tissue by changing the ultrasonic interference patterns externally. Different areas of a brain slice cut in the parasagittal orientation were illuminated (over a $1mm^2$ region) using our ultrasonically sculpted optical waveguides. Blue light at the peak absorption of Channelrhodopsin-2 (ChR2) at $\lambda = 475$ nm was confined and guided within the tissue and the Green Fluorescent Protein (GFP) emission in the target location was imaged with a spatial resolution of 45 μm (see Figure). To prove the efficacy of our method for delivering light deep into the tissue and counterbalancing the scattering within tissue, we also used large artificial tissue phantoms (2 mm thick), having brain-like properties (density ~ 1.03 g/cm^3, acoustic impedance $\sim 1.6x10^6$ $Kg/sec.m^2$, and reduced scattering coefficient ~ 13.5 cm^{-1}), where we observed light confinement and guiding deep into the medium. In the presentation, we will demonstrate optical imaging of the trajectory of the sculpted optical waveguide deep into the tissue using optical reporters such as GFP and mCherry. We will also discuss the potential of this technique for excitation of opsins such as ChR2 and Arch in transgenic mouse brain tissue with high spatial and temporal resolution.



Disclosures: **M. Scopelliti:** None. **E. Conte:** None. **A.H. Gittis:** None. **M. Chamanzar:** None.

Nanosymposium

113. Optical Methods for Connectivity

Location: 150B

Time: *Sunday, November 12, 2017, 8:00 AM - 10:15 AM

Presentation Number: *113.04

Topic: *I.04. Physiological Methods

Support: NSF Award #1512794

Title: Flexible Parylene waveguides monolithically integrated with vertical input/output ports for high-resolution optogenetic stimulation

Authors: ***J. REDDY**[1], M. CHAMANZAR[2]
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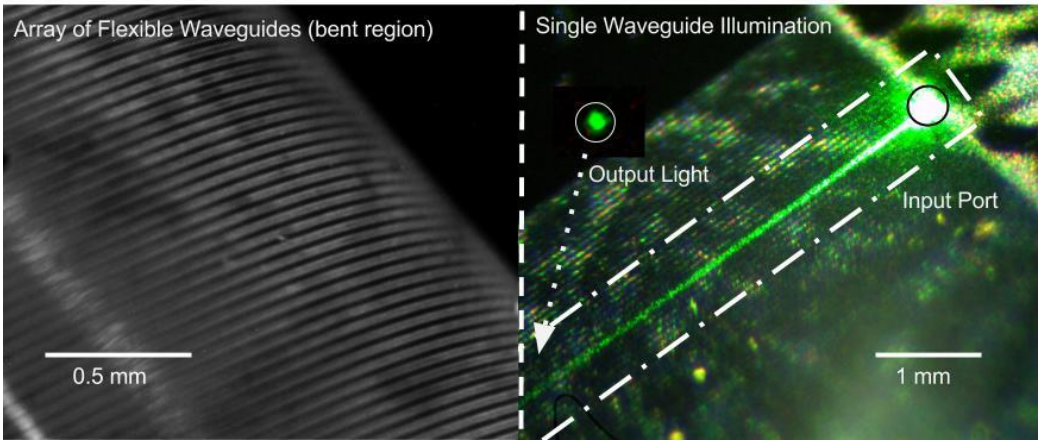
Abstract: To achieve high spatial resolution in optogenetic stimulation, light must be delivered to specific regions within the brain tissue using compact optical waveguides that can be safely implanted with minimal damage to the tissue, for which flexible polymer waveguides are preferred over rigid dielectrics and semiconductor materials. Polymer optical waveguides have previously been demonstrated in SU8 and PDMS. Here, we demonstrate a high-density array of optical waveguides entirely made in Parylene, a biocompatible polymer that is widely used as the insulation layer in neural probes. Taking advantage of the refractive index contrast between Parylene-C and Parylene-N ($\Delta n = 0.022$), we show that light can be confined and guided in

compact (core ~ 5x5 μm) waveguides. Most implementations of optrodes are based on end-fire launching of light out of the waveguide facet to illuminate a volume of brain tissue at the tip of the shank. Here, we present input/output optical ports with integrated micromirrors designed such that the illumination volume is vertical to the flexible probe surface, allowing for the co-location of optical stimulation with additional planar layers of surface recording electrodes. We demonstrate light guiding in a high-density array of compact (5 μm – 30 μm) Parylene waveguides functioning across the range of optogenetic wavelengths (λ= 460 – 630 nm). An example is shown below, where only one waveguide in an array is selectively excited to deliver light over a 2 cm distance. We will discuss the potential application of such waveguides for optogenetic stimulation of Channelrhodopsin-2 (ChR2) in transgenic mouse brain tissue and demonstrate patterned illumination using the waveguide array in brain tissue by imaging the Green Fluorescence Protein (GFP) emission.

An array of high-density waveguides, where a bent region is shown.

A single waveguide excited through a vertical micromirror input port. The output beam (at the end of the waveguide) is shown in the inset.



Disclosures: **J. Reddy:** None. **M. Chamanzar:** None.

Nanosymposium

113. Optical Methods for Connectivity

Location: 150B

Time: *Sunday, November 12, 2017, 8:00 AM - 10:15 AM

Presentation Number: *113.05

Topic: *I.04. Physiological Methods

Title: Pan-neuronal calcium imaging of prey capture and reward circuitry in freely swimming larval zebrafish

Authors: *J. C. MARQUES[1,1], D. KIM[1], I. BIANCO[2], D. ROBSON[1], J. LI[1]
[1]Rowland Inst. at Harvard, Cambridge, MA; [2]Univ. Col. London, London, United Kingdom

Abstract: In order to survive in a changing environment, animals adapt their behaviour in order to maximize rewards. A prevailing view is that reward circuits in the brain evaluate the consequences of actions by computing prediction errors, comparing actual and predicted outcomes and updating the value of actions. Reward-related signals have been observed in many regions of the vertebrate brain and in neurons with various chemical identities. Fundamental questions in neuroscience are 1) what are the specific neural computations that exist in these brain-wide reward networks and 2) how do these neural signals contribute to produce adaptive and flexible behaviours? A prime example of a flexible adaptive behaviour that involves rewards is hunting behaviour in larval zebrafish. While zebrafish is a promising vertebrate system for identifying reward-related signals through whole brain neural imaging, previous studies have been severely limited by the inability to record neural activity from a fast-moving animal during the entire hunting sequence. Using a high-speed tracking microscope, we recorded neural activity across the brains of larval zebrafish at single cell resolution while they hunted paramecia. Larvae captured prey at the same rate under the tracking microscope as on a setup with a stationary stage, indicating that tracking microscopy does not disturb hunting behaviour. By aligning neural activity to specific behavioural events during hunting, we can functionally link neurons throughout the brain to motor sequences and outcomes during prey capture.

Disclosures: J.C. Marques: None. **D. Kim:** None. **I. Bianco:** None. **D. Robson:** None. **J. Li:** None.

Nanosymposium

113. Optical Methods for Connectivity

Location: 150B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***113.06

**Topic: ***I.04. Physiological Methods

Support: Simons Foundation Grant SCGB 324285

Title: Whole brain neural dynamics and behavior in *C. elegans*

Authors: *A. LEIFER, A. LINDER, J. NGUYEN
Princeton Univ., Princeton, NJ

Abstract: How does a simple nervous system generate animal behavior? To tackle this question we developed a suite of optical neurophysiology tools to manipulate and measure neural activity

from populations of neurons in the nematode C. elegans as it crawls freely, including a whole-brain imaging system that records intracellular calcium transients from over 150 neurons as the animal moves. To account for animal motion, we developed a computer-vision and machine-learning based image analysis pipelines that automatically segments and tracks neurons through time even as the brain undergoes very large motion and deformation. We are using this technology platform to investigate how neural dynamics generate animal behavior. We present decoders that predict the animal's current behavior from population neural activity, and show preliminary work investigating neural coordination of longer-timescale behaviors.

Disclosures: **A. Leifer:** None. **A. Linder:** None. **J. Nguyen:** None.

Nanosymposium

113. Optical Methods for Connectivity

Location: 150B

Time: *Sunday, November 12, 2017, 8:00 AM - 10:15 AM

Presentation Number: *113.07

Topic: *I.04. Physiological Methods

Support: Burroughs Wellcome Fund Career Award at the Scientific Interface
NSF Brain Eager Award IOS-1452593
NIH R01NS082525-01A1

Title: Whole-brain imaging in freely-moving *C. elegans*

Authors: ***V. VENKATACHALAM**[1], V. SUSOY[2], M. WU[3], W. HUNG[4], M. ZHEN[4], A. D. SAMUEL[2]
[1]Physics, [2]Harvard Univ., Cambridge, MA; [3]Univ. of Toronto, Mount Sinai Hospital, Lunenfeld-Tanenbaum Res. Inst., Toronto, ON, Canada; [4]Mount Sinai Hospital, Lunenfeld-Tanenbaum Res. Inst., Toronto, ON, Canada

Abstract: The nematode *Caenorhabditis elegans* is an ideal model for systems neuroscience because it offers the possibility of in vivo recording of the activity of the entire brain at a single-neuron resolution in unrestrained animals. Using a customized spinning disk confocal microscope and using newly optimized *C. elegans* strains that express nuclear-localized GCaMP6 for visualization of neuronal activity, we have been able to make extended recordings of the multi-neuronal activity and motor behavior in individual freely moving *C. elegans* across a range of ecologically-relevant conditions. In particular, we have been focusing on the neuronal bases of male mating behavior, perhaps the most complex behavior exhibited by *C. elegans*. During mating, a male worm needs to constantly modify his motor output in response to multiple sensory stimuli to succeed in achieving his goal. We have been able to make recordings of

activity of all neurons in the male tail during the entire sequence of courtship and mating including navigation towards the hermaphrodite, response to contact, turning, vulva location, spicule insertion, sperm release, and a refractory period. Using these recordings of unprecedented detail, completeness, and length, we can now follow the progression of neuronal responses from known sensory inputs to motor outputs and identify relationships between different parts of neuronal networks that result in behavioral transitions.

Disclosures: V. Venkatachalam: None. **V. Susoy:** None. **M. Wu:** None. **W. Hung:** None. **M. Zhen:** None. **A.D. Samuel:** None.

Nanosymposium

113. Optical Methods for Connectivity

Location: 150B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***113.08

**Topic: ***I.04. Physiological Methods

Title: Pan-neuronal calcium imaging in freely swimming larval zebrafish by high speed tracking microscopy

Authors: D. N. ROBSON, D. KIM, J. KIM, J. MARQUES, W. GU, *J. LI
Rowland Inst., Harvard Univ., Cambridge, MA

Abstract: Cellular resolution calcium imaging typically requires an animal to be tethered under a microscope, significantly restricting the range of behaviors that can be studied. To expand the behavioral repertoire amenable to imaging, we have developed a microscope system that enables whole brain calcium imaging in freely swimming larval zebrafish. We use high speed infrared imaging to track the target animal while it moves freely in a 50 mm circular arena, more than 12 times the body length of the animal. Based on the predicted trajectory of the brain, we apply optimal control theory to a motorized stage system to cancel brain motion in three dimensions. This motion cancellation system overcomes the immense technical challenges posed by this animal, including a peak acceleration of 20 m/s^2, similar to the acceleration of a Formula One race car. We have combined this system with Differential Illumination Focal Filtering (DIFF), a variant of HiLo microscopy, which enables us to image the brain of a freely swimming larval zebrafish for over an hour. This work greatly expands the repertoire of natural behaviors that can be studied with cellular resolution calcium imaging, including spatial navigation, social behavior, feeding and reward.

Disclosures: D.N. Robson: None. **D. Kim:** None. **J. Kim:** None. **J. Marques:** None. **W. Gu:** None. **J. Li:** None.

Nanosymposium

113. Optical Methods for Connectivity

Location: 150B

**Time: ***Sunday, November 12, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***113.09

**Topic: ***I.04. Physiological Methods

Support: K25NS083754
R01NS078223
R01NS084028
P30NS098577
14PRE18410013

Title: Hemodynamic mapping of cell-specific and resting-state functional connectivity in the awake mouse brain

Authors: *A. Q. BAUER[1], A. KRAFT[2], G. BAXTER[1], P. WRIGHT[1], M. REISMAN[3], A. BICE[1], A. SNYDER[1], M. BRUCHAS[4], J.-M. LEE[2], J. CULVER[1]
[1]Radiology, [2]Neurol., [3]Physics, [4]Anesthesia, Washington Univ. In St. Louis, Saint Louis, MO

Abstract: FMRI has transformed our understanding of the brain's functional organization. While resting state functional connectivity (RSFC) analyses are efficient for whole-brain mapping, attempts to explain RSFC on the basis of known anatomical connectivity have been only partially successful. Further, mapping subunits of a functional network is difficult with hemoglobin-only imaging paradigms. Still, blood-based methods of brain mapping remain powerful because hemoglobin provides endogenous contrast in all mammalian brains. To add greater specificity to hemodynamic imaging, we combined optogenetics with optical intrinsic signal imaging to create an optogenetic effective connectivity (Opto-EC) mapping assay (**Fig. 1A**). Using mice expressing channelrhodopsin under a Thy1 promoter, we generated Thy1-based EC (Thy1-EC) maps in awake mice that reflect how locally driven excitatory activity influences distant cortical regions. Titrated photostimuli determined which stimulus parameters elicited linear hemodynamic responses (**Fig. 1B**). Optimized stimuli were scanned over the left hemisphere (**Fig. 1C**). Generally, Thy1-EC maps exhibited higher spatial specificity than RSFC maps. Patterns of RSFC exhibited widespread ipsilateral connectivity while Thy1-EC maps contained distinct short- and long-range constellations of ipsilateral connectivity (**Fig. 1D**). Further, RSFC maps were usually symmetric about midline while Thy1-EC maps displayed more heterogeneous contralateral homotopic connectivity. We evaluated the patterns of both modalities against axonal projection connectivity (APC) from the Allen Institute (**Fig. 1E**). Thy1-EC more closely resemble APC than did RSFC. Opto-EC mapping is an efficient method for examining cell-specific connectivity in mice. In less than an hour, Opto-EC can be determined for 100 sites in a single behaving animal, making it considerably more efficient than

ex-vivo methods. Longitudinal application of Opto-EC mapping represents a powerful strategy for examining evolving connectivity-related circuit plasticity within the brain.

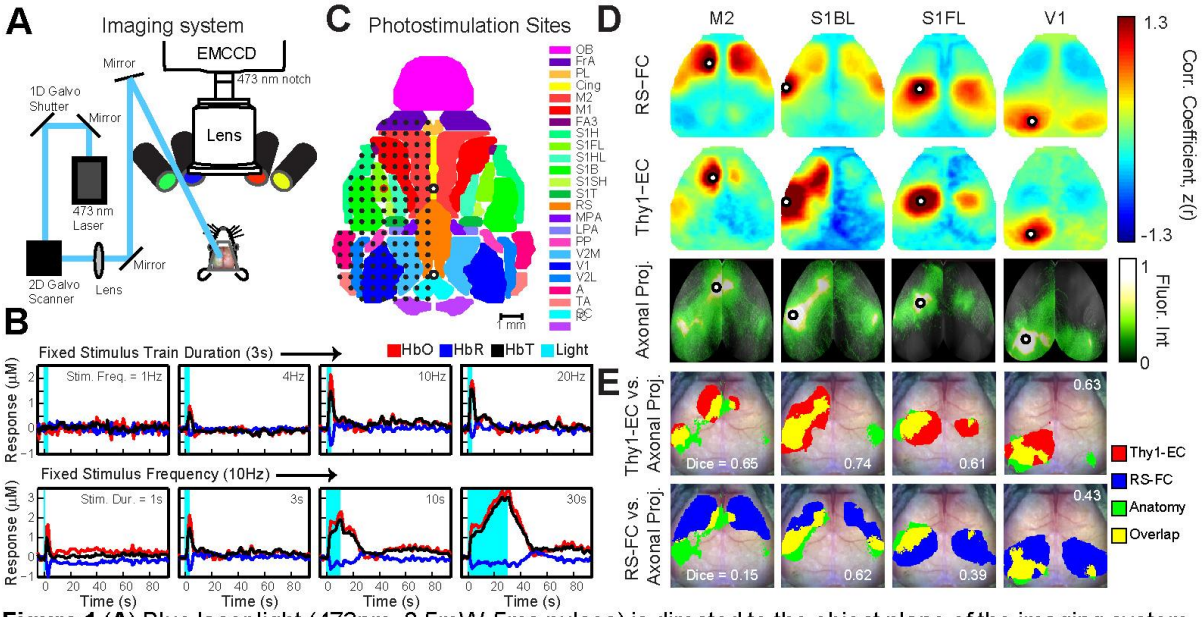


Figure 1 (**A**) Blue laser light (473nm, 0.5mW, 5ms pulses) is directed to the object plane of the imaging system. Prior to imaging, a small Plexiglas window glued to the intact mouse skull is used to secure the mouse head for imaging. (**B**) Hemodynamic responses to titrated doses of stimulus frequency (top) or duration (Bottom). Stimuli with long (>10s) duration reveal different temporal characteristics that what would otherwise be expected from physiological stimulation; therefore, 3 second, 10Hz stimuli were used for all mapping experiemnts. (**C**) Sites selected for optogenetic mapping. (**D**) Top Row: Resting state functional connectivity (RS-FC) maps using 20-30 min of data, Middle row: Maps of Thy1 effective connectivity (Thy1-EC) using 25 seconds of data, and Bottom Row: Maps of axonal projections were collected from the Allen Mouse Brain Connectivity Atlas and co-registered to OIS imaging data. M2: secondary motor; S1Bl: primary somatosensory Barrel (lateral); S1FL: primary somatosensory forelimb; V1: primary visual. (**E**) In order to calculate the spatial overlap between maps, Dice coefficients were calculated for Thy1-EC and RS-FC maps thresholded at z(r)=0.3 and axonal projection images thresholded at 50% max fluorescence intensity. Thy1-EC maps were found to be more topographically similar to structural connectivity images than RS-FC maps.

Disclosures: **A.Q. Bauer:** None. **A. Kraft:** None. **G. Baxter:** None. **P. Wright:** None. **M. Reisman:** None. **A. Bice:** None. **A. Snyder:** None. **M. Bruchas:** None. **J. Lee:** None. **J. Culver:** None.

Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

Location: 152A

Time: *Sunday, November 12, 2017, 1:00 PM - 4:30 PM

Presentation Number: *186.01

Topic: *A.07. Developmental Disorders

Support: R01 NR012686

Civitan Emerging Scholars Grant (AJK)
Pitt-Hopkins Research Foundation (JDS)

Title: Aberrant pain phenotype in a mouse model of the rare autism spectrum disorder Pitt Hopkins Syndrome

Authors: *E. J. RAHN[1], A. J. KENNEDY[2], J. W. LEWIS[1], S. G. DORSEY[3], J. D. SWEATT[4]
[1]Dept. of Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL; [2]Bates Col., Lewiston, ME; [3]Sch. of Nursing and Program in Neurosci., Univ. of Maryland Baltimore, Baltimore, MD; [4]Pharmacol., Vanderbilt Univ. Sch. of Med., Nashville, TN

Abstract: Pitt Hopkins Syndrome, a rare intellectual disability on the autism spectrum caused by haploinsufficiency of transcription factor 4 (TCF4), is purportedly associated with aberrant pain phenotypes. This study evaluated basal nociception and models of inflammatory, post-surgical, and neuropathic pain in B6/129 male mice bred for heterozygous ($^{+/-}$) deficiency in TCF4 expression and characterized relative to wild-type (WT) littermates. Mice were evaluated for basal nociceptive responses to mechanical, cold, and thermal stimuli. Inflammatory-induced acute nociception was assessed with formalin (0.1%, 1%, and 5%) administered unilaterally into the plantar surface of the hind paw. Nocifensive behaviors were recorded for 70 minutes post-formalin. Post-surgical pain was evaluated following unilateral incision of the hind paw (plantar incision model; PIM). Responsivity to mechanical and thermal stimuli in PIM mice and sham controls took place over a 22-day timecourse. Neuropathic pain was assessed utilizing the spared nerve injury (SNI) model. SNI mice and sham controls were evaluated for responses to mechanical, cold, and thermal stimulation 5 months post-injury. Additional behavioral batteries for SNI mice included: elevated plus maze, open field, novel object location memory, and CatWalk. TCF4$^{+/-}$ mice demonstrated hyperreflexivity at baseline to all mechanical, cold, and thermal stimuli with the exception of the spinally-mediated tail-flick response. Attenuated nocifensive behaviors were observed in both Phases I and II post-formalin administration (0.1%, 1%, and 5%) in TCF4$^{+/-}$ mice relative to WT controls. PIM resulted in thermal hyperalgesia and mechanical allodynia up to 7 days post-surgery in WTs. TCF4$^{+/-}$ mice with incised paws had no altered responses to mechanical stimuli relative to baseline, however thermal hyperalgesia developed relative to TCF4$^{+/-}$ shams with a timecourse similar to WTs. SNI produced robust mechanical and cold allodynia in WT mice; however TCF4$^{+/-}$ mice showed no alterations from baseline measures in response to mechanical, cold, or thermal stimulation. Additional behavioral measures in SNI mice revealed only genotypic differences, with the exception of injury-associated alterations in the CatWalk. TCF4$^{+/-}$ mice modeling the intellectual disability Pitt Hopkins Syndrome display hyperreflexive responses to basal nociceptive tests that are supraspinally mediated and attenuated pain responses to acute, post-surgical, and chronic pain models. More work is necessary to characterize this aberrant pain phenotype and determine whether other animal models of intellectual disabilities share similar alterations.

Disclosures: E.J. Rahn: None. **A.J. Kennedy:** None. **J.W. Lewis:** None. **S.G. Dorsey:** None. **J.D. Sweatt:** None.

Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

Location: 152A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***186.02

**Topic: ***A.07. Developmental Disorders

Support: NIEHS Grant ES025585

Title: Environmental contribution to brain transcriptome dynamics in a maternal immune activation mouse model of autism spectrum disorders

Authors: *C.-Y. LAI[1], J. LI[3], J. D. LUCERO[1], R. G. CASTANON[2], J. R. NERY[2], D. A. AMODEO[6], Y. WANG[4], T. J. SEJNOWSKI[1,7], S. B. POWELL[5], J. R. ECKER[2,7], E. A. MUKAMEL[3], M. BEHRENS[1]
[1]Computat. Neurobio. Lab., [2]Genomic Analysis Lab., The Salk Inst. For Biol. Studies, La Jolla, CA; [3]Cognitive Sci., [4]NanoEngineering,, [5]Psychiatry, Univ. of California San Diego, La Jolla, CA; [6]Psychology, California State Univ. San Bernardino, San Bernardino, CA; [7]Howard Hughes Med. Inst., La Jolla, CA

Abstract: Autism spectrum disorder (ASD) is a highly heritable neurodevelopmental condition, characterized by impaired social interaction and restricted-repetitive behaviors. Maternal environmental factors, such as infection and the gut microbiome, have been associated with ASD risk in humans. In rodents, maternal immune activation (MIA) during early embryonic development was also found to cause profound neurodevelopmental alterations in the offspring, which lead to neurochemical and behavioral abnormalities that resemble those of human ASD. However, it is still unclear how activation of maternal immune response interacts with underlying genetic factors to influence observed ASD phenotypes. Recent evidence suggests that dysregulation of epigenetic pathways, and ensuing altered gene expression, could be behind the neurodevelopmental alterations observed in the offspring. Our previous analysis of DNA methylation patterns in mouse brain showed continuous modifications during early development, with thousands of differentially methylated regions remodeling daily during the embryonic stages, and then slowing down during the second postnatal week. The intricate dynamics of methylation and transcriptional changes during brain development makes this period highly vulnerable to disruption by environmental and/or genetic factors. To address this hypothesis, we performed MIA by injecting polyinosinic:polycytidylic acid (PolyI:C) in pregnant mice at embryonic day 12.5. We measured the transcriptome in mouse neocortical tissue of MIA and control offspring by mRNA sequencing (RNA-Seq) at embryonic day 14.5 (E14), postnatal day 0 (P0), and in adults at 27 weeks of age. We characterized social behavior, repetitive grooming, and reversal learning in adult mice and correlated the behavioral phenotype of individual animals with gene transcription. Gene ontology analyses showed that a set of differentially expressed

(DE) genes at P0 and week 27 are involved in biological process of synaptic transmission and behavioral response to stimulus. At E14.5 several genes involved in inhibition of oligodendrocyte differentiation were altered in the MIA pups. We observed a negative correlation between the changes in gene expression at early (E14 and P0) versus adult (week 27) mice. Adult MIA offspring showed deficits in reversal learning, measured as increased trials to criterion, and decreased sniff time with a stranger mouse**.** This study identified altered transcriptome patterns at key developmental time points in the cortex of MIA mouse offspring that can further our understanding of the underlying genetic and environmental etiologies of autism spectrum disorder.

Disclosures: C. Lai: None. **J. Li:** None. **J.D. Lucero:** None. **R.G. Castanon:** None. **J.R. Nery:** None. **D.A. Amodeo:** None. **Y. Wang:** None. **T.J. Sejnowski:** None. **S.B. Powell:** None. **J.R. Ecker:** None. **E.A. Mukamel:** None. **M. Behrens:** None.

Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

Location: 152A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***186.03

**Topic: ***A.07. Developmental Disorders

Support: NIH

Title: Studying somatic mosaicism in normal brain and in neurodevelopmental disorders using neuronal and glial fractions

Authors: *L. FASCHING[1], G. COPPOLA[1], L. TOMASINI[1], A. E. URBAN[2], A. ABYZOV[3], F. M. VACCARINO[4]
[1]Child Study Ctr., Yale Sch. of Med., New Haven, CT; [2]Dept. of Psychiatry and Behavioral Sci. and Dept. of Genet., Stanford Univ. Sch. of Med., Palo Alto, CA; [3]HSR, Harwick 3-12, Mayo Clin., Rochester, MN; [4]Child Study Center, Dept. of Neuroscience, Yale Sch. of Med., Yale Univ., New Haven, CT

Abstract: As members of the Brain Somatic Mosaicism network we are investigating somatic variations in post mortem human brains and their implications in neurodevelopmental disorders. These include single nucleotide variants (SNVs), small insertions/deletions (Indels) and copy number variations (CNVs) that are present only in subset of cells and in different tissues, and arise after fertilization, at different times over the lifespan of an individual. Emerging data strongly suggest that each tissue is a mosaic of different genomes, and individual cells can accumulate as many as 1,000 somatic SNVs that are shared to various degrees between the other

cells in a tissue.
Studying somatic mutations in bulk brain tissue allows only the detection of variants at very high frequency, while the single cell approach is prone to false positive artifacts because of the need to perform whole genome amplification (WGA).
To overcome those issues, we enrich for cell type specific fractions by Fluorescence Activated Nuclei Sorting (FANS) followed by whole genome sequencing (WGS).
We are studying the basal ganglia and the cortex from postmortem brain specimens, two regions that are known to be implicated in neurodevelopmental disorders such as Tourette Syndrome.
To date we have successfully FAN-sorted for interneurons, medium spiny neurons, and oligodendrocytes in the basal ganglia and for interneurons, pyramidal neurons and glia in the cerebral cortex of a post mortem normal control brain. We have validated these results by RNA-seq.
We are currently sorting for nuclear fractions in basal ganglia and cortex of Tourette Syndrome patients and normal control brains. Fractions will be compared to each other and to the bulk brain tissue to discover mosaic genomic variants. The analysis is done by using a pipeline to call for somatic variants that relies on "somatic callers" extensively employed in the cancer field (MuTect, SomaticSniper, Strelka and VarScan). This strategy gives us the advantages to detect also mutations that appear at very low frequency in brain tissue.
We aim to discover lineage and region specific somatic variations in postmortem brain specimens of Tourette Syndrome patients as compared to matched controls and we are going to assess their potential role in disease pathogenesis by comparing frequencies, potential functional impact on transcriptome and epigenome, and by using in vitro modeling.

Disclosures: L. Fasching: None. **G. Coppola:** None. **L. Tomasini:** None. **A.E. Urban:** None. **A. Abyzov:** None. **F.M. Vaccarino:** None.

Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

Location: 152A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***186.04

**Topic: ***A.07. Developmental Disorders

Support: NIH Grant U54NS093793
NIH Grant R24OD022005
NIH Grant R01GM067858
Howard Hughes Medical Institute
Intramural Research Program at NHGRI
Common Fund of the NIH Office of the Director

NIH Grant U01HG007709

Title: Recurrent de novo variants in EBF3 cause a neurodevelopmental syndrome characterized by hypotonia, ataxia, and expressive speech disorder

Authors: *H.-T. CHAO[1], M. DAVIDS[3], E. BURKE[3], J. G. PAPPAS[5], J. A. ROSENFELD[2], A. J. MCCARTY[3], T. DAVIS[3], L. WOLFE[3], C. TORO[3], C. TIFFT[3], F. XIA[2], N. STONG[6], T. K. JOHNSON[7], C. G. WARR[7], S. YAMAMOTO[2], D. R. ADAMS[3], T. C. MARKELLO[4], W. A. GAHL[3], H. J. BELLEN[8], M. F. WANGLER[2], M. C. V. MALICDAN[3]
[1]Pediatrics, [2]Baylor Col. of Med., Houston, TX; [3]NHGRI, Bethesda, MD; [4]NHGRI, Bethesday, MD; [5]NYU Langone Med. Ctr., New York, NY; [6]Columbia Univ., New York, NY; [7]Monash Univ., Melbourne, Australia; [8]Dept Molec & Human Genet., Howard Hughes Med. Inst., Houston, TX

Abstract: Neurodevelopmental disorders encompass clinically and biologically heterogeneous conditions including intellectual disability, autism spectrum disorder, and epilepsy. The advent of whole exome sequencing (WES) provided a powerful tool for discovering disease-associated genes by identifying genetic alterations in individuals with rare disorders or rather non-specific clinical features that hamper phenotypically-driven gene discovery. We retrospectively analyzed data from 7,595 patients referred for clinical or research WES analysis at the Baylor Genetics Laboratory and National Human Genome Research Institute, respectively. De novo variants in genes essential for neurologic function and exhibiting selective restraint, a process where selection reduced functional variation, were evaluated for potential disease association. The functional significance of these variants was evaluated *in vivo* in the fruit fly, *Drosophila melanogaster*. Our analysis identified three unrelated individuals with a syndromic disorder characterized by hypotonia, ataxia, developmental delay, intellectual disability, expressive speech disorder, CNS malformations, and genitourinary abnormalities with recurrent de novo variants in *EBF3*, encoding the transcription factor Early B-cell Factor 3. These variants (c.488G>A, p.Arg163Gln and c.488G>T, p.Arg163Leu) affect an evolutionarily conserved residue in a zinc finger motif crucial for DNA binding that disrupts EBF3-mediated transcriptional regulation *in vitro* and are deleterious *in vivo* in a fruit fly model. Findings in the fruit fly model suggest that these variants disrupt EBF3-mediated regulation of evolutionarily conserved signaling pathways. The coincidental occurrence of three de novo variants affecting the same residue in individuals with similar phenotypes is highly unlikely and statistically significant ($p = 2.1 \times 10^{-3}$). Our findings reveal that impaired EBF3-mediated transcriptional regulation result in a unique genetic syndrome. Furthermore, our results support the efficacy of WES in novel disease gene discovery for neurodevelopmental disorders.

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Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

Location: 152A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***186.05

**Topic: ***A.07. Developmental Disorders

Title: Intervention for viral-induced brain anomaly and intellectual disability by the CRISPR/Cas9 genome editing strategy: Through the study of congenital CMV infection model

Authors: *K. ISHII[1], S. TANKOU[1], M. S. SUZUKI[2], K. ISHIZUKA[1], Q. TANG[3], I. KOSUGI[2], A. SAWA[1]
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Abstract: Congenital cytomegalovirus (CMV) infection is an epidemiologically significant contributor to brain anomalies and intellectual disability, which is a significant health problem worldwide. Clinical disabilities that manifest from congenital CMV infection include microcephaly, seizures, and sensorineural hearing loss. Unlike many other infectious diseases, there is no vaccine and no effective treatment against CMV infection. Thus, elucidating pathological mechanisms is particularly important in the case of CMV infection to develop an effective therapeutic strategy. However, the mechanisms by which the congenital infection results in a wide range of brain dysfunction are unknown. Here we demonstrate a comprehensive analysis, from the molecular to the behavioral, using the intraplacental mouse CMV (MCMV) infection model. We define that MCMV-encoded immediate early protein 1 (IE1) plays a specific role in interfering with a critical cellular cascade involving DISC1 and promyelocytic leukemia (PML), which leads to functional deficits in the neural progenitor cells. Our results also indicate that the MCMV-elicited cellular deficits, in turn, lead to cortical maldevelopment and behavioral deficits in the mouse model. Moreover, our preclinical data supports that depleting the CMV IE1 gene by CRISPR/Cas9 genome-editing system may be effective in blocking the pathological viral-host protein interactions and ameliorating the pathology of congenital CMV infection. Taken together, our data suggest that the specific interaction of host and viral proteins underlie a key mechanism for CMV-elicited neurodevelopmental deficits. Thus, focusing on this particular mechanism may yield as a promising therapeutic target.

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Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

Location: 152A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***186.06

**Topic: ***A.07. Developmental Disorders

Support: 1ZIAMH000889-38

Title: Rates of cerebral protein synthesis measured with the L-[1-^{11}C]leucine positron emission tomography method are decreased in adult subjects with fragile X syndrome

Authors: *C. B. SMITH[1], K. C. SCHMIDT[1], I. LOUTAEV[1], T. J. BURLIN[1], T. HUANG[1], L. KRYCH[1], N. MIAO[2], C. SHEELER[1], D. VESSELINOVITCH[1], Z. XIA[1]
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Abstract: Fragile X syndrome is a developmental disorder resulting in intellectual disability, autistic-like symptoms, sensory hypersensitivity, and in many cases seizure disorders. In fragile X, the gene *FMR1* is silenced, and its protein product FMRP is absent. FMRP is an RNA-binding protein associated with actively translating ribosomes. It is hypothesized that FMRP regulates protein synthesis by stalling translation and decreasing expression of key secondary signaling molecules. In its absence, as in fragile X, investigators infer rates of translation are elevated, and this is considered a core phenotype of the disease. We have reported that, in an *Fmr1* knockout mouse model of the disease, rates of cerebral protein synthesis (rCPS) measured in vivo are elevated in some regions of the brain, particularly the hippocampus (Qin et al., 2005, J Neurosci 25:5087). In the present study, we applied the [^{11}C]leucine positron emission tomography (PET) method to measure rCPS in patients with fragile X syndrome. Six fragile X subjects and ten age-matched healthy controls, 18-24 years of age and free of psychotropic medication, were studied in the awake state. Studies were performed on the ECAT High Resolution Research Tomograph. Studies were initiated with an intravenous infusion of L-[1-^{11}C]leucine and PET data and timed samples of venous blood were collected over the ensuing 60 min. We used a venous sample calibrated population-derived input function and dynamic PET data to estimate kinetic model parameters of the method voxel-wise by means of a basis function method (Tomasi *et al*, 2009, JCBFM 29:1317). All subjects also underwent a structural MRI of the head and regions of interest (ROIs) were drawn on MRI volumes to which PET volumes had been co-registered. Parameter estimates in all voxels within each ROI were averaged for each subject. Contrary to expectations, our results indicate that rCPS are decreased throughout the brain in fragile X patients by 20-30% compared to healthy controls. These results contrast with our findings in the *Fmr1* knockout mouse model. In human brain, absence of FMRP may trigger an imbalance of pathways involved in the regulation of translation.

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Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

Location: 152A

Time: *Sunday, November 12, 2017, 1:00 PM - 4:30 PM

Presentation Number: *186.07

Topic: *A.07. Developmental Disorders

Support: FRAXA Research Foundation
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atural Sciences and Engineering Research Council of Canada (NSERC)

Title: Excitation/inhibition imbalance in humans with Fragile-x syndrome

Authors: F. MORIN-PARENT[1], C. CHAMPIGNY[2], F. CORBIN[2], *J.-F. LEPAGE[3]
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Abstract: Excitation/inhibition (E/I) imbalance is a defining feature of animal models of autism spectrum disorders in general, and of Fragile-X syndrome (FXS) in particular. Indeed, FMR1-KO animals typically display hyperactive glutamatergic process combined with hypoactive GABAergic action. However, these observations have never been validated in humans with FXS, limiting the translational value of E/I imbalance as a potential biomarker of the disorder for clinical research. Here, we used transcranial magnetic stimulation (TMS) to assess the primary neurotransmitter systems involved in the maintenance of E/I in 20 patients with FXS. Our results show that patients with FXS, in comparison to controls, present alterations in glutamatergic, GABAa, and GABAb mechanisms (all $p<0.05$). Moreover, in FXS patients, FMRP levels correlate with resting motor threshold, a measure of NMDAr-mediated synaptic excitability ($p<0.05$). Taken together, these results validate the observations made in animal models regarding E/I imbalance in FXS, and show the potential of TMS for clinical research in FXS.

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Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

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**Presentation Number: ***186.08

**Topic: ***A.07. Developmental Disorders

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Title: Fragile X Syndrome causes widespread epigenetic dysfunction treatable with BET inhibitor JQ1

Authors: *E. KORB, M. HERRE, I. ZUCKER-SCHARFF, J. GRESACK, C. ALLIS, R. DARNELL
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Abstract: Fragile X Syndrome (FXS) is a leading genetic cause of intellectual disability and autism. FXS results from the loss of function of Fragile X Mental Retardation Protein (FMRP), which represses translation of target transcripts. Most of the well-characterized target transcripts of FMRP are synaptic proteins, yet targeting these proteins has not provided effective treatments. We examined a group of FMRP targets that encode transcriptional regulators, particularly chromatin-associated proteins. Loss of FMRP in mice results in widespread changes in chromatin regulation and aberrant gene expression. To determine if targeting epigenetic factors could reverse phenotypes associated with the disorder, we focused on Brd4, a BET protein and chromatin reader targeted by FMRP. Inhibition of Brd4 function through multiple treatment paradigms alleviated the cellular and behavioral phenotypes associated with FXS. We conclude that loss of FMRP results in significant epigenetic misregulation and that targeting transcription via epigenetic regulators like Brd4 may provide new treatments for FXS.

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Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

Location: 152A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

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**Topic: ***A.07. Developmental Disorders

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Texas Children's Hospital

Title: Development of an experimental paradigm to model neurobehavioral outcomes in Fragile X syndrome at advanced ages

Authors: *B. P. VICARI[1], S. VEERARAGAVAN[2], R. C. SAMACO[2]
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Abstract: Fragile X syndrome (FXS) is among the most common causes of intellectual disability in males and occurs due to an expansion of a triplet CGG-repeat in the 5' UTR region of the *FMR1* gene resulting in hypermethylation and subsequent transcriptional silencing. In addition, individuals with FXS display neurobehavioral indications such as ADHD, impaired sociability, and anxiety. For over two decades, the community of researchers and other stakeholders interested in FXS have relied predominantly on a mouse model of *Fmr1* completely lacking the protein product FMRP for both basic science and translational studies. However, although this model recapitulates multiple behavioral features of FXS, including hyperactivity, increased perseverative behavior, and in some cases, learning and memory deficits, nearly all published neurobehavioral studies to date have focused on evaluations conducted on mice less than eight months of age. While findings from these studies are highly informative for modeling the consequences of FMRP deficiency that occur during a period of life spanning childhood through adulthood, a paucity of both animal and human data exists on the outcome of FMRP deficiency during late adulthood. Individuals with FXS have been reported to live a relatively long lifespan, with some cases of people living through the seventh and eighth decade of life. Therefore, as individuals living with intellectual disability continue to live longer and age, there will be a pressing need to better understand the nature and impact of these conditions, such as FXS, on neuro-related outcomes. To this end, we evaluated the neurobehavioral features of naïve *Fmr1* KO mice on a pure C57BL/6J background at approximately 1.5 years of life to investigate the relevance of this mouse model for studying FXS at advanced age. The cross-sectional experimental study was designed to examine multiple behavioral domains. We found that *Fmr1*

KO mice exhibited alterations consistent with previous reports focused on younger animals including reduced anxiety-like behavior, hyperactivity, increased perseverative behavior, and impaired cued fear memory. However, in contrast to some studies, motor coordination and social approach behavior were normal. Taken together, our results suggest that aged *Fmr1* KO mice display behavioral abnormalities that are largely similar to those found in adolescent and younger adult *Fmr1* KO mice and underscore the utility of aged FXS mice for the study of late stage FXS behavioral phenotypes.

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Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

Location: 152A

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**Presentation Number: ***186.10

**Topic: ***A.07. Developmental Disorders

Support: NS034007
NS047384
HD082013

Title: Genome-wide measurement of mRNA translation in Fragile X syndrome

Authors: *S. ARYAL, F. LONGO, E. KLANN
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Abstract: Fragile X Syndrome (FXS) is the most prevalent inherited form of intellectual disability and the leading monogenic cause of autism. FXS is caused by loss of expression of the Fragile X Mental Retardation protein (FMRP), an mRNA-binding protein whose primary function is to regulate translation in neurons. Correspondingly, mouse models of FXS exhibit increased steady state protein synthesis in multiple brain regions. Precise control of translation is especially critical in neurons because rapid *de novo* protein synthesis is required for long-lasting synaptic plasticity and multiple types of memory processes, both of which are impaired in FXS mice. Indeed, there is widespread agreement that aberrant translation underlies a majority of the phenotypes, including autism-like behaviors, exhibited by FXS model mice. Consistent with these observations, genetic deletion of the translation-stimulating p70 S6 kinase 1 (S6K1) rescues a range of phenotypes, including excessive translation, aberrant synaptic plasticity and dendritic morphology, and autism-like behaviors in FXS model mice.
In this study, we sought to determine the identities of the messenger RNAs that exhibit eccentric translation in FXS model mice brains, and to investigate whether genetic deletion of S6K1

normalized their altered synthesis to levels comparable to those in wild-type (WT) littermates. To this end, we carried out ribosome footprint profiling on cortical lysates of ~ P30 WT, *Fmr1* knockout (KO), *Rps6kb1* (S6K1) KO, and double knockout (DKO) mice. Ribosome footprint profiling uses deep sequencing of ribosome-protected mRNA fragments to produce 'snapshots' of actively translating ribosomes on individual mRNAs. We used DeSeq2 on quality-controlled sequencing datasets to identify mRNAs that registered differential normalized ribosome footprint counts across the four genotypes. We also carried out whole-transcriptome RNA-seq of the cortical lysates in order to decouple translational and transcriptional landscapes in FXS model mice. Our findings reveal systems-level insights on both transcriptional and translational dysregulation in the cortex of FXS model mice.

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Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

Location: 152A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

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**Topic: ***A.07. Developmental Disorders

Support: Jérôme Lejeune Foundation Grant 254-CA2014A
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Title: Neurotrophic-mimetic strategy to rescue synaptic plasticity and cognitive functions in a mouse model of Down syndrome

Authors: *A. CONTESTABILE[1], M. PARRINI[1], M. ALBERTI[1], D. GHEZZI[1], G. DEIDDA[1], L. CANCEDDA[1,2]
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Abstract: Down syndrome (DS) or trisomy 21 is the most frequent genetic cause of intellectual disability in children and adults. Although numerous studies have shown that cognitive impairment possibly arises from dysfunction of the hippocampal circuit, there has been little progress in defining effective treatments. Previous studies have shown that impaired synaptic plasticity of mature hippocampal neurons and decreased hippocampal adult neurogenesis are main determinants in reducing cognitive functions in DS animal models. Currently, most preclinical therapeutic approaches in DS mice have focused on rescuing either one or the other of these impairments. Here, we have found that the expression of Brain-Derived Neurotrophic Factor (BDNF) is decreased in the brains of individuals with DS. Interestingly, a large body of literature indicates that BDNF signaling modulates both synaptic plasticity, and adult

neurogenesis. Therefore, we propose here to promote BDNF/TrkB signaling using a BDNF-mimetic drug with the twofold aim of rescuing synaptic plasticity and increase adult neurogenesis toward the rescue of cognitive functions in the Ts65Dn mouse model of DS. Our results indicate that indeed promoting BDNF/TrkB signaling rescued hippocampal synaptic plasticity, increased hippocampal adult neurogenesis and restored cognitive performances in different behavioral tasks in Ts65Dn mice. The molecular mechanisms of impaired BDNF/TrkB signaling in trisomic mice are currently under investigation. Overall, our experiments show in a reliable animal model of DS the efficacy of a novel and multifaceted therapeutic approach with good potential to be translated into clinical practice.

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Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

Location: 152A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***186.12

**Topic: ***A.07. Developmental Disorders

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Intramural Research Program at the National Institute on Drug Abuse

Title: Amelioration of UBE3A-dependent, hippocampal phenotypes in Angelman syndrome mouse model by reduction of RhoA-activating protein Ephexin5

Authors: *G. SELL[1], W. XIN[2], M. A. ZBINDEN[3], E. K. COOK[3], A. BONCI[4], S. S. MARGOLIS[3]
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Abstract: Angelman syndrome (AS) is a neurodevelopmental disorder characterized by deficits in motor coordination, cognition, and speech, as well as seizure susceptibility. Angelman syndrome is in part caused by the loss of the brain-specific maternally expressed and paternally imprinted *UBE3A* gene that encodes for an E3 ubiquitin ligase. In some cases, mutations in the catalytic domain of UBE3A are sufficient for AS-associated phenotypes. A prevailing hypothesis in the AS field is that the absence of UBE3A leads to an increase in its substrates due to a lack in their ubiquitylation and proteasome dependent degradation. This misregulation of these substrates expression might then mediate the heterogeneous phenotypes characteristic of AS.

Although the role of UBE3A in protein degradation is well established, the contribution of elevated UBE3A substrates to AS phenotypes is unknown. One such substrate that we identified is the molecule Ephexin5, a synaptic regulator which is specifically expressed in the hippocampus during development and upregulated in the mouse model of AS. Ephexin5 has dual roles in spine restriction during development as well as activity-dependent spine formation. Here, we show that maternal *Ube3A* deletion is sufficient to cause deficits in motor behaviors and learning and memory tasks. This was accompanied by elevated spine density in the hippocampal CA1 region and a corresponding increase in excitatory synaptic transmission. Genetic removal of Ephexin5 specifically rescued hippocampus-dependent behaviors in AS mice, and normalized the observed changes in spine density and excitatory transmission in CA1 pyramidal neurons. Removal of Ephexin5 did not, however, alter AS-related deficits on non-learning and memory tasks, such as rotarod. We conclude that an increase in the UBE3A substrate Ephexin5 contributes to abnormal hippocampal physiology and hippocampus-dependent behaviors in AS mice. These data provide initial evidence in favor of the idea that UBE3A substrates can in fact play a significant role in AS-related phenotypes and may represent viable therapeutic targets for treating AS.

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Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

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Presentation Number: *****186.13

Topic: *****A.07. Developmental Disorders

Support: CIRM DISC2-09032
FAST-Track Grant
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Title: Development of an artificial transcription factor therapy for angelman syndrome

Authors: ***K. FINK**[1], P. DENG[2], B. PYLES[2], U. BEITNERE[2], H. O'GEEN[2], J. NOLTA[3], D. SEGAL[2]
[1]Dept. of Neurol. and Stem Cell Program, UC Davis Med. Ctr., Sacramento, CA; [2]Genome Ctr., UC Davis, Davis, CA; [3]Stem Cell Program, UC Davis, Sacramento, CA

Abstract: Angelman Syndrome (AS) is a rare (1 in 15,000 births) neurologic disorder characterized by intellectual disabilities, lack of speech, ataxia, and seizures. The genetic cause

of AS is loss of expression in the brain of UBE3A (ubiquitin-protein ligase E6-AP). Due to brain-specific imprinting, the paternal allele is silenced by a long brain-specific RNA transcript that overlaps and is antisense to UBE3A (UBE3A-ATS), thus loss of the maternal allele by mutation or deletion causes UBE3A deficiency throughout the brain. We have demonstrated that a purified zinc finger-based Artificial Transcription Factor (ATF) protein could be injected intraperitoneally (IP) or subcutaneously (SC) into a mouse model of AS, cross the blood brain barrier, enter neurons, and activate widespread expression of paternal Ube3a throughout the brain. Here we focus on translational studies centered on a therapeutically relevant delivery modality that will result in brain-wide distribution and sustained expression of the ATF while providing a functional and molecular rescue of AS-related neuropathology and behavioral phenotypes. We have performed comparative studies using the purified ATF protein, viral vectors, and a stem cell gene therapy-based delivery platform. Wildtype and AS mice received either the ATF, scrambled ATF or sham treatment, and the efficiency of Ube3a activation was quantified using immunohistochemistry and qPCR. In addition to delivery studies in mice, we have also evaluated new ATFs designed for the human AS locus (hATF) and tested their efficacy in human neurons from patient-derived iPSC. The results from these studies will further validate the clinical potential of ATF-based therapies for AS and related disorders.

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Nanosymposium

186. Neurodevelopmental Disorders: Mechanisms

Location: 152A

Time: *****Sunday, November 12, 2017, 1:00 PM - 4:30 PM

Presentation Number: *****186.14

Topic: *****A.07. Developmental Disorders

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Title: Intellectual disability-linked KDM5C loss triggers spurious transcription, prevents germline gene silencing and deregulates activity-driven enhancers

Authors: *A. BARCO[1], ***A. BARCO**[1], M. SCANDAGLIA[1], J. P. LOPEZ-ATALAYA[1], A. MEDRANO-FERNÁNDEZ[1], M. T. LÓPEZ-CASCALES[1], B. DEL BLANCO[1], M. LIPINSKI[1],

E. BENITO[1], R. OLIVARES[1], S. IWASE[2], Y. SHI[3]
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Abstract: Mutations in the lysine demethylase 5C gene (KDM5C) cause a rare X-linked intellectual disability disorder. This enzyme demethylates histone H3 di- or trimethylated at lysine 4 (H3K4me2/3), two histone modifications associated with active transcription. To investigate the differential role of KDM5C in developing and adult brain, we compared the behaviour, transcriptome and epigenomic landscapes of *Kdm5c* null (KO) and forebrain-restricted inducible knockout (ifKO) mice. KOs showed strong neurological phenotypes mimicking patients' symptoms such as decreased learning and memory and increased emotional responses. In contrast, ifKOs were mildly affected in behavioural performance, suggesting a predominant developmental component in KDM5C-associated intellectual disability. Consistent with the proposed general function for Kdm5c as a transcriptional repressor, both KO and ifKO mice showed excessive hippocampal transcription and histone H3K4 tri-methylation at promoters and enhancers. Interestingly, both strains exhibited events of spurious transcription coinciding with local increases of H3K4me3 in non-canonical and cryptic TSSs suggesting an instructive role for this histone mark on transcriptional activation. Furthermore, conventional KOs also showed (i) neuronal expression of germ line genes that escaped developmental silencing by DNA methylation, and (ii) over-activation of activity-regulated enhancers involved in cognitive processes, such as those regulating the Npas4, Arc and Fos loci. In summary, we suggest that Kdm5c plays a critical role during development both as an epigenetic repressor and as a fine-tuner of enhancers. Although the importance of these functions declines after neuronal maturation, Kdm5c still retains a genome surveillance role preventing the illegitimate activation of non-neuronal and cryptic promoters in adult neurons.

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Nanosymposium

187. Current Perspectives on Homeostatic Plasticity and Activity-Dependent Remodeling

Location: 140A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***187.01

**Topic: ***B.08. Synaptic Plasticity

Support: Heep Fellowship Texas A&M

Title: Postsynaptic remodeling of neuromuscular synapses during postnatal synaptic competition

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Abstract: During development of mature neuromuscular synapses, the innervation of skeletal muscles is extensively remodeled: each muscle fiber transitions from receiving innervation by multiple axons at birth to a singly innervated state in the adult. Termed synapse elimination, this process occurs via the loss of redundant motor inputs has typically been characterized as an activity-dependent competition amongst the individual inputs for sole occupation of each muscle fiber endplate. Evidence from our lab indicates an "axo-centric" perspective is an oversimplified explanation for how neuromuscular synapses ultimately become singly innervated. Using light and electron microscopy to investigate mouse neuromuscular junctions (NMJs) during early postnatal development we have found evidence that terminal Schwann cells (tSCs) are capable of altering the competitive balance between inputs. Previously, we have shown how tSCs promote the elimination of inputs, acting as a to drive competition. Additionally, in a series of ongoing experiments we have observed marked differences in the ultrastructure of postsynaptic areas covered by nerve as opposed to tSCs. Our observations indicate muscle fibers undergo extensive remodeling and/or growth, evidenced by pocket-like invaginations in the muscle fiber membrane that appear to be a mechanism for postsynaptic membrane trafficking. Interestingly, pockets appear to contain acetylcholine receptors and are not observed beyond the endplate region at birth. Moreover, within the endplate region pockets are almost exclusively located beneath areas of nerve terminal contact, suggesting a mode of reinforcement through focal expansion of synaptic contact areas. Interestingly, pockets are not distributed evenly amongst the presynaptic inputs, suggesting selective expansion beneath individual inputs. Collectively our observations and analysis indicate a role for the muscle fiber during the early stages of synaptic competition. We propose that the muscle fibers assess the relative firing patterns and levels of activity of individual inputs and respond through differential distribution of newly synthesized and recycled receptors.

Disclosures: I.W. Smith: None. **W.J. Thompson:** None.

Nanosymposium

187. Current Perspectives on Homeostatic Plasticity and Activity-Dependent Remodeling

Location: 140A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***187.02

**Topic: ***B.08. Synaptic Plasticity

Support: NIH Grant R01NS39313
NIH Grant R35NS097212

Title: Retrograde signaling by a secreted Semaphorin and presynaptic Plexin drives homeostatic synaptic plasticity

Authors: *B. O. ORR, R. D. FETTER, G. W. DAVIS
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Abstract: Homeostatic signaling systems function throughout the nervous system to ensure stable, yet flexible neural activity and animal behavior with potential relevance to neurological disease. Presynaptic homeostatic plasticity (PHP) is a conserved form of neuronal homeostatic signaling in organisms ranging from Drosophila to human. PHP can be rapidly induced (seconds to minutes) by pharmacological inhibition of postsynaptic neurotransmitter receptors and is expressed as an offsetting increase in presynaptic release, thereby necessitating a retrograde, trans-synaptic signal of unknown identity. Here, we demonstrate that Semaphorin2b (Sema2b) is a secreted, target-derived signal that acts upon presynaptic PlexinB (PlexB) receptors to mediate the retrograde, homeostatic control of presynaptic neurotransmitter release at the *Drosophila* neuromuscular junction. Sema2b-PlexB signaling regulates the expression of PHP via control of the RIM-dependent readily releasable vesicle pool (RRP), without altering synapse ultrastructure or vesicle number. Additional data regarding the signaling systems that connnect PlexB to the potentiation of the RRP will be presented. During neural development, Semaphorin-Plexin signaling instructs axon guidance and neuronal morphogenesis. Yet, Semaphorins and Plexins are expressed in the adult brain. Our study provides evidence that Semaphorin-Plexin signaling directly controls the homeostatic modulation presynaptic neurotransmitter release and we propose that this may represent a persistent function of Semaphorin-Plexin signaling in the adult brain.

Disclosures: B.O. Orr: None. **R.D. Fetter:** None. **G.W. Davis:** None.

Nanosymposium

187. Current Perspectives on Homeostatic Plasticity and Activity-Dependent Remodeling

Location: 140A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***187.03

**Topic: ***B.08. Synaptic Plasticity

Support: SNSF Professorship Grant PP00P3_144816 3
UZH FK Grant

Title: Long-term depression of a superprimed vesicle pool links presynaptic homeostasis to quantal scaling

Authors: *M. MUELLER[1], J. KEIM[2], S. SYDLIK[2]
[2]IMLS, [1]Univ. of Zurich, Zurich, Switzerland

Abstract: Synaptic efficacy is stabilized by homeostatic mechanisms. While there is ample evidence for presynaptic and postsynaptic forms of homeostatic synaptic plasticity, little is known about the interplay between different forms of homeostatic plasticity. Moreover, it is almost completely unknown how homeostatic plasticity is related to non-homeostatic plasticity. Here we find that at the Drosophila neuromuscular junction, long-term depression (LTD) of a high release probability (pr) vesicle pool links presynaptic homeostatic plasticity to quantal scaling, a postsynaptic form of homeostatic plasticity. First, we observed that high-frequency stimulation protocols induce a ~twofold decrease in EPSP or EPSC amplitude that lasted for up to 30 minutes without apparent changes in mEPSP/C amplitude, indicating a long-term decrease in neurotransmitter release. The decrease in release was independent of initial pr, but correlated with a concomitant reduction in readily-releasable vesicle pool size and pr. Further analysis revealed that LTD was due to a decrease in the size of an EGTA-insensitive pool of 'superprimed' vesicles, independent of apparent changes in the amplitude of presynaptic spatially-averaged calcium transients. Interestingly, we uncovered mEPSP amplitude up-scaling by ~30-40% during LTD at synapses undergoing presynaptic homeostasis induced by glutamate receptor perturbation. Moreover, we detected quantal scaling during LTD in five presynaptic homeostasis mutants (ppk11, rbp, dysbindin, rab3-GAP and snapin-RNAi). Finally, we provide evidence that quantal scaling was independent of apparent changes in glutamate receptor subunit composition, and blocked by limiting glutamate receptor number. Our data are consistent with the idea that quantal scaling or presynaptic homeostatic potentiation counteract LTD of a superprimed vesicle pool. Together, our data provide evidence for an interplay between two forms of homeostatic plasticity during presynaptic LTD.

Disclosures: **M. Mueller:** None. **J. Keim:** None. **S. Sydlik:** None.

Nanosymposium

187. Current Perspectives on Homeostatic Plasticity and Activity-Dependent Remodeling

Location: 140A

Time: *Sunday, November 12, 2017, 1:00 PM - 3:00 PM

Presentation Number: *187.04

Topic: *B.08. Synaptic Plasticity

Support: Simons Foundation Award #: 345485

Title: Reduction in synaptic Shank3 levels disrupts homeostatic synaptic scaling

Authors: *V. TATAVARTY, H. K. LIN, C.-H. WU, G. G. TURRIGIANO
Brandeis Univ., Waltham, MA

Abstract: Synaptic Scaling (SS) is a mechanism of homeostasis employed by neurons to regulate synaptic strength. The goal is to constrain neuronal firing rates in an ideal range to prevent runaway excitation or silencing of networks. Deficits in homeostasis have been proposed to contribute to pathogenesis of Autism Spectrum Disorders (ASDs) (Valakh and Nelson 2015). Mutations in Shank3, a scaffold protein localized to excitatory synapses have been identified in patients suffering from Autism Spectrum Disorders (ASDs). To establish if SS deficits play a role in ASDs we first investigated the role of Shank3 in SS. Short Hairpin directed against Shank3 (Shank3 SH) was used to knock down Shank3 in cortical neurons. Our results show that Shank3 SH-expressing neurons are unable to scale up synaptic strength in response to prolonged activity blockade with TTX as measured by mEPSC recordings and immunocytochemistry. Immunostaining data demonstrates that during SS, Shank3 is redistributed to synapses. Interestingly, treatment of Shank3 deficient cells with lithium, leads to a complete rescue of SS in cultured neurons. Multiple kinases have been identified that are regulated by lithium. We are currently using direct pharmacological blockade/activation of individual kinases that lithium regulates to determine the mechanism of rescue. In order to determine the effect of Shank3 loss on network function *in vivo,* we are recording from awake behaving Shank3 knockout mice. Our results strongly support the role of Shank3 in SS and suggest SS deficits may contribute to dysfunction in ASDs. Furthermore, since SS deficits are rescued by lithium in culture, Lithium may be a potential therapeutic option for ASDs.

Disclosures: V. Tatavarty: None. **H.K. Lin:** None. **C. Wu:** None. **G.G. Turrigiano:** None.

Nanosymposium

187. Current Perspectives on Homeostatic Plasticity and Activity-Dependent Remodeling

Location: 140A

Time: * Sunday, November 12, 2017, 1:00 PM - 3:00 PM

Presentation Number: * 187.05

Topic: * B.08. Synaptic Plasticity

Support: MRC Grant

Title: Experience-dependent homeostatic plasticity of layer 5 IB and RS neurons in visual cortex

Authors: *A. PANDEY[1], K. D. FOX[2]
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Abstract: Cortical layer 5 contains pyramidal neurons that project both to other cortical areas and to subcortical targets. These projection subtypes map onto the electrophysiologically defined classifications of regular spiking (RS) and intrinsic bursting (IB) neurons respectively. Studies in barrel cortex have shown that RS and IB neurones exhibit a different time course of homeostatic plasticity from one another and show different levels of depression and potentiation in response to whisker deprivation. In this study we asked two questions; first, does this plasticity specialisation between RS and IB cells generalise to visual cortex? Second, are the differences in plasticity, property of the projection target subtype or the electrophysiological subtype or both? We tagged the neurons projecting to different areas by injecting retrobeads in their putative targets and induced plasticity by monocular deprivation (MD) for 3, 5 or 10 days during critical period (P24-P34) in C57-Bl6J wild type mice. We recorded from IB and RS neurons from the primary binocular visual area (V1) and neurons projecting to the contralateral V1 (V1c) or superior colliculus (SC) in transverse cortical slices. We compared average amplitudes and cumulative frequency distribution of mEPSC amplitudes between control and MD animals. Our results reaffirm that neurons projecting to the contralateral hemisphere are mostly RS neurons, while neurons projecting to the SC are mostly IB neurons. We observed that both types of neurons show reduction in synaptic amplitudes after 3 days of MD. However, the amplitude of depression is smaller in IB neurons (9.36%) compared to RS neurons (20.22%). Our preliminary data also suggest synaptic depression persists in RS neurons after 5 days of MD. After 10 days of MD amplitude the of depression did not change in the RS neurons (25.16%), while it showed a sign of homeostatic rebound and overshooting the control mEPSC amplitude by 18.09%. Our data show that neurons projecting to the contralateral hemisphere also undergo experience dependent depression in mEPSC amplitude (23.66%) after 3 days of MD. We are also studying homeostatic plasticity in the neurons projecting to superior colliculus using same methodology. Therefore, our preliminary findings suggest that, like RS and IB neurons of barrel cortex layer 5 (Greenhill *et al*, 2015), RS and IB neurons in V1 show a different time course of homeostatic plasticity.

Disclosures: **A. Pandey:** None. **K.D. Fox:** None.

Nanosymposium

187. Current Perspectives on Homeostatic Plasticity and Activity-Dependent Remodeling

Location: 140A

Time: *****Sunday, November 12, 2017, 1:00 PM - 3:00 PM

Presentation Number: *****187.06

Topic: *****B.08. Synaptic Plasticity

Support: NIH NINDS R01NS045500

Title: Sensory experience-dependent circuit refinement requires the cytokine receptor Fn14

Authors: *L. CHEADLE[1], C. TZENG[1], B. T. KALISH[1], S. RIVERA[1], D. HARMIN[1], L. BURKLY[3], C. CHEN[4], M. E. GREENBERG[2]
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Abstract: Neural circuits assembled *in utero* undergo extensive refinement in response to sensory experience during critical periods of postnatal development. The mechanisms by which experience regulates the establishment of circuit connectivity are not well understood but likely involve the induction of functionally important genes in activated neurons. We characterized for the first time the genes induced by visual experience in the dorsal lateral geniculate nucleus (LGN) of the thalamus, a central brain structure that processes visual information downstream of direct input from the retina. Among a cohort of 216 induced genes, we identified the cytokine receptor Fibroblast growth factor-inducible 14, Fn14, as a candidate regulator of refinement. Fn14 mRNA and protein expression are dynamically regulated by vision and peak during the critical period of visual experience-dependent refinement. Combining electrophysiological and structural techniques in mice lacking Fn14, we found that Fn14 is dispensable for early postnatal stages of spontaneous activity-dependent development but required during a subsequent critical period when vision maintains and refines the circuit according to sensory experience. As a result, neurons lacking Fn14 maintain globally weakened contact with an excess of synaptic partners at the close of postnatal development. Depriving mice of visual experience mimics the effect of Fn14 loss-of-function on circuit connectivity. Fn14 is expressed in excitatory relay neurons of the LGN and enriched at synapses during the critical period, consistent with regulation of refinement via a postsynaptic mechanism. This study characterizes Fn14 as a novel molecular link between experience-dependent gene regulation and the development of circuit connectivity in the brain.

Disclosures: L. Cheadle: None. **C. Tzeng:** None. **B.T. Kalish:** None. **S. Rivera:** None. **D. Harmin:** None. **L. Burkly:** A. Employment/Salary (full or part-time):; Employee and stockholder of Biogen. **C. Chen:** None. **M.E. Greenberg:** None.

Nanosymposium

187. Current Perspectives on Homeostatic Plasticity and Activity-Dependent Remodeling

Location: 140A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***187.07

**Topic: ***B.08. Synaptic Plasticity

Support: European Molecular Biology Organization Long term postdoctoral fellowship

NIH RO1 DC009836

Title: Plasticity in cortical fast-spiking GABA networks supports recovered sensory processing following peripheral nerve injury

Authors: *J. RESNIK, R. S. WILLIAMSON, D. B. POLLEY
Otolaryngology, Harvard Med. Sch., Boston, MA

Abstract: The adult sensory cortex exhibits a remarkable plasticity following damage to sensory end organs. Afferent denervation results in a reorganization of cortical maps, a rebalance of network activity and changes in sensory capabilities. These compensatory adaptations have been associated with reduced GABA signaling and cortical hyperexcitability. However, it is unknown how functional modifications in sensory processing and dynamic changes in intracortical inhibition relate to one another during this process. Here, we directly measure changes in parvalbumin-expressing (PV) GABA networks in the adult auditory cortex (ACtx) and relate changes in local inhibition to recovered auditory processing in putative pyramidal (PPy) neurons after a near-complete loss of cochlear nerve afferents. We describe two approaches: 1) An optogenetic strategy to monitor daily changes in the net strength of PV-mediated feedforward inhibition and 2) a chronic cellular imaging approach to directly visualize changes PV and PPy neurons. For the first approach, we made chronic recordings from individual PPy units in the ACtx of awake, head-fixed mice while optogenetically activating PV neurons for a 7-8 week period surrounding profound auditory nerve damage. This approach allowed us to compare distinct forms of plasticity, such as spontaneous rate, sensory gain, PV mediated inhibition and receptive field plasticity, in single PPy units with day-by-day resolution. We found that whereas the status of brainstem-evoked potentials and traditional biomarkers of central auditory hyperactivity did not predict the recovery of sensory responses to surviving nerve fibers, homeostatic adjustments in PV-mediated inhibition during the first days following injury could predict the eventual recovery of cortical sound processing in PPy neurons weeks later. Our findings show a rapid loss and recovery in PV-mediated inhibition that may compensate for a sudden drop in afferent drive and support the progressive recovery of sensory processing. Findings from our optogenetic experiments reveal striking inhibitory dynamics in the first week after auditory nerve injury but are agnostic as to whether these changes reflect postsynaptic changes in PPy neurons or changes in the PV networks themselves. Our ongoing experiments use chronic 2-photon calcium imaging to simultaneously visualize sound-evoked GCaMP signals in genetically identified PV neurons alongside neighboring PPy neurons. Collectively, our work identifies the central importance of rapidly releasing the PV plasticity ‘brake’ to enable recovered sensory processing in the adult cortex following injury.

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Nanosymposium

187. Current Perspectives on Homeostatic Plasticity and Activity-Dependent Remodeling

Location: 140A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***187.08

**Topic: ***H.01. Animal Cognition and Behavior

Support: MESF;2012R1A5A2A44671346

Title: Cerebellar role in emotional memory processing at parallel fiber-Purkinje cell synapses

Authors: *J.-K. HAN[1], S. KIM[2]
[1]Physiol., [2]Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: It is increasingly recognized that there is a critical relationship between cerebellum and emotion, particularly in fear responses and fear memory consolidation. However, underlying mechanism for molecular regulation of memory formation remains unclear. To address this issue, we targeted signal transducer and activator of transcription (STAT) family, which is known as a strong etiological factor for posttraumatic stress disorders (PTSD), characterized by a hypermnesia of the trauma. Herein, we hypothesize that cerebellar STAT3 contributes to PTSD-like memory formation. Using Purkinje cell-specific STAT3 knockout (KO) mice model in fear conditioning paradigm, we found that long-term fear memory was increased in STAT3-deficient group, and avoidance memories were significantly increased in STAT3 KO group after 24 hours. When learned fear, STAT3 KO group showed more exaggerated responses (fear-potentiated responses) than wildtype group. After fear conditioning, long-term potentiation (LTP) was reframed to long-term depression (LTD) at parallel fiber-Purkinje cell synapses of STAT3 KO mice. Reframing LTP/LTD was also confirmed in *in vitro* slice physiology. However, long-term potentiation of inhibitory synapses at molecular layer interneuron-Purkinje cell synapses of STAT3 KO mice were not involved in the consolidation of fear memory. To investigate how Purkinje cell-specific STAT3 modulates bidirectional plasticity in memory formation, we considered the transcriptional regulations mediated by STAT3. Expression level of AMPA receptor gluA1/2 subunits was increased in STAT3 KO mice. All things considered, these results demonstrated that Purkinje cell STAT3 regulates PTSD-like memory formation revealing the novel mechanisms of traumatic memories.
Keywords: Purkinje cell, STAT3, PTSD-like memory, Reframing LTP/LTD, AMPA receptors

Disclosures: J. Han: None. **S. Kim:** None.

Nanosymposium

188. Novel Therapeutics for Neurodegenerative Disorders

Location: 146C

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***188.01

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: European Union's Seventh Framework Programme (FP7/2007-2013)
Biotechnology and Biological Sciences Research Council (Project Grant BB/L01923X/1)

Title: KEAP1 inhibition is neuroprotective and suppresses the development of epilepsy

Authors: *T. SHEKH-AHMAD[1], R. ECKEL[1], S. DAYALAN NAIDU[2], M. HIGGINS[2], M. YAMAMOTO[3], A. T. DINKOVA-KOSTOVA[2,4], S. KOVAC[1,5], A. Y. ABRAMOV[1], W. MATTHEW[1]
[1]Dept. of Clin. and Exptl. Epilepsy, Ucl/Institue Of Neurol., London, United Kingdom; [2]Div. of Cancer Res., Jacqui Wood Cancer Centre, Univ. of Dundee, Dundee, United Kingdom; [3]Dept. of Med. Biochem., Tohoku Univ. Grad. Sch. of Med., Sendai, Japan; [4]Dept. of Pharmacol. and Mol. Sci. and Dept. of Med., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [5]Dept. of Neurol., Univ. of Muenster, Muenster, Germany

Abstract: Epilepsy remains a major neurological disease with 30% of which remains refractory to drug therapy. Hippocampal sclerosis (HS) is a common acquired disease that is one of the major causes of drug resistant epilepsy. A key mechanism that leads from a brain insult to HS is the excessive generation of reactive oxygen species (ROS). There is growing evidence that inhibiting ROS generation can ameliorate neuronal damage in seizures and epilepsy. However, the effects of antioxidant therapy on epileptogenesis have been mixed. This may be partly explained by the short-lived neuroprotective effects of direct antioxidants, because of their consumption in the process of ROS scavenging.
Here we use a novel strategy to increase endogenous antioxidant defenses by upregulating the transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 is negatively regulated by Kelch-like ECH associated protein 1 (Keap1). TSA, a close structural analogue of bardoxolone methyl, is a novel Nrf2 activator that has undergone clinical trials in non-small cell lung cancer and, because of its good CNS penetration, is now undergoing a clinical trial in Friedreich's Ataxia.
Here we show that TSA activates Nrf2 through inhibition of Keap1 through its primary sensor C151.
We next determined the functional effect of Keap1 inhibition by TSA in the low Mg^{2+} *in vitro* epileptiform activity model.
Pre-incubation (200 nM, 24 h) of the cells with TSA did not change the frequency or coastline of

low Mg^{2+}-induced calcium spikes in neuronal culture, suggesting that activation of Nrf2 with 200 nM TSA did not change vesicular glutamate release or activation of NMDA receptors in the low Mg^{2+} model.
Prolonged seizure-like activity induces mitochondrial membrane potential depolarization ($\Delta\psi m$). TSA protected neurons against decrease in $\Delta\psi m$ (from 30% to 10%).
TSA (200 nM, 24 h) significantly reduced the rate of ROS production in neurons during seizure-like activity 2, 10 and 15 min after exposure to low-Mg^{2+} (from 192%, 357% and 564% to 113%, 186 and 291% respectively), and almost completely prevents seizure-like activity induced neuronal cell death.
We then go on to show that, given after status epilepticus in vivo, TSA increased glutathione and ATP, prevented neuronal death and dramatically reduced (by 94%) the frequency of late spontaneous seizures for at least four months following status epilepticus in rats. Thus, acute Keap1 inhibition following status epilepticus exerts a neuroprotective and persistent anti-seizure effect.

Disclosures: **T. Shekh-Ahmad:** None. **R. Eckel:** None. **S. Dayalan Naidu:** None. **M. Higgins:** None. **M. Yamamoto:** None. **A.T. Dinkova-Kostova:** None. **S. Kovac:** None. **A.Y. Abramov:** None. **W. Matthew:** None.

Nanosymposium

188. Novel Therapeutics for Neurodegenerative Disorders

Location: 146C

Time: *Sunday, November 12, 2017, 1:00 PM - 3:15 PM

Presentation Number: *188.02

Topic: *C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH NS060703
American Heart Association

Title: Chemical Nrf2 activators display broad dose-dependent neuroprotection in porcine neonatal hypoxia-ischemia encephalopathy

Authors: ***R. SINGH**[1], B. WANG[2], M. REYES[2], P. SANTOS[2], E. KULIKOWICZ[3], Z.-J. YANG[2], J. K. LEE[2], L. J. MARTIN[4], R. C. KOEHLER[1]
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Abstract: The newborn brain is vulnerable to hypoxia-ischemia (HI), in part, because of incomplete development of antioxidant defenses. Endogenous antioxidant defenses can be

enhanced by activation of the transcription factor Nrf2, which upregulates a wide variety of antioxidant enzymes. Here, we tested two distinct Nrf2 activators: the naturally occurring compound sulforaphane (SFN; 1, 3, 10, and 30 mg/kg), and the more potent synthetic triterpenoid 2-cyano-3-, 12-dioxooleana-1,9 (11)-dien-28-oic-ethyl amide (CDDO-EA 0.3, 1, 3, and 10 mg/kg). We used a porcine model of neonatal HI consisting of 45-min ventilation with 10% O2 plus 8-min airway occlusion. For each drug and sex, piglets were randomized to receive an IV injection of drug or vehicle 1 h after reoxygenation in a blinded fashion, and the density of remaining viable neurons were counted in several brain regions at 4 days. The lowest dose (1 mg/kg SFN; 0.3 mg/kg CDDO-EA) produced marginal protection compared to the two intermediate doses. In somatosensory cortex of males, SFN increased viable neuronal counts from 42±19% (% of sham; ±95% confidence intervals; n=8) with vehicle to 72±27% with 3 mg/kg and to 76±33% with 10 mg/kg SFN. Likewise, CDDO-EA increased cortical viable neurons from 58±21% with vehicle to 73±31% (n=7) with 1 mg/kg and to 72±35% with 3 mg/kg. In thalamus of males, SFN increased viable neurons from 28±30% with vehicle to 48±31% with 3 mg/kg and to 69±30% with 10 mg/kg SFN. Likewise, CDDO-EA increased thalamic viable neurons from 13±13% with vehicle to 43±12% with 1 mg/kg and to 48±17% with 3 mg/kg CDDO-EA. In putamen of males, SFN increased viable neurons from 26±12% with vehicle to 58±30% with 3 mg/kg SFN. Likewise, CDDO-EA increased viable neurons from 15±19% with vehicle to 49±28% with 1 mg/kg CDDO-EA. The highest dose (30 mg/kg SFN; 10 mg/kg CDDO-EA) produced no additional benefit. The neuroprotective effect of CDDO-EA was more prominent in female putamen (79±26%; n=7) with 3 mg/kg than in male putamen (30±20%), suggesting a sex-specific difference in efficacy of Nrf2 activators. This work demonstrates in a translational large animal model that chemical activators targeting Nrf2 protect the immature brain from HI injury, providing evidence for oxidative stress as a mediator of neurodegeneration and as modifiable therapeutic target using endogenous cells signaling pathways.

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Nanosymposium

188. Novel Therapeutics for Neurodegenerative Disorders

Location: 146C

Time: *Sunday, November 12, 2017, 1:00 PM - 3:15 PM

Presentation Number: *188.03

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

Support: Helmholtz Validation Found

Title: Amyloid beta oligomer elimination enhances cognition and impedes neurodegeneration in various Alzheimer's disease mouse models

Authors: *D. WILLBOLD[1,2]
[1]Forschungszentrum Jülich Gmbh, Jülich, Germany; [2]Inst. für Physikalische Biologie, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

Abstract: Several lines of evidence suggest a central role of amyloid-β-peptide (Aβ) in the pathogenesis of Alzheimer's disease (AD). More than Aβ fibrils, small soluble and prion-like propagating Aβ oligomers are suspected to be the major toxic species responsible for disease development and progression. Therefore, eradication of these Aβ oligomers is our principal objective for therapy of AD. Previously, we have identified the fully D-enantiomeric peptide D3 by mirror image phage display selection and showed that it was able to specifically eliminate Aβ oligomers and convert them into non-toxic species. D3 was able to reduce plaque load in transgenic AD mouse models, and improved cognition even after oral application [1]. More recently, we developed derivatives of D3 with improved properties during a lead optimization strategy that focused primarily on the Aβ oligomer elimination efficiency. We used our newly developed Aβ-QIAD (quantitative determination of interference with Aβ aggregate size distribution) to quantitatively measure Aβ oligomer elimination efficiency and thus target engagement [2]. Morris water maze and novel object recognition experiments in several transgenic mouse models were used to measure cognition enhancement of the D3 derivatives. SHIRPA and Rotarod assays were used to follow neurodegeneration in the TBA2.1 mouse model and its inhibition by our compounds. As expected from D-peptides, D3 and its derivatives showed superior pharmacokinetic properties, such as long half-lives and high oral bioavailability [3, 4]. The presented compounds were able to eliminate Aβ oligomers as well as to enhance cognition and slow down neurodegeneration even after oral application. In conclusion, D-enentiomeric peptides that specifically and efficiently eliminate Aβ oligomers are able to enhance cognition and impede neurodegeneration even in old animals with full-blown pathology and even when orally applied. Also, preclinical and clinical data demonstrate safety of the new first-in-class compound. [1] Funke et al., ACS Chem. Neurosci. 1, 639-648 (2010). [2] Brener et al., Sci. Rep. 5, 13222 (2015). [3] Jiang et al., PLoS One 10, e0128553 (2015). [4] Leithold et al., Pharm Res. 33, 33(2):328-336 (2016)

Disclosures: D. Willbold: None.

Nanosymposium

188. Novel Therapeutics for Neurodegenerative Disorders

Location: 146C

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***188.04

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

Support: NIH Grant R01AG038961
Focused Ultrasound Foundation
W. Coulter Foundation

Title: Unilateral focused ultrasound-induced blood-brain barrier opening alters the spatial profile of hyperphosphorylated tau in an Alzheimer's mouse model

Authors: *M. KARAKATSANI[1], T. L. KUGELMAN[1], S. WANG[1], K. E. DUFF[2], E. KONOFAGOU[1,3]
[1]Columbia Univ., Dept of Biomed. Engin., New York, NY; [2]pathology and Cell Biol., Taub Inst. at Columbia Univ/ NYSPI, New York, NY; [3]Columbia University, Dept. of Radiology, New York, NY

Abstract: Focused ultrasound has been shown to interact with Alzheimer's pathology and particularly to trigger the reduction of the amyloid plaque load. However, a less studied interaction is that of ultrasound with the tangle formation that has been implicated in the cognitive decline of Alzheimer's patients. With the current study we investigate the interaction of unilateral focused ultrasound-induced blood-brain barrier opening with the tau distribution in an Alzheimer's mouse model.For this study 5 mice of the rTg4510 line (3.5 months old) were sonicated four times in the hippocampal formation and were compared to 5 control littermates. The day after the last sonication the mice were sacrificed. The brains were sectioned and counterstained for tau protein (AT8) as well as microglia activation (CD68). A customized algorithm was constructed to quantify the number of cells and the axonal distribution of the tau-marker. Figure 1 shows two representative examples of the control and the treatment group. Following the hippocampal formation of the control brain, it can be observed that both somatodendritic and axonal tau (red) are evident. Although the cell bodies affected by tau protein are also evident in the animals that received four sonications, axonal tau was less pronounced. Differences across hemispheres were detectable only in the treated group. In addition, the phagocytic microglia (green) seem almost absent in the control brains while they can be observed in both hemispheres of the treatment group. Quantification of the tau marker showed comparable levels of the cell body count for the two groups but significantly less axonal tau expression for the treated group. Since the cell body count was similar between groups, it can be concluded that the reduced tau protein was not transferred to other cell bodies. Finally, microglia were also significantly activated by the sonication but its relationship to tau re-distribution remains to be established.

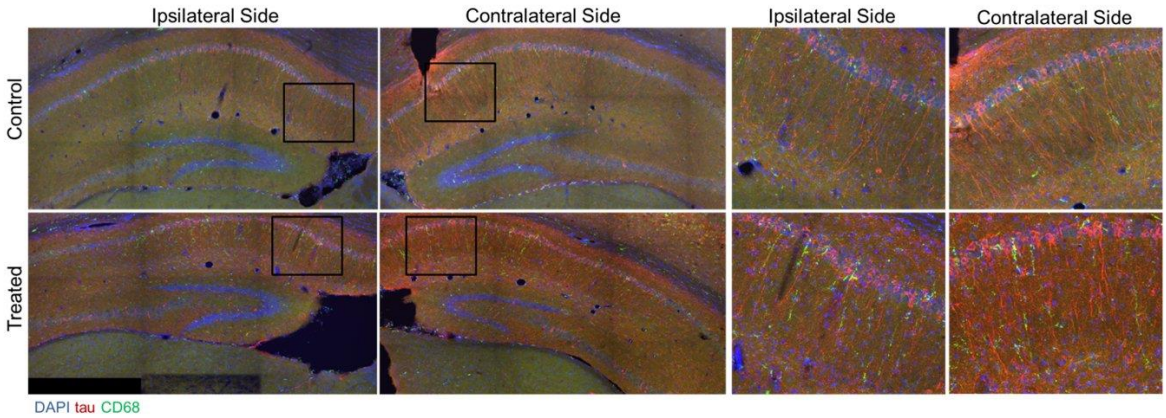

Figure: Hippocampal formation counterstained for tau protein with AT8 (red) and microglia activation with CD68 (green). The first row corresponds to the ipsilateral and contralateral side of a control brain and their magnified regions. The second row corresponds to the ipsilateral and contralateral side of a treated brain and the corresponding magnified regions.

Disclosures: M. Karakatsani: None. **T.L. Kugelman:** None. **S. Wang:** None. **K.E. Duff:** None. **E. Konofagou:** None.

Nanosymposium

188. Novel Therapeutics for Neurodegenerative Disorders

Location: 146C

Time: *Sunday, November 12, 2017, 1:00 PM - 3:15 PM

Presentation Number: *188.05

Topic: *C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONACYT-MEXICO SCHOLARSHIP-339473

Title: Nutritional strategies against synaptic and metabolic alterations in alzheimer´s disease

Authors: *T. SYEDA[1], A. PINEDO-VARGAS[2], S. DIAZ-CINTRA[2], N. TORRES-TORRES[3], C. PEREZ CRUZ[1]
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Abstract: Background: Alzheimer's disease (AD) is the most common form of dementia. Recent investigations described synaptic hyperactivity and metabolic alteration in early stages of the disease. Healthy life style and adherence to Mediterranean diet seems to decrease the incidence of AD. Bioactive components of our daily diet can modulate cellular metabolism and brain function. However, the mechanism of action of bioactive food (BF) remains unclear.

Objective: To elucidate the mechanism by which bioactive food can improve synaptic and metabolic function in 3xTgAD mice. **Method:** BF diet contained dried nopal (5%), chia seed oil (9%), soy protein (19.4%), and turmeric (0.1%). AIN-93 was used as control diet. Both diets were designed to supply same calorie/kg. Two months old female 3xTg-AD (Tg) and Wild Type (WT) mice were used for this study. Tg mice were randomly divided into 2 groups: 1) Tg mice fed control diet (Tg-AIN), and 2) Tg mice fed BF (Tg-BF), both for 7 months. WT animals were fed control diet. Cognitive performance was assessed at 9 months of age by T-maze and water maze. We quantified SIRT1- and PGC-1- inmunoreactivity in hippocampus. Synaptic and metabolism related proteins, inflammation and oxidative stress markers were analyzed in cortex by western blot. Short-chain-fatty acids (SCFAs) were analyzed by UV-HPLC. Gut microbiota composition was evaluated in feaces samples. **Results:** There was a significant improvement in short-term memory in Tg-BF, accompanied by decreased p-Tau, intracellular Aβ load, and neuroinflammation. In addition, BF was able to restore SIRT1 and PGC-1 levels in pyramidal layer. Interestingly, synaptic over excitation (i.e. increased Arc, Glur1 and PSD95 protein content) was reduced after BF ingestion. BF also caused decreased p-AKT and SCFAs receptor (FFAR3) in cortex of Tg mice. SCFAs content and gut microbiota composition was also modulated by BF diet. **Conclusion**: The food combination used in the present study was able to improve cognitive performance and neuronal metabolism in Tg mice. Several components of the BF diet have prebiotic properties. Gut microbiota composition and diversity was modified in Tg mice after BF ingestion. It has been postulated that gut microbiota metabolites can modulate brain function (brain-gut axis). Interestingly, we observed that BF altered levels of SCFAs and proteins related to synaptic function and energy metabolism in Tg mice. Hence, a nutritional portfolio can be proposed as a therapeutic strategy against degenerative diseases and may modulate the course of AD.

Disclosures: T. Syeda: None. **A. Pinedo-Vargas:** None. **S. Diaz-Cintra:** None. **N. Torres-Torres:** None. **C. Perez Cruz:** None.

Nanosymposium

188. Novel Therapeutics for Neurodegenerative Disorders

Location: 146C

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***188.06

**Topic: ***C.01. Brain Wellness and Aging

Support: K99AG051711 (J.M.C.)
AG045034 (T.W.-C.)

Title: Systemic TIMP2 treatment revitalizes hippocampal function in aged mice

Authors: *J. M. CASTELLANO[1], K. I. MOSHER[2], R. J. ABBEY[3], A. A. MCBRIDE[3], M. L. JAMES[4], D. BERDNIK[3], J. C. SHEN[3], B. ZOU[6], X. S. XIE[6], M. TINGLE[5], M. S. ANGST[5], T. WYSS-CORAY[3]
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Abstract: Aging drives changes in neuronal and cognitive function, the decline of which is a major feature of several neurodegenerative diseases, including Alzheimer's disease. Exposure to young blood counteracts aspects of age-related decline, yet characterization of factors promoting plasticity and cognition remains an area of active investigation. We hypothesized that umbilical cord plasma represents a reservoir of 'rejuvenating' factors capable of revitalizing synaptic function in aging and disease. We recently provided the first characterization of a human plasma transfer model using immunodeficient mice as a tool to screen blood-borne rejuvenating activities. Conservation between mouse and human plasma factors was investigated using protein microarrays on hundreds of plasma proteins. Cord plasma improved synaptic and cognitive function compared to plasma treatment with older human donors. Coupling these analyses with array-identified candidates in vivo uncovered blood-borne factors that appeared to activate neuronal activity in vivo, several of which we now report as putative pro-plasticity factors.
We further demonstrate that systemic TIMP2 treatment was sufficient to enhance synaptic plasticity and cognitive performance in aged mice. Conversely, targeting systemic TIMP2 with anti-TIMP2 antibody in young mice resulted in impaired spatial memory in a novel location recognition task. Depletion experiments revealed TIMP2 to be necessary for the hippocampal-dependent cognitive improvements conferred by cord plasma. In the CNS, we find that TIMP2-expressing neurons in the hilus decline gradually with age. Paired with the observation that TIMP2 acting directly on the hippocampus is important for robust long-term potentiation (LTP), these data argue that a more precise understanding of TIMP2's interactions within the CNS will be beneficial. We provide evidence of morphological and gene expression changes within the brain following TIMP2 treatment that may inform cellular targets, while also providing data in other models of synaptic dysfunction.
Together, our results suggest that blood-borne cues modulate the brain's response to aging and its susceptibility to synaptic failure, perhaps providing novel targets for the development of therapies targeting neurodegeneration.

Disclosures: **J.M. Castellano:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest shareholder; co-inventor on patent applications. **K.I. Mosher:** None. **R.J. Abbey:** None. **A.A. McBride:** None. **M.L. James:** None. **D. Berdnik:** None. **J.C. Shen:** None. **B. Zou:** None. **X.S. Xie:** None. **M. Tingle:** None. **M.S. Angst:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest shareholder; co-inventor on patent applications. **T. Wyss-Coray:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest co-founder and shareholder; co-inventor on patent applications.

Nanosymposium

188. Novel Therapeutics for Neurodegenerative Disorders

Location: 146C

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***188.07

**Topic: ***C.01. Brain Wellness and Aging

Title: Enhanced skeletal muscle proteostasis as a determinant of CNS protein quality control and neural function in the aging brain

Authors: *C. J. CORTES[1,2], H. A. TUCKER[1], A. GROMOVA[3], A. R. LA SPADA[2,4]
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Abstract: Proteostasis is essential for cell health and viability, and involves complex and highly conserved networks that regulate protein translation, protein folding, and protein degradation. A decline inproteostasis function is one of the features of aging tissues, particularly of the central nervous system (CNS). Indeed, the aging brain is particularly sensitive to proteotoxic stress, as demonstrated by the high number of age-associated neurodegenerative disorders characterized by protein misfolding and aggregation, including Alzheimer's disease (AD). The regulation of non-cell autonomous proteostasis has recently arisen as a novel mechanism for the modulation of systemic homeostasis in worms and flies, and is postulated to have important organismal effects on metabolism and aging. However, to date, there are no studies addressing the existence and activity of these pathways in mammals, and their potential effects on the aging brain. Transcription Factor E-B (TFEB) is a powerful master transcription factor regulator of proteostasis,integrating autophagy and bioenergetics. We recently derived transgenic mice that moderately overexpress TFEB in skeletal muscle, and discovered that the resulting enhanced skeletal muscleproteostasis function can significantly ameliorate proteotoxicity in the CNS and also improve cognition and memory in aging mice. We have also uncovered changes in soluble TFEB muscle-secreted factors (myokines), suggesting a potential modulation of the observed neuroprotective effects. Identification of pathways regulating cross-talk between skeletal muscle and CNS may yield targets with high therapeutic potential for diseases of the aging CNS.

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Nanosymposium

188. Novel Therapeutics for Neurodegenerative Disorders

Location: 146C

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***188.08

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Reduction of neuropathological deficits in transgenic mouse models of Huntington's disease using solid lipid curcumin particles

Authors: *A. AL-GHARAIBEH[1,2], R. CULVER[1,2], L. PALADUGU[1,2], S. HEILEMAN[1,2], A. OSTERHOUT[1,2], N. MUHN[1,2], N. MUNRO[1,2], D. STORY[1,2], J. ROSSIGNOL[1,2,3], G. L. DUNBAR[1,2,4], P. MAITI[1,2,4]
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Abstract: Huntington's disease (HD) is a genetic neurodegenerative disorder characterized by dysfunction of motor, cognitive and psychiatric behaviors. The hallmark pathology of HD is the aggregation of mutated huntingtin protein in intracellular spaces, which are associated with neuronal degeneration, along with abnormal dendritic arborization and spine loss in the medium spiny neurons (MSNs) of striatum. Although the genetic cause has been identified, the exact pathway for the massive neuronal degeneration is not known. Several efforts have been implicated to prevent or cure the degeneration of MSN in striatum, but no effective therapy is currently available. Recently, curcumin (Cur), a natural polyphenol extracted from the herb *Curcuma longa*, has been used to prevent or delay HD pathology, but due to its solubility and bioavailability issues, solid lipid curcumin particles (SLCPs) were used in the present study. We administered SLCPs (orally;100mg/kg) every other day for 8 weeks duration in the YAC128 mice and 4 weeks in the R6/2 mice (mouse models of HD). We administered a battery of behavioral tests, including accelerating rotarod, and grip strength every other week. After the stipulated period of treatment, the mice were sacrificed, and half of the brains were immersed in Golgi-Cox staining, and the other half were preserved for Western blotting analyses. Although, we did not find any significant change in behavioral analyses in both YAC128 and R6/2 HD mice, there was a significant increase of the number of dendritic spines in MSNs in SLCP-treated mice. In addition, a trend toward an increase in the number of distal dendrites in the treated mice was observed. Western blot results revealed an increase in brain derived neurotrophic factor (BDNF) and its receptor (TrkB), as well as a marker for MSNs (DARPP32) in the striata of SLCP-treated mice. Taken together, our preliminary results suggest that SLCPs might be used to prevent or delay neurodegeneration of MSNs in striatum of mouse models of HD, and provide a new therapeutic strategy for treating HD.

Disclosures: **A. Al-Gharaibeh:** None. **R. Culver:** None. **L. Paladugu:** None. **S. Heileman:** None. **A. Osterhout:** None. **N. Muhn:** None. **N. Munro:** None. **D. Story:** None. **J. Rossignol:** None. **G.L. Dunbar:** None. **P. Maiti:** None.

Nanosymposium

188. Novel Therapeutics for Neurodegenerative Disorders

Location: 146C

Time: *Sunday, November 12, 2017, 1:00 PM - 3:15 PM

Presentation Number: *188.09

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

Support: NIH Grant R01AG033106

Title: One year aerobic exercise increases regional cerebral blood flow in anterior cingulate cortex: a blinded, randomized trial in patients with Mild Cognitive Impairment

Authors: ***B. P. THOMAS**[1], T. TARUMI[5], M. SHENG[1], B. Y. TSENG[5], K. WOMACK[2], M. C. CULLUM[3], B. RYPMA[6], R. ZHANG[5,4], H. LU[7,1]
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Abstract: Individuals with mild cognitive impairment (MCI) are at an early stage of Alzheimer's disease (AD), and have high risk of inevitable decline to AD. Much research has focused on preventing this decline, but negative outcomes from several AD clinical trials has led us to research other alternatives. Aerobic exercise may be effective at preventing AD. It is shown to improve cardiorespiratory and cognitive function in older adults with and without MCI. The mechanisms of cognitive function improvement are not well understood, and are the topic of this research. We hypothesized that aerobic exercise improves cerebrovascular function, which leads to brain function improvement. We used Pseudo-Continuous-Arterial-Spin-Labeling (PCASL) MRI to measure resting cerebral blood flow (CBF) in MCI. Non-aerobic stretching was used as control for comparison. 30 subjects with MCI were recruited and assigned to perform either aerobic exercise, or non-aerobic stretching for one year. Both groups were age, gender, education, BMI, and clinically matched. The aerobic exercise group was trained to maintain their heart rate (HR) within 55-65% of max HR during exercise. The stretch group performed upper and lower body stretching and maintained their HR below 55% of max HR. Both groups began training at 3 sessions per week, 30 minutes per session, and intensity was gradually increased. Resting CBF was measured in all subjects at the start and end of training in a 3T MRI scanner

using a PCASL sequence. For each subject, the CBF map pre training was subtracted from that post training (Post-Pre), to obtain a difference map. CBF maps were then compared between groups to assess changes in CBF due to aerobic exercise compared to stretch (Exercise>Stretch). Cardiorespiratory fitness, was significantly higher ($p<0.05$) in the exercise group alone. Memory function as measured by the logical memory (LM) delayed recall test improved significantly in the aerobic exercise group alone. CBF increased in the exercise group compared to the stretch group in the anterior cingulate cortex (ACC), medial frontal gyrus (MFG, BA32) and inferior frontal gyrus. A voxel-wise regression analysis revealed that improvement in memory function correlated positively with CBF increase in the ACC and MFG (BA6). Chapman et al reported similar exercise induced CBF increase in the ACC in older adults. The ACC and MFG, represent a critical node in working memory, involved in monitoring of memory and allocation of attention supporting memory. In summary, aerobic exercise improved cardiovascular and cognitive function in MCI. Improvement in cognitive function was suggested to be mediated by increases in CBF in the ACC and frontal lobe.

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Nanosymposium

189. Parkinson's Disease: Human Therapeutic Studies

Location: 143A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***189.01

**Topic: ***C.03. Parkinson’s Disease

Title: Single center assessment of deep brain stimulation (DBS) program: Degree, onset and longevity of benefit from subthalamic nucleus (STN) implantation for Parkinson’s disease (PD) as assessed by the universal Parkinson disease rating scale (UPDRS) III

Authors: *E. L. HARGREAVES[1], O. MARK[2], D. P. SCHNEIDER[2], R. J. DIPAOLA[2], S. F. DANISH[3], D. L. CAPUTO[2]
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Abstract: At our center, we administer the UPDRS-III at nearly every patient visit. Now, we report the results from those, who underwent STN DBS implantation between 3 and 4 years ago. The intent was to replicate and extend Weaver et al., (2009) who showed that DBS with medical management outperformed medical management alone 6 months post-DBS. We sought the onset of benefit greater than baseline medical management and continuously tracked the benefit up to now, some 3 years post operatively. The “micro-lesion” effect as reported by Mann et al., (2009)

was also tested.
The charts of 20 patients were reviewed, who were intradepartmental referrals undergoing STN DBS and continued to be followed and managed “in house”. All the “On” UPDRS-III scores during the year prior to STN DBS were aggregated. Additionally, the “On” and “Off” scores of the Dopamine (Da) Challenge performed during DBS candidacy were logged. Post operatively, the UPDRS-III score was logged at the Contact Screen, during the “Off” state. The UPDRS-III score during the visit immediately following the contact screen was logged, as were all subsequent “On” scores aggregated into the first 3 and 6 month intervals, and all 6 month intervals after that, up to 3 years at present. All comparisons were made using paired ttests.
The micro-lesion effect was assessed by comparing the Da Challenge “Off” score to the Contact screen “Off” score, revealing that the post-DBS “Off” score was statistically less than the pre-DBS “Off” score ($t_{(19)}$=2.41; p=0.026). No difference was found between the average UPDRS-III “On” score preceding DBS versus the Da Challenge “On” score (p=0.18), leading to these two scores being aggregated to form a pre-DBS baseline “On” score. This Baseline “On” scores was then contrasted to: 1st visit post-Contact screen (p=0.35), 3 month post DBS (p=0.04), 6 month (p=0.002), 1year (p=0.00003), 1.5 years (p=0.0006), 2 years (p=0.002), 2.5 years (p=0.0007) and 3 years (p=0.009). All statistical differences favored the post-DBS intervals with improved UPDRS-III “On” scores compared to the pre-DBS baseline aggregate “On” score.
Our Center’s long term following of STN DBS Parkinson’s patients verifies the “micro-lesion” effect, and further shows benefit greater than best medical management alone can be obtained from DBS and best medical management by as early as 3 months post-DBS, and can be maintained at similar levels for at least 3 years post DBS.

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Nanosymposium

189. Parkinson's Disease: Human Therapeutic Studies

Location: 143A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***189.02

**Topic: ***C.03. Parkinson’s Disease

Title: Deep brain stimulation battery longevity of medtronic activa PC neurostimulators; parameter contribution using linear regression models

Authors: *R. P. PATEL[1], R. J. DIPAOLA[2], D. P. SCHNEIDER,[2], S. WONG[2], S. F. DANISH[3], E. L. HARGREAVES[1]

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Abstract: Deep Brain Stimulation (DBS) is an adjunct neurosurgical treatment for movement disorders. Medtronic's Activa PC neurostimulator is purported to have a 2-5 year battery life. Previous studies have reported correlation between programmable parameters and the longevity of earlier Medtronic neurostimulators. Here, we have examined 32 patients, who underwent DBS with Activa PC devices, implanted from 2010 to 2014, and have had at least one device replacement. Of the 32 patients, 27 have subthalamic nucleus (STN) lead placement for PD, 1 has ventrointermediate nucleus (VIM) lead placement for ET, and 4 have Globus Pallidium Internal (GPi) stimulation (3 for PD, 1 for Camptocormia). Data were obtained through retrospective chart analysis and consisted of implant and exchange dates, final battery charge, and final contact configuration, impedances and stimulation parameters, selected as representative of stable long term programming. Frequency values ranged from 40 Hz to 200 Hz, mean: 89.22 Hz (sem 7.01). Right amplitude ranged from 1.18 V to 5.2 V, mean: 3.110 V (sem 0.17). Left amplitude ranged from 1.25 V to 5.1 V, mean: 3.31 V (sem .16). Right pulse width (PW) ranged from 60 µs to 140 µs, mean: 87.66 µs (sem 3.80). Left PW ranged from 60 µs to 120 µs, mean: 87.03 µs (sem 2.95). Correlations between individual parameters and device longevity revealed weak, yet statistically significant results. For the left and right amplitude the correlations were r=-0.33 and r=-0.598 respectively, while for the left and right PW correlations were r=-0.44 and r=-0.36. The frequency correlation was r=-0.35. Aggregate measures of left/right parameter settings for amplitude r=- 0.22 and PW r=-0.18 did not fare better. When individual parameters were computationally aggregated to represent the Total Electrical Energy Delivered (TEED) by the neurostimulator, (Koss et al., 2005) for a 1 sec epoch [(amplitude^2 X frequency X PW) / (impedance)], the resulting device output was the strongest predictor (r=-0.72) of device longevity. Further, TEED was found to be strongest predictor of device longevity in forward multiple regression models, in line with previous reports for Medtronic's earlier devices. Of the variables included in the optimal model, TEED was entered first, followed by end battery charge, and finally a unilateral impedance (r=-0.824; Rsquared=0.679). Our analysis and multiple regression models represent a novel approach to predicting device longevity based on multiple contributing variables for Medtronic's Activa PC neurostimulator, and may be able to reduce clinical deterioration and subacute worsening of symptoms associated with battery depletion and failure.

Disclosures: R.P. Patel: None. **R.J. DiPaola:** None. **D.P. Schneider,:** None. **S. Wong:** None. **S.F. Danish:** None. **E.L. Hargreaves:** None.

Nanosymposium

189. Parkinson's Disease: Human Therapeutic Studies

Location: 143A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***189.03

**Topic: ***C.03. Parkinson’s Disease

Support: Leopold Korn and Michael Korn Professor in Parkinson's Disease

Title: Human fetal dopamine cell transplants survive for the lifetime of Parkinson patients independent of the time since transplant or the age of the transplant recipient

Authors: *C. R. FREED[1], R. E. BREEZE[2], B. A. SYMMES[1], S. FAHN[3], D. EIDELBERG[4], W. ZHOU[1]
[1]Div. of Clin. Pharmacol., [2]Neurosurg., Univ. of Colorado, Aurora, CO; [3]Neurol., Columbia Univ., New York, NY; [4]Neurol., Feinstein Inst. for Med. Res., Manhasset, NY

Abstract: Beginning in 1988, we have transplanted human fetal dopamine neurons into 61 subjects with advanced Parkinson’s disease and have shown that transplants can significantly improve signs of Parkinson’s disease up to but not exceeding the best effects of L-dopa. 34 of the 61 subjects received transplants between 1995-1999 under an NIH protocol with tissue fragments from 4 embryos placed via 4 needle tracks through the forehead into the long access of putamen. Most non-NIH subjects received transplants prior to our development of the NIH protocol varying from unilateral into putamen and caudate (2 subjects) to bilateral simultaneous transplants into putamen (25 subjects) using either a vertex (16) or anterior (9) approach. Post-mortem brains have been obtained from 15 subjects who have died 7 months to 27 years after transplant, 8 NIH and 7 non-NIH. Dopamine neurons were identified immunohistochemically in transplant tracks using a primary antibody to tyrosine hydroxylase and a secondary antibody labeled with horseradish peroxidase or fluorescent FITC. Despite the absence of immunosuppression at any time for most subjects, every fragment of human embryonic mesencephalon showed surviving dopamine neurons, indicating that the immune system had not destroyed any transplant. The average number of dopamine neurons surviving per embryo was 9,120 +/- 1110 (mean+/- sem) with no significant difference between NIH and non-NIH subjects (p=0.27 n.s.). Because NIH subjects received tissue from 4 embryos, their total cell counts were 36,290 +/- 8099. Clinical review showed that subjects who were able to discontinue L-DOPA therapy had survival of at least 30,000 dopamine neurons. All transplants showed extensive fiber outgrowth into striatum, indicating that the transplanted dopamine neurons were physiologically functional. Immunostaining for Lewy bodies using antibodies to phosphoserine-129 alpha-synuclein revealed inclusions in about 1% of neurons. Regression analysis showed no relation between dopamine neuron survival and the years since transplant (NIH: R2=0.17, non-NIH: R2=0.02) or the age of the patient at the time of transplant (NIH: R2=0.22, non-NIH: R2=0.02).

These results indicate that patient age is not a factor for successful dopamine neuron transplantation and that there is no progressive loss of dopamine neurons over time. We conclude that transplanted human dopamine neurons survive for the lifetime of Parkinson patients without immunosuppression. Because the percentage of dopamine neurons surviving transplantation is very low, about 5%, methods that improve cell survival at the time of surgery should yield more predictable clinical outcomes.

Disclosures: C.R. Freed: None. **R.E. Breeze:** None. **B.A. Symmes:** None. **S. Fahn:** None. **D. Eidelberg:** None. **W. Zhou:** None.

Nanosymposium

189. Parkinson's Disease: Human Therapeutic Studies

Location: 143A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***189.04

**Topic: ***C.03. Parkinson’s Disease

Title: Six month update on the First-in-Human clinical study of neural stem cells in patients with Parkinson’s disease

Authors: *R. A. KERN[1], I. GARITAONANDIA[1], R. GONZALEZ[1], G. SHERMAN[1], A. NOSKOV[1], D. CARDIFF[1], T. CHRISTIANSEN-WEBER[1], A. SEMECHKIN[1], E. BRAINE[2], A. SHAHRUL[2], G. NAIR[2], A. H. EVANS[2]
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Abstract: Parkinson’s disease (PD) is a devastating neurodegenerative disease with progressive degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta. There are over 10 million people afflicted with PD and the yearly mortality rate is more than 100,000 worldwide. Unfortunately none of the available treatment options have the potential to restore the damaged nigrostriatal pathway. Cell based therapies have shown considerable promise because they can achieve significant biochemical and clinical improvements for several years in some patients. We have demonstrated in preclinical PD models that transplantation of human parthenogenetic derived neural stem cells (ISC-hpNSC) promotes behavioral recovery and increases DA levels, DA neuron innervation and number. Intra-nigrostriatal administration of clinical grade ISC-hpNSC is safe, well tolerated, reduces inflammation, and provides neurotrophic support and neuroregeneration to the nigrostriatal pathway. We are conducting a First-In-Human study to evaluate the safety and functional activity of ISC-hpNSC, making it the world’s first pluripotent stem cell based therapy for PD (ClinicalTrials.gov: NCT02452723). This is a single-arm, open-label, Phase I study evaluating three dose regimens of 30, 50 and 70 million ISC-hpNSC. There are 12 patients in this study divided into 3 cohorts of 4 patients each.

Patients receive immunosuppression and stereotactic bilateral injections of 7 cell deposits per hemisphere into the caudate nucleus, putamen and substantia nigra. Patients are evaluated for 12 months with a 5 year long-term follow-up. The primary endpoint of the study is to assess the incidence of treatment-emergent adverse events. Secondary endpoints evaluate efficacy by measuring the change from baseline in ^{18}F-dopa PET, UPDRS, PDQ-39, BDI, CGI, QUIP-RS, AIMS and MOCA. All four patients from the first cohort have successfully been transplanted with 30 million ISC-hpNSC cells. Delivery of ISC-hpNSC to the striatum and substantia nigra went according to plan without intraoperative complications. No serious adverse events (SAE) associated with ISC-hpNSC or the immunosuppression regimen have been reported. No graft-induced dyskinesia or evidence of tumors, inflammation or infection have been reported. Six month analysis of ^{18}F-dopa PET scans and neurological scores from the first cohort will be presented. In summary, interim data shows that administration of ISC-hpNSC is safe and has the potential to repair the nigrostriatal pathway.

Disclosures: The Disclosure Block has exceeded its maximum limit. Please call Tech support at (217) 398-1792 for more information.

Nanosymposium

189. Parkinson's Disease: Human Therapeutic Studies

Location: 143A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***189.05

**Topic: ***C.03. Parkinson’s Disease

Support: Financial support by Foundation HM and Insightec

Title: Focused ultrasound subthalamotomy restores intracortical inhibition in Parkinson's disease

Authors: *M. DILEONE, R. RODRÍGUEZ-ROJAS, R. MARTÍNEZ-FERNÁNDEZ, J. PINEDA-PARDO, M. DEL ÁLAMO, F. HERNÁNDEZ-FERNÁNDEZ, G. FOFFANI, J. A. OBESO
CINAC, Univ. Hosp. HM Puerta Del Sur, Mostoles, Spain

Abstract: Magnetic resonance imaging (MRI)-guided focused ultrasound has recently been developed to produce focal lesion of deep brain structures without the need for skull incision. The objective of this study was to test the effects of focused ultrasound subthalamotomy on motor cortex excitability in Parkinson’s disease (PD). Short-interval intracortical inhibition (SICI) and short-interval intracortical facilitation (SICF) were measured with paired-pulse transcranial magnetic stimulation (TMS) of the motor cortex before, 24 hours, 3 months and 6 months after focused ultrasound subthalamotomy on the more affected hemisphere in 9 clinically

asymmetric patients with Parkinson's disease. All evaluations were performed OFF medication. In baseline conditions, SICI - but not SICF - was significantly lower in the more affected hemisphere compared to the less affected hemisphere. Six months after subthalamotomy, SICI selectively increased in the more affected hemisphere, reaching values near normality whereas SICF was not significantly modified. The improvement in SICI did not correlate with changes in cortical metabolism, as measured by 18F-flurodeoxyglucose-positron emission tomography (PET), but they did correlate with changes in subthalamic metabolism in the lesion hemisphere, and with reduction in motor scores (UPDRS III). These results suggest that restoring intracortical inhibition by focused ultrasound subthalamotomy is a relevant mechanism underlying clinical improvement.

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Nanosymposium

189. Parkinson's Disease: Human Therapeutic Studies

Location: 143A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***189.06

**Topic: ***C.03. Parkinson's Disease

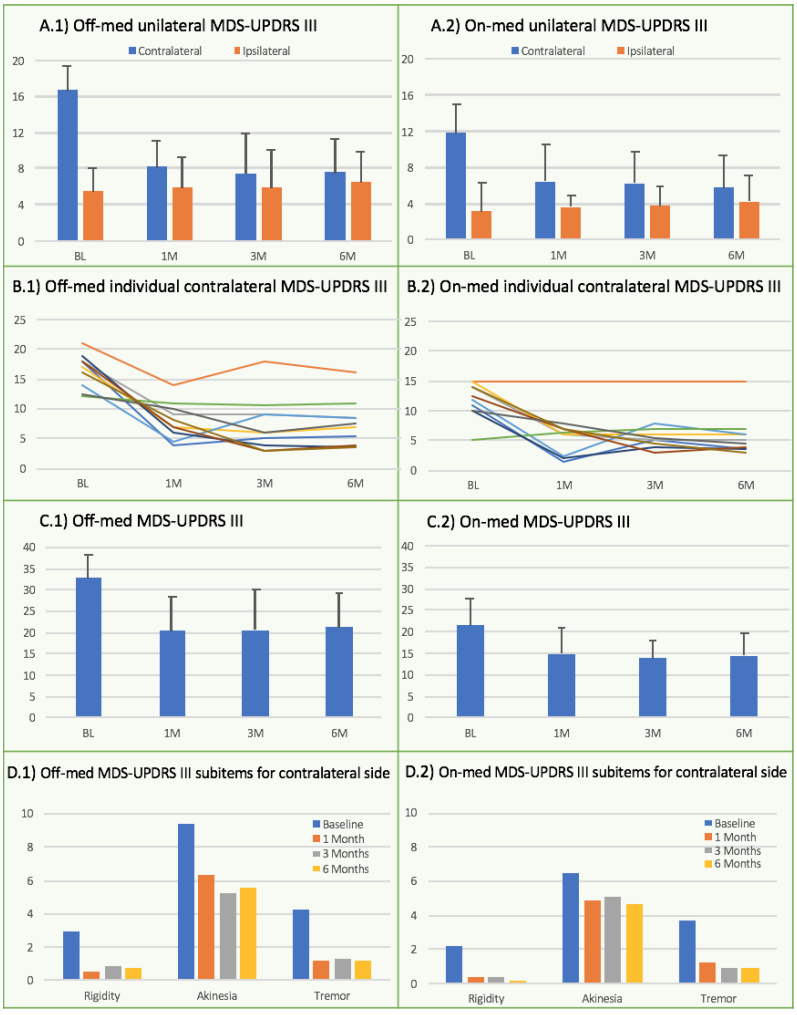
Support: Financial support by Foundation HM and Insightec

Title: Safety and efficacy of focused ultrasound subthalamotomy for the treatment of Parkinson's disease

Authors: *R. MARTINEZ, R. RODRÍGUEZ-ROJAS, M. DEL ÁLAMO, M. DILEONE, F. HERNÁNDEZ-FERNÁNDEZ, J. PINEDA-PARDO, I. OBESO, G. FOFFANI, J. OBESO
Cinac-University Hosp. HM Puerta Del Sur, Mostoles, Spain

Abstract: The development of magnetic resonance (MR)-guided focused ultrasound allows focal lesioning of deep brain structures without skull incision. The aim of this study was to assess the safety and efficacy of unilateral subthalamotomy by MR-guided focused ultrasound to treat motor features of Parkinson's disease(PD).
This is an open-label, single-center study including ten Parkinson's disease patients with markedly asymmetric parkinsonism who were not well-controlled with medication. Motor features were assessed by the MDS-UPDRS III and motor complications were evaluated through MDS-UPDRS IV and the Dyskinesia rating scale. Levodopa daily equivalents were measured. Adverse events were recorded. Neuroimaging and electrophysiological changes were

assessed.MDS-UPDRS III score for the treated body side presented a reduction of 53 and 47% between baseline and 6-month visit in the off and on-medication condition respectively (from 16.6 to 7.5, p=0.005 and from 11.9±3.1 to 5.8±3.5, p=0.011). Total motor MDS-UPDRS improved up to 35 and 25% (from 32.7±5.4 to 21.2±8.2 p=0.005, and from 21.5±6.3 to 14.5±5.3 P=0.007). Rigidity was the most improved motor feature (71% and 88% p<0.001, in the off and on-conditions respectively) while akinesia was the least (36% p=0.015, and 23% p=0.058, respectively). Subthalamotomy resulted in no change in dyskinesia scores whereas off-dystonia improved significantly. Levodopa equivalents were reduced by 24% (p=0.014). One single patient developed upper limb off-dyskinesia five days after treatment that progressively reduced and had disappeared at 6 months.This pilot study suggests that MR-guided focused ultrasound subthalamotomy is feasible, safe and effective for the treatment of Parkinson's disease motor features.



Disclosures: **R. Martinez:** None. **R. Rodríguez-Rojas:** None. **M. del Álamo:** None. **M. Dileone:** None. **F. Hernández-Fernández:** None. **J. Pineda-Pardo:** None. **I. Obeso:** None. **G. Foffani:** None. **J. Obeso:** None.

Nanosymposium

189. Parkinson's Disease: Human Therapeutic Studies

Location: 143A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***189.07

**Topic: ***C.03. Parkinson’s Disease

Title: Investigating possible mechanisms of action of transcranial electric stimulation in parkinson’s disease

Authors: *Y. SALIMPOUR[1,2], K. A. MILLS[3], W. S. ANDERSON[2]
[2]Neurosurg., [3]Neurol., [1]Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: The primary method of treatment for people suffering from Parkinson's disease currently include medication and deep brain stimulation (DBS). Medications may be poorly tolerated and cause side-effects, whereas DBS is relatively invasive and can cause complications associated with brain surgery. Transcranial electric stimulation (TES) and its conventionally used form, transcranial direct current stimulation (tDCS), involves noninvasive cortical stimulation for the adjunctive treatment of movement disorders. In order to evaluate the mechanism of the observed effects of tDCS on PD symptoms, address the open question of possible mechanisms of action of tDCS to improve symptoms of PD, we here explore subcortical structures during DBS surgery. After prepping and draping the subject's scalp for the the surgical procedure, the tDCS electrode is positioned approximately over the hand region of the motor cortex to deliver tDCS to the scalp. The subcortical microelectrode is positioned in the target of interest and recordings of multiunit and field potential activity take place before, during and after the application of tDCS. Additionally, an intracranial strip electrode array implanted over the motor cortex is used to record the Electrocorticography (ECoG) signals in the cortical area for exploring possible changes after stimulation. The preliminary results from PD patients demonstrate a reduction in the coupling between the phase of beta rhythm and the amplitude of gamma oscillation in the recorded ECoG signals from motor cortex during and after tDCS stimulation. The primary goal of this study is to determine the feasibility of applying tDCS on the primary motor cortex of Parkinson disease patients while they undergo deep brain stimulation surgery. Due to the existence of cortical and subcortical interconnections, future clinical cortical level stimulation of the brain could modulate the neuronal activity in these network connections. The secondary goal is to investigate possible relationships between the mechanisms of action of deep brain stimulation and cortical stimulation by using electrophysiological recordings from the subthalamic nucleus neurons. Finally, the results might provide some evidence for the possibility of using both forms of neuromodulation in combination to increase the efficacy of treatment.

Disclosures: Y. Salimpour: None. **K.A. Mills:** None. **W.S. Anderson:** None.

Nanosymposium

189. Parkinson's Disease: Human Therapeutic Studies

Location: 143A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***189.08

**Topic: ***C.03. Parkinson's Disease

Support: NIH Grant R01AA023483
NIH Grant R01MH107197

Title: Accelerometry in Parkinson's disease

Authors: *T. HARRIGAN[1], J. R. BRASIC[2], G. N. MCKAY[2], K. A. MILLS[3], B. J. HWANG[4], C. MISHRA[6], A. PANTELYAT[7], L. FAYAD[5], D. F. WONG[8]
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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 11 patients with Parkinson's disease were instrumented with tri-axial accelerometers on the upper and lower extremities during modified segments of the of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz, 2008). Tests were administered by a board certified neurologist, certified in administration of the MDS-UPDRS. 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 by summing components to get total acceleration and by averaging over movement time. To assess the correlation between accelerometry and clinical observations, significantly or mildly impaired patients were chosen by clinical observation. **Results:** Table 1 shows typical results in a patient with mild impairment and a patient with significant impairment for both the upper extremity supination/pronation test and for a hand motion test (where the patient was asked to open and close his thumb/forefinger as fast and completely as possible). The accelerometer data also shows wrist flexion and larger index finger accelerations than wrist accelerations during supination/pronation in some cases. **Conclusions:** The averaged acceleration correlates with clinical observations, but time patterns offer more information. The accelerations at the wrist in the hand motion test may be useful. The proposed protocol

represents a promising tool to standardize and augment movement ratings in the future. This procedure 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.

Average Acclerations (g)			
Pronation/supination		Left	Right
Minor Impairment	Clinical Score	2	1
Minor Impairment	Finger	1.60	2.40
	Wrist	0.91	1.25
Significant Impairment	Clinical Score	3	2
Significant Impairment	Finger	3.14	1.86
	Wrist	1.01	1.03
Hand Motion			
Minor Impairment	Clinical Score	0	0
Minor Impairment	Finger	1.65	1.43
	Wrist	0.30	0.19
Significant Impairment	Clinical Score	1	1
Significant Impairment	Finger	2.06	1.65
	Wrist	0.40	0.25
1 g = 9,81 m/s^2 (acceleration of gravity)			

Disclosures: T. Harrigan: None. **J.R. Brasic:** None. **G.N. McKay:** None. **K.A. Mills:** None. **B.J. Hwang:** None. **C. Mishra:** None. **A. Pantelyat:** None. **L. Fayad:** None. **D.F. Wong:** None.

Nanosymposium

189. Parkinson's Disease: Human Therapeutic Studies

Location: 143A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:45 PM

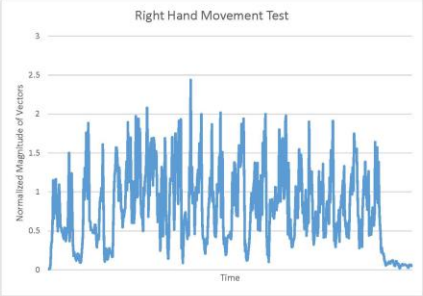
**Presentation Number: ***189.09

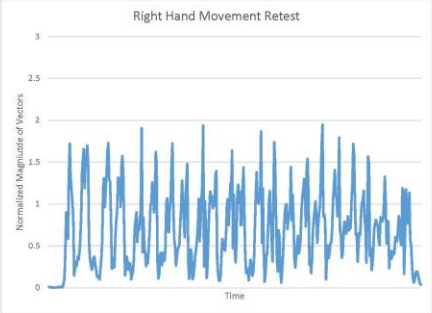
**Topic: ***C.03. Parkinson's Disease

Title: Test-retest of instrumentation to quantitatively measure movements of Parkinson's Disease

Authors: *B. J. HWANG[1], G. N. MCKAY[2], T. HARRIGAN[5], C. MISHRA[2], A. PANTELYAT[3], D. F. WONG[6], J. R. BRASIC[4]
[1]Neurosci., Johns Hopkins Univ., Baltimore, MD; [2]Russell H. Morgan Dept. of Radiology and Radiological Sci., [3]Neurol., [4]Radiology, Johns Hopkins Sch. of Med., Baltimore, MD; [5]REDD, Johns Hopkins Univ. Applied Physics Laborator, Laurel, MD; [6]Radiology, Johns Hopkins Med. Insts., Baltimore, MD

Abstract: Objective To evaluate and correlate the test-retest reliability of an accelerometry-based device and diagnostic criteria guidelines to quantify the severity of motor impairment in patients with Parkinson disease.
Methods: An 83-year-old man with Parkinson disease was evaluated with a protocol to assess live ratings and quantitative accelerometry measurements of the extremities during performance of modified segments of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz, 2008) by the same examiner at baseline and reevaluated 44 days later. The output of the accelerometry-based device for each item was treated as a three-dimensional vector. The data were normalized. The magnitude of the vector was calculated. Normalized data = X - N, where X = a data point, and N = normalizing factor of the average data value two seconds prior to the movement task Magnitude = square root of ($X^2 + Y^2 + Z^2$).
Results: Live ratings were identical for all 22 categories except for rest tremor amplitude right upper limb, (0, 1), right hand movements (2, 1), and left hand movement (1, 0). The percent agreement on live ratings between sessions is 86%. The output from instrumentation on the right hand movements confirmed the live ratings with higher values for the test than the retest in the calculated averages. Visual inspection of the generated continuous curves showed spikes consistent with an abrupt interruption in movement rhythm during the test not present in the retest (See Figure.)
Conclusions: The agreement between live ratings on two sessions by the same rater was good. For the right hand movements, live ratings demonstrated a difference confirmed by instrumentation represented by averages and by visual inspection of the curves. This suggests that instrumentation is comparable to live rating by a board-certified neurologist who is certified in the administration of the MDS-UDPRS. This procedure may facilitate obtaining objective data to monitor movements in people with Parkinson's disease during clinical trials and other interventions.





Disclosures: B.J. Hwang: None. **G.N. McKay:** None. **T. Harrigan:** None. **C. Mishra:** None. **A. Pantelyat:** None. **D.F. Wong:** None. **J.R. Brasic:** None.

Nanosymposium

189. Parkinson's Disease: Human Therapeutic Studies

Location: 143A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***189.10

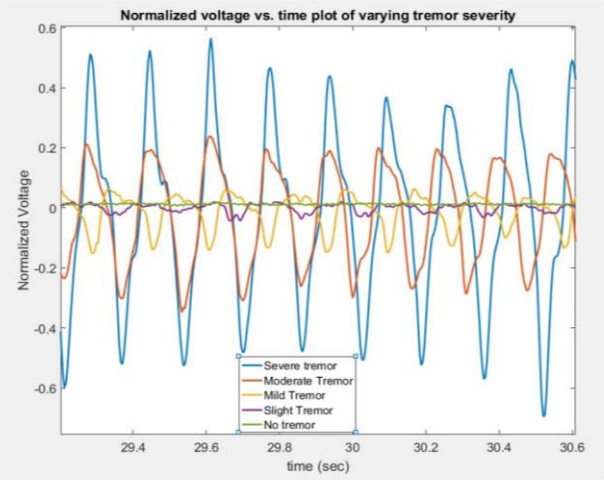
**Topic: ***C.03. Parkinson’s Disease

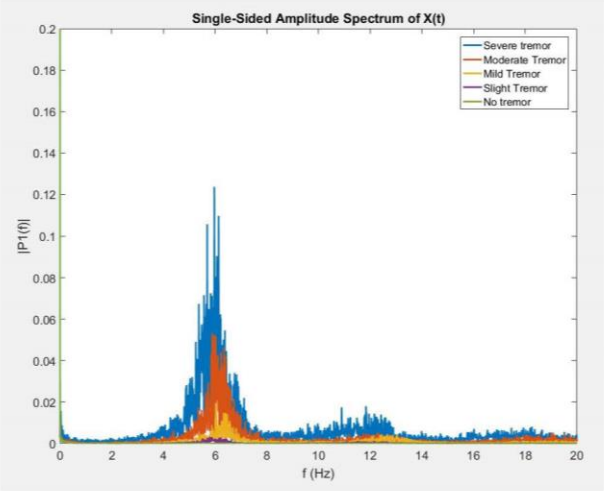
Title: Quantitative continuous measurement of movements in the extremities of people with Parkinson's disease

Authors: *J. R. BRASIC[1], G. N. MCKAY[2], B. J. HWANG[4], T. P. HARRIGAN[5], C. MISHRA[2], K. A. MILLS[3], A. PANTELYAT[3], J. BANG[3], L. ROSENTHAL[3], A. MATHUR[2], K. KITZMILLER[2], D. F. WONG[2]
[2]The Russell H. Morgan Dept. of Radiology and Radiological Sci., [3]Dept. of Neurol., [1]Johns

Hopkins Sch. of Med., Baltimore, MD; [4]Neurosci., Johns Hopkins Krieger Sch. of Arts and Sci., Baltimore, MD; [5]Johns Hopkins Applied Physics Lab., Laurel, MD

Abstract: Objective: To calibrate and evaluate an accelerometry-based device as an instrument to more precisely quantify the assessment of motor function of people with Parkinson's disease (PD). **Methods:** An accelerometry device consisting of a USB-powered data logger (DATAQ DI-710) wired to four 3-axis accelerometers (Analog Devices EVAL-ADXL335Z) was placed on the extremities of a healthy 25-year-old man. The participant moved his hands to simulate the pill-rolling tremor exhibited by people with PD. Signal processing algorithms in MATLAB extracted and analyzed the data generated by hand movements consistent with “no tremor,” “slight tremor,” “mild tremor,” “moderate tremor,” and “severe tremor.” **Results:** The figure demonstrates data of a healthy 25-year-old man mimicking tremors of PD of varying amplitudes. (a) Normalized voltage output of accelerometry device vs. time shows increased tremor acceleration amplitude with increasing tremor severity. (b) Sample signal processing algorithm - fast Fourier transform (FFT) plot of the same data of (a), where the y-axis represents the single-sided amplitude corresponding to the x-axis frequency. **Conclusions:** An accelerometry-based device with signal processing differentiates simulated parkinsonian tremors of varying amplitudes. The level of precision in tremor measurement will allow increased sensitivity for detection of clinical changes correlating with alterations in biological or neurophysiologic measurements during future research. 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.





Disclosures: **J.R. Brasic:** None. **G.N. McKay:** None. **B.J. Hwang:** None. **T.P. Harrigan:** None. **C. Mishra:** None. **K.A. Mills:** None. **A. Pantelyat:** None. **J. Bang:** None. **L. Rosenthal:** None. **A. Mathur:** None. **K. Kitzmiller:** None. **D.F. Wong:** None.

Nanosymposium

189. Parkinson's Disease: Human Therapeutic Studies

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Time: *Sunday, November 12, 2017, 1:00 PM - 3:45 PM

Presentation Number: *189.11

Topic: *C.03. Parkinson’s Disease

Support: NIBIB (K23EB014326)
NINDS (R01NS097782)
American Parkinson Disease Association, Postdoctoral Fellowship

Title: Pallidal deep brain stimulation reduces excessive cortical phase amplitude coupling in parkinson disease

Authors: *M. MALEKMOHAMMADI, N. AUYONG, N. POURATIAN
Neurosurg., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Objective: Although Subthalamic nucleus (STN) and globus pallidus internus (GPi) are both efficacious therapeutic targets for deep brain stimulation (DBS) in Parkinson disease (PD), most studies so far only have focused on understating the mechanisms of action in STN-DBS. Recent studies of STN-DBS suggest that DBS exerts its effect by modulating excessive cortical beta-broadband gamma phase-amplitude coupling (PAC). Motor cortical PAC has been also shown to significantly change with movement of contralateral limb. To further delineate role of cortical PAC in PD pathophysiology and examine generalizability of this finding to other DBS targets, we aimed to study effects of pallidal stimulation on cortical signals. **Methods:** We recorded local field potentials (LFPs) from right sensorimotor cortices through a non-penetrating electrocorticography (ECoG) strip in 10 PD patients undergoing pallidal DBS. Data was recorded during 30-second blocks of rest and contralateral hand movement (finger tapping). We measured beta (13-35 Hz) power using Welch method and beta-broadband gamma PAC in cortical signals using Tort's Modulation index. We examined effect of DBS and movement as well as their interactional effect on cortical beta power and beta-gamma PAC using linear mixed effect (LME) model. **Results:** We found that movement modulates both cortical power and PAC, however pallidal stimulation only results in significant suppression of cortical PAC. LME identified only movement and not the stimulation as the main factor triggering a statistically significant beta power suppression in cortical signals ($P<0.001$). Similar analysis on PAC however showed movement and stimulation both contribute to statistically significant suppression of cortical PAC ($p <0.01$) and that the interaction between the two factors is significant ($P = 0.047$). **Conclusions:** Our results show a similar effect of the palldial DBS to STN-DBS on motor cortical PAC. Significant interaction between movement and stimulation further supports the hypothesis that excessive cortical PAC is a manifestation of motor abnormalities in PD. Therapeutic DBS exerts its effect by modulating motor cortical PAC, regardless of the target. Moreover, similar effects of pallidal and STN DBS on motor cortical PAC may suggest that such phenomenon is less likely to be mediated via modulation of the hyperdirect pathway.

Disclosures: M. Malekmohammadi: None. **N. AuYong:** None. **N. Pouratian:** None.

Nanosymposium

190. Mechanisms of Neurotoxicity and Degeneration

Location: 147A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***190.01

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01NS094402
Shriners Hospitals for Children Grants 85600 PHI

Title: An essential role for palmitoylation-dependent retrograde signaling in developmental axon degeneration

Authors: *J. NIU, S. M. HOLLAND, A. KETSCHEK, K. M. COLLURA, F. I. DESIMONE, G. GALLO, G. M. THOMAS
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Abstract: During development of the peripheral nervous system (PNS), excess neurons are born and then compete for limiting amounts of neurotrophic support. Axons that experience insufficient support initiate retrograde pro-degenerative signals, which trigger a subsequent coordinated breakdown of PNS axons and neuronal cell bodies. Interestingly, this developmental process shares key features with the neurodegeneration seen in several pathological conditions, including critical roles for Dual Leucine-zipper Kinase (DLK) and DLK's downstream target c-Jun N-terminal kinase (JNK). However, it is unclear how retrograde DLK-JNK pro-degenerative signals are conveyed. We recently described a key role for the protein-lipid modification palmitoylation in DLK-dependent responses to axonal injury. Here, using cultured dorsal root ganglion (DRG) sensory neurons, we report that palmitoylation targets not just DLK but also the neural-specific JNK3 to similar axonal trafficking vesicles. Moreover, pharmacologically or genetically preventing palmitoylation of the DLK-JNK3 module blocks both retrograde pro-degenerative signaling and axon degeneration itself. At the molecular level, palmitoylation of DLK and JNK3 is critical to establish a positive feedback loop that maintains the DLK-JNK3 module in a highly active state. Our results reveal a novel role for palmitoylation in developmental axon degeneration, provide new insights into how neurons convey long distance signals, and suggest new therapeutic approaches that may reduce axon degeneration in pathological conditions.

Disclosures: J. Niu: None. **S.M. Holland:** None. **A. Ketschek:** None. **K.M. Collura:** None. **F.I. DeSimone:** None. **G. Gallo:** None. **G.M. Thomas:** None.

Nanosymposium

190. Mechanisms of Neurotoxicity and Degeneration

Location: 147A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***190.02

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Supported by National Institute on Aging (P01AG012411)
UAMS "S.T.O.P. Alzheimer's" Fund

Title: Caveolae as a novel component of proteostasis compromised by excess fatty acids: Relevance to neurodegeneration

Authors: *S. AGHDAM[1], S. AYYADEVARA[1,2], S. T. GRIFFIN[3], S. W. BARGER[4,5]
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Abstract: Inappropriate accumulation of proteins is a common element of CNS aging and several neurodegenerative disorders. A countervailing force, "proteastasis," includes proteolysis via the ubiquitin proteasome system (UPS). Evidence has established solid links between metabolic dysfunction—e.g., as promoted by high-fat diets—and the onset of neurodegenerative conditions such as Alzheimer's disease (AD), and in metabolic syndrome, brain uptake of fatty acids (FA) is elevated. Therefore, we investigated the effects of major dietary FAs—oleic acid and palmitic acid—on UPS function and proteostasis using in vitro neural models, including differentiated human NTera2 neuronal cells (hNT) and rodent primary neurons. Treatment of hNT with a combination of palmitic acid and oleic acid for 24 hours did not significantly increase the amount of ubiquitinylated (Ub-) proteins. To assess changes in the subcellular site of localization of Ub-proteins following FA treatment, the cells were fractionated by sucrose-gradient ultracentrifugation and fractions were probed by Western blot for ubiquitin. Compared to control cells, a considerable amount of Ub-proteins shifted to fractions containing caveolin in the 24-hour FA-treated cells. Treatment of hNT with oleic acid and palmitic acid increased the levels of the detergent-insoluble protein aggregates in whole-cell lysates in a time-dependent fashion. Analysis of the caveolin-positive fractions also revealed a time-dependent increase of detergent-insoluble protein aggregates 6, 12, and 24 hours after FA treatment. The proteasome activator protein PA28β—but not the 20S catalytic core of proteasomes—was detected in caveolin-positive fractions of control and FA-treated hNT cells. In caveolin-positive fractions of hNT cells, FA treatment reduced the protein levels of monomeric PA28β and instead yielded a high-molecular-weight band. Since the majority of the Ub-proteins and their detergent-insoluble derivatives appeared to be in caveolae following FFA treatment, we propose that the shift in the

molecular weight for PA28β represents protein aggregation for this protein within caveolae. In summary, FAs manipulate the UPS activity and promote protein aggregation in neurons. The presence of Ub-proteins, PA28β, and protein aggregates in caveolin-positive fractions and their modulation by FAs indicates a novel role for caveolae in regulating neuronal proteostasis.

Disclosures: S. Aghdam: None. **S. Ayyadevara:** None. **S.T. Griffin:** None. **S.W. Barger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Barger receives royalties from MilliporeSigma Inc. for the sales of secreted amyloid precursor protein.

Nanosymposium

190. Mechanisms of Neurotoxicity and Degeneration

Location: 147A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***190.03

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

Support: NIH Grant P01 AG017617
NIH Grant T32-GM066704

Title: Apolipoprotein E4 expression reduces brain exosome secretion

Authors: *K. PENG[1], M. J. ALLDRED[1], R. PEREZ-GONZALEZ[2], J. MORALES-CORRALIZA[3], M. SAITO[4], M. SAITO[4], S. D. GINSBERG[5], P. M. MATHEWS[6], E. LEVY[4]
[1]Ctr. for Dementia Res., Nathan Kline Inst., Orangeburg, NY; [2]Ctr. for Dementia Res., Nathan S. Kline Inst., Orangeburg, NY; [3]Nathan Kline Institute-New York Univ., Orangeburg, NY; [4]Nathan S Kline Inst., Orangeburg, NY; [5]Ctr. for Dementia Res., Nathan S Kline Institute/NYU Langone Med. Ctr., Orangeburg, NY; [6]Psychiat/Dementia Res., New York Univ. Sch. Med., Orangeburg, NY

Abstract: The ε4 allele of apolipoprotein E (ApoE4), the greatest genetic risk factor for sporadic Alzheimer's disease (AD), is also linked to cognitive vulnerability and functional brain differences that appear to be independent of AD-pathology. Based upon prior findings that ApoE4 expression may affect the neuronal endosomal system, we have investigated the impact of ApoE4 on the levels of brain exosomes. Exosomes are late endosome-derived membrane-bound vesicles secreted from the cell into the extracellular space. Our findings document lower levels of brain exosomes in non-demented human ApoE4 carriers when compared to individuals homozygous for the risk-neutral ε3 allele (ApoE3). Comparing humanized ApoE4 and ApoE3 mouse models that do not develop β-amyloid or tau pathology, we show an ApoE4-driven reduction in brain exosomes that is aging-dependent. Six-month-old ApoE4 mice had the same

levels of brain exosomes as age-matched ApoE3 mice. At 12 months of age, however, a decrease in the levels of brain exosomes was seen in ApoE4 mice. At the protein and mRNA levels, expression of TSG101 (a protein involved in the initial formation of late endosomal intraluminal vesicles destined to be secreted as exosomes) and expression of rab35 (a regulator of exosome secretion) were lower in 12-month-old ApoE4 mouse brains. This finding suggests that a reduction in exosome formation and trafficking out of the cell occurs in the aged ApoE4 brain. Consistent with ApoE's role as a carrier of cholesterol from astrocytes to neurons, cholesterol and ganglioside levels were higher in exosomes isolated from ApoE4 mouse brain when compared to ApoE3. This supports the idea that changes in neuronal lipid levels resulting from ApoE genotype may contribute to alterations in intracellular vesicular trafficking, particularly within the endosomal-exosomal pathways. Our results argue for deficient exosome biosynthesis and release in the brains of ApoE4 carriers, highlighting the vulnerability and importance of the endosomal-exosomal pathways in neurodegenerative processes during aging. Reduced exosome secretion within the brain is likely to impact not only physiological processes such as cell-to-cell communication, but may also contribute to abnormalities within the endosomal pathway from which exosomes are generated, potentially further compromising this system and neuronal function.

Disclosures: K. Peng: None. **M.J. Alldred:** None. **R. Perez-gonzalez:** None. **J. Morales-Corraliza:** None. **M. Saito:** None. **M. Saito:** None. **S.D. Ginsberg:** None. **P.M. Mathews:** None. **E. Levy:** None.

Nanosymposium

190. Mechanisms of Neurotoxicity and Degeneration

Location: 147A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***190.04

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

Support: Bluefield Project to Cure FTD Post-doctoral Fellowship

Title: Accelerated aging in a mouse model of Frontotemporal dementia with progranulin haploinsufficiency

Authors: *M. TELPOUKHOVSKAIA, L. ZHAN, D. LE, Y. LI, Y. ZHOU, C. THEODORIS, D. SRIVASTAVA, L. GAN
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Abstract: Heterozygous mutations in the granulin (*GRN*) gene that lead to lower levels of progranulin protein (PGRN), cause Frontotemporal dementia (FTD); while complete absence of

PGRN leads to neuronal ceroid lipofuscinosis (NCL). We recently reported that FTD patients with PGRN haploinsufficiency present clinicopathological characteristics that are found in NCL. However, mouse models of PGRN haploinsufficiency exhibit little, if any, FTD phenotype. This lack of phenotype poses tremendous challenges to the field, both in basic understanding of the disease mechanisms and modeling the disease.
As a common form of dementia in the elderly, FTD is an aging disease. Telomere shortening is a key feature of aging. Laboratory mice have much longer telomeres compared to humans. We hypothesize that long telomeres protect laboratory mice from neurodegenerative disease caused by PGRN haploinsufficiency. Although neurons do not divide, so the telomeres might not be affected by aging-associated telomere shortening, other cells types including microglia do divide and are likely affected by telomere shortening. Our recent work demonstrated critical role of PGRN deficient microglia in FTD related deficits. To better model PGRN haploinsufficiency in mouse models, we generated PGRN heterozygotes with shortened telomeres. The telomerase knockout mice carry a homozygous deletion for the telomerase RNA component (mTerc) gene, which leads to complete loss of Terc expression and telomerase activity. To assess whether shortened telomeres in PGRN haploinsufficient mice resulted in FTD-like phenotype, we have crossed Terc knockout mice with PGRN haploinsufficient mice for three generations. We will report results from a battery of FTD-related behavioral tests, brain pathology, and characterizations related to microglial function and inflammatory responses.

Disclosures: M. Telpoukhovskaia: None. **L. Zhan:** None. **D. Le:** None. **Y. Li:** None. **Y. Zhou:** None. **C. Theodoris:** None. **D. Srivastava:** None. **L. Gan:** None.

Nanosymposium

190. Mechanisms of Neurotoxicity and Degeneration

Location: 147A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***190.05

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

Support: EU FP7 Marie Curie Industry-Academia Partnerships and Pathways (IAPP) Grant (STEMMAD, PIAPP-GA-2012-324451)
Innovation Fund Denmark (BrainStem, 4108-00008B)

Title: Integrated omics analysis of patient iPSC-derived model for CHMP2B-dependent frontotemporal dementia

Authors: *Y. ZHANG[1], P. JENSEN[2], B. I. ALDANA[1], J. E. NIELSEN[3], B. HOLST[4], P. HYTTEL[1], H. S. WAAGEPETERSEN[1], M. R. LARSEN[2], K. K. FREUDE[1]
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Abstract: One gene affected in familial frontotemporal dementia (FTD) is the charged multivesicular body protein 2B (*CHMP2B*) located on chromosome 3 (FTD3). Patients display global cortical and central brain atrophies, with no apparent amyloid plaque formation or conclusive hyper-phosphorylated tau aggregates. To study the cellular and molecular events of FTD3, we have previously established a well characterized human induced pluripotent stem cells (iPSCs) disease model from patients carrying the heterozygous 31449G>C mutation in *CHMP2B* and isogenic gene-corrected controls generated via the CRISPR/Cas9 system with subsequent *in vitro* neuronal differentiation. In order to systematically decode the pathogenesis, we further integrated high-throughput RNA sequencing, mass spectrometry-based proteomic studies and metabolic assays. Intriguingly we identified several candidate genes and pathways mis-regulated, which are important in celluar organization, subcellular component transportation and neuronal development including neural transmitter transportation. In order to directly decipher impaired protein protein interactions resulting from truncated CHMP2B, homozygous inserted mutant hiPSCs were generated. We subsequently performed affinity-purification mass spectrometry analyses, revealing a list of key proteins, which lost their binding capacities due to the truncation of CHMP2B. These key proteins enabled us to directly align cellular phenotypes with molecular events, indicating that such integrated omics analysis is providing a comprehensive tool for interpreting the role of mutant *CHMP2B* in FTD3 pathogenesis. Strikingly, we found that several dysregulated genes and pathways, which are also, affected in other neurodegenerative disorders. These findings open up for possibilities to develop pharmaceutics targeting several distinct neurodegenerative diseases at once.

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Nanosymposium

190. Mechanisms of Neurotoxicity and Degeneration

Location: 147A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***190.06

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Air Force Office of Scientific Research (EOARD, London, UK), and Air Force Material Command, USAF, under grant number FA8655-05-1-3065;
IT 794/13 (JVL), Government of Basque Country and UFI 11/32 (JVL) University of

Basque Country, Spain
Society for Neuroprotection and Neuroplasticity (SSNN), Romania.

Title: Nicotine neurotoxicity is exacerbated in hypertension

Authors: *S. SHARMA[1,3], D. F. MURESANU[4], J. V. LAFUENTE[5], A. NOZARI[6], A. SHARMA[2], *H. SHARMA[1]
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Abstract: Nicotine smoking is a serous health hazard in human populations resulting in hypertension and related cardiovascular anomalies responsible for further mental and physical health problems. Normally cigarette smoking is done to relieve stress. However, nicotine intake creates several biochemical and function changes that could lead to slowly developing brain pathology. In human populations, cigarette smoking is prevalent in diabetic or hypertensive persons. Although nicotine induces slowly developing hypertension, effects of nicotine in hypertensive cases are not well known. In this investigation we explored the role of nicotine exposure in chronic hypertension with regard to brain pathology in a rat model. Our previous reports show that nicotine exposure (9 mg/kg, s.c.) for 1 week results in blood-brain barrier (BBB) breakdown to Evans blue albumin and induces vasogenic brain edema and neuronal damages. These effects of nicotine were further aggravated in cold (5 °C) and hot (34°C) environment indicating that environmental factors may affect nicotine neurotoxicity. In this study, we evaluated the role of nicotine exposure in renal hypertensive rats. For this purpose rats were made renal hypertensive by using 1 Kidney 1 clip (1K1C) method. Thus, the left renal artery was constricted by placement of a sliver clip (0.5 mm diameter) that restricts blood flow partially to the kidney. This procedure results in slowly developing hypertension (mean arterial blood pressure, MABP 174±8 torr) after 6 weeks. When nicotine was given in these hypertensive rats for 1 week (9 mg/kg, s.c.) a significant increase in the BBB to Evans blue was seen that was 3-to 4-fold higher than normal animal exhibited BBB leakage after identical nicotine exposure. Interestingly, the hypertensive rats by itself did not show any BBB leakage to Evans blue after saline treatment. Immunohistochemical investigation of neuronal nitric oxide synthase (nNOS) shows a massive upregulation in several brain areas in nicotine-exposed rats. The magnitude and intensity of nNOS upregulation was also 2- to 4 fold enhanced in hypertensive rats after nicotine administration. This suggests that oxidative stress and generation of free radicals could play important roles in nicotine-induced neurotoxicity. However, hypertensive rats alone did not show any marked increase in nNOS expression in the brain. This suggests that nicotine somehow stimulates oxidative stress that is further exacerbated by additional stress of hypertension. It remains to be seen whether discontinuation of nicotine intake may reduce nNOS activity and brain pathology over time, a feature that is currently investigated in our laboratory.

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Nanosymposium

190. Mechanisms of Neurotoxicity and Degeneration

Location: 147A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***190.07

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Scoliosis Research Society

Title: Atraumatic spinal cord injury initiates the oxidative stress pathway and metabolic impairments

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Abstract: Tissue damage after spinal cord injury (SCI) results from ischemia, edema, increased excitatory amino acids, and oxidative damage. Uncovering the specific contribution of these events is often complicated by the extensive necrosis induced by common SCI animal models, including contusion, transection, or dislocation. However, in mild hyperflexion or distraction injuries, SCI occurs in absence of overt tissue damage, suggesting that such lesions are mediated by molecular mechanisms induced by hypoxia. We recently reported that mild bidirectional spine distraction in rats, results in spinal cord hypoxia and protein oxidation, indicating mitochondrial oxidative stress. This lesion causes reduction in ventral motor neurons (VMN) size and hind-limb functional deficits, without signs of edema, inflammation or gliosis. Since Riluzole has been shown to activate the antioxidant glutathione in rat cerebral cortex by activating glutamate transporters, we reasoned that this neuroprotective treatment could reduce the oxidative damage observed during atraumatic distraction injuries. Adult rats received either Riluzole (8mg/kg) or vehicle control prior and daily for 7 days after a spinal cord distraction (5mm for 15 minutes). As expected, a significant increase in hydrogen peroxide was observed immediately following spinal cord distraction. In distraction animals, histological evaluation of the spinal cord confirmed significant hypoplasia and pyknosis ($p<0.0001$) of the VMNs, which correlated with gait impairments. In sharp contrast, Riluzole treatment effectively prevented oxidative stress and neural damage. Our data indicates that the neural damage directly results from metabolic stress induced after mild SCI and can be prevented with antioxidant treatments.

Disclosures: E.N. Shimizu: None. **J.L. Seifert:** None. **K.J. Johnson:** None. **M.I. Romero-Ortega:** None.

Nanosymposium

190. Mechanisms of Neurotoxicity and Degeneration

Location: 147A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***190.08

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Neuroprotective effects of nicotinic receptor partial agonist varenicline in aged mice after laparotomy. Implication of prevention for post-operative cognitive dysfunctions

Authors: *R. C. CHANG[1,2], C. HUANG[3,1], J. M. T. CHU[1,3], G. T. C. WONG[3]
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Abstract: Systemic inflammation often leads to neuroinflammation and activation of microglia/astrocytes, which can be found in elderly after surgical treatment. Post-operation after surgery results in cognitive dysfunctions, which is frequently occurred in elderly and is highly related to systemic inflammation. Apart from non-steroid anti-inflammatory ibuprofen, we further investigate whether nicotinic receptor partial agonist varenicline can protect neurons from cognitive dysfunctions after experimental laparotomy in aged mice. We employed 18-month-old C57BL6/N mice for this experiment and sevoflurane as anesthetics. Varenicline was administrated orally and daily from one day before surgery and continuously for 13 days after laparotomy. For cognitive functions, we use novel object recognition test (NOR) and modified Y-maze test. We further use open field test for testing anxiety. We also tested the motor control by rotarod. After euthanization, we harvested the brains at different time points for expression of mRNA for inflammatory cytokines, Western-blot analysis of phosphorylated tau and nuclear tau, immunohistochemical staining for microglia, astrocytes, DNA damage and apoptosis.
Our results showed that laparotomy significantly reduced the latency and error number of our modified Y-maze; and discrimination index in NOR. Varenicline significantly attenuated cognitive dysfunctions in these two tests. For neuroinflammation, there were significant increase in IL-1β, IL-6 and MCP-1 after laparotomy. While varenicline did not significantly reduce cytokine levels back to control levels, it markedly reduced activation of microglia by morphological examination and expression of CD68. Laparotomy triggered phosphorylation of tau and translocation of tau into nucleus. This was in conjunction with DNA damage by an increase of γH2AX expression in the nucleus shown in immunocytochemical staining and presence of cleaved caspase-3 in Western-blot analysis. Varenicline could significantly attenuated all these pathological events.
Taken together, our results demonstrated that nicotinic receptor partial agonist could elicit neuroprotective effects to prevent cognitive dysfunctions, neuroinflammation and even

Alzheimer-like pathology in aged mice after laparotomy. Varenicline has high potential to be developed as therapeutic prevention against post-operative cognitive dysfunctions and the associated adverse effects on the brain.

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Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***191.01

**Topic: ***C.09. Brain Injury and Trauma

Title: Transplanted human iPS cell-derived neuronal precursor cells promote motor functional recovery after chronic spinal cord injury

Authors: *T. OKUBO[1,2,3], N. NAGOSHI[2], J. KOHYAMA[3], O. TSUJI[2], M. MASTUMOTO[2], M. NAKAMURA[2], H. OKANO[3]
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Abstract: [Introduction] Previously we have reported that neural stem/progenitor cells derived from human iPS cells (hiPSC-NS/PCs) pretreated with gamma-secretase inhibitor (GSI), which called human iPS cell-derived neuronal precursor cells (hiPSC-NeuPCs), promoted more neuronal differentiation and maturation *in vitro*. And *in vivo*, transplantation of these cells differentiated into more mature neurons without tumorigenicity and maintained greater functional recovery at sub-acute spinal cord injury (SCI) (*Okubo et al, Stem Cell Reports 2016*). The purpose of the present study was to elucidate the effectiveness of transplanted these cells for chronic SCI in mice.
[Method] To obtain hiPSC-NeuPCs, safe hiPSC (201B7)-NS/PCs were pretreated with GSI for 1 day before transplantation. We induced contusive SCI at T10 level, and transplanted hiPSC-NeuPCs (NeuPC group), hiPSC-NS/PCs (Control group) or PBS (PBS group) at 42 days after injury (n=5 per each group). [Result] At 89 days after transplantation, immunohistochemical findings revealed that the transplanted cells survived and did not cause tumor-like overgrowth. The proportion of pan-ELAVL positive mature neurons were significantly increased in the NeuPC group. More neurofilament 200-kDa-positive neuronal fibers and 5-hydroxytryptamine-positive serotonergic fibers were observed in the NeuPC group. There were also significantly more growth-associated protein 43-positive fibers were observed, indicating that the axonal regrowth was promoted. Quantitative analysis revealed that the transverse area of the spinal cord at lesion epi-center and +4mm caudal were significantly decreased in the other groups compared

with the NeuPC group, suggesting that the NeuPC group transplantation prevented atrophy of the injured spinal cord. Luxol fast blue staining also revealed a greater preservation of myelinated areas in the NeuPC group compared with the other groups. The functional recovery was significantly enhanced at 56 days after transplantation and maintained thereafter in the NeuPC group compared with the other groups.
[Conclusion] These results indicate that only transplantation of hiPSC-NeuPCs differentiated into more mature neurons and maintained functional recovery even at chronic SCI. However, the degree of functional recovery was smaller at chronic phase compared with sub-acute phase. Therefore, we will evaluate efficacy of hiPSC-NeuPC transplantation combined with rehabilitation therapy to enhance greater functional recovery even at chronic SCI.

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Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***191.02

**Topic: ***C.09. Brain Injury and Trauma

Title: Selective ablation of tumorigenic cells following human induced pluripotent stem cell-derived neural stem/progenitor cell (hiPSC-NS/PC) transplantation in spinal cord injury - Suicide genes in stem cell therapy

Authors: *K. KOJIMA[1], H. MIYOSHI[2], S. ITO[2], T. IIDA[4], M. OZAKI[5], S. KAWABATA[6], G. ITAKURA[7], O. TSUJI[3], N. NAGOSHI[5], M. MATSUMOTO[2], M. NAKAMURA[2], H. OKANO[5]
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Abstract: Background
The issue of safety is one of the highest concerns when it comes to the clinical application of hiPS-NS/PC transplantation in treating spinal cord injury (SCI). With certain “tumorigenic cell lines” transplanted into murine SCI models, there is an initial improvement in motor function followed by an abrupt deterioration secondary to the mass effect of the tumor. A significant proportion of these cells remain undifferentiated post transplantation. The aim of this study is to selectively ablate these undifferentiated cells whilst preserving the differentiated cells and hence the motor function.

Methods
Herpes Simplex Virus 1 Thymidine Kinase (HSV-TK) gene is a well-known suicide gene used in the clinical setting. Ganciclovir (GCV), the prodrug of HSV-TK, can be converted to cytotoxic GCV-triphosphate by HSV-TK, thereby killing HSV-TK-expressing cells. It is known to be cell cycle dependent.
In Vitro: We lentivirally introduced the HSV-TK gene into a known tumorigenic line of hiPSC-NS/PCs (hiPSC-NS/PC-HSVTK). GCV was administered 3 weeks after differentiation of these cells.
In Vivo: hiPSC-NS/PC-HSVTK were transplanted into sixteen SCI model mice. GCV was administered to eight of these mice 6 weeks following transplantation. Motor function was evaluated through weekly BMS scoring together with Rotor Rod and Digigait analysis 12 weeks following transplantation.
Results
In Vitro: there was a significant decrease in the percentage of immature Nestin and Ki67 positive cells ($p<0.01$), while the Tuj1 positive neuronal cells were relatively preserved ($p>0.05$) ($n=3$).
In Vivo: In the mice without GCV administration (GCV(-)), an initial improvement in motor function was followed by an abrupt deterioration. In the mice with GCV administration (GCV(+)), however, the improved motor function was well preserved ($p<0.01$). Immunohistochemistry revealed that the immature Nestin, SOX1 and Ki67 positive cells were more abundant in the GCV(-) mice compared to the GCV(+) mice ($p<0.01$). There were no significant differences in the percentage of NeuN positive neuronal cells between the two groups ($p>0.05$).
Conclusion
We were successful in selectively ablating the immature potentially tumorigenic iPS-NS/PCs that had been transplanted into SCI model mice whilst preserving the motor function gained from the treatment.

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Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***191.03

**Topic: ***C.09. Brain Injury and Trauma

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Wings for Life
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
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Title: A sensitized IGF1 treatment restores corticospinal axon-dependent functions

Authors: *Y. LIU[1], X. WANG[1], W. LI[1,2], Q. ZHANG[1,3], Y. LI[1], Z. ZHANG[1], P. WILLIAMS[1], J. R. SANES[4], Z. HE[1]
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Abstract: A major hurdle for functional recovery after both spinal cord injury and cortical stroke is the limited regrowth of the axons in the corticospinal tract (CST) that originate in the motor cortex and innervate the spinal cord. Despite recent advances in engaging the intrinsic mechanisms that control CST regrowth, it remains to be tested whether such methods can promote functional recovery in translatable settings. Here we show that post-lesional AAV-assisted co-expression of two soluble proteins, namely insulin-like growth factor 1 (IGF1) and osteopontin (OPN), in cortical neurons leads to robust CST regrowth, and the recovery of CST-dependent behavioral performance after both T10 lateral spinal hemisection and a unilateral cortical stroke. In these mice, a compound able to increase axon conduction, 4-aiminopyridine-3-methanol, promotes further improvement in CST-dependent behavioral tasks. Thus, our results demonstrate a potentially translatable strategy for restoring cortical dependent function after injury in the adult.

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Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***191.04

**Topic: ***C.09. Brain Injury and Trauma

Support: NIH R01NS094527
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Title: Lysosomal damage after spinal cord injury causes accumulation of RIPK1 and RIPK3 proteins and potentiates necroptosis

Authors: *M. M. LIPINSKI[1], S. LIU[1], C. SARKAR[1], Y. LI[1], A. I. FADEN[1], E. Y. KOH[2], J. WU[1]
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Abstract: Necroptosis, a form of regulated necrosis mediated by the receptor-interacting protein kinases 1 and 3 (RIPK1 and RIPK3, respectively), is induced following spinal cord injury (SCI) and thought to contribute to neuronal and oligodendrocyte cell death. However, mechanisms leading to activation of necroptosis after SCI remain unclear. We have previously shown that autophagy, a catabolic pathway facilitating degradation of cytoplasmic proteins and organelles in a lysosome-dependent manner, is inhibited following SCI in the rat. Our current data confirm that inhibition of autophagy is also occurring after T10 contusive SCI in the mouse model, as indicated by accumulation of both the autophagosome marker, LC3-II and autophagy cargo protein, p62/SQSTM1. This was most pronounced in the ventral horn motor neurons and was caused by rapid lysosomal membrane damage and inhibition of lysosomal function after SCI. Interestingly, RIPK1, RIPK3 and the necroptosis effector protein MLKL also rapidly accumulated after SCI and specifically localized to motor neurons with disrupted autophagy, suggesting that the two events may be related. To determine if lysosomal dysfunction could contribute to induction of necroptosis, we treated PC12 cells and cultured rat cortical neurons with lysosomal inhibitors, Bafilomycin A and Chloroquine. Both treatments led to rapid accumulation of RIPK1 and RIPK3, confirming that they are normally degraded by the lysosomal pathway. In PC12 cells lysosomal inhibition also sensitized cells to necroptosis induced by TNF-αlpha and caspase inhibitor Boc-D. Imaging studies confirmed that RIPK1 partially localized to lysosomes in both untreated and lysosomal inhibitor treated cells. Similarly, we observed accumulation of RIPK1 in both cytosol and lysosomes after SCI *in vivo*. Therefore, lysosomal dysfunction after SCI may contribute to both inhibition of autophagy and sensitize cells to necroptosis by promoting RIPK1 and RIPK3 accumulation.

Disclosures: M.M. Lipinski: None. **S. Liu:** None. **C. Sarkar:** None. **Y. Li:** None. **A.I. Faden:** None. **E.Y. Koh:** None. **J. Wu:** None.

Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***191.05

**Topic: ***C.09. Brain Injury and Trauma

Support: NIH R01 NS091218
Maryland Stem Cell Research Grant 2016-MSCRFE-2747

Title: cPLA2 activation leads to lysosomal damage and autophagy impairment after TBI

Authors: *C. SARKAR[1], J. W. JONES[2], N. U. HEGDEKAR[1], J. PETER[1], A. KUMAR[1], M. A. KANE[2], A. I. FADEN[1], M. M. LIPINSKI[1]
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Abstract: Dysregulation of autophagy, a lysosome dependent major cellular degradative process, has been implicated as one of the major causes of neuronal cell death in several neurodegenerative diseases. We also have demonstrated impairment of autophagy following controlled cortical impact (CCI) induced traumatic brain injury (TBI) in mice. We observed block of autophagosome degradation mainly within neuron at early time point after TBI. Our data indicated that it is at least in part due to lysosomal dysfunction, as evidenced by lower lysosomal enzyme activity in injured cortex at day 1 after TBI. We observed leakage of lysosomal content into the cytosol due to lysosomal membrane damage after brain injury. In order to explore the mechanism of lysosomal damage we analyzed lipid content of lysosomal membrane isolated from the cortices of naive and injured mice using LC-MS technique. We detected increase in lysophospholipid and decrease in glycerophosphlipids in the lysosomal fraction of injured mouse cortex as compared to that of naive mice. This correlated with the activation of cytosolic phospholipase A2 (cPLA2), an enzyme that cleaves fatty acyl linkage in the phospholipid releasing fatty acid mostly arachidonic acid and leaving lysophopholipid in the cellular membranes. We observed enhanced phosphorylation of cPLA2 within mouse cortex soon after injury. We also observed markedly higher level of phospho-cPLA2 in the lysosomal fraction of injured mouse cortex indicating involvement of cPLA2 in lysosomal damage following TBI. Consistently lysosomal damage was detected *in vitro* in H4 cells and rat cortical neurons treated with cPLA2 activator ceramide-1-phosphate (C1P) leading to the accumulation of autophagosomes. siRNA mediated knock down of cPLA2 or pretreatment of cells with cPLA2 inhibitor arachidonyl trifluoromethyl ketone (AACOCF3) substantially prevented autophagosome accumulation in C1P treated H4 cells and rat cortical neurons. *In vivo,* AACOCF3 treatment significantly lowered the level of lysophosphlipid in the lysosomal membrane of injured mouse cortex as detected by LC-MS analysis. We also observed significant decrease in accumulation of autophagosomal substrate p62 in the injured cortex of mice treated with AACOCF3. Moreover we observed improvement in motor and cognitive function in injured mice when treated with AACOCF3. Taken together these data indicate that cPLA2 activation leads to lysosomal damage causing autophagosome accumulation in the cortex and contributing to neuronal cell death after TBI. Thus we propose, that inhibiting cPLA2 early after TBI may restore autophagosome clearance and decrease neuronal cell loss.

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Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***191.06

**Topic: ***C.09. Brain Injury and Trauma

Support: NIH R01 NS094527

Title: cPLA2 activation after spinal cord injury contributes to lysosomal defects and impairment of autophagy

Authors: *Y. LI[1], J. W. JONES[3], C. SARKAR[1], S. LIU[1], M. A. KANE[3], A. I. FADEN[1], E. Y. KOH[2], M. M. LIPINSKI[1], J. WU[1]
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Abstract: The autophagy-lysosomal pathway plays an essential role in cellular homeostasis and a protective function against a variety of diseases. However, under certain circumstances pathologically increased autophagy can contribute to cell death. This may occur particularly when lysosomal function is impaired and autophagic degradation is not able to proceed to completion, leading to pathological accumulation of dysfunctional autophagosomes. We have previously shown that autophagy is inhibited and contributed to injury after SCI. Here we examine mechanism of autophagy and lysosomal defects following SCI. Expression levels and processing of the lysosomal enzyme cathepsin D (CTSD) were decreased at 2h after SCI. Enzymatic activity of CTSD and another lysosomal enzyme, alkaline phosphatase, were decreased 24h post-injury, indicating lysosomal damage. Sub-cellular fractionation confirmed lysosomal membrane permeabilization (LMP) and leakage of lysosomal content into the cytosol. cPLA2 is an enzyme that cleaves fatty acyl linkage in the phospholipids of cellular membranes and increased activity of cPLA2 may be involved in membrane damage. cPLA2 was activated in the lysosomal fraction, accompanied by increased accumulation of the autophagosomal marker LC3-II and its substrate p62. To directly assess the extent and mechanism of damage to lysosomal membranes, mass spectrometry (MS)-based lipidomics was applied to compare the lipid composition of lysosomal membranes purified from sham or injured spinal cord at 2h post-injury. Our data demonstrate increases in several classes of lysosophospholipids- the products of phospholipases (PLAs), as well as accumulation of PLA activator, ceramide. Inhibition of cPLA2 decreased lysosomal damage, restored autophagic flux, and reduced neuronal cell damage. Taken together our data implicate lysosomal defects in the pathophysiology of SCI and further indicate that cPLA2 activation leads to lysosomal damage that causes neuronal autophagosome accumulation associated with neuronal cell death.

Disclosures: **Y. Li:** None. **J.W. Jones:** None. **C. Sarkar:** None. **S. Liu:** None. **M.A. Kane:** None. **A.I. Faden:** None. **E.Y. Koh:** None. **M.M. Lipinski:** None. **J. Wu:** None.

Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

Time: *Sunday, November 12, 2017, 1:00 PM - 4:30 PM

Presentation Number: *191.07

Topic: *C.09. Brain Injury and Trauma

Support: Craig H. Neilsen Foundation Postdoctoral Fellowship

Title: Optical control of neural ablation in zebrafish as a model for secondary injury mechanisms

Authors: ***K. MRUK**[1], P. PIZA[2], J. K. CHEN[1]
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Abstract: During SCI, the primary injury occurs unexpectedly; therefore, understanding and combating the secondary injury mechanisms that occur after the initial trauma has the most therapeutic potential. However, the self-propagating nature and complexity of SCIs makes it challenging to dissect cellular responses during and after injury. Taking advantage of the transparency of zebrafish larvae, we developed an optogenetic method to induce cellular ablation in zebrafish larvae. This light-inducible system, offers many advantages over traditional injury models. First, transcription is spatiotemporally controlled giving a more reproducible injury. Second, the system is modular, enabling tissue-specific ablation in concert with an assortment of toxins. Third, this method is compatible with tools used in regenerative studies including locomotor assays and calcium imaging permitting real-time visualization of the CNS response to injury and repair. Lastly, this method works with commercially available transgenic zebrafish lines containing *UAS* transgenes and can be modified for use with other *Gal4*-compatible species. Combining the ability to control light in both space and time with tissue-specific promoters allows us to create reproducible ablation, thus sparing the surrounding tissue and allowing us to decouple the complex secondary events that occur after injury.

Disclosures: **K. Mruk:** None. **P. Piza:** None. **J.K. Chen:** None.

Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***191.08

**Topic: ***C.09. Brain Injury and Trauma

Support: UTS CHT Grant

Title: The nature of the inflammatory response to spinal cord injury differs between mature and developing rats

Authors: *T. SUTHERLAND, C. GORRIE
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Abstract: Spinal cord injury (SCI) is a severe and life-long condition that places great burden on the individual and society. A SCI results in loss of tissue, varying degrees of functional impairment and exhibits only limited repair which has great effect on patients' quality of life. The immune and inflammatory response plays a significant role in the progression of the secondary injury phase of SCI. This is an area of great interest in SCI research and it still remains to be fully elucidated the role this response plays in the larger picture, and also whether this cascading immune response is beneficial or detrimental to recovery. Previous work from this laboratory has used immunohistochemistry to show a decreased inflammatory response at both acute and chronic time points, demonstrated by decreased neutrophil infiltration, macrophage and microglial activation in infants, compared to their adult counterparts.
A mild contusion SCI was surgically induced using a NYU impactor in adult (10 weeks of age) and infant (P7-9) Sprague-Dawley rats (n=98). The spinal cord was then removed fresh 1hr, 24hrs and 1wk post-injury to be assessed using flow cytometry to quantitate different phenotypes of macrophages, neutrophils and T-lymphocytes within the injured tissue and multiplex cytokine ELIZA on the tissue supernatant.
This animal model showed some significant differences in the nature and progression of both the cellular and molecular inflammatory response between infants and adults. There were greater leukocyte numbers in the injured adult cord than the infants. The adults also showed higher M1-like than M2-like macrophage percentages of the total leukocyte population at all time points. This trend was reversed in the infants. Neutrophils peaked at 24hrs in both age groups but were present in higher numbers in the adults. T-lymphocytes were highest at 24 hrs in the adults and 1 hr in the infants. Prominent pro-inflammatory cytokine expression (IL-1α, β, IL-6, IL-12) was higher and more sustained in the adults than the infants, while the infants showed a steady increase in IL-4 and IL-13 as well as sustained IL-10 expression.
The results of this study re-enforce our previous studies suggesting the inflammatory response is significantly different in developing and mature spinal cords; the infant response appears more

balanced and potentially more beneficial to injury resolution than that displayed by the adults. This may be a contributor to the observed trend for a better functional recovery in younger patients, compared to adults, which is also reported for animal studies and may point to the manipulation of the inflammatory response as a potential avenue for SCI therapies.

Disclosures: T. Sutherland: None. **C. Gorrie:** None.

Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***191.09

**Topic: ***C.09. Brain Injury and Trauma

Support: UU Radiology/Neurosciences Pilot Grant
UU Neurosurgery Pilot Grant

Title: MRI-guided high intensity focused ultrasound to improve drug delivery in spinal cord injury

Authors: *D. J. CROSS, A. H. PAYNE, M. A. OSTLIE, G. G. GARWIN, E. C. REICHERT, Y. ANZAI, G. W. J. HAWRYLUK
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Abstract: Introduction
Spinal cord injury (SCI) affects thousands of people each year. Treatment is currently limited to supportive care which has only a modest effect on neurological outcome. MRI-guided high intensity focused ultrasound (MRg-HIFU), clinically used for noninvasive ablation of uterine fibroid and treatment of essential tremor, has been applied in the brain with microbubbles to generate sonoporation, resulting in transient, focal blood brain barrier permeability that increases drug delivery. The goal of this preliminary study was to show the feasibility of targeting HIFU to various spinal cord regions in uninjured rats as a non-invasive approach to increase blood-spinal cord barrier (BSCB) permeability for localized drug delivery in SCI.
Methods
Rats (n=5) were positioned on a MRg-HIFU system in a 3T MR scanner. 3D T1w images were used to position the rat and to assess the efficacy of the BSCB opening, which was achieved using a 256-element phased-array transducer (f=940 kHz, intensity FWHM = 1.8x2.5x10.9 mm). The cervical spine was targeted in 2 rats and thoracic in 3 (1 rat had HiFU in both regions) with 3-4 sonications consisting of 20 ms bursts applied at a 1 Hz pulse repetition frequency for 3 min. The acoustic power was 3-5 W. Optison microbubbles (0.02 mL/kg) were injected before each

sonication. BSCB opening was confirmed using Prohance (0.25 mL/kg) contrast-enhanced T1w images and 1% Evans blue (EB) dye in ex vivo cord samples. One rat had SHAM HIFU. Neurological function was assessed following the procedures and cords were removed at 2 days post-HIFU.
Results
Increased signal on T1W imaging was seen in 4/5 target areas (40.2 ± 19%, mn±sd range 18-68%) from 200-300s after sonication. EB was seen in 3 of 4 obtained targets (one subject did not receive dye). EB deposition qualitatively agreed with signal increase locations. The SHAM rat showed no T1W signal increase or presence of dye ex vivo. No subjects exhibited abnormal neurological function post HiFU.
Conclusion
This preliminary study indicates that different spine regions can be successfully targeted with MRg-HIFU to achieve BSCB opening. Feasibility of this technique is apparent despite technical challenges such as the small target and surrounding bone. Subsequent studies will use MRg-HIFU in a rat SCI model and in combination with therapeutics. The results from this research could have a significant impact on treatment options following SCI.

Disclosures: D.J. Cross: None. **A.H. Payne:** None. **M.A. Ostlie:** None. **G.G. Garwin:** None. **E.C. Reichert:** None. **Y. Anzai:** None. **G.W.J. Hawryluk:** None.

Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***191.10

**Topic: ***C.09. Brain Injury and Trauma

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Patient organizations “Verticale” [to FEP and HNN]

Title: RNA-Seq analysis of microglia and astrocytes reveal time- and injury-dependent activation of specific genetic program following spinal cord injury

Authors: *H. NORISTANI[1,2,3], Y. N. GERBER[2,3,5], J.-C. SABOURIN[6], H. BOUKHADDAOUI[4], H. E. HIRBEC[7], F. E. PERRIN[8,9,6]

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Abstract: The precise role of glial reaction after spinal cord injury (SCI) has been debated for a long time. Using two models of SCI (lateral hemisection and transection) and cell-specific RNA sequencing in glial populations, we first demonstrate that microglial response after injury is time-dependent, whilst astrocytes undergo heterogeneous time- and severity-dependent activations. Early transcriptomic response of microglia after SCI involves proliferation and neuroprotection, which is then switched to neuroinflammation at later stages. Early after spinal cord hemisection astrocytes undergo moderate activation and do not promote an immune response by 2 weeks after injury. Contrary, at 1 week following spinal cord transection astrocytes undergo marked activation and actively promote immune response/inflammation followed by reduced extracellular membrane breakdown at 2 weeks after FT.

We then demonstrate that SCI induces an autologous microglial expression of astrocytic markers with over 6% of microglia expressing glial fibrillary acidic protein and vimentin. Concomitantly, over 10% of astrocytes undergo an autologous transdifferentiation, expressing classical neuronal progenitor markers including βIII-tubulin and doublecortin with typical immature neuronal morphology. Lineage tracing confirmed that the origin of these astrocytes is resident mature, rather than newly formed astrocytes. Astrocyte-derived neuronal progenitors subsequently express GABAergic, but not glutamatergic-specific markers. Furthermore, we have identified the neural stem cell marker fibroblast growth factor receptor 4 (*Fgfr4*) as a potential autologous modulator of astrocytic transdifferentiation following SCI. Finally, we establish that glial transdifferentiation starts as early as 72 hours and continues to a lower degree up to 6 weeks post-lesion. Our data provide the first transcriptomic analyses of microglia and astrocytes at multiple stages after different SCI severities. We thus demonstrate for the first-time autologous injury-induced astroglial transdifferentiation. Enhanced autologous glial transdifferentiation may represent a novel therapeutic approach to promote functional recovery following SCI.

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Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***191.11

**Topic: ***C.09. Brain Injury and Trauma

Support: NIH R21

Title: Delayed radial sorting and re-myelination in a 4cm long gap repair despite synergistic effect of neurotrophins and pleiotrophins in nerve regeneration

Authors: *G. S. BENDALE[1], N. ALSMADI[2], R. GRANJA-VAZQUEZ[3], E. HOR[4], M. ROMERO-ORTEGA[2]
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Abstract: Despite the robust regenerative capacity of the adult peripheral nervous system, long-gap nerve defects fail to self-repair, resulting in permanent sensory and motor deficits. Autologous nerve grafts are the gold standard for the surgical treatment of such injuries, but sacrificial nerves are limited and this approach only provides limited functional recovery, prompting the need for bioengineered alternatives. The addition of neurotrophic factors to nerve conduits has proven to be effective, but not superior, to autografts in long-gap injury models. Here, we evaluated the combinatorial effects of neurotrophins and pleiotrophins in the repair of a 4 cm gap in the rabbit peroneal nerve injury model. The effect of PTN, GDNF and PTN-GDNF was compared to bovine serum albumin (BSA) and to a cut/re-suture positive control. Twenty weeks post-injury, histological evaluation of the nerve showed that the number of axons in the proximal end were similar among all groups, but re-myelination was deficient in the BSA, and PTN groups, and was enhanced by GDNF. In the distal stump, however, the number of axons did not seem to be influenced by the growth factors, and re-myelination was absent. However, PTN or GDNF doubled, and the combination of these factors significantly tripled the average axon diameter observed in the distal stump compared to BSA ($P<0.001$). Electron microscopy analysis revealed a comparable number of Schwann cells in all treatments in the distal stump. However, Remak bundles in the BSA group were smaller in size, containing mostly small diameter axons. In sharp contrast, those treated with GDNF and PTN showed large diameter axons in Remak bundles, with some sorted out from those bundles and re-myelinated in the PTN-GDNF group. Behavioral analysis using toe-spread index confirmed the synergistic effect of the combined neurotrophin and pleiotrophin treatment in enhancing nerve regeneration across a critically long nerve defect. Together, our results indicated that growth factor support is necessary but not sufficient for inducing normal functional nerve regeneration across a critically long gap, and that

factors that can accelerate axonal sorting from Remak bundles may be beneficial as additional targets for long gap repair.

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Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***191.12

**Topic: ***C.09. Brain Injury and Trauma

Support: JSPS KAKENHI Grant Number JP26670044
Discretionary Funds of the President and Budget for Functional Enhancement by University of Toyama in 2015–2017

Title: Acteoside improves chronic spinal cord injury via a skeletal muscle-secreted new myokine

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Abstract: Spinal cord injury (SCI) causes serious locomotor dysfunction due to the disruption of descending motor tracts at the lesion site. There is no successful medication showing enough effect on chronic SCI. To discover the new approach for medication, we focused on skeletal muscle atrophy as a detrimental condition in chronic SCI. Therefore we aim to find a drug that improves skeletal muscle atrophy and promotes the releases of axonal growth factors from skeletal muscle because skeletal muscle constitutively secretes myokine to maintain skeletal muscle function and possibly neuronal function. We screened herbal extracts to look for myokine release activity. Primary cultured myocytes from newborn mice hindlimb skeletal muscle were treated by herbal extracts, and conditioned medium (CM) was prepared. CM was treated to primary cultured cortical neurons to evaluate axonal growth activity. CM from Cistanchis herba extract treated-myocytes induced axonal growth. Acteoside was identified as an active compound in Cistanchis herba. Acteoside enhanced also proliferation of primary cultured myocytes. Acteoside was administered (3 times/week) intramuscularly to SCI mice (T12 contusion injury) from 45 days after injury. During observation period (for 130 days after the injection start), locomotor function was significantly improved by acteoside. At the end point of the observation, wet weights of skeletal muscle were significantly increased compared with vehicle-treated group. Released factors from myocytes by acteoside stimulation were investigated, and PKM2 was identified. Recombinant PKM2 enhanced axonal growth in primary

cultured cortical neurons. In the present study, we discovered a drug acting skeletal muscle, that improves locomotor dysfunction and skeletal muscle atrophy in chronic SCI, and new myokine PKM2 may play a role in the recovery phenomena.

Disclosures: **A. Kodani:** None. **C. Tohda:** None.

Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

Time: *Sunday, November 12, 2017, 1:00 PM - 4:30 PM

Presentation Number: *191.13

Topic: *C.09. Brain Injury and Trauma

Support: CNMPB
UFMG

Title: Role of autophagic protein ULK1 in axonal degeneration and regeneration after traumatic lesion to the central nervous system

Authors: ***V. T. RIBAS**[1], B. VAHSEN[2], C. LENZ[3], U. MICHEL[2], H. URLAUB[3], M. BÄHR[2], P. LINGOR[2]
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Abstract: Traumatic lesion to the central nervous system (CNS) usually results in permanent deficits. The understanding of mechanisms involved in degenerative and regenerative events in the CNS is pivotal for developing novel therapeutic strategies. Autophagy is a cellular degradation process responsible for the turnover of proteins and organelles and is regulated by Unc-51-like kinase 1 (ULK1), which is a key protein involved in autophagy induction. Recently, we demonstrated that autophagy is increased in degenerating axons after spinal cord lesion. Therefore, autophagy might be an important mechanism regulating axonal degeneration following traumatic lesion and its inhibition could be promising in order to promote axonal stabilization and further improve axon regeneration. Whether modulation of ULK1 could be beneficial in blocking axonal degeneration and promoting axon regrowth has not been evaluated so far. Thus, we generated adeno-associated viral vectors expressing a dominant-negative form of ULK1 (ULK1.DN) to decrease autophagy specifically in neurons and study the role of autophagy in axonal degeneration and regeneration *in vitro* and *in vivo*. First, we show significant changes in autophagy-associated protein levels by ULK1.DN. Then, we show that expression of ULK1.DN in primary cortical neurons cultured in a microfluidic chamber decreases axonal degeneration after axotomy. Moreover, overexpression of ULK1.DN in retinal

ganglion cells attenuates axonal degeneration of proximal axons after optic nerve crush assessed by *in vivo* live imaging. Overexpression of ULK1.DN in rubrospinal neurons protects the proximal axons from degeneration after spinal cord injury. Axon regeneration was improved by ULK1.DN expression after axotomy of primary cortical neurons cultured in a microfluidic chamber. Employing a proteomics analysis, we found significant changes in the proteome by ULK1.DN expression. Finally, we could additionally detect several significant regulations in protein levels by immunoblotting which are connected to axonal outgrowth. Taken together, these findings provide new knowledge about the role of ULK1 in axonal degeneration and regeneration, and point to ULK1 as a potential therapeutic target for traumatic injury to the CNS.

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Nanosymposium

191. Spinal Cord Injury: Mechanisms and Repair

Location: 144A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***191.14

**Topic: ***E.09. Spinal Cord Injury and Plasticity

Support: NMRC Grant: M4061864.120.703012

Title: Aligned fiber-mediated microRNA delivery in promoting neurite outgrowth in CNS neurons

Authors: N. ZHANG[1], *S. CHEW[2], J. CHIN[1]
[1]Sch. of Chem. and Biomed. Engin., [2]Nanyang Technological Univ., Singapore, Singapore

Abstract: The first step of axon regeneration after axotomy is the formation of a new growth cone. This is a crucial structure for subsequent axon extension and microRNAs (miRs) play significant roles in determining regeneration outcomes by controlling local protein synthesis at growth cones. Specifically, miR-21, miR-222, miR-132 and miR-431 have been shown to regulate local axon protein synthesis and promote axon regrowth after injuries. In this study, we hypothesized that a combination of miRs and substrate topography would enhance axon regeneration. In particular, aligned fiber-mediated delivery of miRs would increase axon regrowth through the synergistic effects of contact guidance and sustained miR signaling. Additionally, scaffold-mediated miR delivery would enhance the efficiency of non-viral gene silencing in neurons. To find out which combination of miRs could result in the longest neurite extension, we screened all possible combinations of the 4 reported miRs in vitro by using E14 or P1 rat cortical neurons. After absorbing miR mimics onto mussel-inspired bio-adhesive 3,4-

dihydroxy-L-phenylalanine (DOPA) coated aligned fibers, a uniform distribution of oligonucleotides was detected. In addition, neurons cultured on the aligned fibers exhibited longer neurite outgrowth as compared to the ones cultured on glass coverslips. Moreover, gene expression analyses showed that fiber-mediated miR delivery exhibited 2-4 fold enhancement in target gene knockdown as compared to the bolus delivery on 2D cultures. The neurite length in each group showed similar trends between P1 and E14 cortical neurons. Among all the groups, the withdrawal of miR-21 appeared the most potent in promoting neurite outgrowth followed by the withdrawal of miR-222 (the withdrawal of miR-21:319.1±7.706 μm vs. negative miR: 233.7±4.711 μm, $p < 0.001$; the withdrawal of miR-222: 302.1±6.609 μm vs. neg miR: 233.7±4.711 μm, $p < 0.001$). For individual miR treatment, miR-21 and miR-132 were more effective than miR-222 and miR-431. For 2 miR combinations,miR-222/431 showed the best result while the shortest outgrowth was observed in miR-21/431 treated groups (miR-222/431: 280.2±5.663μm vs. neg miR: 233.7±4.711 μm, $p < 0.001$). The combination of 4 miRs did not show synergistic effects on enhancing axon regeneration. In conclusion, the results demonstrated the efficacy of aligned fibers in guiding and enhancing axon growth, as well as promoting non-viral gene transfection. These aligned fibers allow the incorporation of different combinations of miRs. Such platforms facilitate the feasibility of carrying out miR screening, and are easily translated to in vivo for future in vivo screening.

Disclosures: **N. Zhang:** None. **S. Chew:** None. **J. Chin:** None.

Nanosymposium

192. Representation of Faces and Bodies

Location: 147B

Time: *Sunday, November 12, 2017, 1:00 PM - 4:30 PM

Presentation Number: *192.01

Topic: *D.07. Vision

Title: Coding of faces by tensor components

Authors: ***S. R. LEHKY**[1,2], A. PHAN[3], A. CICHOCKI[3], K. TANAKA[2]
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Abstract: Neurons selectively responsive to faces exist in the ventral visual stream of both monkeys and humans. However, the characteristics of face cell receptive fields are poorly understood. Here we use tensor decompositions of faces to model a range of possibilities for the neural coding of faces that may inspire future experimental work. Tensor decomposition is in some sense a generalization of principal component analysis from 2-D to higher dimensions. For this study the input face set was a 4-D array, with two spatial dimensions, color the third

dimension, and the population of different faces forming the fourth dimension. Tensor decomposition of a population of faces produces a set of components called tensorfaces. Tensorfaces can be used to reconstruct different faces by doing different weighted combinations of those components. A set of tensorfaces thus forms a population code for the representation of faces. A special feature of the tensor decomposition algorithm we used was the ability to specify the complexity of the tensorface components, measured as Kolmogorov complexity (algorithmic information). High-complexity tensorfaces have clear face-like appearances, while low-complexity tensorfaces have blob-like appearances that crudely approximate faces. For a fixed population size, high-complexity tensorfaces produced smaller reconstruction errors than low-complexity tensorfaces when dealing with familiar faces. However, high-complexity tensorfaces had a poorer ability to generalize to handling novel face stimuli that were very different from the input face training set. This raises the possibility that it may be advantageous for biological face cell populations to contain a diverse range of complexities rather than a single optimal complexity.

Disclosures: **S.R. Lehky:** None. **A. Phan:** None. **A. Cichocki:** None. **K. Tanaka:** None.

Nanosymposium

192. Representation of Faces and Bodies

Location: 147B

Time: *Sunday, November 12, 2017, 1:00 PM - 4:30 PM

Presentation Number: *192.02

Topic: *D.07. Vision

Title: The consequence of data demeaning on inferences regarding mirror-symmetric coding in the macaque face-processing system

Authors: ***F. M. RAMIREZ**[1,2], E. F. RODRIGUEZ[2]
[1]Bernstein Ctr. for Computat. Neurosci., Berlin, Germany; [2]Pontificia Univ. Catolica de Chile, Santiago, Chile

Abstract: Electrophysiological measurements from macaques have shown that the anatomical location of distinct face-selective cortical patches is associated with a specific functional identity [Freiwald WA, Tsao DY (2010). Functional Compartmentalization and Viewpoint Generalization Within the Macaque Face-Processing System. Science 330:845-851]. While neurons in the middle face patches (ML, middle lateral, and MF, middle fundus) were unimodally tuned to a single preferred orientation, neurons in the anterior lateral face patch (AL) were bimodally tuned to mirror-symmetrically oriented faces—e.g., the left and right profiles of a face. Recently, studies combining fMRI and multivariate pattern analysis (MVPA) methods including representational similarity analysis (RSA) aimed to describe the form of tuning of

neural populations in the human face-processing network. Conclusions across studies diverged, however, in all core face-selective areas. By analysing population responses of single-neurons recorded in macaques (data: Freiwald and Tsao, 2010) we investigated the impact of (i) choice of pattern dissimilarity measure and (ii) cocktail demeaning prior to subjecting the data to RSA. Cocktail demeaning refers to the practice of subtracting the mean pattern across conditions from that associated with each condition prior to pattern analyses. This pre-processing step and mathematically related variants continue to be used by some researchers. Here, re-sampling was used to simulate the impact of the fMRI measurement process on inferences regarding neural coding. Depending on the level of pooling of single-cell responses, using Euclidean distances led to incompatible inferences regarding the underlying form of tuning in MF and AL. Such inconsistencies were not observed when relying on the cosine distance (an angular distance). That is, unless cocktail-demeaning was implemented. As hypothesized by Ramírez (2016) [Doctoral Thesis, Psych. HU-Berlin] on the basis of simulations, implementing cocktail-demeaning prior to RSA led to erroneous conclusions regarding mirror-symmetric coding also when using the cosine distance. These findings demonstrate the risks of inaccurate estimates of neuronal response-patterns on inferences regarding neural coding, generally bear on the interpretation of MVPA analyses by demonstrating the need to distinguish effects reflecting the direction of a population vector in multidimensional space from those associated with its length (and mean), and suggest a unified interpretation of otherwise inconsistent conclusions regarding viewpoint generalization in humans.

Disclosures: F.M. Ramirez: None. **E.F. Rodriguez:** None.

Nanosymposium

192. Representation of Faces and Bodies

Location: 147B

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***192.03

**Topic: ***D.07. Vision

Support: Scientific Research on Innovative Areas “Sparse Modeling” (25120004) from MEXT, Japan

Title: A computational approach to predict view tuning and face inversion effect of face neurons in inferior temporal cortex

Authors: Y. NAM[1], G. UCHIDA[2], *T. SATO[3], M. TANIFUJI[4]
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Abstract: View tuning and inversion effect are the unique response properties of face neurons in inferior temporal cortex. However, the features of face neurons that determine the response properties has not been well understood. In the present study, we recorded responses of face neurons to more than 1000 objects including faces with various views and non-face objects. We used a previously proposed computational method (Owaki et al., 2012) to identify the features that maximally explain the variance of recorded responses to objects. Here, we assumed that the feature can be recovered from a dictionary consisting of a massive number of candidate features generated from natural image fragments. We applied a Gabor filter and a local max operation to the image fragments to generate candidate features comprising combinations of local orientations and colors. To quantify object responses predicted by candidate features, we apply the same filter and max operation to object stimuli, calculated Euclidian distances against candidate features, and normalized the distances within a range of 0 to 1 using a radial basis function. We then searched for the feature that provides predicted object responses that are highly correlated with neural responses. In this way, we identified features with significant correlation coefficient between predicted and neural responses. To test the identified features explained view tuning of face neurons, we made additional recording from the neurons with systematically controlled views of faces. For these responses, we investigated correlation in view tuning between the predicted responses from identified features and actual neural responses. We found the responses showed significant correlation ($p<0.05$) for 60% of recordings. We also recorded neural responses to upright and inverted faces, and identified feature predicted the inversion effect of the neurons in 80% of cases. Thus, the features that comprise specific, moderately complex combinations of local orientations and colors enable us to predict facial view tuning curves and inversion effect. The specific combination of local orientation essential for these response properties will be discussed.

Disclosures: **Y. Nam:** None. **G. Uchida:** None. **T. Sato:** None. **M. Tanifuji:** None.

Nanosymposium

192. Representation of Faces and Bodies

Location: 147B

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Presentation Number: *192.04

Topic: *D.07. Vision

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R01MH111425
HHMI

Title: Recordings from macaque face and body patches in the upper bank of the superior temporal sulcus reveal strong species selectivity

Authors: *L. SHE, D. TSAO
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Abstract: Recordings from the "classic" macaque face patch system, consisting of six face patches in the fundus and lower bank of the superior temporal sulcus (STS) as well as the inferotemporal gyrus, indicate a major role in coding invariant facial identity. Furthermore, these six patches appear to be species-agnostic, responding approximately equally on average to human and monkey faces (Moeller and Tsao, SFN 2011). Beyond these six classic face patches, several face-selective patches have been identified by fMRI in the macaque brain including a patch in the upper bank of the STS, a patch in perirhinal cortex, and three patches in prefrontal cortex. Here, we targeted an upper bank face patch with anterior-posterior location approximately the same as face patches AF/AL for single-unit recordings. We found that cells in this patch had several distinctive properties. Cells responded selectively to monkey faces but not human faces. Adjacent to this cluster of face cells, we identified a cluster of body-selective cells. Analogous to the upper bank face patch cells, these body cells responded specifically to monkey bodies and not to human bodies. In a second animal, fMRI revealed the existence of adjacent face and body patches in the upper bank of the STS. Overall, our results suggest the existence of two modules in the upper bank of the STS that may be specialized for coding social signals conveyed by faces and bodies of conspecifics.

Disclosures: L. She: None. **D. Tsao:** None.

Nanosymposium

192. Representation of Faces and Bodies

Location: 147B

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**Topic: ***D.07. Vision

Support: NIH Grant DC013906

Title: Multiplexing in face selective cortex: Evidence of flexible trial-by-trial and sub-trial representations of multiple stimuli

Authors: *V. C. CARUSO[1], A. F. EBIHARA[4], S. TOKDAR[2], W. FREIWALD[5], J. M. GROH[3]
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Abstract: Much of our knowledge of how the brain encodes visual information comes from experiments in which one stimulus is presented on each trial. However, in the real world, many stimuli are present at the same time. How does the brain represent multiple simultaneous stimuli, particularly when they recruit an overlapping population of neurons?
Our group has recently showed that the primate auditory system can represent two synchronous sounds by interleaving in time the responses to each (Caruso et al, biorxiv, 2017). Such time division multiplexing of responses effectively increases the capacity of single neural channels, permitting more than one item to be represented across time in a neural population.
Here we test whether a similar encoding mechanism occurs in higher visual cortical areas thought to be dedicated to encoding face stimuli. We analyzed single cell activity from two face selective cortical areas, the medial fundus (MF) and anterior lateral (AL) patches, while monkeys viewed a “preferred” face stimulus, chosen to elicit a high response, a “non-preferred” face or object, or both.
When pooled across time and trials, the activity of MF and AL neurons during dual-stimulus presentations was intermediate between the responses to each stimulus alone (Ebihara’s doctoral thesis, 2015). However, two novel statistical analyses that investigate activity fluctuations within and across trials (Caruso et al., biorxiv, 2017), suggest that activity in these structures varied across time, potentially allowing both stimuli to be represented. MF showed greater incidence of fluctuating activity than AL, and trial-by-trial fluctuations were more prevalent for face-face stimulus pairs, which presumably recruit a more overlapping population, than for face-object pairs, for which the overlap would be less.
REFERENCES
Ebihara, AF, "Normalization Among Heterogeneous Population Confers Stimulus Discriminability on the Macaque Face Patch Neurons" (2015). *Student Theses and Dissertations*.278. http://digitalcommons.rockefeller.edu/student_theses_and_dissertations/278
VC Caruso, JT Mohl, C Glynn, J Lee, SM Willett, A Zaman, R Estrada, S Tokdar, JM Groh Evidence for time division multiplexing of multiple simultaneous items in a sensory coding bottleneck, bioRxiv doi:10.1101/107185

Disclosures: V.C. Caruso: None. **A.F. Ebihara:** None. **S. Tokdar:** None. **W. Freiwald:** None. **J.M. Groh:** None.

Nanosymposium

192. Representation of Faces and Bodies

Location: 147B

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***192.06

**Topic: ***D.07. Vision

Title: Diverse response properties of face-selective cells in the human fusiform face area

Authors: *S. KHUVIS, E. M. YEAGLE, A. D. MEHTA
Dept. of Neurosurg. and Feinstein Inst. for Med. Res., Hofstra Northwell Sch. of Med., Hempstead, NY

Abstract: Both fMRI and intracranial EEG studies have demonstrated that the human fusiform face area (FFA) responds differently to visual presentation of faces vs non-face images. However, single-unit recordings confirming such selectivity have heretofore only been performed in the macaque homologue of human FFA, the middle face patch.
Here, we report on single units recorded from the FFA regions of four patients undergoing invasive monitoring for medically-refractory epilepsy. Within four left and two right FFA areas, we identified 36 visually-responsive units, of which 24 (67%) distinguished between faces and non-face stimuli. Of stimulus-selective cells, 10 (41%) demonstrated an increased firing rate in response to face stimuli relative to non-face image stimuli, while 8 (33%) showed decreased firing. A subset of these cells sustained their selective activity after the offset of the visual stimulus (8 cells, 33%). Furthermore, some selective FFA neurons showed tuned responses specifically to image stimulus offset: some showed greater activity following the offset of face images relative to non-face images (3 cells, 13%), while others showed the reverse trend (2 cells, 8%).
We propose a preliminary taxonomy of neurons in the human FFA based on the broad range of tuning properties exhibited by these cells.

Disclosures: S. Khuvis: None. **E.M. Yeagle:** None. **A.D. Mehta:** None.

Nanosymposium

192. Representation of Faces and Bodies

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**Topic: ***D.07. Vision

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NTU CoHASS Incentive Scheme
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Title: Spatial and temporal ensemble coding in face adaptation

Authors: *H. XU, H. YING, E. BURNS
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Abstract: The human visual system is bombarded by massive amounts of information every day. Through ensemble coding our brains can easily obtain the gist of the information presented in a scene (e.g., an angry mob) rapidly and automatically without having to examine each individual facial expression. In three studies, we explored how this ensemble coding might arise both spatially and temporally to affect face perception. We first found that adapting to attractiveness or emotion during an RSVP face sequence biased the judgment of subsequently presented faces in a way that suggested ensemble coding was occurring temporally during RSVP. In a second experiment, we found that ensemble coding of facial attractiveness can arise spatially when judging a face viewed within a group. In a final experiment, spatial ensemble coding crossed over temporally through adaptation to influence the attractiveness perception of subsequently presented faces, with the ensemble coding effects in these latter two experiments associated with one another. Ensemble coding must therefore occur both spatially and temporally and indicates high level visual processing, in comparison to center-surround inhibition, when processing faces in a group or in a sequence.

Disclosures: H. Xu: None. **H. Ying:** None. **E. Burns:** None.

Nanosymposium

192. Representation of Faces and Bodies

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**Topic: ***D.07. Vision

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Title: Elucidating temporal processing in human high-level visual cortex using fMRI and encoding approaches

Authors: *A. STIGLIANI, B. JESKA, K. GRILL-SPECTOR
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Abstract: How is temporal information processed in high-level visual cortex? Early and intermediate retinotopic areas show separable responses to transient and sustained visual stimuli. However, the temporal processing characteristics of high-level visual areas involved in processing faces, bodies, or characters are poorly understood. To fill this gap in knowledge, we measured cortical responses with fMRI (N = 8) to time-varying stimuli that were either transient (30 stimuli/trial; duration: 33 ms each; inter-stimulus interval (ISI): 67, 133, 300, or 633 ms), sustained (1 stimulus/trial; duration: 3, 5, 10 or 20 s), or contained both transient and sustained stimulation (30 stimuli/trial; duration: 67, 133, 300, or 667 ms each; ISI: 33 ms). Then we

implemented a novel encoding model to test if and how transient and sustained temporal channels contribute to responses in high-level visual cortex. Different than the standard linear model, which predicts responses directly from the stimulus, the encoding approach first uses a 2 temporal-channel model to predict neural responses to the stimulus with fine temporal precision and then derives fMRI responses from the neural predictions. Results show that an encoding model not only explains responses to time varying stimuli in face and body-selective regions, but also finds differential temporal processing across high-level visual cortex. That is, temporal processing differs both across anatomical locations as well as across regions that process different domains. Specifically, (1) face- and body-selective regions in lateral temporal cortex (LTC) are dominated by transient responses, but face- and body-selective regions in lateral occipital cortex (LOC) and ventral temporal cortex (VTC) illustrate both sustained and transient responses, and (2) face-selective regions in LOC and VTC illustrate larger sustained responses than neighboring body-selective regions. Together, these results suggest that domain-specific regions in high-level visual cortex are organized in parallel processing streams with differential temporal characteristics and provide evidence the human visual system contains a separate lateral processing stream that is attuned to changing aspects of the visual input.

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192. Representation of Faces and Bodies

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NIH Grant 1R01EY02391501A1
China NSF Grant 31470055

Title: Microstructural development of vertical connections impacts functional selectivity in face and reading networks

Authors: ***Z. ZHEN**[1,2], J. GOMEZ[3], V. S. NATU[2], M. BARNETT[4], B. L. JESKA[2], K. S. WEINER[2], K. GRILL-SPECTOR[2,3]
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Abstract: It is well-established that both anatomical and functional features of the human brain develop from childhood to adulthood. However, the development of functional regions relative to large-scale and fine-scale white matter anatomical properties is poorly understood. To fill this gap in knowledge, we examined the relationship of functional regions within high-level visual cortex that process faces and words relative to three vertical white matter fasciculi: the vertical occipital fasciculus (VOF), the posterior arcuate fasciculus (pAF), and the arcuate fasciculus (AF). We asked three main questions: (1) Is the large-scale organization of face- and word-selective regions relative to vertical white matter tracts different between children and adults? (2) Are there large-scale (e.g. all tracts and all regions) or fine-scale (e.g. tract- and/or region-specific) differences in microstructural properties between children and adults? (3) Can a model of white matter properties predict functional selectivity in children and adults? To address these questions, we used functional magnetic resonance imaging (fMRI), diffusion MRI (dMRI), and quantitative MRI (qMRI) in 23 children (5-12) and 23 adults (22-28). After localizing ventral face and word-selective regions in each participant, we used dMRI and ensemble tractography to define the VOF, pAF, and AF in order to (1) identify portions of these fascicles that connect with each of the functional regions (referred to as functionally defined fasciculi, FDF) and (2) test how anatomical properties of these FDFs change across development. We report three main findings. First, different portions of the VOF, pAF, and AF each intersect with face- and word-selective regions. This large-scale organization is similar for children and adults as there is no difference in the spatial layout or volume of these FDFs. Second, independent measures of diffusivity and T1 relaxation show a significant decrease within these FDFs from childhood to adulthood, which is consistent with increased myelination. Finally, a data-driven approach using a principal component analysis of fascicle properties reveals that the two main components explaining the difference between white matter properties in children and adults are weighted by both diffusivity and T1 relaxation. Intriguingly, separate scores of these components in functionally defined portions of the VOF are significantly correlated with face- and word-selectivity, respectively. These results indicate that microstructural development of vertical fasciculi affects the function of networks in high-level visual cortex.

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Nanosymposium

192. Representation of Faces and Bodies

Location: 147B

**Time: ***Sunday, November 12, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***192.10

**Topic: ***D.07. Vision

Title: The dorsal and ventral visual pathways exchange information during configural face processing

Authors: *V. ZACHARIOU, N. P. MLYNARYK, L. G. UNGERLEIDER
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Abstract: Configural face processing, the processing of the spatial relationships among the features of a face, is considered essential for face perception. If configural face processing depends on spatial information, might this process involve interactions between the face-processing regions of the ventral stream and visuospatial processing regions of the dorsal stream? Here, we used thetaburst TMS (TBS) with fMRI to examine how interference of localized spatial-processing regions of the dorsal stream affects the BOLD activity and pattern of functional connectivity of face-processing regions in the ventral stream during a same-different face detection task. Participants were presented with two face exemplars, appearing simultaneously on a screen that could differ in terms of the shape (featural differences) or the spatial configuration of their features (configural differences; Zachariou et al. 2016). Featural and configural differences were matched in difficulty as measured by RT and accuracy separately for each participant. Dorsal spatial-processing regions were the active TBS sites and the vertex was the control site. When TBS was applied on the location-processing regions, the magnitude of the BOLD activity within the right occipital face area (OFA) and right anterior inferior temporal (aIT) regions decreased in response to configural but not featural face processing. This effect was not observed for the vertex control site. TBS on the location-processing regions also decreased the functional connectivity between bilateral OFA, aIT, right fusiform face area (FFA), and the location-processing regions (the TBS targets) significantly more for configural than featural face processing. No changes in functional connectivity were observed when TBS was delivered on the vertex control site for either face task. We conclude that the location-processing substrates of the dorsal stream exchange visusospatial information with face-processing regions of the ventral stream during configural face processing.

Disclosures: V. Zachariou: None. **N.P. Mlynaryk:** None. **L.G. Ungerleider:** None.

Nanosymposium

192. Representation of Faces and Bodies

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Kavli NSI Post-doctoral fellowship (to JS)
Women in Science Post-doctoral fellowship (to JS)

Title: Comparing human and monkey neural circuits for processing social scenes

Authors: *J. SLIWA[1], S. R. MARVEL[2], W. A. FREIWALD[1]
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Abstract: Recognizing agents, their actions, and their interactions is essential for understanding the world around us. In the monkey brain, these cognitive steps engage serially three distinct neural circuits: The face and body patches, the Mirror Neuron System (MNS) and finally the Exclusively Social Interaction Network (ESIN), a putative precursor of the Theory of Mind (ToM) network in monkeys (Sliwa J and Freiwald WA, 2017). It remains unknown however whether homologous brain regions are involved in humans, or whether humans and monkeys employ different neural strategies to process social scenes. To answer these questions we scanned twenty-six human subjects for fMRI acquisition in two sessions, while they were presented with the same videos as the ones presented to monkeys, and additionally with videos of social scenes involving human actors. Whole-brain activity for watching blocks of human or monkey individuals, their actions and their interactions was compared to the activity for watching control videos of objects' still, moving and interacting, using Random Effects (RFX) Generalized Linear Model (GLM) group analysis. We show that similarly to monkeys, humans 1) engage face and body areas (mapped independently using a classic localizer) in all social video conditions, and 2) engage the MNS (mapped independently using a classic localizer) in a generic manner for watching agent-object, agent-agent and object-object interactions. Yet contrary to monkeys, humans 1) spontaneously engage the ToM network (mapped independently using a classic localizer) even when watching non-acting agents, and 2) equally enhance the activity of the ToM network when watching agents performing goal-directed actions and social interactions. These preliminary results identify which neural strategies are shared and which ones adapted to the specific needs of the species, and specifically emphasize the uniquely human interest in understanding peers' goal-directed actions.
Sliwa J, Freiwald WA (2017) A dedicated network for social interaction processing in the primate brain. Science

Disclosures: **J. Sliwa:** None. **S.R. Marvel:** None. **W.A. Freiwald:** None.

Nanosymposium

192. Representation of Faces and Bodies

Location: 147B

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**Topic: ***D.07. Vision

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Title: Characterizing the response to face pareidolia in human category-selective visual cortex

Authors: *S. WARDLE[1], K. SEYMOUR[2], J. TAUBERT[3]
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Abstract: Face pareidolia is the perception of illusory faces in inanimate objects such as food, trees, and the well-known "Man in the Moon". Pareidolia is typically a spontaneous and persistent phenomenon, and the object is perceived simultaneously as both an illusory face and an inanimate object. In the human brain, ventral visual areas such as the lateral occipital complex (LOC) and fusiform face area (FFA) in occipital-temporal cortex are category-selective and respond to either objects or faces respectively. It is unclear how these regions process stimuli with a dual face/object identity. Here we used fMRI to determine how category-selective regions process stimuli that elicit face pareidolia. We collected 56 photographs of naturally occurring examples of face pareidolia in objects such as food, accessories, and appliances. For each object with an illusory face, we found a similar image of the same category of object but without an illusory face. Thus this yoked image set of 56 images was matched for object content and visual features but did not contain any illusory faces. We used a yoked block design to measure patterns of fMRI BOLD activation in response to the 112 photographs of objects where pareidolia was present or absent. Participants performed a standard 1-back task in the MRI scanner to maintain attention throughout each run. Category-selective areas were defined in each participant in separate runs using standard functional localizers comprised of photographs of real faces, scenes, objects, and scrambled objects. We used a linear support vector machine (SVM) to attempt to decode the presence of illusory faces from the patterns of BOLD activation in each region-of-interest. With leave-one-run out classification, the classifier could successfully discriminate between blocks containing objects with illusory faces versus non-face objects from activity in both early visual cortex (V1), and higher-level category-selective areas (LOC and FFA). We used cross-classification (training and testing the classifier on blocks containing different images) to determine whether the presence of an illusory face was decodable from these regions across images with different visual properties. In both LOC and FFA the classifier could successfully decode the presence or absence of pareidolia faces in new image sets that were not

used for training the classifier, demonstrating generalization. Notably the presence of an illusory face could not be decoded in V1 when different image sets were used for training versus testing the classifier. Together, the results suggest that both FFA and LOC (but not V1) respond to the presence of illusory faces in inanimate objects.

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Nanosymposium

192. Representation of Faces and Bodies

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**Topic: ***H.01. Animal Cognition and Behavior

Support: NIMH Intramural Research Program

Title: Monkeys experience face pareidolia

Authors: *J. TAUBERT[1], S. WARDLE[2], M. FLESSERT[3], D. A. LEOPOLD[4], L. G. UNGERLEIDER[5]
[1]The Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Dept. of Cognitive Sci., Macquarie Univ., Sydney, Australia; [3]Lab. of Brain and Cognition, NIMH/NIH/DHHS, Bethesda, MD; [4]NIMH, Bethesda, MD; [5]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Face pareidolia, or the misperception of faces in inanimate objects, can be considered as an error of the face detection system. Examination of these errors can potentially reveal new insight into the organizing principles that underlie higher-level visual processing in the primate brain. Here we begin our investigation of face pareidolia by reporting that this illusion is not unique to humans. First, we collected 15 examples of face pareidolia that occurred by chance in a wide variety of everyday objects. For each example of an illusory face in an object, we found a matched object of the same object category with similar visual features, but without a face. During a looking preference paradigm, we presented examples of face pareidolia, matched objects, and monkey faces in pairs to five male rhesus macaques while recording their natural eye movement behavior. All monkeys looked longer at objects that were judged to contain illusory faces by human observers than at matched objects (t_4 =10.23, P <.001, η^2 =.96) or monkey faces (t_4 =5.52, P =.005, η^2 =.88). We also examined their eye gaze patterns. We tallied the distribution of fixations directed towards each of the 45 stimuli across all trials. For each subject, we created a 2-dimensional density plot, normalized to the maximum number of fixations, and averaged these across all five subjects. The density plots highlight that monkeys made frequent fixations of the “eye” and “mouth” regions for both the monkey faces and the

illusory faces, which is consistent with human gaze behaviour when viewing real faces. A support vector machine classifier successfully predicted whether each monkey was viewing an object with an illusory face or not, based on the fixation density plots (all *P*s >.001). Overall, our results indicate that monkeys also see face configurations in non-face objects and, as such, provide the first compelling evidence of face pareidolia in any species other than our own.

Disclosures: J. Taubert: None. **S. Wardle:** None. **M. Flessert:** None. **D.A. Leopold:** None. **L.G. Ungerleider:** None.

Nanosymposium

192. Representation of Faces and Bodies

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**Topic: ***D.07. Vision

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Title: Action categories are represented as distributed patterns in ventral and dorsal structures: A high field and high resolution fMRI (7T) study

Authors: *M. ZHAN, R. GOEBEL, M. VAESSEN, B. DE GELDER
Cognitive Neuroscience, Fac. of Psychology and Neurosci., Maastricht Univ., Maastricht, Netherlands

Abstract: In daily life various bodily displays are effortlessly understood, indicating combined processing of information about the object category, movement, action type and emotional significance. Until recently, the assumption was that each type of information of the bodies was represented in dedicated brain areas, showed by studies with different focuses: the action-related information was found a fronto-parietal network being activated when observing actions, including the intraparietal sulcus (IPS), the dorsal and ventral premotor areas (PMd, PMv); the body-form information as a visual object category was found in body/body parts-sensitive regions in the ventral-lateral pathway, including the extrastriate body area (EBA) and the fusiform body area (FBA); the biological motion-information was found in regions in the posterior superior temporal sulcus (pSTS) sensitive to the motion of both faces and bodies. Some of those areas were also consistently activated during emotional experience. In this high-field and high-resolution 7T fMRI study, we challenged this category specificity model using representational similarity analysis (RSA) to discover common and specific areas representing

ten different action categories and their properties. Stimuli consisted of whole body postures of neutral, instrumental and affective actions controlled for actor identity. We show that the 10-action-category structure was represented in body-form and motion related areas (fusiform, EBA, pSTS), in motor-related areas (anterior IPS, primary motor cortex), and in attention-related areas (V3a/V7, posterior IPS, superior parieto-occipital junction), while these areas were distinctively involved in representing other properties of the bodies. In addition, the searchlight RSA revealed the 10-action-category structure in medial brain areas (along the cingulate, medial prefrontal areas) subcortical (thalamus, head of the caudate) and cerebellar areas. Our findings indicate that perception of the action categories involves a large distributed network of areas that are differently involved in representing each of the categories and their properties.

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Nanosymposium

193. Sleep: Key Advances

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Time: *Sunday, November 12, 2017, 1:00 PM - 3:15 PM

Presentation Number: *193.01

Topic: *F.08. Biological Rhythms and Sleep

Support: HHMI

Title: Hypothalamic switch of REM sleep

Authors: ***K.-S. CHEN**[1,2], M. XU[1,2], Y. DAN[1,2]
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Abstract: Mammals have three distinct brain states - wakefulness, rapid eye movement (REM) sleep and non-REM sleep. The dorsomedial hypothalamus (DMH) has been proposed to be involved in sleep regulation, while the neural mechanism remains unknown. Here we showed that a subtype of inhibitory neurons in the dorsomedial hypothalamus (DMH) projecting to the preoptic area or the brainstem have opposite functions in REM sleep regulations. Virus-based tracing demonstrated that these two groups of neurons have distinct collateral projections. Using cell-type specific, retrograde in vivo microendoscopic calcium imaging, we found that preoptic area projectors have the lowest activities during REM sleep, while brainstem projectors have the highest activities during REM sleep. Selectively optogenetic activation of preoptic area projectors suppressed REM sleep while activation of brainstem projectors promoted REM sleep. Complementary optogenetic inhibitions indicated that the activities of these neurons are required for corresponding REM sleep regulatory functions. These findings provide a novel neural

mechanism for REM sleep regulation through the DMH, a site of divergence for circuits switching REM sleep on and off.

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Nanosymposium

193. Sleep: Key Advances

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Topic: *F.08. Biological Rhythms and Sleep

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Harvard Mind Brain Behavior
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Title: Tracking fluctuating thalamocortical dynamics during the transition into sleep through high temporal resolution neuroimaging

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Abstract: Sleep onset is a gradual process marked by changes in electrophysiological dynamics and a progressive decline in behavioral responsiveness. Prominent EEG signatures of sleep, such as spindles and slow waves, reflect oscillatory interactions across cortical and thalamic structures. However, typically only coherent cortical activity can be detected in the scalp EEG, whereas activity in deeper brain regions is challenging to measure, so little is known about how large-scale thalamocortical dynamics change during the process of sleep onset. This study aimed to track shifts in thalamocortical dynamics at high temporal resolution within the human brain during sleep onset. We developed a new approach to imaging local thalamocortical dynamics in the 0.1-1 Hz range by performing simultaneous EEG and fast (TR=367 ms) fMRI, allowing rapid imaging of local thalamic and cortical activation patterns in concert with electrophysiology. We scanned ten subjects with simultaneous EEG-fMRI at 3 Tesla during sleep onset, beginning at

midnight. We found that shifts in arousal during sleep onset, as defined by loss of the occipital alpha rhythm, are marked by an increase in the spatial coherence of slow cortical dynamics detected in the fMRI signal. The phase of the fMRI signal oscillation was coupled to the spectral content of the EEG, suggesting a correspondence with local neural excitability. We additionally performed EEG-fMRI at 7 Tesla in two subjects to take advantage of the higher sensitivity provided by ultra high field imaging, while they performed a breath-counting task to track behavioral state. We found that the cortical fMRI rhythm tracked fluctuations in behavioral performance, and identified an analogous oscillatory fMRI signal in thalamic structures with a 1-2 second delay. Measuring BOLD impulse responses in visual thalamus demonstrated that its hemodynamic response peaked earlier than in cortex, suggesting that the lag in thalamic activity during sleep was linked to neural rather than hemodynamic delays. We conclude that transitory shifts in the coherence of local slow thalamocortical dynamics predict the onset of sleep and the decline of behavioral performance. These results demonstrate that rapid changes in large-scale network function can be detected through new techniques for fast whole-brain neuroimaging, and suggest that the onset of coherent thalamocortical slow dynamics occurs earlier in sleep than classically proposed, as these neural activity patterns foreshadowed the transition into sleep.

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Nanosymposium

193. Sleep: Key Advances

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Topic: *F.08. Biological Rhythms and Sleep

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NIH DP2MH104119

Title: Parvalbumin interneuron-driven theta oscillations are sufficient for network stabilization leading to contextual fear consolidation independent of sleep

Authors: ***N. OGNJANOVSKI**[1], M. ZOCHOWSKI[2], S. J. ATON[1]
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Abstract: Sleep is thought to play a critical role in promoting various forms of learning and memory. Hippocampal oscillations occurring in either rapid eye movement (REM) or non-REM (NREM) sleep have been proposed to play a role in contextual and spatial memory formation,

possibly due to the role of these oscillations in patterning ensemble activity. Here we show that immediately following contextual fear conditioning (CFC), parvalbumin-expressing (PV+) interneurons in hippocampal area CA1: 1) are necessary during NREM sleep, but not REM sleep or wakefulness, to establish fear memory, 2) coordinate NREM-REM oscillations of delta, theta, and SPWR frequencies, 3) can generate oscillations that are sufficient to rescue memory deficits due to sleep deprivation, and 4) can stabilize patterns of neuronal communication and induce long-lasting changes in the strength of functional connectivity relationships between CA1 neurons We employed state-targeted optogenetic manipulations of PV+ interneuron activity in CA1 following learning using mice expressing Archaerhodopsin (Arch) in PV+ interneurons (*PV:Arch*). We found that PV+ interneuron activity during NREM sleep, but not wake or REM sleep, is critical for CFM consolidation. We also observe REM theta increases following CFC are suppressed when PV+ interneurons are inhibited during prior bouts of NREM. Following NREM-targeted optogenetic inhibition, there was also a decrease in the stability of CA1 network connectivity patterns across time. Under normal conditions, network stability increases in CA1 for up to 24-h post-CFC - a change predictive of successful memory consolidation. We also test whether rhythmic activation of the hippocampal network is sufficient to overcome oscillatory and CFM consolidation deficits caused by sleep deprivation (SD) in mice expressing Channelrhodopsin 2 in PV+ interneurons (*PV:ChR2*). Critically, in SD mice, theta frequency stimulation of CA1 PV+ interneurons rescues CFM to levels seen in freely-sleeping animals, and restores persistent decreases in NREM delta power and SPWRs that extend into recovery sleep following SD. This manipulation also increased the stability and strength of network connectivity following CFC to a level comparable to that observed in freely-sleeping animals. These data suggest that PV+ interneurons are necessary and sufficient to amplify NREM sleep-associated CA1 network oscillations and regulate spike timing in a manner that promotes systems-level memory consolidation.

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**Topic: ***F.08. Biological Rhythms and Sleep

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Title: A high-throughput non-invasive screen to measure both sleep and circadian parameters in IMPC knockout mouse lines

Authors: *P. M. NOLAN[1], N. HORNER[1], P. LAU[1], L. BROWN[2], S. PEIRSON[2], S. WELLS[1], G. BANKS[1]
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Abstract: Advances in genomics, high throughput sequencing and bioinformatics have enabled the rapid identification of genes associated with a number of physiological parameters in humans, including those associated with circadian rhythms and sleep. However unless a clear function can be assigned to each gene it can be difficult to interpret a relevant pathology and its clinical implications. Numerous studies have demonstrated that the mouse is a highly tractable and versatile model organism for the functional characterisation of specific genes. To this effect the International Mouse Phenotyping Consortium (IMPC) has been established with the aim of providing phenotyping data for a knock out of every gene in the mouse genome. While the IMPC phenotyping pipeline provides a platform for numerous behavioural, physiological and histopathological phenotypes, at present sleep and circadian phenotyping of these mouse lines is limited as standard tests for these parameters are low-throughput and involve the use of invasive procedures. The recently developed COMPASS system uses passive infrared monitoring to track the movement of singly-housed mice in the home cage and uses computer-based algorithms to extract numerous circadian rhythm and sleep related parameters from the data. We are using this novel technique to screen selected IMPC mouse lines for sleep and circadian rhythm phenotypes. Mouse lines are selected on the basis of known function and gene expression. Cohorts of homozygous mutants are screened for five days in a 12 hour light dark cycle and then an additional nine days in constant darkness. Activity data is collected throughout this time and analysed for changes in sleep and circadian rhythms. Here we present data on the first cohorts of mutants that we have studied and demonstrate the range of abnormal phenotypes we have identified. We also demonstrate how this data can be integrated with information from primary IMPC phenotyping pipelines to provide a systematic assessment of gene function on a genome-wide level.

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**Presentation Number: ***193.05

**Topic: ***F.08. Biological Rhythms and Sleep

Support: HHMI

Title: Identification of preoptic sleep neurons using retrograde labeling and gene profiling

Authors: *S. CHUNG[1,2], F. WEBER[1,2], P. ZHONG[2], C. TAN[3], T. NGUYEN[4], K. T. BEIER[5], N. HÖRMANN[2], W.-C. CHANG[2], Z. ZHANG[2], J. DO[2], S. YAO[4], M. J. KRASHES[6], B. TASIC[4], A. CETIN[4], H. ZENG[4], Z. A. KNIGHT[3], L. LUO[5], Y. DAN[2]
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Abstract: In humans and other mammalian species, lesions in the preoptic area (POA) of the hypothalamus cause profound sleep impairment, indicating a crucial role of the POA in sleep generation. However, the underlying circuit mechanism remains poorly understood. Electrophysiological recordings and c-Fos immunohistochemistry showed the existence of sleep-active neurons in the POA, especially in the ventrolateral preoptic area (VLPO) and median preoptic nucleus (MnPO). However, the sleep-active neurons are spatially intermingled with wake-active neurons, making it difficult to target the sleep neurons specifically for circuit analysis. Here, we have identified a population of POA sleep neurons based on their projection target and discovered their molecular markers. Using a lentivirus expressing channelrhodopsin-2 (ChR2) or a light-activated chloride channel (iC++) for retrograde labeling, bidirectional optogenetic manipulation, and optrode recording, we showed that the POA GABAergic neurons projecting to the tuberomammillary nucleus (TMN) are both sleep active and sleep promoting. Cell type- and projection-specific circuit tracing revealed their presynaptic inputs and postsynaptic targets. Furthermore, translating ribosome affinity purification (TRAP) and single-cell RNA-seq identified several candidate markers for these neurons; optogenetic and pharmacogenetic manipulations of the POA neurons labeled by these markers confirmed their sleep-promoting effects. Together, these findings provide easy genetic access to sleep-promoting POA neurons and a valuable entry point for dissecting the sleep control circuit.

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**Topic: ***F.08. Biological Rhythms and Sleep

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Title: Enhancement and stabilization of visual perceptual learning during sleep are subserved by different mechanisms

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Abstract: Visual perceptual learning (VPL) refers to a long-lasing performance improvement on a visual feature after visual experience. Accumulating behavioral evidence indicates that sleep plays important roles in facilitating VPL. There are two different types of facilitatory roles of sleep: performance enhancement and stabilization. Performance enhancement should be associated with high plasticity, which is opposite to stabilization. Nevertheless, the mechanisms of these two roles of sleep have not been clearly distinguished. In the present study, we investigated neural mechanisms involved in each of the plasticity and stabilization processes of VPL during sleep by taking advantage of a widely known interference paradigm. In VPL, learning of a texture discrimination task (TDT), a standard task in VPL (Karni and Sagi, 1991), can be interfered with by immediate successive training on another TDT. This occurs when the orientations of the background elements in the TDT stimuli used in two successive trainings are orthogonal to each other (two-block paradigm). In Experiment 1, we investigated whether slow wave activity, sleep spindle activity during NREM sleep, or theta activity during REM sleep is involved in the plasticity process during sleep. There were two groups with a two-block paradigm (learning vs. no-learning groups) where we manipulated background orientations with the same number of trials so that the homeostatic process during sleep should be equated but the amount of learning after sleep should be different between the two groups. If there are some types of spontaneous oscillations whose strengths are different between groups during sleep, such oscillations should be specifically involved in the learning facilitation. We found that two types of spontaneous oscillations, sleep spindle activity during NREM sleep and theta activity during REM sleep, were involved in the plasticity process, where retinotopic enhancement was in correlation with post-sleep VPL only for the learning group. In Experiment 2, we separated two blocks of training by a 120-min interval during which subjects slept. The post-sleep training was assumed to interfere with the pre-sleep VPL if the stabilization process did not occur during sleep. We found that theta activity during REM sleep showed retinotopic enhancement in correlation with the resilience of pre-sleep VPL. Additionally, post-sleep training disrupted pre-sleep VPL when the sleep period between training did not include REM sleep. Together, these results suggest that the plasticity process involves both sleep spindle and theta activities whereas the stabilization process involves only theta activity in VPL.

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**Topic: ***F.08. Biological Rhythms and Sleep

Support: Supported by NIH IRP (Y1AA3009) and Piramal Pharma Inc.

Title: Effects of acute and chronic sleep on beta amyloid accumulation and glucose metabolism in the brain

Authors: *E. SHOKRI-KOJORI[1], G.-J. WANG[1], C. E. WIERS[1], S. B. DEMIRAL[1], M. GUO[1], S. KIM[1], V. RAMIREZ[1], E. LINDGREN[1], G. MILLER[1], C. FREEMAN[1], A. ZEHRA[1], S. DE SANTI[3], D. TOMASI[1], H. BENVENISTE[4], N. D. VOLKOW[2]
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Abstract: While there has been a growing interest in the relationship between brain beta amyloid (AB) accumulation and risk for Alzheimer's disease in older individuals, these associations have not been fully investigated in a wider age range. More importantly, it is not clear whether higher regional AB accumulation would negatively affect brain function (as indexed by cerebral metabolic rate of glucose metabolism: CMRglc). Brain glymphatic system has been suggested as a mechanism through which AB peptide is cleared from the brain, particularly during sleep. It has been shown that both age and sleep quality lead to higher AB accumulation in the brain. It is not clear whether acute sleep deprivation (SD) contributes to AB accumulation in regions such as the hippocampus and precuneus which are affected by the Alzheimer's disease. Here we investigated the effect of one night SD on brain AB accumulation as measured by [18F]florbetaben (FBB) in participants (n = 20, 10 males, age = 43.35±13.3 years) after rested-wakefulness (RW) and after SD. FBB binding was assessed with the ratio of standard uptake value (SUVr) using cerebellum as a reference region. CMRglc was calculated using [18F]fludeoxyglucose (FDG) images that were collected on a separate day (n = 18). FSL and FreeSurfer were used for segmentation of structural MRI, for alignment of PET and MRI, and normalization to the MNI space. Voxel-wise analysis revealed a cluster including the left hippocampus and caudate with higher FBB SUVr during SD than RW ($p_{FWE} < 0.01$, cluster-level). Next, we correlated how sleep quality (Pittsburgh sleep quality index: number of sleep hours) was associated with FBB SUVr during RW. Lower FBB SUVr in bilateral hippocampus ($p_{FDR} < 0.05$, peak-level) and right precuneus ($p_{FWE} < 0.01$, cluster-level) were associated with higher sleep-hours. Similar FBB associations were also found with other measures of sleep. Finally, we characterized voxel-wise associations between CMRglc and FBB during RW. After correction for partial-volume effects, we found negative correlations between CMRglc and FBB

SUVr in brain regions including bilateral occipital, precuneus, and middle frontal gyrus, together with left prefrontal cortex and right hippocampus and fusiform gyrus ($p_{FWE} < 0.05$, cluster-level). Moreover, higher CMRglc in these regions including left prefrontal and right precuneus was associated with more sleep-hours ($p < 0.01$). Our findings provide evidence that acute sleep deprivation increases AB accumulation in the hippocampus while better sleep quality results in lower regional FBB SUVr (e.g., precuneus) that was also linked with higher brain function as indexed by glucose metabolism.

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Topic: *F.08. Biological Rhythms and Sleep

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Title: Neonatal sleep fragmentation results in reduced EEG power bands and long-term behavioral consequences

Authors: ***S. J. BERTRAND**[1], S. R. KUDCHADKAR[2], Z. ZHANG[2], N. PUNJABI[2], S. KANNAN[2]
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Abstract: Sleep is important for neural and behavioral development. Slow wave, or delta, activity increases in the first years of life and decreases after a peak in puberty, although the precise role of delta activity is not well understood. Sleep fragmentation (SF) is a common comorbidity of many disease states, including neurodevelopmental disorders, and frequently occurs in the pediatric intensive care unit (PICU). SF differs from sleep deprivation in that it results in an increase in arousals throughout the night, but the overall length of sleep remains unchanged. SF in adults results in acute behavioral changes such as impaired performance on

vigilance, attention and memorytasks. The effects of SF on development were examined using the orbital shaker method of sleep fragmentation in post-natal day 3 New Zealand white rabbit kits. During fragmentation a there was a significant increase in open field activity in the SF kits, and there was a significant reduction in EEG delta power. The increase in activity returns to baseline levels within one week post-fragmentation, however there is a significant presence of activated microglia and an increase of pro-inflammatory cytokines at one week post-fragmentation. In a novel object task SF kits spend significantly less time with the novel object compared to control and sham kits two weeks post-fragmentation, suggesting impairments in working memory. In an alternating T-maze task three weeks post-fragmentation, SF kits alternate at comparable rates as control and sham kits however it takes significantly longer for SF kits to choose an arm, if they choose at all. Finally, SF kits have sustained increases inflammatory cytokines TNF-α and INF-γ, and TSPO, a marker of microglial activation, marking a sustained inflammatory profile within the hippocampus and cortex. Together, the data suggest that sleep fragmentation and the resulting reduction in EEG power and sustained neuroinflammation interrupts the development of key memory processes.

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Topic: *F.08. Biological Rhythms and Sleep

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Title: Decoding material-specific memory reprocessing during sleep in humans

Authors: ***M. SCHÖNAUER**[1], S. ALIZADEH[1], H. JAMALABADI[1], A. ABRAHAM[2], A. PAWLIZKI[2], S. GAIS[1]
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Abstract: Experiments in animals found that learning-related neuronal activity is replayed during sleep. This process is thought to stabilize new memories. Activity on the level of brain areas suggests similar reactivation in humans. Whether brain activity in human sleep actually reflects the specific content of previous learning episodes, however, remains unclear. To detect such material-specific memory reprocessing, we developed a multivariate pattern classification

(MVPC) algorithm that can determine what type of images participants had viewed in a learning session based solely on brain activity during sleep. In our experiment, 32 subjects learned pictures of either faces or houses before an 8-h period of nighttime sleep during which brain activity was recorded with high-density EEG. We then employed MVPC methods to test whether electrical brain activity contains information specific to the previously learned material. We find significant patterns of learning-related processing in the EEG of rapid eye movement (REM) and non-REM (NREM) sleep, which are generalizable across subjects. This reprocessing occurs in a cyclic fashion during time windows congruous to critical periods of synaptic plasticity. Its spatial distribution over the scalp and frequency composition differ between NREM and REM sleep. Moreover, only the strength of reprocessing in slow-wave-sleep predicts later memory performance, speaking for at least two distinct underlying mechanisms in these states. We thus demonstrate that memory reprocessing occurs in both NREM and REM sleep in humans, and that it pertains to different aspects of memory consolidation.

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Nanosymposium

194. Memory Retrieval

Location: 150A

Time: *Sunday, November 12, 2017, 1:00 PM - 3:00 PM

Presentation Number: *194.01

Topic: *H.02. Human Cognition and Behavior

Title: Neural dissociation of stimulus memorability and subjective recognition during episodic retrieval

Authors: ***W. A. BAINBRIDGE**[1], J. RISSMAN[2]
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Abstract: While much of memory research takes a subject-centric focus, recent work has also pinpointed important item-centric effects on memory, driven by how intrinsically memorable or forgettable a stimulus is. Specifically, recent neuroimaging research finds that perceptual and memory-related regions of the brain show sensitivity to the memorability of a stimulus early on during encoding. However, no research has investigated the neural correlates of memorability during memory retrieval, as well as how such correlates may relate to subjective ratings of memory strength. In the current study, stimuli and neuroimaging results from a fMRI experiment (N=16) on retrieval of studied faces images (Rissman et al., 2010) were reanalyzed using a framework based on memorability. Memorability scores were obtained through a memory test on Amazon Mechanical Turk (N=872) for 400 face images from the fMRI study. We conducted

representational similarity analyses (RSAs) across the brain to identify which regions showed higher neural pattern similarity for more memorable images, as well as which regions showed higher pattern similarity for images that were successfully remembered by each participant. We find two largely non-overlapping sets of regions, with memorability-related information existing predominantly within ventral and medial temporal lobe regions and memory retrieval outcome-related information existing predominantly in fronto-parietal regions. Memorability-based effects persisted regardless of whether studied faces were correctly recognized (hits) or unstudied faces were correctly rejected. These results were confirmed using support vector regressions, which identified regions able to predict memorability score as a continuous variable. In sum, we find strong stimulus memorability effects during the retrieval of an image, which seem to differ from those activation patterns associated subjective memory strength.

Disclosures: W.A. Bainbridge: None. **J. Rissman:** None.

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194. Memory Retrieval

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**Presentation Number: ***194.02

**Topic: ***H.02. Human Cognition and Behavior

Support: Wellcome Trust Grant WT089049AIA

Title: Temporal dynamics of episodic memory reinstatement revealed by scalp and intracranial eeg

Authors: *M. S. TREDER[1], I. CHAREST[1], D. ROLLINGS[2], V. SAWLANI[2], R. CHELVARAJAH[2], M. WIMBER[1], S. HANSLMAYR[1], B. STARESINA[1]
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Abstract: Episodic memories are hallmarked by the vivid reinstatement of past experiences. While previous fMRI work has pointed to a role of hippocampal pattern completion in coordinating cortical reinstatement, the precise mechanisms of episodic reinstatement remain elusive. Here, we used high-density scalp EEG in healthy participants (n=22) and intracranial EEG (iEEG) in presurgical epilepsy patients (n=5) to investigate the oscillatory underpinnings of episodic reinstatement. The combination of both scalp and intracranial EEG allowed us to interrogate the temporal dynamics of cortical areas as well as medial temporal lobe (MTL) subregions with high fidelity. In an associative learning paradigm, participants first encoded trial-unique object-scene pairs. After a delay period, participants were presented with either the

object or the scene image as a cue and indicated via a button press whether or not they remembered the associated target image. The (i)EEG signals were filtered into standard frequency bands and frequency-specific covariance matrices were calculated within 300 ms windows for each time point in a retrieval trial. We then used a novel geometric approach based on Riemannian manifolds to map matrices into a linear tangent space. The vectorised matrices were used as features for training a shrinkage Linear Discriminant Analysis (LDA) classifier to differentiate between either remembered vs. forgotten trials or between remembered objects vs. scenes. In the scalp EEG data, we first found that successful reinstatement was associated with patterns of oscillatory activity in alpha, beta, and gamma bands. Second, within these oscillatory patterns, distinct neural signatures for successfully reinstated objects vs scenes were observable. Intriguingly, employing event-locked analysis of the intracranial MTL data, we found a switch in neural representation from the physical cue stimulus to the retrieved target stimulus during successful recollection. These results shed new light on the hippocampal-neocortical dynamics of episodic pattern completion across time.

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194. Memory Retrieval

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**Presentation Number: ***194.03

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH Grant R01 AG034580

Title: Search and recovery of autobiographical and laboratory memories: Shared and distinct neural components

Authors: *Z. A. MONGE[1], *Z. A. MONGE[1], E. A. WING[1], J. STOKES[2], R. E. CABEZA[1]
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Abstract: Functional neuroimaging evidence suggests that there are differences in the neural correlates of episodic memory for laboratory stimuli (*laboratory memory*) and for events from one's own life (*autobiographical memory*). However, this evidence is scarce and often confounded with differences in memory testing procedures. Here, we directly compared the neural mechanisms underlying the search (finding the memory target) and recovery (accessing the memory traces; i.e., ecphory) of autobiographical and laboratory memories while minimizing

testing differences. Before scanning, participants studied four-word "chains" spread across three semantically-related word pairs (e.g., *rubber-hose, hose-garden, garden-plant*). During scanning, participants completed a laboratory memory task, in which they recalled the word chains, and an autobiographical memory task, in which they recalled specific personal events associated with word cues (e.g., *dog*). Importantly, response times were similar in the two tasks, allowing for a direct comparison of the activation time courses. In the examination of task shared brain activation, we found that bilateral inferior frontal gyri and sensory-related regions (e.g., occipital pole, inferior temporal/fusiform gyri) were activated similarly during both the autobiographical and laboratory tasks. In the examination of task distinct brain activation as a function of memory stage (search vs. recovery), intriguingly, we found during search, similar brain regions were activated during both the autobiographical and laboratory tasks, whereas during recovery, clear differences emerged: regions of the default mode network (DMN) exhibited greater activity for autobiographical than laboratory memory, whereas bilateral superior parietal lobules exhibited greater activity for laboratory than autobiographical memory. Also, graph theory-based, multivariate functional connectivity analyses revealed that the DMN exhibited a more integrated topology (i.e., had higher participation coefficients) in the functional network underlying autobiographical (vs. laboratory) memory recovery. These findings further characterize the shared and distinct neural components underlying autobiographical and laboratory memories, and suggest that differences in autobiographical vs. laboratory memory brain activation previously reported in the literature reflect memory recovery rather than search differences.

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Title: A necessary role for the left angular gyrus in episodic memory and episodic simulation

Authors: ***P. P. THAKRAL**, K. P. MADORE, D. L. SCHACTER
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Abstract: Functional magnetic resonance imaging (fMRI) studies indicate that episodic memory (i.e., remembering specific past experiences) and episodic simulation (i.e., imagining specific future experiences) are associated with enhanced activity in a common set of neural regions,

referred to as the core network. This network comprises the hippocampus, medial prefrontal cortex, and left angular gyrus, among other regions. Because fMRI data are correlational in nature, it is unknown whether activity increases in core network regions are necessary for episodic memory and simulation. In the current study, we employed MRI-guided transcranial magnetic stimulation (TMS) to assess whether temporary disruption of the left angular gyrus would impair both episodic memory and simulation. For each of two TMS runs, 1 Hz repetitive TMS was applied for 10 minutes to the left angular gyrus and then to a control site (vertex) where stimulation was followed by task and a recovery period. During the task period, participants performed three tasks: an episodic memory task, an episodic simulation task, and a non-episodic control task (generating free associates). In each task, participants were shown a cue word (noun) for 30 seconds. For each cue, participants either verbally recalled a personal memory from the past few years related to the cue (i.e., the episodic memory task), imagined a personal event in the next few years related to the cue (i.e., the episodic simulation task), or generated words related to the cue (i.e., the free associate task). After each trial, participants judged how difficult it was to perform the task on a 5-point scale ranging from very easy to very difficult. Responses were audio-recorded and transcribed. Memory and simulation tasks were coded for internal (i.e., episodic) details and external details (i.e., semantic, repetitive, or off-topic information). Results demonstrated that, relative to TMS to the vertex, disruption of the left angular gyrus significantly reduced the number of internal details produced for both the memory and simulation tasks, with a concomitant increase in external detail production, reflected by a significant detail by TMS site interaction. In addition, difficulty in the memory and simulation tasks increased following TMS to the left angular gyrus relative to the vertex. By contrast, performance in the non-episodic control task did not statistically differ as a function of TMS site (i.e., number of free associates produced or difficulty in performing the free associate task). Taken together, these results are the first to demonstrate that the left angular gyrus is necessary for both episodic memory and episodic simulation.

Disclosures: **P.P. Thakral:** None. **K.P. Madore:** None. **D.L. Schacter:** None.

Nanosymposium

194. Memory Retrieval

Location: 150A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***194.05

**Topic: ***H.02. Human Cognition and Behavior

Support: NSERC RGPIN-04241

Title: Retrieving autobiographical memories under stress: Examining the effects of cortisol on retrieval and reconsolidation processes

Authors: *S. SHELDON[1], S. CHU[1], J. NITSCHKE[1], J. BARTZ[1], J. C. PRUESSNER[2]
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Abstract: A well-established finding is that elevated cortisol levels in response to a stressor hinder hippocampally-dependent processes which specifically affects episodic memory functioning. In this study, we tested the impact of stress on episodic processes during autobiographical memory retrieval. Based on current research that has indicated that the act of retrieval causes a memory to become liable and subject to alterations, we also determined how stress affects the reconsolidation of autobiographical memories. Healthy young male participants were tested in a between-subjects experiment that consisted of two sessions. In session one, participants completed either a psychological stress induction or a control task followed by an autobiographical memory test. In this test, participants were shown emotional and non-emotional cue words. To each cue, participants retrieved as well as described an autobiographical memory and then rated their experience of retrieving that memory on a number of dimensions. Cortisol levels were measured throughout this session. Session two took place three to four days later. During this session, participants described the same memories from session one and then rated their remembering experience. All memory descriptions were transcribed and scored for the amount of specific (episodic) detail. Participants under stress were slower to access memories in response to the cues than the participants not under stress. We also found that reaction times to access a memory was linked to cortisol responses to stress. Although participants under stress described memories with more specific detail than those not under stress, their memories changed less from session one to session two than the participants not under stress. These findings contribute to current understandings of the effects of the cortisol stress-response on memory and reconsolidation processes.

Disclosures: S. Sheldon: None. **S. Chu:** None. **J. Nitschke:** None. **J. Bartz:** None. **J.C. Pruessner:** None.

Nanosymposium

194. Memory Retrieval

Location: 150A

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***194.06

**Topic: ***H.02. Human Cognition and Behavior

Title: Differences in retrieval of what, where, and when components of recently-formed episodic memories

Authors: *J. J. SAKON, R. KIANI
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Abstract: Episodic memory refers to the capacity to store various streams of information into a linked, coherent episode for later recall. At a minimum, a memory is considered episodic if a subject can encode and later retrieve what, where, and when components from a single event (Nyberg et al., 1996). However, few studies have investigated memory performance differences between these components. That is: **do we remember the what, where, and when of episodic memories equally?**

We developed a novel task to address this question. In the encoding phase, human subjects (N=5) view a movie of 3-6 shapes that appear and disappear sequentially at varying locations on a central sphere. During the retrieval phase, subjects are cued about a particular time in the movie and then shown a static image of a shape at a location on the sphere. They indicate whether the shape and location match those shown in the movie at the cued time. Half of the retrieval images match locations and shapes for the cued time. The other half mismatch in various ways, enabling us to test different components of memory: "what" by showing non-matching shapes in time-matching locations, "where" by showing time-matching shapes in non-matching locations, and "when" by showing images from different times in the movie.

Subjects show equivalent accuracy across each trial type, suggesting that the brain attempts to encode components of episodic memory with equal fidelity. However, more refined analyses reveal key distinctions. 1) The retrieval accuracy of the three components is differentially affected by the gap between the cued time and the beginning (primacy) or end of the movie (recency). In particular, primacy and recency are stronger for trials probing "when" compared to "where". 2) In a variant of our task in which two of the shapes in the movie resemble each other through a parametric variation, subjects show better accuracy for "where" compared to "when" memory. This suggests increased similarity of "what" components differentially influences "where" and "when" components. 3) As the number of intervening shapes between the parametric pair increases in the movie, performance gets better on "when" retrieval trials and worse on "where" retrieval trials, showing more evidence for differential interactions of memory components.

Our results support the hypothesis that—while the engrams of episodic memories encapsulate what, where, and when of events for accurate recall—these components are not inseparably linked. Different computations underlie the memory of each component and are distinctly susceptible to interference, leading to unequal fidelity of memory components depending on order and complexity of memorized events.

Disclosures: J.J. Sakon: None. **R. Kiani:** None.

Nanosymposium

194. Memory Retrieval

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**Topic: ***H.02. Human Cognition and Behavior

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Title: Brain functional and structural changes over learning and sleep

Authors: *S. BRODT[1], J. BECK[2], M. ERB[3], K. SCHEFFLER[3], S. GAIS[1], M. SCHÖNAUER[1]
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Abstract: Traditional models of learning and memory consolidation postulate two interacting memory systems, with rapid encoding supported by the hippocampus (HC) and only gradually developing, stable storage in neocortical circuits. In a recent fMRI study we have shown rapidly emerging memory-related activity in the posterior parietal cortex (PPC) that over learning repetitions becomes independent of HC signaling and fulfills all criteria for a long-term memory representation. Besides changes in functional activity, the site where a memory representation is stored for the long-term should also undergo structural changes. These changes can be assessed by diffusion MRI already several hours after learning. In the current study, we investigated functional and structural changes in the HC and neocortex over the course of learning. Additionally, we were interested in the impact of sleep on memory systems consolidation. Two groups of human subjects (n=41) learned object-place associations over 8 learning-recall repetitions in two sessions spaced 13 hours apart. The wake group had the first session in the morning, spent the day awake and returned in the evening for the second session. The sleep group learned in the evening, slept during the night and returned in the morning. Neural activity during learning and recall was tracked with fMRI. To assess structural changes, dMRI was acquired at three time points: immediately before the first learning session, 90 minutes after the first learning session and again before the second learning session. Confirming our previous results, functional activity in the PPC increases rapidly over learning repetitions and mirrors the progression of recall performance rates. The same holds true for functional activity during recall. Concerning structural changes, when controlling for circadian effects in gray matter, PPC areas also show a decrease in mean diffusivity after the first learning session. Conversely, HC functional activity declines only over the first learning session. Analysis of beta estimates over all 8 learning repetitions shows a steep decline in functional activity only from the first to the second learning repetition. Sleep affected behavior, as the performance of the wake, but not the

sleep group worsens over the retention interval between sessions and functional activity in posterior parietal areas. The simultaneous investigation of functional and structural changes confirms the rapid build-up of a long-term memory representation in posterior parietal areas, which is further stabilized by sleep. The contribution of the HC to encoding, however, seems to be confined to the very first encounter with new information.

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Nanosymposium

194. Memory Retrieval

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Title: Olfactory cues evoke stimulus-specific replay in the sleeping human brain to enhance memory recall

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Abstract: Odors have been previously shown to be key agents in targeted memory reactivation (TMR), a technique used to influence sleep-based memory consolidation. During olfactory TMR, an odor is delivered during encoding, and then again during subsequent sleep (i.e., reactivation). TMR often results in improved performance for the associated memory task upon waking, but the neural mechanism underpinning this memory boost is not well understood. Researchers speculate that reactivation cues bias memory replay toward associated memory traces, resulting in privileged consolidation for those targeted memories. Here, we designed a novel olfactory TMR paradigm to test the hypothesis that odors delivered during sleep induce replay of associated memories in the human brain. First, subjects learn the grid locations of pictures belonging to specific categories during fMRI scanning. Next, subjects learn to associate each of the picture categories with a different category-specific odor. During reactivation, half of the category-specific odors are presented in sleep during simultaneous EEG-fMRI recording. In line with previous TMR studies, our behavioral data suggest that reactivation improves memory

performance specifically for targeted picture categories. Moreover, in an interference test following reactivation, subjects take longer to place pictures from targeted picture categories on the grid, potentially reflecting a struggle to override the strengthened memories. Finally, we use multivoxel pattern analysis of fMRI data to show that encoding category-specific pictures elicits unique ensemble patterns of neural activity during learning, and that these same patterns reemerge following odor presentation during sleep.

Disclosures: L.K. Shanahan: None. **E. Gjorgieva:** None. **T. Kahnt:** None. **J.A. Gottfried:** None.

Nanosymposium

195. Corticolimbic Circuits in Decision Making

Location: 150B

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Title: Medial prefrontal cortex shapes hidden state inference in the midbrain dopamine system

Authors: *C. K. STARKWEATHER[1], S. J. GERSHMAN[2], N. UCHIDA[3]
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Abstract: Midbrain dopamine (DA) neurons signal reward prediction error (RPE), or actual *minus* expected reward. The vast majority of experiments examining DA RPEs have utilized classical conditioning paradigms in which reward timing and/or probability are fixed. In contrast, in the real world, the true state of the environment (e.g. “will reward come, or not?”) may be hidden and must be dynamically inferred across time. Mounting evidence suggests that hidden state inference shapes DA RPEs, although the brain regions involved remain unknown. We asked whether the medial prefrontal cortex (mPFC) shapes hidden state inference in the DA system. We trained animals on two classical conditioning tasks that varied the time interval between cue and reward across trials (**Fig. 1a,b**). Similar to our previous work (Starkweather et al, 2017), the passage of time had opposing effects on DA RPEs, depending on whether reward was delivered in a deterministic manner. In the 100% Rewarded condition, post-reward RPEs

decreased as a function of time (**Fig. 1c,** $F_{8,377} = 6.1$, $P = 9 \times 10^{-16}$, 2-way ANOVA – factors: time, neuron). In the 90% Rewarded condition, post-reward RPEs *increased* as a function of time (**Fig. 1d,** $F_{8,377} = 3.9$, $P = 2 \times 10^{-4}$). We modeled this result by incorporating the animals' intra-trial inference that reward may not arrive in the 90% Rewarded task. Strikingly, upon chemogenetically inactivating the mPFC, the pattern of positive temporal modulation in the 90% Rewarded condition was abolished (**Fig 1f**, $F_{8,431} = 0.6$, $P = 0.8$), while the pattern of negative temporal modulation in the 100% Rewarded condition persisted (**Fig 1e** , $F_{8,341} = 11.8$, $P = 1.9 \times 10^{-15}$). Through modeling, we show that our result supports a circuitry in which the mPFC shapes hidden state inference in the DA system.

Figure 1

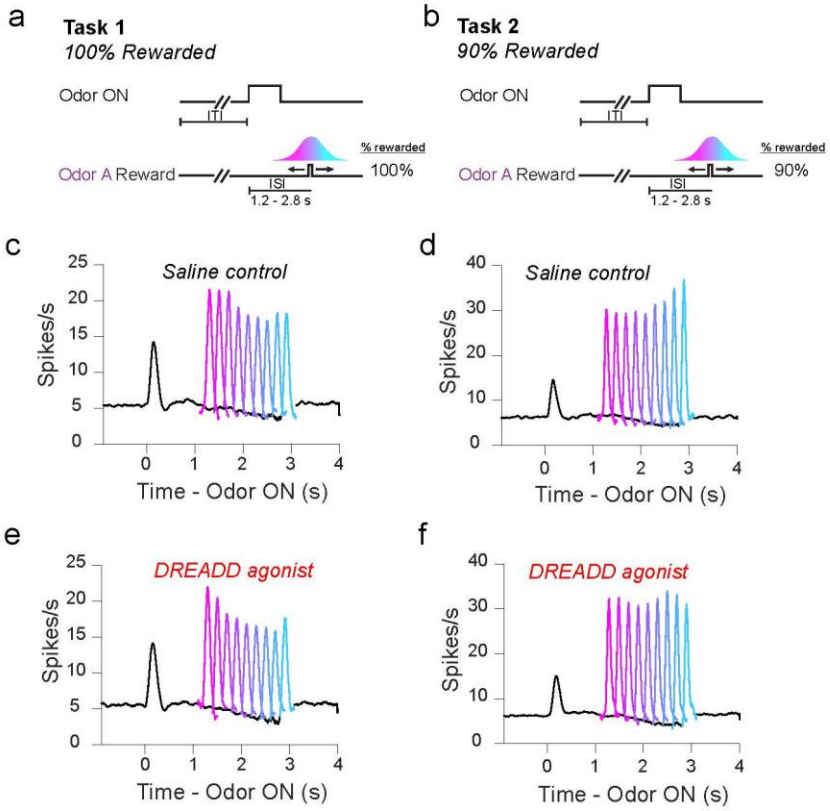

Figure 1 a. Task 1 (100% Rewarded). **b.** Task 2 (90% Rewarded). **c.** Phasic RPEs in response to reward delivery (colored lines) are negatively modulated over time in Task 1. **d.** Phasic RPEs in response to reward delivery are positive modulated over time in Task 2. **e.** Negative temporal modulation of phasic RPEs in Task 1 is spared upon inactivation of mPFC by a chemogenetic method (DREADDs). **f.** Positive temporal modulation of phasic RPEs in Task 2 is abolished upon inactivation of mPFC by DREADD agonist injection.

Disclosures: C.K. Starkweather: None. **S.J. Gershman:** None. **N. Uchida:** None.

Nanosymposium

195. Corticolimbic Circuits in Decision Making

Location: 150B

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**Presentation Number: ***195.02

**Topic: ***H.01. Animal Cognition and Behavior

Support: NIMH F32 MH107159

Title: Decoding the nature of hierarchical representations in distributed cortical structures during complex behaviors

Authors: *S. A. MCKENZIE[1], D. F. ENGLISH[1], G. BUZSÁKI[1], H. B. EICHENBAUM[2]
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Abstract: Memory guided behavior depends upon information transforms across multiple brain regions. To understand such transformations, we recorded from populations of neurons in the dorsal and ventral hippocampus, the rhinal cortices, and the orbital frontal cortex (OFC) as rats performed a task in which a food reward was contingent upon correct identification of particular object and location combinations. Across brain regions, neurons showed time evolving, multi-modal receptive fields. In each brain region, populations of such mixed-selectivity neurons simultaneously represented multiple aspects of a subject's experience. Importantly, these regions differed by the hierarchical degree to which different task features influenced neural activity, where the dorsal and ventral hippocampus along with the medial entorhinal cortex encoded Context > Position > Object/Reward, the lateral entorhinal and perirhinal cortices encoded Context > Object/Reward > Position, and the OFC encoded Reward > Object > Position.
The nature of each region's representation was derived from similarity analysis of population firing rates. However, the true nature of the neural code must be understood by how one brain region "reads out" the pattern of activity from its inputs. We present the first step in deriving such an input/output transformation through the analysis of how single neurons respond to different patterns of mono-synaptic input. We identify a manifold of firing patterns that yields an equivalent likelihood of post-synaptic activity defined by the precise spike timing intervals between pre-synaptic inputs. These results suggest that a lot is missed in an analysis limited to the rate code, though formidable challenges lie ahead if we are to decode information from the relative timing of large numbers of neurons.

Disclosures: S.A. McKenzie: None. **D.F. English:** None. **G. Buzsáki:** None. **H.B. Eichenbaum:** None.

Nanosymposium

195. Corticolimbic Circuits in Decision Making

Location: 150B

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**Presentation Number: ***195.03

**Topic: ***H.01. Animal Cognition and Behavior

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Title: Task specific value encoding in the orbitofrontal cortex

Authors: *E. L. RICH[1], E. F. CHANG[2]
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Abstract: The orbitofrontal cortex (OFC) is required for making adaptive choices based on past experience. Animal studies have shown that OFC encodes learned stimulus values, but these signals might contribute to a larger role in encoding one's current state in a task. As such, it is predicted that OFC should be modulated by the relationship between stimuli and the context in which they are experienced. We investigated how OFC responds to identical stimuli experienced in different contexts, and how responses change during learning.
Five human subjects undergoing evaluation for epilepsy surgery were implanted with electrocorticography (ECoG) arrays in multiple brain regions including OFC, and experienced task stimuli in passive and learning conditions (8 to 64 OFC electrodes per patient). Initially, patients listened to a random presentation of 3 novel stimuli, which were nonsense speech sounds (vowel-consonant-vowel conjunctions). Next, each stimulus was assigned a positive, negative or neutral point value, and patients learned by trial and error to choose the more valuable of two presented options. By the end of the session (last 5 trials) all patients chose >= 80% correct. After learning, patients again passively listened to randomly ordered stimuli.
We analyzed high-gamma (HG) frequencies (70-150 Hz), which correlate with local neural activity, and found that value learning had no effect on OFC responses when stimuli were passively perceived. During pre- and post-learning passive conditions, HG on each electrode did not differ by stimulus identity, task block, or their interaction ($p > 0.01$). During learning, OFC responses were more dynamic. Most commonly, HG changed across epochs within trials, such that 69% of electrodes showed significant effects (from 33% to 100% per patient), primarily in epochs surrounding a choice. In addition, on 32% of electrodes (25% to 50% per patient) HG changed across trial blocks within the learning condition. To further analyze these across-trial

effects, we modeled each patient's learning with a temporal difference (TD) model, so that optimized parameters estimated the learned value of stimuli on each trial. Many electrodes (70%) were modulated by the value of chosen stimuli at some time in the trial, mostly preceding feedback. Thus, stimulus values were encoded during learning, but not in the passive context. Interestingly, TD model fits improved when HG activity from OFC was added to the learning model, suggesting that OFC conveys information about ongoing choice behavior beyond what is captured by simple prediction-error based models of learning.

Disclosures: E.L. Rich: None. **E.F. Chang:** None.

Nanosymposium

195. Corticolimbic Circuits in Decision Making

Location: 150B

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**Presentation Number: ***195.04

**Topic: ***H.01. Animal Cognition and Behavior

Support: NIH grant R01DA042065

Title: Dynamic neural representation of reward predictions

Authors: *A. LANGDON[1], Y. K. TAKAHASHI[2], M. R. ROESCH[3], G. SCHOENBAUM[2], Y. NIV[1]
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Abstract: Adaptive behavior relies on the formation and updating of accurate predictions about upcoming rewards. Theoretical and empirical work has suggested that the ventral striatum (VS) is an important source of reward predictions, providing these predictions to dopamine neurons in the midbrain for the computation of reward prediction errors. We recently demonstrated that signaling of dopaminergic prediction errors due to changes in the time of reward delivery requires the VS, suggesting that VS activity encodes expectations about when upcoming rewards are expected (Takahashi, Langdon et al., 2016).
Here, we apply multiclass classification techniques to decode the predicted latency of reward delivery (short vs long) and the chosen reward well (left vs right) from the pattern of firing activity in pseudoensembles of VS neurons, recorded from rats as they performed the same odor-guided choice task used in prior work, in which the timing of reward delivery was manipulated across blocks of trials. We show that after initial learning, the expected time of reward delivery can be reliably decoded from ensemble VS activity throughout a trial, including during reward expectation, that is, after a choice has been made and before reward has been delivered. In

addition, the neural representation of predicted reward reliably dissociates between within-block and other-block choice options, even before trial onset, indicating that reward predictive neural activity in the VS reflects the block-wise structure of the task.
We also find that the neural representation of the predicted time of reward is unstable: reward predictions at the end of the reward-expectation window cannot be reliably decoded using classifiers trained on the neural representation isolated at the start of the expectation window. This indicates that the neural representation of predicted reward in the VS dynamically evolves during reward expectation, suggesting an implicit code for expectations about reward time.
We conclude that firing activity in the VS ensemble jointly and dynamically represents the (to be) chosen well and the expected delay to reward. Such a joint representation might reflect a 'state' representation, hypothesized by reinforcement learning theories (Wilson, et al. 2014), in which reward predictions are bound to a representation of the current structure of the task. Overall, these findings provide critical insight into how neural activity in the VS represents both immediate reward predictions and the higher order structure of the learning task, and provide an empirical test of computational theories of the role of the VS in reward prediction and learning.

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Nanosymposium

195. Corticolimbic Circuits in Decision Making

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John Templeton Foundation

Title: Sequential replay of non-spatial task states in the human hippocampus

Authors: *N. SCHUCK, Y. NIV
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Abstract: Neural replay of activation patterns in the hippocampus during wakeful rest is considered an important process in memory and decision making. Whereas much research has investigated replay of spatial experiences using electrophysiological recordings in animals, little is known about hippocampal replay in humans and whether it also applies to non-spatial task states. In this study, we investigated sequences of fMRI BOLD activation patterns during wakeful rest following a sequential, non-spatial decision-making task in humans. A pattern-

recognition algorithm was trained on task data and applied to individual volumes of fMRI data that were acquired during rest. This analysis revealed that the order of pattern activations in the hippocampus reflected previously experienced sequences of mental task states. The strength of hippocampal pattern sequenceness during rest was related to better on-task decoding of task states in the orbitofrontal cortex, a brain area known to play an important role in decision making by representing a cognitive map of the current task. Control analyses showed that no evidence for replay was found when the same analysis was performed on hippocampal resting state data acquired before task experience from the same participants and no effect was found in resting state data from the orbitofrontal cortex. Our data are the first to demonstrate sequential reactivation of non-spatial decision-making states in humans. This finding suggests a role of the human hippocampus in replaying abstract task states in order to elaborate the current decision making policy. In addition, our data establish that it is feasible to investigate internally generated neural event sequences with fMRI despite its substantial temporal limitations.

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

Nanosymposium

195. Corticolimbic Circuits in Decision Making

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Title: Orbitofrontal ensembles encode current state or "place" within an odor sequence task

Authors: ***J. ZHOU**[1], T. STALNAKER[1], S. RAMUS[2], G. SCHOENBAUM[1,3,4]
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Abstract: Orbitofrontal cortex (OFC) has been proposed to encode a cognitive map of task space. This map is thought to be particularly important when the current state or local position in the map cannot be derived from observable external events alone. If this is true, it is important to determine how such a cognitive map handles value representations and how it differs from maps in other areas, such as hippocampus. To begin to address these questions, we developed an odor sequence task in which a cognitive map of the “place” in the sequence could be used to facilitate performance. Rats sampled one of 16 odors on each trial and made a go or no-go response to

obtain reward or avoid a prolonged ITI. The 16 odors were organized in 4 different 6-odor sequences (1a, 1b, 2a, and 2b). The odors in the first 2 positions of each sequence (S1, S2) were unique, like the unique arms of a spatial maze. The odors in the other 4 positions (S3 - S6) were shared across two sequences (1a and 1b, 2a and 2b), like common arms in a maze. In sequences 1a and 1b, the shared odors made identical reward predictions, whereas in sequences 2a and 2b, some made opposing predictions. On these trials, the rats had to recall past information to make correct choices on these trials. With sufficient training, rats made correct responses on >75% of all the trial types generally and >90% in many sessions. This included trial types that required them to "look back" several trials to the unique arms of the sequence to make the correct response. This indicates that rats maintained information about their current state or place in the sequence, even when that information was hidden or unobservable from current events. We recorded more than 1000 single units in the OFC from these rats (n=7) and performed a decoding analysis to investigate how representations of the different states were organized by neural activity in OFC. As expected, we found that OFC neurons represented both odor and reward information on individual trials. In addition to this, ensembles also distinguished the rats' position within the odor sequence at multiple time periods in the trial. Further these representations of current state or place were present when this information was critical for correct performance and when it was not. These data show that OFC represents the rats place within a cognitive map of a non-spatial task and does so even when that information is not immediately necessary for predicting reward.

Disclosures: J. Zhou: None. **T. Stalnaker:** None. **S. Ramus:** None. **G. Schoenbaum:** None.

Nanosymposium

195. Corticolimbic Circuits in Decision Making

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**Presentation Number: ***195.07

**Topic: ***H.01. Animal Cognition and Behavior

Title: Hippocampal sequences and model-based planning in the rat

Authors: *K. J. MILLER[1,2], J. BOYD-MEREDITH[2], M. M. BOTVINICK[3], C. D. BRODY[4]
[2]Princeton Neurosci. Inst., [1]Princeton Univ., Princeton, NJ; [3]DeepMind, London, United Kingdom; [4]Princeton Neurosci. Inst. and Dept of Mol. Biol., HHMI / Princeton Univ., Princeton, NJ

Abstract: Hippocampal sequences, in which place cells "sweep out" trajectories through space while an animal is at rest, have been proposed to play a key computational role in model-based planning (Foster & Knierim, 2012). Here, planning is defined as the process of action selection

that leverages an internal model of the environment - that is, the use of an internal "cognitive map" to inform choice. Research into the role of sequences in planning, and into the neural mechanisms of planning in general, has been hampered by a lack of tasks for animal subjects which both demonstrably elicit planning and are suitable for neural recordings. In recent work, we have lifted this limitation, adapting advances from work with humans (Daw, et al., 2011) to develop a multi-step decision task for rats, and demonstrating that they adopt a strategy of planning which is hippocampus-dependent (Miller, Botvinick, & Brody, bioRxiv & submitted). Here, we report the results of electrophysiological recordings made in dorsal hippocampus during planning behavior. We find that individual cells encode the states of the task, and that hippocampal sequences take place during "sharp wave ripple" events at the conclusion of each trial. We are currently characterizing the content of these sequences in terms of the states of the task, to shed light on the computational role in planning that they may play.

Disclosures: K.J. Miller: None. **J. Boyd-Meredith:** None. **M.M. Botvinick:** None. **C.D. Brody:** None.

Nanosymposium

195. Corticolimbic Circuits in Decision Making

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**Presentation Number: ***195.08

**Topic: ***H.01. Animal Cognition and Behavior

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Title: Human hippocampal theta oscillations reflect sequential dependencies in deep planning

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Abstract: Human hippocampal theta oscillations in the 3-8 Hz range have been linked to memory performance and choice certainty, but it remains unclear whether changes in theta power are associated with specific aspects of decision making. Notably, rodent hippocampal theta oscillations are related to sweeps of place cell activity that could be used to plan trajectories. This raises the possibility that associated increases in human hippocampal theta

power also relate to on-the-fly planning of forward trajectories. To identify the neuronal correlates of online planning, we tested human subjects on a deep planning paradigm, while recording the hippocampal local field potential (LFP); either invasively, using intracranial electroencephalography (iEEG); or non-invasively, using whole-head magnetoencephalography (MEG). In each case, subjects were instructed to make a ~3s visual search for the shortest path between a starting and target location - within novel mazes that afforded multiple paths. Subjects were subsequently asked which direction they would go from one of two choice points along the shortest path. Crucially, the mazes were designed to induce forward planning in terms of a two-level tree search, where subjects needed to maintain the decisions they made at each choice point. This allowed us to dissociate the correlates of planning both initial (first choice point) and prospective (second choice point) components. We used iEEG recordings from the hippocampus of two pre-surgical epilepsy patients to identify a time-frequency window of interest for our MEG data, and subsequently observed a task-related increase in 2.5-6 Hz hippocampal theta power during the first half of the visual search period. Next, using MEG beamformer source reconstruction in 22 healthy volunteers, we found that theta power in both the hippocampus and retrosplenial cortex was differentially modulated by initial and prospective choices (i.e., path-length differences). Crucially, hippocampal theta power was highest when subjects viewed mazes with ambiguous prospective choices that were preceded by a more straightforward initial choice. Additionally, we found that hippocampal theta power in both iEEG and MEG recordings correlated with faster reaction times, with most participants performing the task close to ceiling. Together, these results suggest that the human hippocampal theta rhythm is associated with a restriction of decision spaces - to focus on subgoals/bottlenecks during deep planning.

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Nanosymposium

195. Corticolimbic Circuits in Decision Making

Location: 150B

Time: *Sunday, November 12, 2017, 1:00 PM - 3:45 PM

Presentation Number: *195.09

Topic: *H.01. Animal Cognition and Behavior

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Title: Evidence for distinct hippocampal representations of current location and distance to goal

Authors: *J. L. GAUTHIER, D. W. TANK
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Abstract: The hippocampus is critical for learning to navigate to hidden goals that occur at fixed locations, such as the escape platform of a water maze. This is believed to be related to the hippocampal encoding of place, but the hippocampus might also represent variables specific to the task, such as distance to goal. It can be difficult to confirm such representations experimentally, since the hippocampus contains many cells with spatially-modulated firing; this makes it ambiguous whether a neuron encodes a specific location in the environment, or whether it reflects an estimate of current distance to the fixed reward location. To address this problem, we exploited natural behavioral variability to tease apart the neural representations of location and distance to goal. Head-fixed mice with hippocampal windows were trained to traverse a virtual linear track, and a water reward was delivered at a fixed virtual location. Anticipatory licking of the reward tube occurred on almost every trial, and the location of licking onset was assumed to reflect the subjective estimate of reward location. While mice performed the task, optical recordings were made from large populations of CA1 neurons, many of which exhibited spatially-modulated activity. In most virtual place cells, the trial-to-trial variability of the activity location was not correlated with licking onset. But in a small fraction of cells, activity location was highly correlated with the onset of licking, an observation confirmed using cross-validation. Some licking-correlated place cells had fields more than a meter earlier than the reward site and they were active up to 4 seconds earlier than licking, indicating they could not have been driven by motor events associated with licking. As the mouse traversed the track, the sequential activity of licking-correlated cells diverged from the sequence of other place cells, being collectively active earlier or later than average, in a way that predicted the location of licking onset. These observations suggest that the hippocampus maintains an explicit estimate of a task-relevant variable, distance to the reward location, that is distinct from its representation of place.

Disclosures: J.L. Gauthier: None. **D.W. Tank:** None.

Nanosymposium

195. Corticolimbic Circuits in Decision Making

Location: 150B

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**Topic: ***H.01. Animal Cognition and Behavior

Support: NIH Grant 5T32NS047987-10

Title: Reward identity and value prediction errors differentially update task state representations in human orbitofrontal cortex and amygdala

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Abstract: Goal-directed behavior requires flexible neural representations of task structures, including associations between predictive events and expected outcomes. Recent studies have highlighted a critical role of the orbitofrontal cortex (OFC) in signaling these variables, which together comprise a task state. However, the specific parameters that define a given state representation in OFC, and the error signals that drive updating of state representations when task parameters change unexpectedly, are not known. To address these questions here we implemented a transreinforcer reversal learning task in which hungry human participants (N=23) chose between two visual conditioned stimuli to receive either high-intensity (i.e. high-value) or low-intensity (i.e. low value) versions of sweet or savory food odors (2 value x 2 identity) while undergoing functional magnetic resonance imaging (fMRI). Occasionally throughout the task, either the value of the expected outcome (but not its identity), or the identity of the expected outcome (but not its value) was changed, signaling a transition into a new task state. Analysis of the choice data revealed that participants reliably chose to smell high-intensity odors, and switched their choices accordingly when the value associations changed. These choices were well explained by a reinforcement learning (RL) model which was fitted to the behavioral data. Using multivoxel pattern analysis of the imaging data, we found that task states differing only in the identity of the outcomes associated with the cues, but not their values, could be decoded in the OFC. Conversely, task states differing only in which cues were associated with the high and low value outcomes, but not their identity, could be decoded in the amygdala. Intriguingly, by regressing outcome-evoked fMRI activity against estimates of prediction errors derived from the RL model, we observed signals related to errors in reward identity and reward value prediction in OFC and amygdala, respectively, and in the midbrain for both. Our findings demonstrate that distinct task state parameters are encoded differentially in the OFC and amygdala. They further raise the possibility that transitions between states rely on dopaminergic prediction error signals projecting from a common midbrain origin to either OFC or amygdala depending on which type of reward information is updated on a given trial.

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Nanosymposium

195. Corticolimbic Circuits in Decision Making

Location: 150B

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***195.11

**Topic: ***H.01. Animal Cognition and Behavior

Title: An acquired choice: Reduced corticostriatal excitability during delay-contingency learning steepens reward discounting

Authors: *M. R. CARR[1], M. J. N. BAELDE[2], Y. VAN MOURIK[2], T. S. HEISTEK[3], H. MANSVELDER[3], T. J. DE VRIES[2], T. PATTIJ[2]
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Abstract: We often encounter situations presenting two desirable alternatives, where we must evaluate whether it is worthwhile waiting for a larger pay-off. Both rodents and humans alike despise waiting, and quickly discount preference for a larger reward option as a function of the increasing delay they must endure until reinforcement. Rodent lesion studies have revealed the importance of the frontal-striatal-limbic circuitry in biasing reward preferences in the delayed reward task (DRT), a paradigm measuring delay-aversive choice impulsivity. Here, we alter circuit activity with a dual virus approach to target neurons sending projections from the dorsomedial Prefrontal Cortex (dmPFC), a major neuroanatomical input to the Nucleus Accumbens Core (NAcC). In these projection neurons we express both the inhibitory Kappa-Opioid (KORD) and excitatory human Muscarinic (hM3Dq) Designer Receptors, which are Exclusively Activated by Designer Drugs (DREADDs). Their pharmacologically inert Designer Drugs, SalvinorinB (SalB) and Clozapine-N-Oxide (CNO), respectively, are injected systemically at different time points to exert bidirectional control of neuronal excitability in the targeted cell populations. Inhibiting these corticostriatal pathways by SalB during reward-delay contingency learning impacts the development of discounting behaviour in rodents. Later at stable DRT performance, those rodents that had experienced corticostriatal hypoexcitability specifically during acquisition remained the steeper discounters of the larger reward. Later manipulations by SalB or CNO injection once the animals had established their large reward preferences did not appear to alter impulsive choice measures. These early findings suggest a role for dmPFC projections to the NAcC in establishing delay discounting behaviours following instrumental delay contingency learning, however appear less influential once the animal is well-trained in the task.

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Nanosymposium

196. Methods for Combined Analysis of Genetic Information

Location: 152B

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**Topic: ***I.01. Molecular, Biochemical, and Genetic Techniques

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Title: Enigma: Imaging & genetics of 18 brain diseases in 50,000 people worldwide

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Abstract: The ENIGMA Consortium (http://enigma.usc.edu) is an international consortium of over 900 scientists studying 18 brain diseases using neuroimaging, genetics and clinical data to answer questions about the brain over the human lifespan. Started in 2009, the Consortium grew to 340 institutions spanning 35 countries. Its 37 working groups published the largest imaging studies to date for 5 major disorders - major depression, bipolar disorder, schizophrenia, OCD, and ADHD. Additional working groups conduct global imaging studies of PTSD, addiction (including substance use disorder), anxiety disorders (including panic and generalized anxiety disorder), neurodevelopmental disorders (including autism spectrum disorders and 22q deletion syndrome), epilepsy, ataxia, stroke recovery, and Parkinson's disease. Here we explain how these working groups analyze brain MRI, diffusion MRI, and resting state fMRI, and coordinate hundreds of secondary projects relating brain metrics to cognition and behavior, and to common and rare genetic variation. ENIGMA's genome-wide association studies of MRI, DTI and EEG measures show overlap in genetic determination between specific imaging markers and schizophrenia, ADHD, Alzheimer's disease, and Parkinson's disease. ENIGMA studies normal brain variation and left-right hemisphere laterality on an unprecedented scale (20,000+ brain MRIs); ENIGMA-Plasticity conducts the largest GWAS to date of longitudinal brain measures, probing genomic factors that affect brain changes over time. We summarize ENIGMA's 3 areas of study - disease, imaging, and genetics - and how ENIGMA partners with genomics consortia to relate imaging and genetic information in neuroscience. New mathematical opportunities arise in genetic analyses of brain scans, including "image-wide genome-wide" searches, "connectome-wide genome-wide" searches, and genetic clustering of imaging traits and network metrics. ENIGMA's global analyses of 18 major diseases have revised current thinking on imaging correlates of psychiatric illness, and how these vary by sex, duration of illness, treatment, and with genetic risk. Cross-Disorder Working Groups now compare the neurobiology of diseases with overlapping characteristics, using MRI, GWAS, and functional MRI. We compare affective disorders to compulsivity/impulsivity disorders suggesting common and distinct patterns in imaging and genomics. ENIGMA is beginning to show how brain diseases inter-relate in terms of the brain systems and circuits affected, revealing factors that affect their emergence and progression in populations worldwide. [ENIGMA members are listed at enigma.usc.edu].

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Nanosymposium

196. Methods for Combined Analysis of Genetic Information

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Title: Gene expression associates with aspects of cortico-striatal networks in the human brain

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Abstract: The human striatum is connected to cortex through multiple functional pathways that process limbic, sensory, and multimodal information. Although the architecture of cortico-striatal networks is well characterized, relatively little is known about the molecular mechanisms supporting their organization. Here, using the Allen Institute's human brain transcriptional atlas, we demonstrate that spatial patterns of gene expression show strong correspondence to limbic and somato/motor cortico-striatal functional networks. Observed network-specific expression profiles were consistent across independent human datasets and evolutionarily conserved in non-human primates. Genes preferentially expressed within the limbic network (encompassing nucleus accumbens, orbital/ventromedial prefrontal cortex, and temporal pole) were related to neuronal ion channels, psychiatric illness, and the organization and function of cortical networks. These analyses indicate that gene expression patterns recapitulate the topography of distributed brain networks and provide novel insights into potential molecular mechanisms supporting cortico-striatal circuitry in health and disease.

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Nanosymposium

196. Methods for Combined Analysis of Genetic Information

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**Topic: ***I.01. Molecular, Biochemical, and Genetic Techniques

Support: MRC Grant MR/K020706/1
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Title: Genomic drivers of neuroimaging phenotypes in health and disease

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Abstract: Graph theoretical methods are increasingly being used to study biomedical problems at a systems level. In the brain, understanding the connectivity between brain regions at the macroscopic level is proving especially useful for characterizing distributed brain changes such as those taking place during development and ageing or in neurodevelopmental disorders such as schizophrenia. However developing principled prognostics and interventions will require linking these macroscopic brain markers to biological processes at the cellular and molecular scale. In this talk I will describe a novel framework for exploring associations between comprehensive maps of brain gene expression (from the Allen Institute's Human Brain Atlas) and network features of brain structure and function observed through MRI. I will first present some proof-of-concept studies for these methods in healthy volunteers. For example, we showed that highly connected hub regions of human functional brain networks also exhibit high expression levels of genes enriched for oxidative metabolism. This provides the first biological evidence for the influential hypothesis that long-distance connections in functional brain networks are energetically costly to maintain. In a second study, we identified a distinctive gene expression profile underpinning the consolidation of hub regions in structural brain networks during

adolescence. Interestingly, these results implicate a significant subset of the recently discovered risk genes for schizophrenia, suggesting that the same genes also play a key role in healthy adolescent changes in brain structure and potentially explaining why adolescence is a particularly vulnerable period for the onset of schizophrenia. I will then go on to discuss how this framework can be applied more directly to gain novel insights into the genomic underpinnings of a variety of psychiatric conditions, highlighting the challenges and opportunities that lie ahead.

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Nanosymposium

196. Methods for Combined Analysis of Genetic Information

Location: 152B

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**Topic: ***I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH MH046729
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Title: Neurotrophin-3 signaling in the dorsal amygdala decreases early-life anxious temperament in non-human primates

Authors: *A. S. FOX[1], T. SOUAIAIA[2], J. A. OLER[4], R. KOVNER[5], J. KIM[3], M. RIEDEL[6], E. FEKETE[5], P. H. ROSEBOOM[7], J. A. KNOWLES[2], N. H. KALIN[5]
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Abstract: Early-life dispositional anxiety is a risk factor for the later development of anxiety, depressive, and substance abuse disorders. Children with an extremely anxious temperament (AT), react to novelty with increased behavioral inhibition and increased levels of physiological arousal. Our group has extensively validated a nonhuman primate model of early-life AT, and identified the central nucleus of the amygdala (Ce) as a critical part of AT's neural substrates. Here, we leverage the nonhuman primate model of AT to uncover molecular substrates of AT

within the dorsal amygdala Ce-region using RNA-seq. Specifically, in 46 young rhesus monkeys (Macaca Mulatta) we combined RNA-seq of dorsal amygdala tissue with brain imaging and behavioral assessments to investigate the molecular underpinnings of AT in the primate. Using real-time MRI guided surgery and an AAV5 vector, we tested our RNA-seq derived hypothesis in 5 young rhesus monkeys.
RNA-seq identified many AT-related molecules, including both well-established and novel candidates. Interestingly, dorsal amygdala RNA-seq data demonstrated an inverse association between expression levels of specific neurotrophin receptor kinase 3 (NTRK3) exons and AT ($t=-2.76$, $p=0.009$). To test the involvement of the NTRK3 pathway, we overexpressed the ligand for the NTRK3 receptor, Neurotrophin-3 (NTF3), in the dorsal amygdala region. Results demonstrated the dorsal amygdala NTF3 overexpression to decrease early-life AT (Mann-Whitney=4.0, $p=0.047$).
Together, these data provide compelling evidence that activation of the NTF3/NTRK3 pathway is capable of decreasing anxiety in young primates, and take an important step toward understanding the molecular underpinnings of early-life AT that can guide the development of novel treatments to prevent the development of stress-related psychopathology.

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Nanosymposium

196. Methods for Combined Analysis of Genetic Information

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Topic: *I.01. Molecular, Biochemical, and Genetic Techniques

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NIH R01 DA17305

Title: Genome-wide association study of conduct disorder and extension to emotional brain function

Authors: ***C. E. CAREY**[1], A. AGRAWAL[2], B. ZHANG[3], N. VAKKALAGADDA[1], E. DRABANT CONLEY[4], A. R. HARIRI[5], E. C. NELSON[2], R. BOGDAN[1]
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Abstract: Conduct disorder (CD) is a moderately heritable childhood externalizing disorder associated with substantial personal and societal burden. Here, we sought to examine its molecular genetic architecture and neural mechanisms that may underlie associations between genetic risk and disorder expression. We performed a genome-wide association study (GWAS) of CD among Australians of European ancestry who completed the Comorbidity and Trauma Study (n_{cases}=680, $n_{controls}$=995). We then tested genetic risk factors identified from the GWAS for association with self-reported psychopathy as well as regional differences in brain activity to emotional facial expressions in an independent sample of 406 non-Hispanic Caucasian U.S. college students.The major A allele of the intergenic rs12536973 polymorphism was associated with increased risk for CD at genome-wide levels of significance, and gene-based analyses revealed an association with *GOLM1*. Annotation revealed that rs12536973 is an eQTL for *PHF14* and may differentially affect transcription binding. In the independent college sample, rs12536973 genotype and CD polygenic risk scores (PRS) derived from our GWAS were associated with variability in psychopathy scores. Further, higher CD PRS were associated with decreased left anterior insula activity to emotional faces in whole-brain analyses. Post hoc conjunction analyses showed that both CD PRS and self-reported psychopathy were associated with reduced activation in overlapping clusters not only within bilateral anterior insula but also supramarginal gyri. Collectively, these results provide insight into the genetic architecture of CD risk and suggest that blunted neural responses to affective social stimuli in regions linked to empathy may represent a neural mechanism through which genomic risk may promote its phenotypic expression.

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Nanosymposium

196. Methods for Combined Analysis of Genetic Information

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Title: A novel polygenic score for molecular vulnerability to depression modulates amygdala reactivity and anhedonic symptoms

Authors: *Y. S. NIKOLOVA[1], A. BAKHT[1], L. FRENCH[1], A. R. HARIRI[2], E. SIBILLE[3]
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Abstract: Background: Neuroimaging studies have associated major depressive disorder (MDD) with dysregulation of the corticolimbic system, within which the amygdala serves as a hub. A recent meta-analysis of case-control postmortem gene expression studies has identified consistent depression-related changes in the corticolimbic transcriptome. Here we hypothesized that subtle genetically driven shifts toward a more depression-like corticolimbic transcriptome would modulate corticolimbic function in vivo. **Methods:** We focused our analysis on a previously published list of 566 genes, the expression of which is reliably associated with MDD across 3 corticolimbic regions (amygdala, subgenual ACC and dlPFC). We used PrediXcan with cis-eQTL SNPs generated from the "cortex" tissue samples in the Genotype-Tissue Expression (GTEx) project to impute brain-level expression of 106 genes in participants of the Duke Neurogenetics Study. Imputed gene expression values were summed into a weighted polygenic score (PS), which was then mapped onto amygdala activity assayed with fMRI. We focused our analysis on Non-Hispanic Caucasians (n=483, 228 men, mean age 19.78±1.23) to match the predominant racial and ethnic background of the postmortem datasets. **Results:** While there was no main effect of PS on amygdala reactivity, a significant sex-by-PS interaction emerged ($p<0.04$) wherein, in men only, higher PS was associated with relatively blunted reactivity to novel, neutral facial expressions ($R^2=0.026$, $p=0.0144$). This PS-modulated amygdala reactivity, in turn, mapped onto increased anhedonic symptoms in men as well as women ($p<0.02$). **Discussion:** Our results suggest that a peripherally indexed genetic shift toward a depression-like corticolimbic transcriptome is associated with relatively blunted amygdala reactivity to novel, neutral social stimuli and associated anhedonic symptoms, a pattern that may be specific to men. Our findings suggest a putative sex-specific pathway of genetic risk for depression.

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Nanosymposium

196. Methods for Combined Analysis of Genetic Information

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Support: James S. McDonnell Foundation 220020467

Title: Altered human brain gene expression correspondence with resting state brain activity in autism

Authors: *G. KONOPKA[1], S. BERTO[1], Y. FETAHI[1], A. KULKARNI[1], M. J. GANDAL[2], A. MONTILLO[1]
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Abstract: Genetic studies have identified specific genomic loci associated either with cognition in general or with cognitive disorders such as autism or schizophrenia. However, the functional consequences of these genetic variants remain mostly to be determined. In particular, the normal expression and function of these identified genes in the human brain and whether these patterns are altered in cognitive diseases is an ongoing field of inquiry. We have shown that post-mortem human brain gene expression can be harnessed to provide insight into active human brain states. There is direct correspondence between human brain gene expression and resting-state brain activity as assessed by fMRI. Unanswered questions remain though such as whether these correlations change in individuals who have cognitive disorders. Here, we investigate whether there are genes that have differential correlation with human brain activity in the resting state in patients with autism by correlating post-mortem RNA-sequencing data with fMRI data. We identify differential correlation of gene expression with brain activity in autism samples compared to matched controls, strengthening the importance of altered functional connectivity in autism pathophysiology as a consequence of disrupted gene expression networks. These data provide functional confirmation of the genetic basis of cognition and cognitive disorders.

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Nanosymposium

196. Methods for Combined Analysis of Genetic Information

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Title: Intrabody-dependent activation of cell-specific gene expression in CNS

Authors: *A. VENKATARAMAN[1], *A. VENKATARAMAN[1], E. CAMPBELL[2], A. KOIDE[3], S. KOIDE[3], S. ANDERSON[2], S. BLACKSHAW[1]
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Abstract: Individual CNS cell types can be labeled and manipulated using transgenic and knock-in animals, but this approach, is slow, expensive, and limited in scope. Furthermore, it cannot be applied to higher primates or humans. We aim to develop an approach that will allow the selective targeting of individual CNS cell types in wildtype individuals, from a range of mammalian species. This is a modification of a technology known as CRE-DOG that uses pairs of camelid nanobodies to scaffold assembly of functional split Cre recombinase in the presence of GFP. We will use this general approach to target endogenous cell subtype-specific transcription factors using Fn3-based recombinant monobodies, which can be rapidly produced and screened in vitro, and use these to induce assembly of split Cre and Dre recombinase. These reagents can then be used to induce cell-specific activation of expression of reporter and effector constructs delivered by electroporation or viral vector. As proof of principle for this approach, we first used Fn3-based pairs of anti-GFP monobodies to scaffold assembly of split Cre in vivo. We will next raise pairs of monobodies against cell-specific retinal transcription factors, and demonstrate that these can scaffold assembly of functional Cre recombinase. Next, we will develop expression constructs that allow Cre-dependent expression of these reagents to avoid potential disruptive effects of monobody expression. Following this, we will demonstrate that these reagents direct cell-specific Cre activation in neonatal retina. Finally, if proven successful, we will generate a toolbox of reagents that will enable selective activation of reporter and effector constructs in the major cell types of retina and cerebral cortex, in both mice and humans.

Disclosures: A. Venkataraman: None. **E. Campbell:** None. **A. Koide:** None. **S. Koide:** None. **S. Anderson:** None. **S. Blackshaw:** None.

Nanosymposium

196. Methods for Combined Analysis of Genetic Information

Location: 152B

**Time: ***Sunday, November 12, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***196.09

**Topic: ***I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIMH IRP

Title: Human brain and skull shape is related to percentage of Neanderthal-derived DNA

Authors: *M. D. GREGORY[1], J. S. KIPPENHAN[2], D. P. EISENBERG[3], P. D. KOHN[1], D. DICKINSON[1], V. S. MATTAY[5], Q. CHEN[5], D. R. WEINBERGER[5], Z. S. SAAD[6], K. F. BERMAN[4]
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Abstract: Before Neanderthals disappeared from the fossil record approximately 40,000 years ago, admixture occurred between this archaic species and the ancestors of present-day humans. The result of this gene flow persists through Neanderthal-derived variants that survive in modern human DNA; however, the neural implications of this inheritance are uncertain. Here, using MRI in a large cohort of healthy individuals of European-descent, we investigated whether the percentage of Neanderthal-derived polymorphisms carried in living humans is related to cranial and brain morphology. We collected T1-weighted MRI scans and genome-wide SNP data on 221 Caucasian individuals. After imputation, we calculated the load of Neanderthal-derived genetic variants ("NeanderScore") in each individual. First, to test our in vivo methods against known fossil remains, MRI data were used to create 3D-skull surfaces using an in-house pipeline. Next, gray-matter volume, white-matter volume, sulcal depth and gyrification index maps were derived. NeanderScore was correlated with each measure to determine brain and skull regions associated with Neanderthal-derived SNP load. Results were thresholded at $p<0.05$ FWE-corrected for multiple comparisons. The first component from a principal components analysis of all significant brain and skull measures was used as a quantitative trait in a genome-wide association study of Neanderthal-derived variants to identify the shared genetic influences on these findings. Examining the skulls of living humans, we found that greater NeanderScore was associated with skull shapes resembling those of Neanderthal cranial remains, particularly in occipital and parietal bones. Additionally, we found convergent NeanderScore-related features in the brain (gray-matter volume, white-matter volume, sulcal depth, and gyrification index), which localized to the visual cortex and intraparietal sulcus, directly underlying the region that showed maximal skull shape change. A GWAS examination of all Neanderthal-derived variants identified a 53kb LD-block of chromosome 10 (overlapping the *GPR26* gene; $p<0.013$, Bonferroni-corrected) that was significantly associated with the shared variance of the brain and skull findings. This work provides insights into ancestral human neurobiology and suggests that Neanderthal-derived genetic variation is neurologically functional in the contemporary population. The findings indicate that this inheritance is particularly implicated in the visual system. The *GPR26* gene, which has functions in affective and energy homeostatic functions, may have been particularly central to these evolutionary changes.

Disclosures: M.D. Gregory: None. **J.S. Kippenhan:** None. **D.P. Eisenberg:** None. **P.D. Kohn:** None. **D. Dickinson:** None. **V.S. Mattay:** None. **Q. Chen:** None. **D.R. Weinberger:** None. **Z.S. Saad:** None. **K.F. Berman:** None.

Nanosymposium

271. Cellular Mechanisms in Neurogenesis

Location: 152B

**Time: ***Monday, November 13, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***271.01

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: NSFC Grant 81271261

Title: ADAM10-initiated intramembrane proteolysis controls radial migration of cortical neurons

Authors: *X. CHENG[1], P.-F. LI[2], Z.-Q. XIONG[2]
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Abstract: Membrane signal paradigms are essential strategies that migrating neurons converge extracellular stimuli thereby formulating instructive orders to directing internal molecular machinery. Mutations of associated genes usually cause severe migration defects. Regulated intramembrane proteolysis (RIP) is one of the critical paradigms that regulate migration, whereas its function and underlying mechanisms remain largely unknown. We identified ADAM10-initiated RIP as a critical regulator of cortical neuron migration,by cleaving Notch to release its intracellular domain(NICD) . Moreover, ADAM10 deficiency led to reduced neuronal motility and disrupted microtubule (MT) structure, which were associated with downregulated expression of acetylated tubulin and MT-associated proteins. Specifically, the NICD/RBPJ complex bound directly to the promoter, and regulated the neuronal expression level of doublecortin (DCX), a modulator of the MT cytoskeleton. Furthermore, giving the many substrate protein that would be cleaved by ADAM10-initiated RIP, unveiling the versatile downstream effective mechanisms is crucial to understand how RIP acts in regulating neuron migration.We found that ADAM10 initiated RIP of Robo2 in cortical neurons release the ectodomain into the extracellular space. Interestingly, the function of Robo2 in regulating neuron migration did not rely on the receptor function of Robo2, but instead depended on the soluble Robo2-ECD, which might binds to another membrane partner, thereby controlling neuron migration. This effective mechanism is different from that of ADAM10-initiated RIP of Notch, which releases NICD into cytosol and NICD in turn translocates into the nucleus. Our work expands the conceptual frame of membrane signal network that regulates the neuron migration of cerebral cortex.

Disclosures: X. Cheng: None. **P. Li:** None. **Z. Xiong:** None.

Nanosymposium

271. Cellular Mechanisms in Neurogenesis

Location: 152B

**Time: ***Monday, November 13, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***271.02

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: FCT MDPhD Scholarship PD/BD/113766/2015

Title: Differential roles for dynein light intermediate chain orthologues in neocortex development

Authors: *J. C. GONCALVES[1,2,3], R. B. VALLEE[1]
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Abstract: Cytoplasmic dynein is the major retrograde microtubule motor and participates in several aspects of neocortex development. These include Radial Glial Progenitor (RGP) cell cycle-dependent interkinetic nuclear migration (INM) and division, the multipolar-to-bipolar transition of newborn neurons, axon extension, and neuronal migration to the cortical plate (CP). The dynein light intermediate chains (LICs) are dynein cargo-binding subunits. The relative roles of the two LIC genes, LIC1 and LIC2, are not well understood in general, and we wished to test whether they play overlapping or distinct roles *in vivo*. To address these questions we used *in utero* electroporation in E16 rat embryos injected intracerebrally with LIC1 and/or LIC2 shRNAs. We analyzed the brain tissue subsequently by fixed and live imaging. LIC1 RNAi led to a marked decrease in mitotic RGP cells, though little to no effect was observed with LIC2 depletion. Furthermore, RNAi for LIC1 or LIC1+LIC2, but not for LIC2 alone, strongly interfered with apical INM. Co-expression of the nuclear envelope dynein recruitment factor and known LIC interactor, BicD2, which rescues defects in other apical INM genes (Hu et al 2013, Cell; Doobin et al 2016; Nat. Commun.), had no effect in this case. LIC1 RNAi also arrested postmitotic multipolar neurons in the Sub Ventricular Zone (SVZ) and lower Intermediate Zone (IZ), and the number of bipolar migrating neurons in the CP was markedly reduced. Moreover, expression of truncated LIC1, lacking the cargo binding domain, caused to an accumulation of cells in the SVZ/IZ, highlighting the importance of cargo binding function of LIC1 for the progression of the newborn neurons to the CP. In contrast, there was little apparent effect of LIC2 depletion in the conversion of multipolar to bipolar neurons, though the number of neurons reaching the CP upper region was reduced. Co-expression of RNAi-insensitive LIC1 partially rescued the neuronal migration phenotype. Notably, cross rescue experiments with exogenous LIC2 was similar to LIC1 rescue. Despite the greater severity of LIC1 *vs.* LIC2 knockdown effects, the ratio of LIC1:LIC2 protein levels was unaltered in during the late embryonic period

(E16-E20), and even in the adult rat. Overall, our data suggest that LIC1 and LIC2 have distinct roles during brain development. LIC1 is important for apical nuclear migration in RGP cells and for the multipolar to bipolar transition of post-mitotic neurons in the SVZ/IZ, while LIC2 caused an accumulation of cells in the lower CP.

Disclosures: J.C. Goncalves: None. **R.B. Vallee:** None.

Nanosymposium

271. Cellular Mechanisms in Neurogenesis

Location: 152B

**Time: ***Monday, November 13, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***271.03

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: FWO G0A0513
IAP-P6/31 and P7/10
IWT O&O JJDDIPS

Title: Beta1 integrins control microglial migration in an age-specific manner during embryonic neurodevelopment

Authors: *B. BRONE[1], S. M. T. SMOLDERS[1], N. SWINNEN[1], S. KESSELS[1], K. ARNOUTS[1], S. SMOLDERS[1], B. LE BRAS[2], J.-M. RIGO[1], P. LEGENDRE[2]
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Abstract: Microglia, the brain phagocytes, take part in brain development and homeostasis. They derive from primitive myeloid progenitors that originate in the yolk sac and colonize the brain mainly through intensive migration. During cortical development, the microglial migration speed declines, which suggests a change in interaction with the microenvironment during embryogenesis. However, the mechanisms allowing dispersion within the parenchyma are unclear. Recent evidence points to a functional role of microglia-fibronectin interactions for migration. α5β1 integrins contribute to the microglia-fibronectin interactions during migration in the developing neocortex on embryonic day (E) 13.5, 15.5 and 17.5. Using blocking antibodies in 2-photon time-lapse microscopy on acute brain slices, we reveal a surprising age-specific regulation of α5β1 function during embryonic microglial cortex colonization. At E13.5, α5β1 blockage inhibits while from E15.5, it promotes migration. α5β1 integrin does however not seem to play a role in mediating contact between microglia and blood vessels. General β1 blockage, targeting microglial interactions with extracellular matrix molecules such as laminin and

vitronectin besides fibronectin, suggests opposing roles for other integrin subtypes in mediating migration from E15.5 onwards.

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Nanosymposium

271. Cellular Mechanisms in Neurogenesis

Location: 152B

**Time: ***Monday, November 13, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***271.04

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: USUHS RO709J14

Title: KCC2 manipulation alters migration of interneurons

Authors: F. T. DJANKPA[1], M. CHATTERJEE[2], *S. L. JULIANO[3]
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Abstract: KCC2 is a brain specific chloride-potassium cotransporter that affects development of the cerebral cortex, including aspects of neuronal migration and cellular maturation and differentiation. KCC2 modulates chloride homeostasis by influencing the action of GABA from depolarizing in young neurons to hyperpolarizing in mature neurons. The polarity switch contributes to guidance cues that modulate termination of neuronal migration. KCC2 expression during the migration of interneurons correlates with the ability of these cells to respond to GABA as a stop signal, suggesting that KCC2 alters GABA from acting as a motogen to becoming a signal that slows migrating neurons and causes them to begin differentiating. Manipulation of KCC2 expression early in development affects various aspects of migrating neurons including their speed and exploratory activity. Bisphenol A (BPA) is an estrogenic chemical used in making polycarbonate and epoxy resins lining food and beverage cans and bottles and also influences KCC2 expression. Emerging evidence indicates that BPA is a potential gene toxicant during embryonic development. Here we show (using western blot) that a 50-100nM treatment of BPA on P0 ferret organotypic slice cultures decreases KCC2 protein levels significantly. Time-lapse video imaging analysis of organotypic slices treated with 50-100nM of BPA shows a significant increase in the speed and step size of migrating neurons leaving the ganglionic eminence at P0 in ferrets compared to control. Similarly, migrating interneurons treated with BPA show abnormal exploratory behavior compared with controls. These findings continue to implicate KCC2 in mediating migratory behavior of neurons moving

into the neocortex. Our findings also further expose the effect of environmental toxins on brain development and their implication in the pathogenesis of neurodevelopmental disorders.

Disclosures: F.T. Djankpa: None. **M. Chatterjee:** None. **S.L. Juliano:** None.

Nanosymposium

271. Cellular Mechanisms in Neurogenesis

Location: 152B

**Time: ***Monday, November 13, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***271.05

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: NRF-CRP 002-082
NMRC/CBRG/0094/2015
MOE2015-T2-1-022

Title: Rab23 regulates radial migration of projection neurons via PDGFRα-mediated expression of N-cadherin

Authors: *C. HOR[1,2], E. L. K. GOH[1,2,3,4]
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Abstract: ABSTRACT
Radial migration of cortical projection neurons is a prerequisite for shaping a distinct multi-layered cerebral cortex during mammalian corticogenesis. Members of Rab GTPases family were reported to regulate radial migration. Here, *in vivo* conditional-knockout or *in utero* knockdown (KD) of Rab23 in mice neocortex causes aberrant polarity and halted migration of cortical projection neurons. Further investigation of underlying mechanism reveals down-regulation of N-cadherin in the Rab23-deficient neurons, which is a cell adhesion protein previously known to modulate radial migration (Shikanai et al., 2011). Interestingly, pharmacological inhibition of ERK1/2 also decreases the expression of N-cadherin, implicating an upstream effect of ERK1/2 on N-cadherin and also suggesting a link between Rab23 and ERK1/2. Further biochemical studies showed that silencing of Rab23 impedes activation of ERK1/2 via perturbed PDGFRα signaling. Restoration of the expression of Rab23 or N-cadherin in Rab23-KD neurons could reverse neuron migration defects, indicating that Rab23 modulates migration through N-cadherin. These studies suggest that cortical neuron migration is mediated by a molecular hierarchy downstream of Rab23 via PDGFRα signaling pathway.

Disclosures: **E.L.K. Goh:** A. Employment/Salary (full or part-time):; Duke-NUS Medical School.

Nanosymposium

271. Cellular Mechanisms in Neurogenesis

Location: 152B

Time: *Monday, November 13, 2017, 8:00 AM - 9:45 AM

Presentation Number: *271.06

Topic: *A.01. Neurogenesis and Gliogenesis

Support: DAAD Doctoral scholarship
DFG Heisenberg Program BL767/2-1
Maria von Linden Program, University of Bonn
BONFOR, Medical Faculty, University of Bonn

Title: Molecular mechanisms underlying migration of midbrain dopaminergic neuronal subpopulations in the developing brain

Authors: ***A. R. VASWANI**[1], P. MOCELLIN[1], M. K. SCHWARZ[2], H. FRIED[3], S. BLAESS[1]
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Abstract: Midbrain dopaminergic neurons (MbDNs) are involved in the regulation of voluntary movement, reward behavior and cognitive processes. MbDNs are generated from the floor plate of the ventral midbrain from where they migrate to form the substantia nigra (SN) and ventral tegmental area (VTA). Precursors of VTA MbDNs migrate radially from the floor plate, while those that form the SN migrate first radially and then tangentially to take up lateral positions. As they migrate, MbDNs simultaneously start to extend their axonal projections towards their forebrain targets. The molecular mechanisms that regulate MbDN migratory behavior and initial axonal outgrowth are not well understood. We are investigating the role of the Reelin signaling pathway in these processes. Reelin is an extracellular matrix protein regulating neuronal migration and morphology in several brain regions. Reelin binds to its receptors ApoER2 and VLDLR, activating the downstream intracellular adaptor protein disabled 1 (Dab1). To examine the role of Reelin signaling in MbDN migration, we generated mouse models in which Dab1 is conditionally inactivated in differentiated MbDNs (Dab1 cko). In Dab1 cko brains, differentiated MbDNs are medially clustered and fail to migrate to the SN, a phenotype similar to the one observed in Dab1 null mice, indicating a direct requirement for Reelin signaling in MbDN migration. To investigate how the loss of Dab1 affects the cellular dynamics of migrating

MbDNs and their forebrain projections, we labeled precursors of the SN in wild-type or Dab1 null embryos in a mosaic manner using genetic fate-mapping. By combining time-lapse imaging in organotypic slices, and imaging of the developing dopaminergic system in cleared whole-mount brains, we monitor the morphology, process orientation and axonal projections of the fluorescently labeled MbDNs. Analysis of 4D datasets of migrating MbDNs shows that, in the absence of Reelin signaling, cells spend more time at rest, have aberrant orientations and abnormally long leading processes. We will present the imaging techniques, data analysis methods and results that we have established in time-lapse imaging of organotypic slices and in 3D visualization of the developing dopaminergic system.

Disclosures: A.R. Vaswani: None. **P. Mocellin:** None. **M.K. Schwarz:** None. **H. Fried:** None. **S. Blaess:** None.

Nanosymposium

271. Cellular Mechanisms in Neurogenesis

Location: 152B

**Time: ***Monday, November 13, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***271.07

**Topic: ***A.01. Neurogenesis and Gliogenesis

Title: Heterogeneity of glial progenitors in the developing cortex revealed by single cell RNA sequencing

Authors: *R. Q. LU[1], J. WANG[1,2]
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Abstract: The major glial cell types in the mammalian cerebral cortex, oligodendrocytes and astrocytes, are critical for normal brain functions including axon ensheathment, synaptogenesis and neurotransmission. However, the identity of the glial progenitors and their developmental potentials are not fully understood. Here, we use single-cell RNA sequencing to characterize molecular identities of glial cells in the postnatal mouse cortex. Single cell population analysis and genetic tracing studies indicate that the glial progenitor cells have a potential to give rise neuroblasts, and this capacity is a stage-dependent. We identify a rare population of bipotent progenitors that may give rise to oligodendrocytes and neuroblasts. Our findings further uncover unique driving networks for astrocyte and oligodendrocyte development. Thus, our data reveal the heterogeneity of glial progenitor cells and identify previously unrecognized bipotential progenitors in the developing cortex.

Disclosures: R.Q. Lu: None. **J. Wang:** None.

Nanosymposium

272. Postnatal Neurogenesis and Stem Cell Functions

Location: 146C

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***272.01

**Topic: ***A.02. Postnatal Neurogenesis

Support: This study was supported by the Janet and Edward Gilda Charitable Foundation and in part by the Department of Veterans Affairs

Title: Regenerative capacity of adult mouse brain

Authors: M. V. SEMENOV[1], K. SMITH[1], O. L. BORDIUK[1], P. J. MORIN[1], *J. M. WELLS[2]
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Abstract: Cell death in the mouse adult brain is observed among neurons and glial, microglial and blood vessel cells. At the same time, the brain has been shown to have an intrinsic ability to replace these lost cells. In our study we evaluated the regenerative capacity of the adult mouse brain and how it changes in the mouse from 1 month old to 2.5 years old. We developed a technique that allows us to count and map the location of all proliferating cells in the entire brain of adult mice. Next we identified neurogenic proliferative zones in the mouse brain using doublecortin immunostaining. We found that neurogenesis occurs at two locations in the mouse brain. The larger area we define as the main proliferative zone (MPZ). This zone includes the lateral walls of the lateral ventricles, often called subventricular zone. The smaller one corresponds to the subgranular zone (SGZ) in the dentate gyrus of the hippocampus. Next we classified proliferating cells into 3 categories based on their location in the MPZ, SGZ and the parts of the brain outside of neurogenic zones. We found that the number of proliferating cells in the neurogenic zones progressively decreases as the mouse ages. The extent of this decrease is about 15-times in the MPZ and even greater in the SGZ where it is about 64-times. Previously it was shown that with an increase in age neuronal losses increase. At the same time, the brain's ability to produce new neurons appears to be decreasing. One might speculate that this misbalance could be a contributing factor for a cognitive decline in aged mice. Unlike neural progenitors, the number of cells that proliferate outside of neurogenic zones remains fairly stable from the age of 2 months to the age of 2.5 years showing that the rate of replacement of non-neural cells such as cells of blood vessels and microglia remains at the same level during the entire mouse lifespan. In summary, our data show that the activities of stem cells in the MPZ, SGZ and areas outside of neurogenic zones change differently as the mouse ages indicating that their age-dependent activity might be regulated by different mechanisms.

Disclosures: M.V. Semenov: None. **K. Smith:** None. **O.L. Bordiuk:** None. **P.J. Morin:** None. **J.M. Wells:** None.

Nanosymposium

272. Postnatal Neurogenesis and Stem Cell Functions

Location: 146C

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***272.02

**Topic: ***A.02. Postnatal Neurogenesis

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John G. Bowes Research Fund
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NSFC 31630032

Title: Neurogenesis in the human hippocampus declines sharply during infancy to extremely low levels in children and undetectable levels in the adult

Authors: *S. F. SORRELLS[1], M. F. PAREDES[2], A. CEBRIAN-SILLA[5], K. SANDOVAL[1], D. QI[6], K. KELLEY[1], D. JAMES[1], S. MAYER[3], J. W. CHANG[7], E. F. CHANG[1], K. I. AUGUSTE[1], A. J. GUTIERREZ MARTIN[8], A. R. KRIEGSTEIN[3], G. W. MATHERN[7], M. C. OLDHAM[1], E. J. HUANG[4], J. M. GARCIA-VERDUGO[5], Z. YANG[6], A. ALVAREZ-BUYLLA[3]
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Abstract: In many vertebrate species, new neurons continue to be produced in the adult hippocampus, a region of the brain important for learning and memory. In rodents, adult neurogenesis is increased by environmental enrichment, exercise, and seizures but decreased in animal models of depression and by chronic stress or inflammation. It has been suggested that adult neurogenesis also continues in humans to a similar or possibly even greater extent; however there are very few histological studies in humans. In this study we examined the development of the human fetal and infant hippocampus to look for dividing neural precursors in the dentate neuroepithelium, hilus and granule cell layer (GCL). We found that unlike in the rodent, a proliferative population of cells did not coalesce to form a neurogenic niche in the human sub-granular zone (SGZ). Instead, cells expressing progenitor markers or Ki67 were widely distributed throughout the hilus, GCL, and molecular layer and decreased sharply in number during the first month of postnatal life. During the first year of life, cells expressing

doublecortin (DCX) and polysialyated neural cell adhesion molecule (PSA-NCAM) were present in the hilus and GCL, but these cells were not dividing and diminished in number during childhood. We found only a few rare DCX+PSA-NCAM+ cells at 13 years of age, but in adults (between 18 and 77 years) DCX+PSA-NCAM+ cells were not present in the hippocampus. These results indicate that the GCL in humans forms during fetal development; that a proliferative SGZ does not coalesce in the human hippocampus either during gestation or early infancy; the immature neurons in this region disappear during childhood; and adult hippocampal neurogenesis in humans is either extremely rare or non-existent.

Disclosures: **S.F. Sorrells:** None. **M.F. Paredes:** None. **A. Cebrian-Silla:** None. **K. Sandoval:** None. **D. Qi:** None. **K. Kelley:** None. **D. James:** None. **S. Mayer:** None. **J.W. Chang:** None. **E.F. Chang:** None. **K.I. Auguste:** None. **A.J. Gutierrez Martin:** None. **A.R. Kriegstein:** F. Consulting Fees (e.g., advisory boards); Neurona Therapeutics. **G.W. Mathern:** None. **M.C. Oldham:** None. **E.J. Huang:** None. **J.M. Garcia-Verdugo:** None. **Z. Yang:** None. **A. Alvarez-Buylla:** F. Consulting Fees (e.g., advisory boards); Neurona Therapeutics.

Nanosymposium

272. Postnatal Neurogenesis and Stem Cell Functions

Location: 146C

Time: *Monday, November 13, 2017, 8:00 AM - 10:00 AM

Presentation Number: *272.03

Topic: *A.02. Postnatal Neurogenesis

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RSCF 17-15-01426

Title: Complex 4D patterns of cell proliferation in the whole brain revealed by WM-CLICK

Authors: *A. LAZUTKIN[1,2,3,4], S. SHUVAEV[1,3], I. DORONIN[1], E. AMELCHENKO[4], K. ANOKHIN[1,2,5], G. ENIKOLOPOV[1,3,4]
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Abstract: In the developing and adult nervous system neural stem and progenitor cells divide in restricted regions and migrate along intricate trajectories to reach distant areas of the brain. Efficient visualization, quantification, and analysis of cell proliferation in whole brain may

reveal dynamics and hidden patterns of neurogenesis during development, aging, disease, or in response to therapies.
We developed new histological techniques for 3D visualization and analysis of proliferating cells in the whole brain of developing and adult mice, based on labeling the dividing cells with 5-ethynyl-2'-deoxyuridine (EdU) and detecting them with fluorescent azide using whole-mount click-reaction (WM-CLICK). We also developed a novel method for automatic volume warping and morphing. We applied these techniques, combined with light-sheet microscopy and two-photon tomography for visualizing patterns of cell division in the mouse brain.
We observed three proliferation/migration streams in the subventricular zone (SVZ) of adult mouse brain - lateral, medial and ventral which merge together into a common rostral migration stream. We also observed profound changes in the patterns of cell division at the perinatal age in two brain regions - SVZ, where streams are gradually formed during development, and cerebellum, where we observed heterochrony in proliferation intensity in the lateral and medial parts. The resulting data can be presented as pseudo time-lapse movie, thus allowing 4D representation of the dynamics of developmental changes in cell division and neurogenesis.

Disclosures: **A. Lazutkin:** None. **S. Shuvaev:** None. **I. Doronin:** None. **E. Amelchenko:** None. **K. Anokhin:** None. **G. Enikolopov:** None.

Nanosymposium

272. Postnatal Neurogenesis and Stem Cell Functions

Location: 146C

Time: *Monday, November 13, 2017, 8:00 AM - 10:00 AM

Presentation Number: *272.04

Topic: *A.02. Postnatal Neurogenesis

Support: Whithall Foundation
NIH NINDS R15NS096562

Title: Neonatal subventricular zone neural stem cells release extracellular vesicles that function as a non-canonical microglial morphogen

Authors: ***D. M. FELICIANO**[1], M. MORTON[2], V. NECKLES[2], C. SELUZICKI[2]
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Abstract: Subventricular zone (SVZ) neural stem cells (NSCs) are the cornerstone of the perinatal neurogenic niche. The anatomical limits of the niche are defined by the NSC apical projecting process which projects to the lateral ventricles and a basal projecting process that terminates at blood vessels. Microglia are resident immune cells that are enriched within the perinatal neurogenic niche, and although they regulate NSCs, there are few studies that

demonstrate bi-directional communication. Extracellular vesicles (EVs) classified as exosomes and ectosomes are particles that are proposed to transfer miRNA and proteins from donor cells to recipient cells. EVs are proposed to carry neurogenic, angiogenic, and immuno-modulatory molecules. Considerable debate exists regarding whether EVs represent a novel mode of communication or whether they are cellular debris. Here, evidence is provided that the EV tetraspanin protein CD9 is expressed within a subpopulation of perinatal SVZ NSCs. Neonatal CD9 is localized to the soma of NSCs but also to regions of the apical and basal projecting processes. Neonatal electroporated NSCs engineered to express fluorescent CD9 release particles within the SVZ. The fluorescent particles are subsequently cleared. Transplanted EVs are selectively transferred to SVZ microglia and heterchronic EV transplantations shift the appearance and timing of microglia within the SVZ. These results demonstrate a novel mechanism by which EVs function as a morphogenic cue for microglia within the neonatal brain.

Disclosures: D.M. Feliciano: None. **M. Morton:** None. **V. Neckles:** None. **C. Seluzicki:** None.

Nanosymposium

272. Postnatal Neurogenesis and Stem Cell Functions

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**Topic: ***A.02. Postnatal Neurogenesis

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NIH Grant EY025638
NIH Grant EY023665
RPB Wasserman Merit Award

Title: Apical cell-cell adhesions reconcile symmetry and asymmetry in zebrafish neurulation

Authors: *X. WEI, C. GUO, J. ZOU
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Abstract: The symmetric tissues and body plans of animals are paradoxically constructed with asymmetric cells. To understand how the yin-yang duality of symmetry and asymmetry are reconciled, we asked whether or not apical polarity proteins orchestrate mirror-symmetric neural tube development in zebrafish by hierarchically modulating apical cell-cell adhesions. We found that apical polarity proteins localize by a pioneer-intermediate-terminal order. Pioneer proteins establish the mirror symmetry of the neural rod by initiating two distinct types of apical adhesions: The parallel apical adhesions (PAAs) cohere cells of parallel orientation, and the

novel opposing apical adhesions (OAAs) cohere cells of opposing orientation. Subsequently, intermediate proteins selectively enhance the PAAs when the OAAs dissolve by endocytosis. Finally, terminal proteins inflate the neural tube by generating osmotic pressure. Our findings suggest a general mechanism to construct mirror symmetric tissues: Tissue symmetry can be automatically established by simply aligning cellular asymmetry opposingly via adhesions.

Disclosures: **X. Wei:** None. **C. Guo:** None. **J. Zou:** None.

Nanosymposium

272. Postnatal Neurogenesis and Stem Cell Functions

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Presentation Number: *272.06

Topic: *A.02. Postnatal Neurogenesis

Support: KAKENHI JP 00376534
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KAKENHI-PROJECT-26290003

Title: Clonal analysis of newborn neurons in the adult telencephalon in medaka fish

Authors: ***Y. ISOE**[1], R. NAKAMURA[2], T. OKUYAMA[3], Y. KAMEI[4], S. NONAKA[4], T. KUBO[2], H. TAKEDA[2], H. TAKEUCHI[5]
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Abstract: In vertebrates, the basic brain architectures are organized during embryonic development. The brain growth spurt occurs postnatally, accompanied by the rapid increases in cell number and brain volume. It remains unknown, however, how postnatal (post-hatch) neurogenesis contributes to the construction of the adult brain structures, such as sub-divisions (anatomical regions) of the telencephalon. To address this subject, we have been focusing on medaka fish (*Oryzias latipes*), because medaka fish shows prominent post-hatch brain growth and the sub-divisions (anatomical regions) of the telencephalon can be easily observed. To visualize newborn neurons in the brain after hatch, we prepared transgenic medaka fish (HuC:loxP-DsRed-loxP-GFP) that HuC promoter drives specifically in newborn neurons. We induced stochastic Cre recombination by micro-injection of Cre mRNA into the one cell stage embryos and found that a subset of clonally-related cells (a clonal unit) of newly-born neurons was located in a compartmented region in the adult telencephalon. Next, we used a transgenic

line (HSP:Cre) which allowed us to induce stochastic recombination by heat-shock and to identify clonal units of newly-born neurons in the adult brain using a large number of samples. Systematic analysis of clonal units revealed that the dorsal telencephalon (the pallium) of the adult brain was constituted by almost 40 clonal units and that a single traditional anatomical region was composed of a few clonal units. On the other hand, in the ventral telencephalon (the sub-pallium), the distribution of clonal units was not restricted to anatomical regions, and some clonal units were mixed. Furthermore, we investigated which transcriptional regulatory pathway could generate the structural difference between the dorsal and ventral telencephalon. ATAC-seq and RNA-seq showed the existence of some transcriptional regulatory pathways specific to the dorsal or ventral telencephalon. Also, to examine which transcriptional regulatory pathway could determine the lineage of individual clonal units, we performed the same experiments using a single clonal unit. Our study might lead to an understanding of how to generate the structural difference between the pallium and subpallium as well as how to generate subdivision of the pallium postnatally.

Disclosures: **Y. Isoe:** None. **R. Nakamura:** None. **T. Okuyama:** None. **Y. Kamei:** None. **S. Nonaka:** None. **T. Kubo:** None. **H. Takeda:** None. **H. Takeuchi:** None.

Nanosymposium

272. Postnatal Neurogenesis and Stem Cell Functions

Location: 146C

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Presentation Number: *272.07

Topic: *B.14. Neuro-Oncology

Support: R01NS072427

Title: Inactivation of HIPPO signaling components LATS1/2 initiates aggressive peripheral nerve malignancy

Authors: ***L. WU**, Q. LU
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Abstract: Malignant peripheral nerve sheath tumors (MPNSTs) are highly aggressive nerve-associated sarcomas with poor prognosis. The molecular events underlying SC lineage cell-to-MPNST transformation are incompletely defined. Here, we show that human MPNSTs exhibit elevated expression of HIPPO-TAZ/YAP activity and that TAZ/YAP hyperactivity in SCs caused by LATS1/2 loss potently induces high-grade nerve-associated tumors with full penetrance. LATS1/2 deficiency converts SCs to a cancerous, progenitor-like, phenotype and promotes hyperproliferation. Conversely, disruption of TAZ/YAP activity alleviates tumor

burden in LATS1/2-deficient mice and inhibits proliferation of human MPNST cells. Moreover, the TAZ/YAP-TEAD1 axis directly targets and activates oncogenic pathways in SCs including PDGFR signaling. Co-targeting TAZ/YAP and PDGF activity efficaciously reduces tumorigenicity in LATS1/2-deficient tumors. Thus, our findings establish a previously unrecognized link between HIPPO-TAZ/YAP activation and MPNST pathogenesis and suggest that combined inhibition of TAZ/YAP/PDGF signaling may be beneficial in MPNSTs.

Disclosures: L. Wu: None. **Q. Lu:** None.

Nanosymposium

272. Postnatal Neurogenesis and Stem Cell Functions

Location: 146C

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***272.08

**Topic: ***A.07. Developmental Disorders

Title: AhR suppresses tumour progression in Shh class medulloblastoma

Authors: *N. SARIC[1], B. PIJUAN SALA[2], S. CLIFFORD[3], G. STOCKINGER[4], C. HOGSTRAND[1], A. BASSON[1]
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Abstract: The class of tumors known as medulloblastomas (MBs) represent the most common pediatric brain tumors. These tumors are molecularly heterogeneous and can be classified into four distinct subclasses depending on their transcriptional signature. These are the Wnt, Shh, group 3 and group 4 MBs. The Shh group MBs are known to arise from aberrantly increased proliferation and neoplastic transformation of cerebellar granule precursors (GCPs). We have identified a role for the AhR (aryl hydrocarbon receptor) during GCP development in the postnatal cerebellum. Our data indicates that conditional AhR deletion causes premature GCP cell cycle exit and reduced proliferation through enhanced activation of the Tgf beta-Smad3 pathway. Mechanistically this likely occurs on a post-transcriptional level with loss of AhR leading to either hyperphosphorylation of Smad3 or maintenance of phospho-Smad3 levels. The Tgf beta pathway is known to have important and differential effects during tumorigenesis. To further investigate the AhR-Tgf beta link in a tumor context we generated double conditional Ptch1 (Patched1)/AhR knockout mice which allowed us to model the Shh subclass MB and pose the question of whether the AhR pathway is able to influence the process of MB development. We found that AhR loss of function led to reduced survival rates and increased tumor incidence in Shh MB models. MB cell proliferation was reduced and this was correlated with heightened

phospho-Smad3 in the AhR null MBs. This phenotypic effect could arise due to enhanced metastasis or augmented tumor initiation in AhR deficient MBs, which is currently being investigated. Understanding the precise contributory mechanism may allow for development of therapeutic strategies targeting aggressive subclasses of Shh MBs.

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Nanosymposium

273. Transplantation and Regeneration

Location: 147B

Time: *Monday, November 13, 2017, 8:00 AM - 10:00 AM

Presentation Number: *273.01

Topic: *A.04. Transplantation and Regeneration

Support: ISF 1053/15

Title: Functional magnetically oriented collagen scaffolds for neuronal regeneration

Authors: ***O. SHEFI**, M. ANTMAN-PASSIG
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Abstract: The ability to manipulate and direct neuronal growth has great importance in the field of tissue engineering, both for neuronal repair and potential medical devices. Following nerve injury, such as peripheral nerve injury, spinal cord injury and neurodegenerative diseases, spontaneous nerve regeneration is often partial and limited, arising the need to develop technologies for optimal regrowth conditions. Neuronal growth, directionality, effective elongation, and level of connectivity play a key role in recapitulating functional capabilities. Major efforts have been devoted to the development of techniques to control cell growth, showing enhanced regeneration on anisotropic and oriented substrates. These include bio-mimetic scaffolds, nano-fibrous constructs and gels or gel filled tubes, offering a mechanical guide to the regenerating axons. Orienting collagen fibers within 3D gels has been explored by several groups including our own. Recently, a novel approach of injectable hydrogels, to be incorporated directly into the injured site has been presented as a promising regenerative therapeutic route. We have previously developed an injectable 3D collagen hydrogel combined with magnetic nanoparticles (MNPs) with fiber structure that can be aligned in situ dynamically and remotely in response to an external magnetic field. We now report the enrichment of the gel platform with biomolecules conjugated MNPs for promoting directed differentiation. Conjugation of trophic factors to nanoparticles has been investigated, including by our group, as a leading approach for sustained delivery to injury sites, thus, the combination of functionally

coated MNPs with the magnetically aligned collagen gel system presents a smart delivery system of biomolecules, together with integral guidance cues. We utilized variously coated MNPs as actuators for gel alignment. Coating of MNPs, as well as field strength, present a critical element in alignment efficiency. PC12 cells grown within magnetically aligned gels with functionally coated MNPs present an elongated and directed growth.

Disclosures: O. Shefi: None. **M. Antman-Passig:** None.

Nanosymposium

273. Transplantation and Regeneration

Location: 147B

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**Presentation Number: ***273.02

**Topic: ***A.04. Transplantation and Regeneration

Support: Department of Defense - JWMRP (W81XWH-13)
National Institutes of Health (F31-NS090476)

Title: Tissue engineered "pioneer" axons as regenerative bridges to guide modality-specific axonal regeneration following peripheral nerve injury

Authors: *K. KATIYAR[1,2,3], M. R. GROVOLA[1,2], L. A. STRUZYNA[1,2], D. P. BROWN[1,2], J. C. BURRELL[1,2], C. K. WALLACE[2,4], K. D. BROWNE[1,2], D. K. CULLEN[1,2]
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Abstract: Peripheral nerve injuries (PNIs) are surprisingly common as they present in 3-5% of all trauma cases. In cases requiring surgical repair of long segmental defects (>3-5cm), the current gold standard is the sensory nerve autograft although functional outcomes are generally unsatisfactory due to the long regenerative distances required for axons to reach distal targets. To address this need, we have developed living tissue engineered nerve grafts (TENGs) consisting of aligned axonal tracts which we routinely generate in custom-built mechanobioreactors at densities of >100,000 axons and lengths of ≥5cm within 2 weeks through the controlled process of axon “stretch-growth”. TENG axons mimic the developmental action of “pioneer” axons, where targeted axonal outgrowth can be achieved along pre-existing axonal tracts *in vivo*. We previously reported that TENGs generated using sensory DRG axons effectively bridged 5cm segmental nerve defects and facilitated muscle reinnervation in a porcine model of major PNI. However, our prior work demonstrated the preferential regeneration of sensory axons along sensory TENGs. Therefore, the scope of the current study is to construct TENGs using motor

axons and evaluate their efficacy in preferentially driving host motor axonal regeneration following major PNI. Motor TENGs were developed using spinal motor neurons (from rats or pigs) and successfully "stretch-grown" resulting in long, aligned axonal tracts expressing motor axon-specific markers. Regeneration of motor axons along these motor TENGs was assessed both *in vitro* and *in vivo,* revealing preferential growth of motor axons along our engineered motor axonal tracts versus sensory axonal tracts. Based on the developmental literature, we hypothesize that this disparity in regeneration was due to differences in the spatial presentation of surface attractive and repulsive cues on motor versus sensory axons. As such, we are quantifying the spatial presentation and expression of specific surface proteins implicated in axon guidance, such as neural cell adhesion molecules, using high-resolution confocal microscopy and stochastic optical reconstruction microscopy (STORM). This work will aid in elucidating the molecular mediators of this newfound mechanism of "axon-facilitated axon regeneration". With further development, tissue engineered "living scaffolds" exploiting this mechanism may be useful for targeted modality-specific axonal regeneration to facilitate functional recovery following neurotrauma or neurodegenerative disease.

Disclosures: K. Katiyar: None. **M.R. Grovola:** None. **L.A. Struzyna:** None. **D.P. Brown:** None. **J.C. Burrell:** None. **C.K. Wallace:** None. **K.D. Browne:** None. **D.K. Cullen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axonova Medical.

Nanosymposium

273. Transplantation and Regeneration

Location: 147B

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***273.03

**Topic: ***A.04. Transplantation and Regeneration

Title: The role of poly ADP-ribosylation in axon regeneration

Authors: *A. B. BYRNE
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Abstract: To regain function after injury or disease, our adult nervous systems must regenerate damaged axons and rebuild synapses with interacting cells. However, axon regeneration is inhibited after injury by both extrinsic and intrinsic mechanisms. Identifying and characterizing the mechanisms that inhibit axon regeneration will enhance our understanding of axon plasticity in the adult nervous system and inform approaches to treat the injured and diseased nervous system. We found poly (ADP-ribosylation) functions intrinsically to regulate axon regeneration of severed neurons in vivo in *C. elegans* and in vitro in mammalian cortical neurons. In addition,

we found chemical inhibition of poly (ADP-ribosylation) enhances functional regeneration of injured GABA neurons. Ongoing studies explore the mechanisms by which poly (ADP-ribose) polymerases and poly (ADP-ribose) glycohydrolases, which add and remove poly (ADP-ribose) from substrate proteins in an Nad^{+}-dependent manner, inhibit and enhance axon regeneration, respectively. Defining how poly (ADP-ribosylation) regulates axon regeneration will both add to our understanding of the intrinsic mechanisms that regulate neuronal repair and contribute to strategies to improve regeneration after injury.

Disclosures: A.B. Byrne: None.

Nanosymposium

273. Transplantation and Regeneration

Location: 147B

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***273.04

**Topic: ***A.04. Transplantation and Regeneration

Title: Fabrication of cerebral organoid by using a 3D bio-printer and its maturation *In vitro* and *In vivo*

Authors: *N. FUJITA[1], Y. MASUI[2], J. CHAMBERS[3], K. UCHIDA[3], R. NISHIMURA[3], Y. KUNITOMI[4], K. NAKAYAMA[5]
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Abstract: [Background]Recently, a 3D bio-printer have been newly developed and used to create various scaffold-free tissues such as liver and cartilage. These tissues have three-dimensional construct and can reproduce the development of tissue. However, the application of a 3D bio-printer to create neural tissue have not yet been reported. In this study, we tried to create cerebral organoids by fabricating neurospheres derived from human induced pluripotent stem cells (hiPSCs) and histopathologically evaluated the maturation of the cerebral organoids in vitro and in vivo.
[Materials and Methods]Neurospheres were cultured from neural stem cells (4×10^4 each) derived from hiPSCs. To create cerebral organoids, 12 neurospheres were skewered onto a fine needle and arranged in two layers consisting of three rows longitudinally and two rows horizontally by using a 3D bio-printer (Regenova®, Cyfuse biomedical). Cultures were maintained by differentiation medium and histopathological evaluation was performed after 2,3,4,8 and 12 weeks. To evaluate in vivo maturation, cerebral organoids were implanted into a defect of the cerebral cortex of Bulb/c nu/nu mice. After 4, 8, and 12 weeks, implanted cerebral organoids

were collected and histopathologically evaluated.
[Results]Neurospheres were fused each other and one construct was foamed in a week. The diameter was gradually increased over time, however, histopathological evaluation revealed the expansion of internal cavitation. Internal necrosis was concurrently observed after 4 weeks. After 8 and 12 weeks, organoids were formed by a thin layer consisting of nerve fiber with a large internal cavity. However, these necrotic changes were not observed implanted organoids until 12 weeks after implantation. Histopathological evaluation revealed that infiltration of vessels and glial cells from host tissue and maturation of cerebral organoid over time. Although regular layer formation observed in the process of brain development was not detected, a layer resembling marginal zone was observed in the surface of the implanted organoids.
[Discussion]We demonstrated the fabrication of cerebral organoids by using a 3D bio-printer. Although constructed organoids could not be maintained under the culture condition used in this study, implanted organoids could be established and gradual maturation was observed. It was suggested that filtration of vessels and glial cells from host tissue played an important role to maintain implanted organoids. Further, histological features mimicking cerebral development suggest that implantation of cerebral organoids can offer a good model for developmental brain disorders.

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Nanosymposium

273. Transplantation and Regeneration

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Topic: *A.04. Transplantation and Regeneration

Support: Department of Veterans Affairs Rehabilitation R&D Career Development Award (CDA2) IK2-RXX002013 to HIC

Title: Transplantation of human cortical organoid tissue for reconstruction of rat visual cortex

Authors: ***D. JGAMADZE**[1], N. BILICI[3], J. T. LIM[1], C. ADAM[1], C. LIU[4], D. CONTRERAS[2], J. A. WOLF[1,5], H. CHEN[1,5]
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Abstract: Introduction: Cell replacement therapies remain one of the more promising methods for replacing lost brain tissue and restoring neurological function. Recent advances in generating cerebral organoids (CO) from pluripotent stem cells have opened up the prospect of transplanting autologous neural tissue constructs that emulate aspects of brain architecture, especially the layers of cerebral cortex. In this study, we investigated the feasibility of transplanting COs into secondary visual cortex (V2) in rats and assessed measures of graft survival and integration.
Methods: COs were generated from a federally approved human embryonic stem cell line modified to express green fluorescent protein (H9-GFP). Adult male rats (200-250g) were anesthetized, a craniotomy was performed, and an aspiration lesion in V2 was made using a 2-mm diameter tissue biopsy punch to a depth of 2 mm. A similarly sized core of organoid tissue (differentiation day 60-100) was then transplanted into the cortical cavity. Immunosuppression was achieved by daily administration of cyclosporine A (IP, 10 mg/kg). Animals were survived for 2 months post-transplantation. A cohort of 3 animals were re-anesthetized for acute electrophysiological recordings using a laminar 32 channel multi-electrode silicon probe. All animals were sacrificed for immunohistochemical analysis.
Results: Organoid grafts survived in 63% (7/11) of cases. We observed extensive graft neurite outgrowth into the host brain. Most of these processes were short, but some projections extended up to 1.5 mm away from the graft site into the corpus callosum. A majority of the cells in transplanted organoids were of neuronal origin as demonstrated by beta-3-tubulin stain. We also observed progenitor cell populations (Pax6 positive cells) present within the organoid, suggesting that organoid maturation had not yet been finalized. We did not observe any spontaneous or induced unit activity in the transplanted organoid. However, activity resembling local field potentials were recorded spontaneously and in response to visual stimulation of the contralateral eye and electrical stimulation of the ipsilateral lateral geniculate nucleus and primary visual cortex, suggesting potential integration of host axons with the transplanted CO.
Conclusion: Our findings show that human COs survive at least 2 months after transplantation in immunosuppressed rats, grow projections into the host brain, and may integrate into the visual network. Additional studies are needed to further assess the functional integration of the COs with brain networks, and examine their capacity to restore lost function in host animals.

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Nanosymposium

273. Transplantation and Regeneration

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National Science Foundation [Graduate Research Fellowship DGE-1321851 (Struzyna)]

Title: Tissue-engineered nigrostriatal pathway for tract reconstruction in Parkinson's disease

Authors: *L. A. STRUZYNA[1,2,4], K. D. BROWNE[2,4], Z. D. BRODNIK[5], J. C. BURRELL[2,4], J. P. HARRIS[2,4], H. I. CHEN[2,4], J. A. WOLF[2,4], K. V. PANZER[1], J. E. DUDA[3,4], R. A. ESPAÑA[5], D. K. CULLEN[2,4]
[1]Bioengineering, [2]Neurosurg., [3]Neurol., Univ. of Pennsylvania, Philadelphia, PA; [4]Michael J. Crescenz Veterans Affairs Med. Ctr., Philadelphia, PA; [5]Drexel Univ., Philadelphia, PA

Abstract: OBJECTIVE: The classic motor symptoms of Parkinson's disease (PD) result from selective degeneration of the nigrostriatal pathway, including dopaminergic neurons in the substantia nigra and their long-distance axonal inputs to the striatum. We are developing a micro-tissue engineering strategy to directly reconstruct the lost nigrostriatal pathway and, as a result, restore motor function following PD neurodegeneration.
METHODS: We created micro-tissue engineered neural networks (micro-TENNs), which are living 3-D neural constructs comprised of a tubular hydrogel shell (398μm diameter) containing an extracellular matrix (ECM) core that supports robust axonal extension. Dopaminergic neurons were isolated from transgenic embryos, purified via fluorescence activated cell sorting, mechanically re-aggregated, precisely delivered to one end of the micro-TENN, and then cultured for 4-60 days based on desired length of axon growth. The resulting micro-TENN cytoarchitecture is designed to consist of a population of dopaminergic neurons at one end with long axonal tracts extending through the lumen to the other end. For transplantation, adult rats were anesthetized, and preformed micro-TENNs were microinjected to span the nigrostriatal pathway.
RESULTS: These miniaturized living neural constructs have been constructed with dopaminergic neurons and unidirectional axonal tracts. These dopaminergic axonal tracts have spanned more than 1 cm at average axon growth rates of 430 microns/day through the ECM-lumen. The neuronal-axonal architecture of these dopaminergic micro-TENNs was verified via immunocytochemistry. Moreover, fast scan cyclic voltammetry was utilized to measure evoked dopamine release following stimulation of the neuronal somata. Following transplantation to physically reconstruct the nigrostriatal pathway in rats, dopaminergic micro-TENNs survived and maintained their axonal architecture for at least 1 month with evidence of neurite outgrowth from the constructs into the host brain. Ongoing studies are assessing behavioral, electrophysiological, and histological outcomes to determine functional integration of preformed micro-TENNs in a rat model of PD.
CONCLUSIONS: Our custom process to generate micro-TENNs *in vitro* enables a precisely engineered structure where the number of neurons and generation of dopamine can be known

prior to implantation. By virtue of their long axonal tracts, micro-TENNs may be capable of replacing circuitry lost in PD to restore dopaminergic inputs to the striatum. Therefore, micro-TENNs may provide a transformative and scalable solution to alleviate the cause of motor symptoms in PD.

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Nanosymposium

273. Transplantation and Regeneration

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**Topic: ***A.04. Transplantation and Regeneration

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ERC grant 309712
Swedish Research Council (VR, K2014-61X-20391-08-4 and K2012-99X-22324-01-5

Title: Converted human neurons mature in adult rat hippocampus

Authors: *M. S. ANDERSSON[1], N. AVALIANI[1], U. PFISTERER[2], A. HEUER[1], M. P. PARMAR[3], M. KOKAIA[4]
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Abstract: Direct conversion of human somatic cells to induced neurons (iNs), using lineage specific transcription factors have opened new opportunities for cell therapy in a number of neurological diseases, including epilepsy. In most severe cases of epilepsy, seizures often originate in the hippocampus, where populations of inhibitory interneurons degenerate. Thus iNs could be of potential use to replace these lost interneurons. It is not known, however, if iNs survive and maintain functional neuronal properties for prolonged time periods in *in vivo*. We transplanted human fibroblast-derived iNs, into the adult rat hippocampus and observed a progressive morphological differentiation, with more developed dendritic arborisation at six months as compared to one month. This was accompanied by mature electrophysiological properties and fast high amplitude action potentials at six months after transplantation. This

proof-of-principle study suggests that human iNs can be developed as a candidate source for cell replacement therapy in temporal lobe epilepsy.

Disclosures: **M.S. Andersson:** None. **N. Avaliani:** None. **U. Pfisterer:** None. **A. Heuer:** None. **M.P. Parmar:** None. **M. Kokaia:** None.

Nanosymposium

273. Transplantation and Regeneration

Location: 147B

Time: *Monday, November 13, 2017, 8:00 AM - 10:00 AM

Presentation Number: *273.08

Topic: *A.04. Transplantation and Regeneration

Support: Neurological Foundation Gillespie Postgraduate Scholarship
Health Research Council Programme Grant

Title: High-resolution mass spectrometry imaging of the human subventricular zone lipidome

Authors: ***M. HUNTER**[1], R. L. M. FAULL[1], N. J. DEMARAIS[2], A. C. GREY[3], M. A. CURTIS[1]
[1]Ctr. for Brain Res., [2]Dept. of Physics, [3]Dept. of Physiol., Univ. of Auckland, Auckland, New Zealand

Abstract: The brain is replete in lipids, where these diverse molecules regulate an array of cell biological and physiological processes. Adult neural stem and progenitor cells are dependent on autonomous lipid synthesis, suggesting a role for lipids in neurogenesis. Accordingly, we hypothesised the existence of specialised lipid microenvironments within neurogenic niches such as the subventricular zone (SVZ). The objective of this study was to characterise the lipidome of the human SVZ using high-resolution matrix-assisted laser desorption/ionisation (MALDI) imaging mass spectrometry. Fresh-frozen caudate nuclei from four deceased, neurologically normal donors (three males, one female) were obtained from the Neurological Foundation Douglas Human Brain Bank. Cryostat-cut sections were thaw-mounted on target slides and 1,5-diaminonaphthalene or 2,5-dihydroxybenzoic acid matrices applied by sublimation. MALDI imaging was performed using a Bruker UltrafleXtreme at 10 µm raster width. Spectra were aligned using FlexAnalysis and pre-processed and analysed in SCiLS Lab. Luxol fast blue and haematoxylin and eosin micrographs were co-registered with MALDI images to delineate the SVZ and its constituent layers. High-dimensional features of the data were explored using principal component analysis, whereas co-localisation of mass signals with the SVZ used Pearson correlation, receiver-operating characteristics and t statistics. Species of interest were identified by liquid chromatography-tandem mass spectrometry and database searching of

accurate masses derived by Fourier transform ion cyclotron resonance. The SVZ showed a distinct lipidomic signature, where principal component analysis discriminated the SVZ from the underlying parenchyma of the caudate nucleus. Sixty mass signals were significantly co-localised with the SVZ, while a further 12 signals were deficient within the SVZ. Among the most prominent observations, the SVZ was rich in sphingomyelins, phosphatidylserines and phosphatidic acids but low in triglycerides and select ceramide phosphates. Focused analysis of the constituent layers of the SVZ identified the ependymal layer to be rich in phosphatidylinositol, whereas the hypocellular and astrocytic layers were less lipidomically distinct. The transition zone (myelin layer) showed high concentrations of phosphatidylinositol and sulphatides, in addition to a differential abundance of many other species. This study is the first to characterise the lipidomic architecture of the SVZ in a human series and may reveal new insights into the molecular biology of neurogenesis in one of the key neurogenic niches in the human adult brain.

Disclosures: **M. Hunter:** None. **R.L.M. Faull:** None. **N.J. Demarais:** None. **A.C. Grey:** None. **M.A. Curtis:** None.

Nanosymposium

274. Cellular and Subcellular Synapse Organization: From Super-Resolution Imaging to Circuit Function

Location: 140A

Time: *Monday, November 13, 2017, 8:00 AM - 10:00 AM

Presentation Number: *274.01

Topic: *B.07. Synaptic Transmission

Support: Center for Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB), Cluster of Excellence 171, DFG Research Center 103

Title: STED nanoscopy reveals the ultrastructure of the postsynaptic density protein PSD-95 in living mice

Authors: ***J.-M. MASCH**[1], D. KAMIN[1], H. STEFFENS[1], J. FISCHER[2], J. ENGELHARDT[2], N. T. URBAN[1], M. KRATSCHKE[3], N. KOMIYAMA[3], S. G. N. GRANT[3], S. W. HELL[1,2]
[1]NanoBiophotonics, Max Planck Inst. For Biophysical Chem., Goettingen, Germany; [2]Optical Nanoscopy Div., German Cancer Res. Ctr. (DKFZ), Heidelberg, Germany; [3]Ctr. for Clin. Brain Sciences, Edinburgh Univ., Edinburgh, United Kingdom

Abstract: The ultrastructural arrangement of the postsynaptic scaffolding protein PSD-95 (postsynaptic density 95) is smaller than the optical diffraction limit and hence cannot be resolved by conventional light microscopy. Recently, optical nanoscopy studies in the

hippocampus of fixed brain slices reported that PSD-95 was organized into nanoclusters (Broadhead et al, 2016). To date, these observations have not been verified *in vivo*.
To study the ultrastructure of PSD-95 *in vivo*, we performed STimulated Emission Depletion (STED) nanoscopy through a cranial window in anesthetized transgenic mice (3 to 6 months old). The mice were engineered to express endogenous PSD-95 in fusion with the self-labeling enzyme HaloTag. A fluorogenic HaloTag-fluorophore was injected into the primary visual cortex one hour prior to imaging. In contrast to available far-red fluorescent proteins, the use of an organic, cell-permeable HaloTag ligand enabled an efficient, bright, and specific labeling of the protein of interest with low background and increased photostability.
Using this approach, we studied the shape, size, and distribution of endogenous PSD-95 in cortical dendrites of pyramidal neurons at 5-25 µm below the brain surface. The ultrastructural arrangement of PSD-95 was highly diverse and varied considerably in shape and size. In the majority of synaptic sites, PSD-95 appeared as a straight or curved line, or a thin ellipse. Frequently, we also observed a complex, oval or ring-like ultrastructure with irregular borders and perforations, which could not be resolved using confocal microscopy. Notably, the PSD-95 substructures appeared continuous, not clustered, in shape.
In conclusion, the combination of STED nanoscopy with the HaloTag fusion technology allowed us to perform the first super-resolution study of an endogenously tagged synaptic protein in living mice. Our results highlight the presence of differences between the organization of postsynaptic sites *in vitro* and *in vivo*, and therefore the necessity to scrutinize these nanoclusters with more detail. Essentially, this study demonstrates the importance of *in vivo* nanoscopy and introduces a novel approach for future investigations of synaptic protein organizations in living animals.
Reference: Broadhead et al. (2016), *Sci. Rep.*, 6:24626

Disclosures: J. Masch: None. **D. Kamin:** None. **H. Steffens:** None. **J. Fischer:** None. **J. Engelhardt:** None. **N.T. Urban:** None. **M. Kratschke:** None. **N. Komiyama:** None. **S.G.N. Grant:** None. **S.W. Hell:** None.

Nanosymposium

274. Cellular and Subcellular Synapse Organization: From Super-Resolution Imaging to Circuit Function

Location: 140A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***274.02

**Topic: ***B.07. Synaptic Transmission

Support: NINDS, NIBIB intramural research programs
US NIMH Grant MH-38256 (R.A.N.).

Title: Identifying NMDARs by EM tomography in the glutamatergic excitatory postsynaptic density

Authors: *X. CHEN[1], S. INCONTRO[2], C. WINTERS[1], M. ARONOVA[3], R. D. LEAPMAN[3], R. A. NICOLL[2], T. S. REESE[1]
[1]Lab. Neurobiol, NINDS-NIH, Bethesda, MD; [2]Dept Cell & Mol Pharmacol, UCSF, San Francisco, CA; [3]Lab. of Cell. Imaging and Macromolecular Biophysics, NIBIB-NIH, Bethesda, MD

Abstract: The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and the *N*-methyl-D-aspartate receptors (NMDARs) are the two major types of ionotropic glutamate receptors embedded in the membrane of the excitatory postsynaptic density (PSD) where they mediate essentially all the synaptic transmission at excitatory synapses. While AMPARs are responsible for vast majority of the charge transfer at resting membrane potential, NMDARs, acting as coincident detectors, allow calcium influx that triggers cascades of events critical for long-term potentiation (LTP). To positively identify NMDARs in EM tomograms of the PSD , a CRISPR-Cas9 lenti viral construct was used to knockout the NR1 subunit obligatory for the assembly of NMDARs, thus eliminating NMDARs in neurons. Electrophysiology measurements show that over 14 days in vitro, NMDA mediated activity at synapses is essentially eliminated, while AMPARs appear to increase. Using dark-field scanning transmission electron microscopy (STEM) tomography, we compared the detailed changes of the core structural elements at the PSD under control and knockout conditions. Rat hippocampal cultures were prepared by high pressure freezing, freeze substitution and low temperature embedding in Lowicryl. Sections 160-400 nm thick were imaged by dark field STEM tomography, which significantly improved the signal to noise ratio compared with both TEM tomography and bright field STEM tomography. Our results provide confirmation that the transmembrane structures with bulky cytoplasmic aspects correspond to NMDARs while those with thinner, flat cytoplasmic aspects correspond to AMPARs. Knocking out NMDARs leads to significant reorganization of the core elements of the PSDs; most notably an increase, right at the post-synaptic membrane, in AMPARs and core scaffolding structures. Our work using improved imaging by dark field STEM opens up the possibility of tracking changes in the macromolecular organization of PSDs down to the level of individual glutamate receptors, information needed to interpret synaptic plasticity at the molecular level.

Disclosures: X. Chen: None. **S. Incontro:** None. **C. Winters:** None. **M. Aronova:** None. **R.D. Leapman:** None. **R.A. Nicoll:** None. **T.S. Reese:** None.

Nanosymposium

274. Cellular and Subcellular Synapse Organization: From Super-Resolution Imaging to Circuit Function

Location: 140A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***274.03

**Topic: ***B.08. Synaptic Plasticity

Support: NIH Grant 610510800060039275

Title: Fast and furious: Imaging dendritic spinule dynamics in cortical mouse neurons using rapid three dimensional structured illumination microscopy

Authors: *C. R. ZACCARD, K. MYCZEK, P. PENZES
Physiol., Northwestern Univ., Chicago, IL

Abstract: Dendritic spinules are fine, transient membranous protrusions that originate from neuronal dendritic spines and can project into invaginations of adjacent axon terminal or glial cell membranes. Current literature shows that these structures are induced by synaptic transmission, and their proposed functions include synaptic plasticity, cell signaling, and membrane recycling. Dendritic spinules are generally thinner than filopodia and less than 1 µm in length, and their nano-scale necessitates resolution beyond the light diffraction limit. Hence, the bulk of our current knowledge of dendritic spinule structure and function is derived from static serial section electron microscopy. The recent advent of structured illumination microscopy (SIM), stimulated emission depletion, and localization map-based super-resolution methods have theoretically enabled live nano-scale imaging, but their practical application for studying rapid biological processes has so far been limited. Recent improvements in SIM systems, though not yet widely available, have overcome slow acquisition speed, which represents the main barrier to live, time-lapse SIM. Herein, we balanced the need for fast frame rates to capture highly transient events against the need to collect high volume images to encompass entire spines and their trajectories. We were therefore able to utilize rapid 3D SIM to track individual dendritic spinules in cultured pyramidal mouse cortical neurons that expressed DsRed-Express2. Similar to previous studies, we report that spinules were most commonly formed on large mushroom-shaped dendritic spines. We measured changes in length, width, and volume over time, as well as determining the lifespan of individual dendritic spinules, which typically ranged from seconds to several minutes. We next transfected mature neurons with EGFP-tagged intrabodies to label endogenous post-synaptic density protein 95, to determine the dendritic spinule origin in relation to the post-synaptic density. Finally, dendritic spinule number and dynamics were compared in control neurons to those treated with Transforming Growth Factor-β1, a neurotrophic and neuroprotective cytokine with an established role in synaptic transmission, synaptic plasticity, and memory. Our study demonstrates the utility of rapid 3D

SIM for studying individual dendritic spinules in living neurons under varied conditions, while advancing our current understanding of their dynamics in cortical pyramidal mouse neurons.

Disclosures: C.R. Zaccard: None. **K. Myczek:** None. **P. Penzes:** None.

Nanosymposium

274. Cellular and Subcellular Synapse Organization: From Super-Resolution Imaging to Circuit Function

Location: 140A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***274.04

**Topic: ***B.07. Synaptic Transmission

Support: NIMH (R01MH101218, R01 MH100561)
U. S. Army Research Office under contract number W911NF-12-1-0594 (MURI)
Fondation pour la Recherche Médicale (FRM)
Philippe Foundation

Title: Modeling the nano-physiology of dendritic spines with electro-diffusion

Authors: *T. LAGACHE[1], K. JAYANT[2], R. YUSTE[3]
[1]Biol. Sci., [2]Electrical Engin. and Biol. Sci., [3]Columbia Univ., New York, NY

Abstract: Dendritic spines are characterized by a bulbous head linked to the parent dendrite by a thin neck. The neck biochemically isolates the head from the parent dendrite [1]. However, to what extent the spine neck electrically influences synaptic transmission is unclear and controversial. Estimates of spine electrical properties have been very variable, and the corresponding diversity in biophysical models has precluded a quantitative understanding of charging dynamics in the spine. To capture the effects of the peculiar nanostructure of the spine on its electrical properties, we have developed a new type of model that links ion dynamics and electrical potential by using a coupled system of differential equations the Poisson (P) equation that links the electrical potential to ion concentration, and the Nernst-Planck (NP) formulation that combines Brownian diffusion and the electrical field [2]. We find that ion diffusion alone cannot account for the rapid kinetics of spine head voltages (~ 1ms) [3] and the large electrical current that flows across the neck. We show that the neck resistance can be high (> 200 MΩ), is proportional to neck length and inversely to the cross-sectional radius, but also critically depends on net ions concentration and their diffusion coefficients. Our spine resistance estimates are larger than the assumed input resistance of a pyramidal neuron and its thick dendritic arbors, causing a substantial membrane depolarization (>20 mV) in the spine head during synaptic input. This large excitatory post-synaptic potential (EPSP) magnitude has fundamental implications on

spine ion dynamics: a rapid (<1ms) and large (50-100 pA) electrical current across the neck and a rapid collapse of the driving force and synaptic entry of ions. This latter effect in turn leads to a decreased dendritic current and accounts for the reduced somatic EPSP and electrical isolation observed in spines with long and thin necks [4]. Finally, we find agreement between our model and recently published electrical measurements of spine head ion dynamics [3].
[1] Yuste and Denk, Nature 375, 682-684. (1995).[2] Holcman, and Yuste, R., Nature Rev. Neurosci. 16:685-92 (2015)[3] K. Jayant et.al., Nat. Nanotech, 12, 335-342 (2017)[4] Araya R, Vogels TP, Yuste R. Proc Natl Acad Sci U S A. 111, E2895-904 (2014)

Disclosures: **T. Lagache:** None. **K. Jayant:** None. **R. Yuste:** None.

Nanosymposium

274. Cellular and Subcellular Synapse Organization: From Super-Resolution Imaging to Circuit Function

Location: 140A

Time: *****Monday, November 13, 2017, 8:00 AM - 10:00 AM

Presentation Number: *****274.05

Topic: *****B.08. Synaptic Plasticity

Support: NIH R01MH077303
UT BRAIN Award
Brain and Behavior Research Foundation
Sealy Center for Structural Biology and Molecular Biophysics

Title: Molecular mechanism of MDGA1: Regulation of neuroligin-neurexin trans-synaptic bridges

Authors: ***G. RUDENKO**[1], S. GANGWAR[1], X. ZHONG[1], S. SESHADRINATHAN[1], H. CHEN[2], M. MACHIUS[1]
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Abstract: Synaptic adhesion and synaptic organizing molecules, also known as ‘synaptic organizers’, play an essential role in promoting synapses. The synaptic organizers, neuroligins and neurexins, promote synapse development and validation. Their extracellular domains protrude into the synaptic cleft where they bind each other and form trans-synaptic macromolecular bridges that span the synaptic cleft. Select pairs promote excitatory and inhibitory synapses, respectively, with neuroligin 2 (NLGN2) limited to inhibitory synapses and neuroligin 1 (NLGN1) dominating at excitatory synapses. Recently, it was discovered that the cell surface molecules, MAM domain-containing glycosylphosphatidylinositol anchor 1

(MDGA1) and 2 (MDGA2), regulate trans-synaptic adhesion between neurexins and neuroligins, impacting NLGN2 and NLGN1, respectively. MDGA1 binds specifically to NLGN2 with nanomolar affinity, but not to NLGN1 or NLGN3, forming a side-by-side (*in-cis*) complex involving the extracellular domains; by contrast, MDGA2 prefers to interact with NLGN1. The interaction of MDGA1 with NLGN2 blocks the ability of NLGN2 to form a trans-synaptic bridge with neurexins, thus downregulating the ability of NLGN2 to promote inhibitory synapse development, on the other hand, there is consensus that MDGA2 downregulates excitatory synapse formation. Because these molecules impact the development of excitatory synapses and inhibitory synapses differentially, it is thought that malfunction of these molecules leads to an imbalance in excitation versus inhibition disrupting neural circuits critical to cognition and behavior. Indeed, neuroligins, neurexins and MDGAs are implicated in many neuropsychiatric diseases, including autism spectrum, disorder, and schizophrenia.
We have determined the molecular mechanism of MDGA action. MDGA1 Ig1-Ig2 is sufficient to bind NLGN2 with nanomolar affinity. The crystal structure of MDGA1 Ig1-Ig2 reveals an unusual locked rod-shaped array. The crystal structure of MDGA1 Ig1-Ig2 in complex with NLGN2 reveals a unique molecular arrangement whereby two MDGA1 Ig1-Ig2 molecules each span the entire NLGN2 dimer. Strikingly, Ig1 from MDGA1 binds to the same region on NLGN2 as neurexins do. Thus, MDGAs regulate the formation of neuroligin-neurexin trans-synaptic bridges by sterically blocking access of neurexins to neuroligins, and provide a molecular mechanism to downregulate inhibitory versus excitatory synapse development, selectively.

Disclosures: **G. Rudenko:** None. **S. Gangwar:** None. **X. Zhong:** None. **S. Seshadrinathan:** None. **H. Chen:** None. **M. Machius:** None.

Nanosymposium

274. Cellular and Subcellular Synapse Organization: From Super-Resolution Imaging to Circuit Function

Location: 140A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***274.06

**Topic: ***B.07. Synaptic Transmission

Support: HHMI/Janelia Research Campus

Title: Branch- And input-specific synaptic clustering by single axons on CA1 pyramidal cell dendrites

Authors: *E. BLOSS, S. VISWANATHAN, B. KARSH, J. COLONELL, R. FETTER, N. SPRUSTON
Janelia Res. Campus, Ashburn, VA

Abstract: Feature selectivity in CA1 pyramidal cells is thought to depend on supralinear synaptic integration in individual branches driven by spatially clustered, temporally synchronous, and functionally related excitatory input. From the connectomics perspective, our understanding as to how axonal wiring patterns might provide such input remains incomplete. A simple way this input structure could be achieved is by single axons forming multiple, spatially clustered synapses onto the same dendritic branch; such an organization would have the corollary benefit of producing both anatomically and functionally related synaptic clusters. Using electron microscopy, we show that this form of connectivity is present in high density on distal, but not proximal dendrites. These coupled sets of connections in the distal dendrites were formed selectively onto large dendritic spines with distinctive pre- and postsynaptic ultrastructural features. Using large-scale array tomography, which enabled the visualization of axons from defined projections to CA1, we show that these coupled connections are formed more often by cortical inputs than by thalamic inputs. Collectively, these data suggest a simple wiring rule that enables the anatomical clustering of functionally related synaptic input onto individual branches of pyramidal cell dendrites.

Disclosures: E. Bloss: None. **S. Viswanathan:** None. **B. Karsh:** None. **J. Colonell:** None. **R. Fetter:** None. **N. Spruston:** None.

Nanosymposium

274. Cellular and Subcellular Synapse Organization: From Super-Resolution Imaging to Circuit Function

Location: 140A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***274.07

**Topic: ***B.08. Synaptic Plasticity

Support: F31 MH103902/MH/NIMH
R01 MH098016/MH/NIMH
R01 MH109341/MH/NIMH
NSF GRFP

Title: Post-transcriptional control of gene target specificity in neuronal plasticity

Authors: *T. R. GAMACHE, D. PHAM, A. AMEN, R. ROTH, G. DIERING, R. L. HUGANIR, M. K. MEFFERT
Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Long-term memories and the associated enduring changes in synaptic connectivity and function have been shown to require *de novo* protein synthesis in many settings. Activity-dependent responses also demonstrate input-specificity and can be restricted to the level of single dendrites and even single dendritic spines, implying the existence of mechanisms for compartment-selective regulation of the neuronal proteome during maintained forms of plasticity. Local protein synthesis constitutes one process that could allow for selective regulation of a subset of plasticity-related proteins only at activated synapses. However, mechanisms to specify and coordinate plasticity-related gene programs at the level of protein synthesis are not fully understood. We previously reported a post-transcriptional mechanism for generating pro-growth gene programs in neurons involving differential regulation of the biogenesis of microRNAs (miRNAs), which are small RNA molecules that can bind targeted mRNAs to repress and inhibit their translation. Brain-Derived Neurotrophic Factor (BDNF) was shown to exert dual regulation of neuronal miRNA biogenesis by rapid induction of two RNA-binding proteins, Dicer and Lin28a. Dicer upregulates the biogenesis of mature miRNAs in a relatively non-selective manner, while Lin28a selectively inhibits the maturation of only a subset of miRNAs. Lin28-targeted miRNAs include those of the Let-7 family, which regulate pro-growth genes associated with neuronal plasticity. We find that BDNF mediates rapid induction of Lin28a downstream of mitogen-activated protein kinase (MAPK) pathway activation through stabilization of Lin28a protein in a complex with Dicer and Dicer co-factor, TRBP. MAPK cascade activation is implicated as a hub in controlling neuronal plasticity in numerous settings. In ongoing work, we test the potential of the Lin28 / Let-7 pathway to confer compartment-restricted regulation of plasticity, miRNA biogenesis, and gene target specificity.

Disclosures: T.R. Gamache: None. **D. Pham:** None. **A. Amen:** None. **R. Roth:** None. **G. Diering:** None. **R.L. Huganir:** None. **M.K. Meffert:** None.

Nanosymposium

274. Cellular and Subcellular Synapse Organization: From Super-Resolution Imaging to Circuit Function

Location: 140A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***274.08

**Topic: ***B.07. Synaptic Transmission

Support: NINDS Grant 1F31NS101820

NINDS Grant 9R01NS089456

Title: Whole-cell mapping of excitatory and inhibitory synapses in layer 2/3 pyramidal neurons reveals structured synaptic organization

Authors: *D. IASCONE[1], Y. LI[2], U. SUMBUL[1], H. CHEN[2], V. ANDREU[3], F. GOUDY[3], L. PANINSKI[1], H. PENG[4], F. POLLEUX[1]
[1]Columbia Univ., New York, NY; [2]Computer Sci., Univ. of Georgia, Athens, GA; [3]Barnard Col., New York, NY; [4]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Proper function of neural circuits requires spatially and temporally balanced development of both excitatory and inhibitory synapses. Despite its importance for dendritic integration and information processing, very little is known about the subcellular organization of excitatory and inhibitory synapses that arise during circuit development in mammals. Studying the function of proteins involved in synaptic development *in vivo* is stymied by the difficulty of quantifying the distribution of all excitatory and inhibitory synapses across the entire dendritic arbor of single neurons. We recently overcame this limitation by developing Synapse Detector, a software toolkit capable of annotating the position and morphology of all synapses across the dendritic arbor of whole neurons genetically labeled *in vivo* using sparse *in utero* electroporation. As part of the Vaa3D image annotation platform, Synapse Detector is completely open source. We find that in layer 2/3 pyramidal neurons, both excitatory and inhibitory synapses exhibit structured organization across dendritic domains and individual dendritic segments. Interestingly, excitatory and inhibitory synaptic density is inversely correlated across basal dendritic domains, but covaries within individual dendritic segments. While inhibitory synaptic density increases towards distal apical tufts, we find that large (i.e. stronger) inhibitory synapses tend to be weighted towards intermediate segments proximal to the soma. Additionally, large excitatory and inhibitory synapses are distributed at high density only along a subset of dendritic segments i.e. are significantly more segregated than would be expected by random chance. This is consistent with previous reports that specific dendritic segments can be potentiated to fire dendritic spikes more readily than other segments even within the same branch order. We also observe a high density of dually innervated spines in apical oblique and tuft terminal dendrites consistent with thalamic innervation of these segments. Our results suggest that synaptic distribution across pyramidal cell dendrites is more precise and spatially segregated than previously appreciated, and that this degree of synaptic organization may have significant functional implications for dendritic integration and information processing.

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Nanosymposium

275. Proteinopathy Other Than Abeta and Tau

Location: 150B

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***275.01

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

Support: NIA AG12411
The Windgate Foundation
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NSF CRI CNS-0855248, EPS-0701890, EPS-0918970, and MRI CNS-0619069

Title: Defining the aggregate interactome in models of alzheimer amyloidopathy

Authors: M. BALASUBRAMANIAM[1,2], S. AYYADEVARA[1], X. DU[2], *S. T. GRIFFIN[1], R. SHMOOKLER REIS[1]
[1]Geriatrics, Univ. of Arkansas for Med. Sci., Little Rock, AR; [2]Bioinformatics & Genomics, Univ. of North Carolina, Charlotte, NC

Abstract: Age-progressive, protein-aggregation forming neurotoxic inclusions is the hallmark pathology in neurodegenerative diseases. Post-translational modifications (including phosphorylation, acetylation, and oxidation) can disrupt normal protein folding, and modified/misfolded proteins can interact to form insoluble complexes that contribute to aggregation. Comparing aggregate proteomics across diverse neuro-degenerative diseases has identified many common proteins, a high fraction of which appeared causal in nematode models of neuropathic protein aggregation. These results imply that aggregation is not a "random" event but instead may depend on a preferred sequence of protein-protein interactions. We sought to define and analyze aggregate architecture by constructing an "interactome" based on proteomic identification of cross-linked peptides, isolated from insoluble protein aggregates of SY5Y-APP_{Sw} cells. These cells, expressing a mutant APP identified in familial AD, form extracellular amyloid deposits, and thus provide a robust model system in which to develop a novel approach to aggregate analysis — defining protein-protein interfaces that are unique to specific aggregates. The resulting data were used to construct an AD/amyloid-specific interactome for identification of novel "hub" proteins and their interacting partners, most of which differed from previously defined "aggregation-seed" proteins such as Aβ or tau. Knock-down in *C. elegans* neurodegenerative-disease models, of the nematode orthologs of these particular "hub" proteins produced significant reductions in aggregates and important associated behavioral traits, thus implicating a subset of hub-hub interactions as pivotal in aggregate formation. Molecular-dynamic simulations predicted details of protein-protein interactions that were consistent with

cross-linking data, and also predicted misfolding consequences of observed post-translation modifications and their impacts on those interactions. Using such interactomes allows for identification of "hot-spot" regions critical to protein interactions. Such interactions may then serve as attractive drug targets for preventing aggregation or disrupting aggregates and, in this way, act to prevent or treat neurodegenerative diseases.

Disclosures: M. Balasubramaniam: None. **S. Ayyadevara:** None. **X. Du:** None. **S.T. Griffin:** None. **R. Shmookler Reis:** None.

Nanosymposium

275. Proteinopathy Other Than Abeta and Tau

Location: 150B

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***275.02

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

Support: Alzheimer’s Association AARG-17-499682

Title: The Parkinson's-associated protein TMEM230 accumulates in granulovacuolar degeneration bodies and dystrophic neurites of Alzheimer’s Disease

Authors: *X. WANG
Pathology, Case Western Reserve Univ., Cleveland, OH

Abstract: Transmembrane Protein 230 (TMEM230) is a newly identified protein associated with Parkinson's disease (PD) found in Lewy bodies and Lewy neurites of patients with PD or dementia with Lewy body disease. However, TMEM230 has not yet been investigated in the most common neurodegenerative disorder Alzheimer's disease (AD). Alzheimer's disease (AD) is the leading cause of dementia in the elderly. It is characterized by two pathologic hallmarks: neurofibrillary tangles (NFTs) and senile plaques (SPs), and is usually accompanied by other prominent pathological changes such as neuronal loss, granulovacuolar degeneration (GVD) and dystrophic neurites (DNs). NFTs are intracellular aggregates composed of bundles of paired helical filaments. In contrast, SPs are spherical extracellular lesions made up of bundles of amyloid-β (Aβ) peptide fibrils. Similar to NFTs, GVD bodies are also intracellular lesions, and defined as dense granules within large membrane-bound cytoplasmic vacuoles mainly seen in the CA1 and subiculum regions of the hippocampus. DNs are another prominent AD feature often found accumulating around SPs in the hippocampus and cortex, usually manifested as thickened and tortuous neuronal processes with either dendritic or axonal origin. Here, we demonstrate that the expression of TMEM230 is specifically increased in neurons in AD patients. Importantly, both GVD and dystrophic neurites, two prominent characteristic pathological structures

associated with AD, contain TMEM230 aggregates. TMEM230 immunoreactivity can be detected in neurofibrillary tangles-containing neurons and hyperphosphorylated tau positive DNs. TMEM230 accumulation is also noted around senile plaques. These findings identifying TMEM230 as a component of GVD and DNs suggest TMEM230 dysregulation as a likely mechanism playing an important role in the pathogenesis of AD.

Disclosures: X. Wang: None.

Nanosymposium

275. Proteinopathy Other Than Abeta and Tau

Location: 150B

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***275.03

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

Support: GACR Grant 16-15915S

Title: Pin1 and CDK5 regulates stability and solubility of phosphorylated CRMP2A in neurons

Authors: *M. BALASTIK, B. ELIASOVA, R. WEISSOVA, M. KLEISNEROVA, J. ZIAK
Mol. neurobiology, Inst. of Physiology, CAS, Praha, Czech Republic

Abstract: Collapsin Response Mediator Protein 2 (CRMP2) is a microtubule associated protein promoting microtubule assembly and axon growth. Its activity is negatively regulated by CDK5 and GSK3β phosphorylation inducing growth cone collapse. In Alzheimer's disease (AD), CRMP2 is present in neurofibrillary tangles (NFT) and its hyperphosphorylation is an early event in AD mouse model pathology. CRMP2 has two isoforms CMRP2A and B. Recently, we have shown that CRMP2A has a novel CDK5 target site - Ser27 (S27) phosphorylation of which leads to CRMP2A degradation. At the same time S27-phosphorylated CRMP2A is specifically bound and stabilized by prolyl isomerase Pin1. Physiological function of S27 phosphorylation or its role in AD pathology has not yet been shown.
Now we demonstrate that Pin1 not only stabilizes S27-phosphorylated CRMP2A, but also regulates its solubility. We show that in aging phosphorylated CRMP2A levels drop in triton soluble fraction, (similar to Pin1 levels) and that this decrease is even more prominent in Pin1 KO mice. Moreover, expression of p25, a CDK5 activator, elevates phospho-S27 levels in soluble fraction already in the young animals, but simultaneous Pin1 knockout (in double mutant mice) reduces the elevated levels. In contrast, the levels of triton insoluble phospho-S27 are not elevated in young p25tg mice but simultaneous Pin1 knockout leads to their increase already in the young mice. Similar increase in the insoluble phosphoS27 CRMP2 is seen only in the older WT and p25tg mice, possibly due to Pin1 level reduction. Finally, we show that, in 3xTgAD

mice, levels of both soluble and insoluble phospho-S27 are significantly elevated, S27 phosphorylation is visible mainly in the vicinity of senile plaques and it is present also in AD patient brains. These data indicate that Pin1 is important for maintenance of the soluble phosphoS27-CRMP2A and that Pin1 deficiency together with CDK5 hyperactivity could contribute to AD related CRMP2 pathology.

Disclosures: **M. Balastik:** None. **B. Eliasova:** None. **R. Weissova:** None. **M. Kleisnerova:** None. **J. Ziak:** None.

Nanosymposium

275. Proteinopathy Other Than Abeta and Tau

Location: 150B

Time: *Monday, November 13, 2017, 8:00 AM - 10:00 AM

Presentation Number: *275.04

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

Title: von Economo neurons and fork cell degeneration in right anterior insula is associated with network-based atrophy and impaired empathy in patients with frontotemporal dementia

Authors: ***L. PASQUINI**[1], A. NANA LI[1], G. TOLLER[1], J. DENG[1], J. BROWN[1], E.-J. KIM[1], S. E. GAUS[1], H.-H. HWANG[1], I. ALLEN[1], G. MARX[1], H. H. ROSEN[1], B. L. MILLER[1], K. RANKIN[1], W. W. SEELEY[1,2]
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Abstract: Frontotemporal dementia (FTD) is an umbrella term for a group of clinical syndromes resulting from neurodegeneration within rostral cortical, subcortical, and limbic structures. The behavioral variant (bvFTD) is characterized by loss of social-emotional functions and by structural and functional disruptions of the salience network, a large-scale brain system anchored by the right anterior insula (rAI) and anterior cingulate cortex. At the neuropathological level, more than 50% of patients with bvFTD show neuronal inclusions containing TDP-43, which selectively target von Economo neurons (VENs) and fork cells (FCs). These unique neuronal morphotypes are located primarily in the anterior insula and anterior cingulate cortex. Because these cells are absent in the brains of most laboratory mammals, little is known about VEN and FC axonal projections. We reasoned that the large-scale structural correlates of VEN and FC degeneration might shed light on the neural systems and functions to which these neurons contribute. Here, we combined antemortem neuroimaging and social cognitive data with postmortem neuropathological data to investigate the relationship between rAI VEN and FC vulnerability, regional atrophy, and impaired empathy in 16 patients with bvFTD or amyotrophic lateral sclerosis due to an underlying TDP-43 proteinopathy. Structural MRI was used to

quantify grey and white matter atrophy, and the interpersonal reactivity index, empathic concern subscale, was used to quantify emotional empathy. In postmortem tissue, systematic, unbiased counting was used to estimate the proportion of VENs and FCs containing TDP-43 inclusions within layer 5 of the rAI. A voxel-wise regression analysis revealed a significant correlation between the proportion of TDP-43-inclusion bearing VENs and FCs and atrophy within the rAI; frontal areas including the anterior cingulate, medial prefrontal, frontal pole, and orbitofrontal cortices; and thalamus. At the group level, atrophy in those regions correlated with empathic concern. A path analysis confirmed a model in which TDP-43-inclusion bearing VENs and FCs mediate widespread network degeneration, which, in turn, contributes to a loss of empathic concern in bvFTD spectrum illness. In conclusion, this study is the first to link VEN and FC degeneration to brain regional atrophy and impaired empathy. The findings suggest that VENs and FCs make an important contribution to large-scale networks on which social-emotional functions rely.

Disclosures: L. Pasquini: None. **A. Nana Li:** None. **G. Toller:** None. **J. Deng:** None. **J. Brown:** None. **E. Kim:** None. **S.E. Gaus:** None. **H. Hwang:** None. **I. Allen:** None. **G. Marx:** None. **H.H. Rosen:** None. **B.L. Miller:** None. **K. Rankin:** None. **W.W. Seeley:** None.

Nanosymposium

275. Proteinopathy Other Than Abeta and Tau

Location: 150B

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***275.05

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

Support: Mext Grant-in-aid project, Scientific Research on Innovation Area (Brain Protein Aging and Dementia control).
the Strategic Research Program for Brain Sciences and Brain/MINDS of the Ministry of Education, Culture, Sports, Science and Technology of Japan
the Japan Agency for Medical Research and Development

Title: FUS and ELAV-like proteins cooperatively control SynGAP isoform alpah2 in a 3'UTR length-dependent manner to promote dendritic spine maturation and cognitive function

Authors: *S. YOKOI[1], T. UDAGAWA[3], Y. FUJIOKA[2], D. HONDA[2], H. OKADO[4], H. WATANABE[2], M. KATSUNO[2], S. ISHIGAKI[2], G. SOBUE[2]
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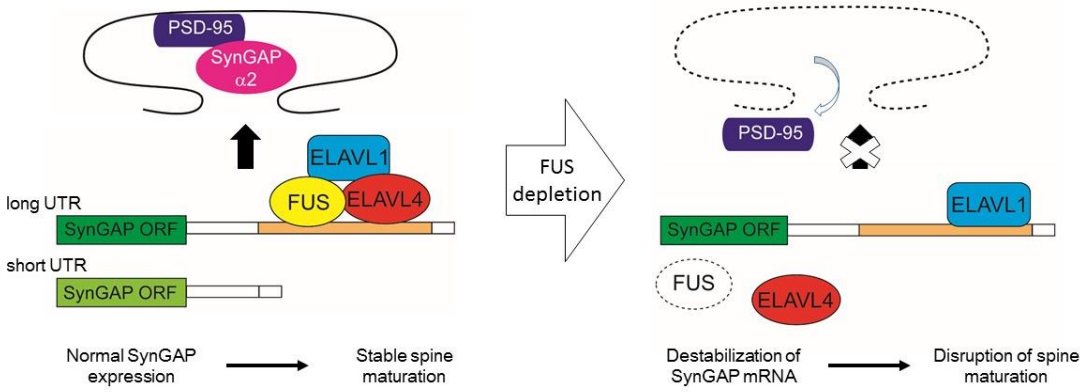
Abstract: FUS is an RNA-binding protein associated with frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). Previous reports demonstrated intrinsic roles of FUS in synaptic function. However, the mechanism of FUS regulation of spine morphology and its relation to FTLD/ALS pathogenesis remained unclear. We show that FUS depletion results in reduced mature spines with internalization of PSD-95 within the dendritic shaft, without affecting the expression level of PSD-95. These data suggest that FUS regulates PSD-95 binding partners, not PSD-95 itself. Mass spectrometry of PSD-95-interacting proteins identified SynGAP, whose expression is reduced upon FUS depletion. Moreover the expression of alternatively spliced SynGAP mRNA isoform α2, but not α1, is regulated by FUS, together with ELAV-like proteins in a 3'UTR length-dependent manner. SynGAP α2 is the dominant isoform with the long 3'UTR, while SynGAP α1 mainly contains alternatively spliced short 3'UTR. FUS and ELAVL4 cooperatively binds with SynGAP long 3'UTR specifically, and stabilizes α2 isoform. In contrast, ELAVL1 is recruited to SynGAP long 3'UTR when FUS is depleted and destabilizes SynGAP α2 mRNA. Finally, we show that FUS conditional knockout mice exhibits abnormal spine maturation and FTLD/ALS-like behavioral phenotypes, including disinhibition without memory deficits, which are ameliorated by SynGAP α2 supplementation. Our findings establish a novel link between FUS and ELAVL proteins for mRNA stability control at the 3'UTR and imply that this mechanism is crucial for maintaining synaptic morphology and cognitive function.



Disclosures: **S. Yokoi:** None. **T. Udagawa:** None. **Y. Fujioka:** None. **D. Honda:** None. **H. Okado:** None. **H. Watanabe:** None. **M. Katsuno:** None. **S. Ishigaki:** None. **G. Sobue:** None.

Nanosymposium

275. Proteinopathy Other Than Abeta and Tau

Location: 150B

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***275.06

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

Support: American Heart Association Predoctoral Grant 16PRE31130009
STSI Pilot Award 2016
NIH Grant R01 DK046335
Damon Runyon Postdoctoral Fellowship (DRG-2230-15)

Title: Circulating misfolded transthyretin oligomers detected by peptide probes decrease upon disease modifying therapies

Authors: *C. MONTEIRO[1], J. SCHONHOFT[1], X. JIANG[3], J. CHAPMAN[3], M. NOVAIS[4], E. T. POWERS[2], T. COELHO[4], J. W. KELLY[2]
[1]The Scripps Res. Inst., LA Jolla, CA; [2]The Scripps Res. Inst., La Jolla, CA; [3]Misfolding Diagnostics, Inc., La Jolla, CA; [4]Hosp. de Santo Antonio, Porto, Portugal

Abstract: The Transthyretin Amyloidoses are a group of degenerative diseases linked to the misfolding and misassembly of the plasma protein transthyretin (TTR). As with other amyloidoses, the mechanism of how TTR amyloidogenesis leads to loss of post-mitotic tissue is not completely understood. Increasing evidence supports the hypothesis that the major toxic species in a variety of neurodegenerative diseases are soluble misfolded oligomers. However, very few studies provide direct support of this hypothesis in humans, mainly because i) the availability of biological fluids / tissues relevant to each disease is limited and ii) the conformational probes needed for selectively detecting distinct and potentially toxic structures are generally not available. Hence, understanding the structure-proteotoxicity relationships driving amyloid diseases remains challenging, hampering the development of early diagnostic strategies, as well as response-to-therapy biomarkers. We have recently developed fluorescently tagged peptide-based probes that selectively bind to and label misfolded TTR oligomers circulating in the plasma of TTR hereditary amyloidosis patients presenting with a predominant neuropathic phenotype. These probes reveal that misfolded TTR oligomer levels are much lower in healthy controls and in asymptomatic carriers than in symptomatic polyneuropathy patients. We used the peptide-based probes to analyze a cohort of patients before and after treatment with tafamidis, a TTR kinetic stabilizer that slows the progression of neuropathy. The circulating misfolded TTR oligomers in the plasma of these patients decreased after tafamidis treatment, consistent with results shown using conformation specific antibodies. This correlation suggests that the circulating misfolded TTR oligomers could be a driver of pathology. Furthermore, quantification of plasma oligomer levels by these methods could become an early diagnostic

strategy, a response-to-therapy biomarker, and a useful tool for continuing the pursuit of understanding structure-proteotoxicity relationships in the TTR amyloidoses.

Disclosures: C. Monteiro: None. **J. Schonhoft:** None. **X. Jiang:** A. Employment/Salary (full or part-time):; Misfolding Diagnostics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Misfolding Diagnostics, Inc. **J. Chapman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Misfolding Diagnostics, Inc.. **M. Novais:** None. **E.T. Powers:** None. **T. Coelho:** None. **J.W. Kelly:** None.

Nanosymposium

275. Proteinopathy Other Than Abeta and Tau

Location: 150B

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***275.07

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

Support: -Spanish Ministry of Economy and Competitiveness (SAF-2014-53040-P, Jesús Ávila)
-Spanish Ministry of Economy and Competitiveness (RYC-2015-17189 (María Llorens-Martín)
-Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED, Spain) (Jesús Ávila)
-Alzheimer´s Association (2015-NIRG-340709 (María Llorens-Martín))
-The Association for Frontotemporal Degeneration (2016 Basic Science Pilot Grant Award (María Llorens-Martín)).

Title: Versatile use of rtTA-expressing retroviruses in the study of adult neurogenesis and neurodegenerative diseases

Authors: *M. LLORENS-MARTÍN[1,2,3], C. M. TEIXEIRA[4], J. TERREROS-RONCAL[5], N. PALLAS-BAZARRA[5], J. AVILA[3]
[1]Mol. Neurobio., Ctr. De Biología Mol. severo Ochoa CBMSO, Madrid, Spain; [2]Mol. Biol., Univ. Autónoma de Madrid, Madrid, Spain; [3]Ctr. de Investigación Biomédica en Red enfermedades neurodegenerativas, CIBERNED, Madrid, Spain; [4]Emotional Brain Inst., New York, NY; [5]Ctr. de Biología Mol. “Severo Ochoa”, Madrid, Spain

Abstract: New neurons are generated in the hippocampal dentate gyrus (DG) throughout adulthood. Newly generated granule neurons become fully integrated in the trisynaptic circuit

and are functionally indistinguishable from surrounding mature neurons at the end of the maturational process. Tetracycline-regulated systems have been traditionally used to drive conditional gene expression both in vivo and in vitro. The regulation of these systems is achieved through the Tetracycline-regulated transactivator (tTA) element, which binds to the tetO operator (tetR) sequence and induces transcription of the transgene of interest. Numerous combinations of mice engineered by tTA/ TetR systems have been generated in order to model different aspects of neurodegenerative diseases. In this regard, a model of particular relevance in the study of Alzheimer disease (AD) is the GSK-3 Beta overexpressing (GSK-3-OE) mouse, in which GSK-3 is overexpressed in hippocampal and cortical neurons. Although these mice mimic numerous features of the AD brain, a series of non-cell autonomous effects, such as neuroinflammation and microglial activation also occur in their brain and may act as a confounding factor under certain circumstances. In order to avoid these indirect effects, and exploiting the fact that tTA can be delivered to target cells by viral vectors, we have recently developed a novel strategy, which, to the best of our knowledge, has not been applied to the study of adult hippocampal neurogenesis (AHN). This strategy is based on the use of tetR-GSK-3 mice and the hippocampal delivery of rtTA by means of an rtTA-IRES-GFP-expressing retrovirus. Using this system, we achieved rapid and selective in vivo overexpression of GSK-3 in the newborn granule neurons infected by the retrovirus. Using this innovative strategy, we found that GSK-3 caused a cell-autonomous impairment of the morphological and synaptic maturation of newborn granule neurons. In addition, we examined whether GSK-3 overexpression limits the stimulatory actions of physical activity on these cells. While physical exercise increased the connectivity and morphological maturation of tet-OFF cells, these effects were not triggered in tet-ON cells. Thus, we have designed an innovative methodology by which to induce selective GSK-3 overexpression in newborn granule neurons. This strategy allows for the selective study of the cell-autonomous effects caused by this protein in newborn granule neurons in absence of non-cell-autonomous effects such as neuroinflammation. Given that the activity of GSK-3 is increased in the brains of individuals with AD, these data may be relevant for non-pharmacological therapies for AD.

Disclosures: M. Llorens-Martín: None. **C.M. Teixeira:** None. **J. Terreros-Roncal:** None. **N. Pallas-Bazarra:** None. **J. Avila:** None.

Nanosymposium

275. Proteinopathy Other Than Abeta and Tau

Location: 150B

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***275.08

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

Support: National Institute of Neurological Disorders and Stroke (NS085770)

National Institute on Aging Northwestern University Alzheimer's Disease Center (AG013854)

Title: Inverse relationship between TDP-43 pre-inclusions and mature inclusions in primary progressive aphasia with FTLD-TDP pathology

Authors: *G. KIM, K. BOLBOLAN, T. GEFEN, S. WEINTRAUB, E. BIGIO, M.-M. MESULAM, C. GEULA
Cognitive Neurol. and Alzheimer's Dis. Ctr., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Phosphorylated 43-kDa TAR DNA-binding protein (TDP-43)-positive "pre-inclusions" (diffuse nuclear and/or cytoplasmic staining) have been described in recent years, suggesting that TDP-43 inclusions develop in stages similar to the progressive accumulation of phosphorylated tau in pre-tangles and tangles in Alzheimer's disease (AD). The purpose of this study was to investigate the relationship between the accumulation of TDP inclusions and pre-inclusions. Subtypes of TDP-43 pre-inclusions were identified and quantitatively examined for their regional and hemispheric distribution in primary progressive aphasia (PPA), a dementia syndrome characterized by gradual dissolution of language as the most salient clinical feature. Immunohistochemistry was performed using an antibody against hyperphosphorylated TDP-43 (pS409/410-2) on 40-µm whole-hemisphere sections from the brains of five PPA participants with post-mortem diagnoses of frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP). Four were right-handed and had asymmetric left hemisphere atrophy, while the fifth subject was left-handed with right hemisphere language dominance and asymmetric right hemisphere atrophy. Unbiased stereology was used to quantify both inclusions and pre-inclusions in a region of high mature TDP inclusion density and a region with low mature TDP inclusion density, as well as the contralateral homologues, in each case. Seven morphologic subtypes of cortical TDP pre-inclusions were identified: smooth, granular/dot-like, or fibrillar staining with localization to the nucleus, cytoplasm, or both. Quantitation revealed an inverse relationship between TDP inclusions and pre-inclusions: regions with lower burden of mature TDP inclusions were characterized by higher densities of pre-inclusions, while increasing burden of mature inclusions corresponded to lower densities of pre-inclusions. Mature inclusions showed significant asymmetry that favored the language-dominant hemisphere ($p<0.01$), while pre-inclusions displayed the opposite pattern ($p<0.01$), with higher densities of pre-inclusions in the non-dominant hemisphere than their contralateral homologues. Additionally, within each hemisphere, the area with higher mature inclusion density displayed lower pre-inclusion counts ($p<0.05$). These results suggest that pre-inclusions are present in greater abundance prior to the formation of mature TDP inclusions, and develop through progressive stages into dark neuritic, intracytoplasmic, or intranuclear aggregates. It remains to be seen whether the observed inverse relationships are common to all TDP-43 proteinopathies.

Disclosures: G. Kim: None. **K. Bolbolan:** None. **T. Gefen:** None. **S. Weintraub:** None. **E. Bigio:** None. **M. Mesulam:** None. **C. Geula:** None.

Nanosymposium

276. Tauopathies

Location: 147A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***276.01

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: AHA-11BGIA (ZZ)
NIH R01HL092071 (MVP)
Anesthesiology Department Duke

Title: Annexin-A1 tripeptide attenuates microglia activation after cardiac surgery in rats

Authors: *Z. ZHANG[1], Q. MA[1], B. SHAH[1], G. MACKENSEN[2], D. LO[1], J. P. MATTHEW[1], M. V. PODGOREANU[1], N. TERRANDO[1]
[1]Duke Univ. Med. Ctr., Durham, NC; [2]Univ. of Washington Med. Ctr., Seattle, WA

Abstract: Background: Cardiac surgery often leads to cognitive impairments, including delirium and postoperative cognitive dysfunction (POCD). We developed a model of cardiopulmonary bypass with deep hypothermic circulatory arrest (DHCA) and tested the pro-resolving effects of a novel bioactive Annexin-A1 tripeptide (ANXA1sp) on neuroinflammation and cognition.
Methods: Male rats underwent 60 min DHCA at 18°C and received either vehicle or ANXA1sp (2 mg/kg, iv) followed by timed reperfusion ranging from 3 hr to 7 days (n=5 to 11/group/timepoint). BV2 microglial cells were used to test the effects of ANXA1sp (10 μM) on oxygen-glucose deprivation followed by reoxygenation from 3-24 hr in vitro. Neuronal apoptosis (TUNEL), necrosis (acid fuchsin-celestine blue), microglial activation (IBA1), NF-kB activity, cytokine production and leukocyte extravasation (MPO) were assessed in tissue and cell culture.
Results: Rats treated with ANXA1sp showed improved neurological scores and shorter latency in the Morris Water Maze at 3 and 7 days post-reperfusion. ANXA1sp reduced cortical and hippocampal neuronal apoptosis and necrosis at 24 hr and 7 days ($p \leq 0.05$). This was associated with a reduction in microglia morphology (Fig), inhibition of NF-κB activation, and suppression of downstream pro-inflammatory cytokines ($p \leq 0.05$), which were replicated in vitro using BV2 cells.
Conclusions: Our findings provide evidence that treatment with a novel bioactive Annexin-A1 tripeptide prevents POCD by attenuating microglial activation and resolving neuroinflammation after cardiac surgery.

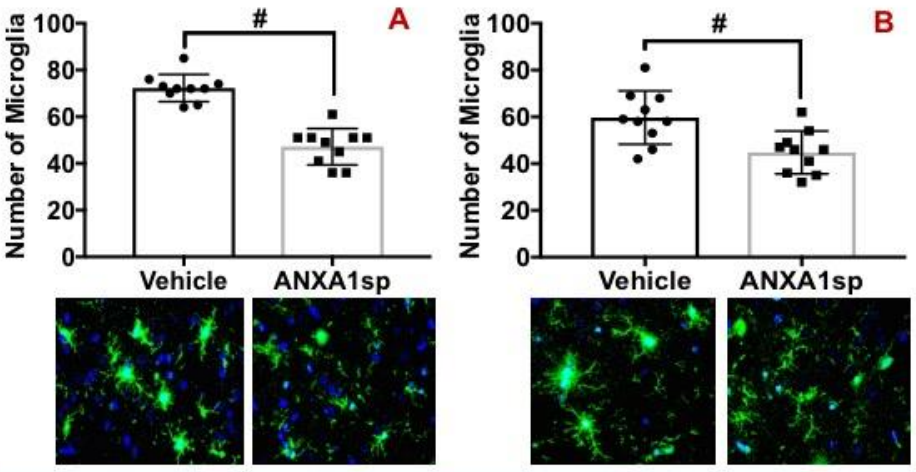


Figure. Annexin-A1 tripeptide (ANXA1sp) attenuated microglia activation induced by cardiac surgery by reducing the number and body size of the activated microglia at both cortex (A) and hippocampus (B) in rats at 24 hours after CPB/DHCA. Results are presented as mean ± SD. #p < 0.01, n = 10. For immunostaining protocol (*top panels*), IBA1 in green for microglia; DAPI in blue for Nucleic DNA.

Disclosures: Z. Zhang: None. **Q. Ma:** None. **B. Shah:** None. **G. Mackensen:** None. **D. Lo:** None. **J.P. Matthew:** None. **M.V. Podgoreanu:** None. **N. Terrando:** None.

Nanosymposium

276. Tauopathies

Location: 147A

Time: *Monday, November 13, 2017, 8:00 AM - 10:15 AM

Presentation Number: *276.02

Topic: *C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant GM107469
NIH Grant AG048410
Whitehall Foundation Research Grant
CNPq fellowship-Brazil

Title: CX_3CR1^+ monocytes modulate learning and learning-dependent synapse remodeling via TNFα

Authors: *G. YANG, H. MOURA SILVA, J. J. LAFAILLE, J. GARRÉ
New York Univ. Sch. of Med., New York, NY

Abstract: Impaired learning and cognitive function often occurs during systemic infection or inflammation. However, the underlying mechanisms remain poorly understood. Here we show that systemic immune challenge causes synapse loss, impairments in learning-dependent synapse formation and deficits in multiple learning tasks in mice. These synaptic alterations observed in the cortex are mediated by peripheral blood monocytes and do not require microglial function in the central nervous system. We further show that activation of CX_3CR1^{high} monocytes impairs motor learning and learning-related synapse structural plasticity through tumor necrosis factor (TNF)-α-dependent mechanisms. Together, our results highlight CX_3CR1^{high} monocytes and TNFα as potential therapeutic targets for preventing peripheral inflammation-induced cognitive dysfunction.

Disclosures: **G. Yang:** None. **H. Moura Silva:** None. **J.J. Lafaille:** None. **J. Garré:** None.

Nanosymposium

276. Tauopathies

Location: 147A

Time: *Monday, November 13, 2017, 8:00 AM - 10:15 AM

Presentation Number: *276.03

Topic: *C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant R01GM088801
NIH Grant R01AG041274
NIH Grant R01HD086977

Title: Tau communicates between neuron and microglia to generate neuroinflammation

Authors: ***Z. XIE**[1], Y. DONG[2], F. LIANG[3], Q. QUAN[3]
[1]Anesthesia, Critical Care and Pain Med., [2]Massachusetts Gen. Hosp. and Harvard Med. Sch., Charlestown, MA; [3]Rowland Inst. at Harvard Univ., Cambridge, MA

Abstract: Sevoflurane anesthesia induces cognitive impairment, Tau phosphorylation and increase in interleukin-6 (IL-6) levels in young mice (*1*). However, the underlying mechanism by which Tau (primarily existed in eurons) interacts with IL-6 (mainly generated in microglia cells) remains unknown. Primary neurons and microglia cells were harvested from wild-type and Tau knockout mice. The neurons or microglia cells or the combination of them were treated with sevoflurane. Same anesthesia was received by young mice (6 day-old). Tau phosphorylation, levels of Tau, IL-6, LDH, and NF-κB were then determined by Western blot analysis, ELISA, immunohistochemistry and nano technology. The sevoflurane anesthesia induced Tau phosphorylation in neurons and increased total Tau levels (but not LDH levels) in the cultured media of the neurons, which were inhibited by lithium, the inhibitor of GSK3β. In addition, the

sevoflurane anesthesia increased the levels of Alix and Flotillin-2, the markers of Extracellular Vesicles (EV), as well as the phospohorylated Tau inside the EV. The sevoflurane anesthesia increased extracellular IL-6 levels in the combination of neurons plus microglia cells, but not alone. Using both immunohistochemistry and nanosensor technology, Tau levels inside the microglia cells harvested from the Tau KO mice were detected after treatment of the conditioned media from sevoflurane treated neurons. Thus, the sevoflurane-induced increases in the IL-6 levels werepotentially mediated by the interaction of neuron and microglia cell through Tau protein. The sevoflurane anesthesia also activates NF-κB signaling pathway, which was also inhibited by lithium. Finally, the sevoflurane anesthesia increased Tau levels in the blood of the young mice. These data suggest that sevoflurane induces Tau phosphorylation via GSK3β. The phosphorylated Tau then exits from neurons via EV. The existed phosphorylated Tau can enter microglia cells to generate IL-6 via NF-κB signaling pathway. These results reveal that Tau protein may serve as a "messenger" to communicate between neurons and microglia cells, leading to euroinflammation in young mice. **References** 1. G. Tao *et al.*, Sevoflurane induces tau phosphorylation and glycogen synthase kinase 3beta activation in young mice. *Anesthesiology* **121**, 510-527 (2014).

Disclosures: **Z. Xie:** None. **Y. Dong:** None. **F. Liang:** None. **Q. Quan:** None.

Nanosymposium

276. Tauopathies

Location: 147A

Time: *****Monday, November 13, 2017, 8:00 AM - 10:15 AM

Presentation Number: *****276.04

Topic: *****C.10.Tauopathies, Tau-dementias, and Prion diseases

Title: Isoflurane reduces brain-derived neurotrophic factor release leading to inhibition of glutamate exocytosis

Authors: K. W. JOHNSON[1], F. S. LEE[2], H. C. HEMMINGS, Jr[1], *J. PLATHOLI[1]
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Abstract: General anesthetics modulate synaptic transmission by acting on multiple pre- and postsynaptic targets including neurotransmitter release, neurotransmitter receptors, and dendritic spine dynamics. Inhibition of glutamate release is one of many ways general anesthetics depress excitatory synaptic transmission but the underlying cellular and molecular targets remain unclear. We hypothesized that isoflurane, a common general anesthetic, reduces brain-derived neurotrophic factor (BDNF) release, resulting in decreased presynaptic Ca^{2+} entry and glutamate release. Dissociated hippocampal neurons from wild-type and loss-of-function BDNF Val66Met knock-in mice with reduced BDNF secretion were used to test this. Isoflurane-induced changes

in BDNF release were measured using the genetically encoded biosensor BDNF-pHluorin. Neurons in culture with varying levels of BDNF secretion were used to determine the effect of reduced endogenous BDNF amounts on Ca^{2+} entry and glutamatergic synaptic vesicle exocytosis, using the fluorescent Ca^{2+} indicator MgGreen and vGlut1-pHluorin, respectively. Our results show that isoflurane attenuates BDNF release and identifies a new molecular signaling pathway contributing to inhibition of glutamate release by isoflurane.

Disclosures: K.W. Johnson: None. **F.S. Lee:** None. **H.C. Hemmings:** None. **J. Platholi:** None.

Nanosymposium

276. Tauopathies

Location: 147A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***276.05

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant R01 GM084979

Title: Effect of general anesthetic on cognitive impairments and synaptic deficits in triple transgenic Alzheimer's mouse

Authors: G. LIANG[1], D. J. JOSEPH[3], C. LIU[4], J. PENG[5], *R. G. ECKENHOFF[6], H. WEI[2]
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Abstract: Inhalational anesthetics can accelerate or attenuate the progression of neuropathology and cognitive impairment in Alzheimer Disease (AD), but the mechanisms are unclear. We examined the association between the isoflurane-mediated effects on neuropathology, cognition, and synaptic physiology in the triple transgenic Alzheimer disease model (3xTgAD) in young, postnatal day 7 (P7) and aged mice (14+ months). Male and female C57BL6/J (NonTg) and 3xTg-AD mice were anesthetized with 1.5% isoflurane for 2 h/day for five consecutive days. Plasma levels of S100β, measured by the enzyme-linked immunosorbent assay 6 h after anesthesia, were elevated in both the young and aged groups in both genotypes, but this elevation was greater in the 3xTg-AD mice. Immunohistochemical analysis detected significantly more amyloid beta accumulation in young and old 3xTgAD mice exposed to isoflurane. Spatial memory, measured by the Morris Water Maze 30 days after the last anesthetic exposure, showed impaired reference memory learning, short-term and working memory in both young NonTg and

3xTg-AD mice compared to age-matched controls. No differences were found in extracellular field recordings conducted in the CA1 region in hippocampal slices from P7 NonTg and 3xTg-AD mice exposed in vivo to isolfurane, but untreated aged 3xTg-AD mice exhibited hyperexcitable basal synaptic transmission, unstable LTP, and reduced paired pulse facilitation (PPF) compared to untreated aged NonTg mice. Isoflurane depressed basal synaptic transmission and PPF in both ages and genotypes, but a stronger depression of synaptic transmission and PPF was noted in the aged 3xTg-AD mice. Isoflurane impaired LTP in young 3xTgAD and in both young and aged NonTg mice as reflected by the lack of change in extracellular field potential (fEPSP) slope from baseline. By contrast, isoflurane normalized and potentiated fEPSP slope in aged 3xTgAD mice to control levels. Finally, acute application of isoflurane to hippocampal slices from aged NonTg as well as from both young NonTg and 3xTg-AD mice previously exposed to the same anesthetic, suppressed LTP. However, aged 3xTg-AD control mice, previously exposed to air, exhibited normal LTP during this acute isoflurane application, but aged 3xTg-AD mice, previously exposed to isoflurane, displayed severely reduced LTP in response to acute isoflurane application. Our results indicate that isoflurane-mediated neuropathologic and cognitive defects in AD mice are associated with synaptic pathologies in an age-dependent manner. Based on these findings, the extent of this association with age and, possibly, treatment paradigms warrant further study.

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Nanosymposium

276. Tauopathies

Location: 147A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***276.06

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH R01 GM098308 and R21 AG047472

Title: Amantadine attenuates sepsis-induced cognitive dysfunction: Contribution of inhibiting toll-like receptor 2

Authors: *Z. ZUO[1], W. XING[2], P. HUANG[2]
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Abstract: Amantadine has been shown to reduce anesthesia and surgery-induced neuroinflammation and cognitive dysfunction. It is known that sepsis can impair brain function. Here, we showed that cecal ligation and puncture (CLP) induced neuroinflammation and cognitive dysfunction. CLP also increased the expression of toll-like receptor 2 (TLR2), TLR4 and TLR9 in CD-1 male mice. These three TLRs are the major ones in the brain. Amantadine attenuated these effects of CLP. A TLR1/TLR2 inhibitor also attenuated sepsis-induced neuroinflammation and cognitive dysfunction. Similarly, sepsis also induced neuroinflammation and cognitive dysfunction in the C57BL mice. Although sepsis also induced neuroinflammation and cognitive dysfunction in the TLR2 knockout mice, the effects of amantadine on the neuroinflammation and cognitive dysfunction were minimal. These results suggest that amantadine attenuates sepsis-induced neuroinflammation and cognitive dysfunction at least partly by inhibiting TLR-2.

Disclosures: Z. Zuo: None. **W. Xing:** None. **P. Huang:** None.

Nanosymposium

276. Tauopathies

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**Presentation Number: ***276.07

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH grant R01GM088801
NIH grant R01AG041274
NIH grant R01HD 086977
Young investigator research grant No. 81400879 from National Natural Science Foundation of China

Title: Cyclophilin D-associated mechanism of sevoflurane-induced inhibition of neurogenesis

Authors: *Y. ZHANG[1,2], J. ZHENG[3], Z. XIE[4]
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Abstract: Introduction: Children who have multiple exposures to anesthesia and surgery may have an increased risk of developing a learning disability [reviewed in [1]]. Our previous studies showed that anesthetic sevoflurane-induced cognitive impairment [2] and inhibited neurogenesis [3]. However, the underlying mechanism remains largely unknown. Cyclophilin D (CypD), a

component of mitochondrial permeability transition pore (mPTP), is critical for cognitive function [4]. Therefore, we set out to assess whether sevoflurane inhibits neurogenesis via CypD/mPTP-regulated reduction in neural progenitor cells (NPCs) proliferation, leading to cognitive impairment in young mice.

Methods: Wild-type (WT) and CypD knockout (KO) mice received 3% sevoflurane 2 hours daily for 3 days from postnatal day (P)6 to P8. We administered 5-Bromo-2'-deoxyuridine (Brdu) (50 mg/kg) to the mice 30 minutes before each of the sevoflurane treatment. We then assessed the effects of the sevoflurane on neurogenesis and cognitive function was determined by using immunohistochemistry and Morris Water Maze. NPCs harvested from WT and CypD KO mice were treated with 4.1% sevoflurane for 6 hours. We then determined the mitochondrial functions, DNA damage and proliferations of the NPCs using flow cytometer, Western blot, and immunocytochemistry, respectively.

Result: The sevoflurane decreased Nestin- and Brdu-positive cells in the brain slices of P8 or P31 mice, and increased the CypD levels, induced opening of mPTP, caused DNA damage, decreased NPC proliferation, and induced cognitive impairment in the WT mice. These effects were mitigated by knockout of CypD.

Conclusion: These data suggest that sevoflurane may increase CypD level, which then causes mPTP opening, leading to DNA damage of NPCs. The damaged DNA decreases NPC proliferation, ultimately leading to cognitive impairment in the young mice.

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Disclosures: Y. Zhang: None. **J. Zheng:** None. **Z. Xie:** None.

Nanosymposium

276. Tauopathies

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**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant AG31742
Foundation for Anesthesia Education and Research
Austin Lamont Endowment, Department of Anesthesiology and Critical Care at the University of Pennsylvania Perelman School of Medicine

Title: Effects of propofol and surgery on neuropathology and cognition in the 3xTgAD Alzheimer transgenic mouse model

Authors: *M. F. ECKENHOFF, F. MARDINI, J. X. TANG, J. C. LI, M. J. ARROLIGA, R. G. ECKENHOFF
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Abstract: Prior work suggests that surgery with volatile general anesthetics amplifies the neuropathology and cognitive impairment of animals made vulnerable by age or specific transgenes. We hypothesize that surgery under propofol anesthesia, a widely used intravenous general anesthetic, will have fewer delayed cognitive and neuroinflammatory sequelae in a vulnerable transgenic mouse model. We conducted sterile cecal ligation and excision surgery in cognitively presymptomatic (11 months) 3xTgAD mice under intraperitoneal propofol anesthesia. Aged matched 3xTgAD control mice received vehicle or propofol without surgery. Morris water maze testing was conducted at 3 weeks and 15 weeks post-operatively (PO). Brains were examined with quantitative immunohistochemistry for amyloid beta plaques, tau pathology, and microglial activation. Acute changes in neuroinflammatory cytokines were assessed in separate cohorts at 6h PO. We detected no significant differences between groups in escape latencies at either 3 or 15 weeks PO, but detected a significant effect of surgery in the probe test at both 3 and 15 weeks PO. Spatial working memory was unaffected at 16 weeks PO in any group. No effects of either propofol alone or surgery were detected on plaque formation, tau aggregates, or neuroinflammation. Acute biochemical assays detected no effects in brain interleukin-10 or interleukin-6 levels. In conclusion, surgery in a vulnerable transgenic animal under propofol anesthesia was associated with minimal to no changes in short and long term behavior and no changes in neuropathology. This suggests that propofol anesthesia is associated with better cognitive outcomes in the aged, vulnerable brain as compared with inhalational anesthesia.

Disclosures: M.F. Eckenhoff: None. **F. Mardini:** None. **J.X. Tang:** None. **J.C. Li:** None. **M.J. Arroliga:** None. **R.G. Eckenhoff:** None.

Nanosymposium

276. Tauopathies

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**Presentation Number: ***276.09

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH R01GM103842

Title: Mitochondrial PKA activation in the developing murine brain during exposure to isoflurane with carbon monoxide

Authors: *R. J. LEVY, A. WANG, Y. LONG
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Abstract: Background: Oxidative stress has been implicated in anesthesia-induced neurotoxicity and ROS arise from mitochondria in this setting. We have previously shown that isoflurane overactivates cytochrome oxidase (CcOX) resulting in lipid peroxidation in newborn mouse forebrain. Importantly, combined exposure to isoflurane with carbon monoxide (CO), a known modulator of CcOX, prevented CcOX stimulation and limited oxidative stress via CcOX tyrosine phosphorylation. Tyrosine phosphorylation of CcOX subunit I, the active site, is thought to occur via a cAMP-dependent pathway, however, the mechanism of hyperphosphorylation during combined exposure to isoflurane with CO is unknown. We hypothesized that CO would activate the cAMP-PKA pathway within forebrain mitochondria of newborn mice during isoflurane exposure. We aimed to identify components of the adenylyl cyclase-cAMP-PKA pathway within mitochondria, to quantify mitochondrial cAMP levels, and to measure PKA activity. Methods: 7-day old C57Bl/6 mice underwent 1-hour exposure to 0 ppm (air), 5 ppm, or 100 ppm CO in air with or without isoflurane. Steady-state levels of sAC, AKAP121, and PKA within forebrain mitochondria were determined via immunoblot analysis. Mitochondrial cAMP levels and PKA activity measured via ELISA and 5'AMP determined with a modified Malachite Green assay. We evaluated 4-6 animals per group. Significance was assessed with Kruskal-Wallis test and post hoc Bonferroni correction and set at $P < 0.05$. Results: Each component of the adenylyl cyclase-cAMP-PKA pathway localized within forebrain mitochondria without differences in steady-state levels of sAC, AKAP121, or PKA between cohorts. Forebrain mitochondrial PKA activity was significantly increased in animals exposed to 100 ppm CO with isoflurane. However, mitochondrial levels of cAMP decreased significantly in both cohorts exposed to CO with isoflurane versus isoflurane-exposed animals. Significant increases in 5'AMP levels were seen in both cohorts exposed to 100 ppm CO. Conclusions: Activation of mitochondrial PKA occurred in immature mice exposed to isoflurane with 100 ppm CO with a concomitant decline in mitochondrial cAMP levels. Decreases in cAMP in this cohort reflected accelerated hydrolysis given the increase in 5'AMP. The data suggest cAMP-dependent tyrosine phosphorylation of

CcOX subunit I during combined exposure to CO with isoflurane. The work provides insight into how combined exposure to CO with isoflurane confers anti-oxidant neuroprotection in the developing brain via a key regulatory mechanism.

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Nanosymposium

277. Representation of Objects and Scenes

Location: 150A

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**Presentation Number: ***277.01

**Topic: ***D.07. Vision

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NIH-NEI- R01-EY014970-11A1
European Union's Horizon 2020 research and innovation programme under grant agreement No 705498

Title: Does the primate ventral stream need cortical feedback to compute rapid online image-by-image object identity?

Authors: *K. KAR[1], J. KUBILIUS[1,3], K. SCHMIDT[1], E. B. ISSA[1], J. J. DICARLO[2,1]
[1]McGovern Inst. for Brain Res., [2]Brain & Cognitive Sci., MIT, Cambridge, MA; [3]Brain and Cognition, KU Leuven, Leuven, Belgium

Abstract: Object identities across different images are represented in the pattern of neural responses in primate inferior temporal (IT) cortex. The algorithms that best approximate these neural responses in the primate (macaque) IT belong to the family of hierarchical convolutional neural networks (HCNN) with predominantly feedforward architectures. However, there is strong anatomical evidence of both local recurrent and long-range feedback connections within the primate ventral visual cortex. We hypothesized that the impact of these feedback connections would be most relevant at later time points in the stimulus driven IT responses. Therefore image representations that critically rely on these feedback computations will require additional processing time (beyond the initial evoked response at 70-100 ms; feedforward pass) to emerge in IT. To test this hypothesis, we measured neural activity (chronically implanted multielectrode arrays; 288 electrodes/monkey) from IT cortex in two monkeys, while they simultaneously performed an image by image object identity estimation task (~3000 images, each containing 1 of 10 possible objects, randomly interleaved to neutralize attention). We first observed that monkeys outperform most HCNNs (e.g. AlexNet, VGG, GoogleNet) on a significant number of images (‘challenge images’). Consistent with previous results, we observed that the top layers of

performance optimized HCNNs predict ~50% of IT neural variance during the feedforward pass. However, their predictions significantly worsened (< 20% explained variance) at later time points (140-200 ms) from the image onset. Taken together, this suggests that, during these later time points, monkeys might be benefitting from additional computations from feedback and lateral connections (unavailable in the feedforward HCNNs which results in their poor prediction of IT responses) that help boost their object identification performances over that of HCNNs. Consistent with this hypothesis, we also observed that object identity decodes from IT neural populations for the challenge images took ~20-30ms longer to emerge (peaking around 150-180 ms from stimulus onset) compared to images where monkeys and HCNNs perform equally ('control images'). These observed neural decoder latency differences were not explained by individual neural response latencies or low-level image property differences like contrast, luminance or spatial frequency. These results imply the importance of feedback in ventral stream object inference, and the observed image-by-image differences constrain the next generation of ventral stream models.

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Nanosymposium

277. Representation of Objects and Scenes

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**Topic: ***D.07. Vision

Support: NIH Grant NCT01617408

Title: A functional dissociation of category-selective brain areas based on their response to moving and static stimuli

Authors: *D. PITCHER[1], *D. PITCHER[1], G. R. IANNI[2], L. G. UNGERLEIDER[3]
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Abstract: Functional magnetic resonance imaging (fMRI) studies have identified brain areas that respond selectively to different categories of visual stimuli. Multiple face-, body- and scene-selective areas are found across the brain, but the functional distinctions between these areas remain unclear. To address this issue, we measured the fMRI response to dynamic and static stimuli in category-selective regions involved in face, body and scene perception. Human participants (N=22) were scanned using fMRI at 7 Tesla while viewing short video clips

containing faces, bodies, scenes, objects or scrambled objects, as well as static images taken from these videos. Results demonstrated a functional dissociation between category-selective areas. Lateral areas, including face-selective regions of interest (ROIs) in the posterior and anterior superior temporal sulcus (STS), the extrastriate body area (EBA) and the occipital place area (OPA) responded more to moving than static stimuli. By contrast, ventral and medial category-selective regions, including the fusiform face area (FFA), occipital face area (OFA), face-selective voxels in the amygdala, fusiform body area (FBA), retrosplenial complex (RSC) and parahippocampal place area (PPA) all responded equally to moving and static stimuli. This dissociation across brain areas that respond selectively to different visual categories suggests that face, body and scene-selective networks may be functionally organized along a common dimension in the human brain.

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Nanosymposium

277. Representation of Objects and Scenes

Location: 150A

**Time: ***Monday, November 13, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***277.03

**Topic: ***D.07. Vision

Support: NWO Rubicon Grant
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Title: Stimulus effects dwarf task effects in visual regions

Authors: *M. C. MUR[1], D. J. MITCHELL[1], S. BRUEGGEMANN[1,2], J. DUNCAN[1,3]
[1]MRC Cognition and Brain Sci. Unit, Cambridge, United Kingdom; [2]Univ. of Hong Kong, Department of Psychology, Hong Kong; [3]Dept. of Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom

Abstract: Task context affects object responses in human ventral visual cortex (e.g. Cukur et al., 2013). This suggests that behavioral goals shape brain representations in sensory regions. Flexibility is desirable for adaptive behavior, but representations should also support stable perception. What balance does the visual system strike between flexibility and stability? In other words, how strongly does task affect visual representations?
We address this question using functional magnetic resonance imaging (fMRI) and analysis of representational variance. We acquired whole-brain 3T fMRI data in 14 human subjects. Subjects viewed object images and words, and performed multiple 2-way categorization tasks on

the stimuli. We extracted activity patterns for each stimulus in each task from visual regions V1, V2, V3v, V4 and IT, and for comparison, from cognitive-control regions IPS and IFJ. We computed activity-pattern dissimilarities to characterize representational content, and used repeated-measures ANOVA to determine the relative contributions of stimulus, task, and their interaction, in explaining dissimilarity variance.

Consistent with previous studies, all visual regions show stimulus effects, and higher-level visual regions V4 and IT show significant task and interaction effects ($p < .05$). However, stimulus effects dominate task and interaction effects in all visual regions ($p < .01$, bootstrap test), accounting for 97 percent of explained dissimilarity variation in V1 and V2, and for 90 percent in V3v, V4, and IT (Fig. 1). In contrast, cognitive-control regions either do not show significant differences (IPS) or show the opposite pattern, with task and interaction effects dominating stimulus effects (IFJ, $p < .05$) (Fig. 1).

Our findings show that task only subtly affects object representations in higher-level visual cortex, suggesting that the visual system favours stable representations. These representations likely serve as input to cognitive-control regions, for conjunctive coding with task context to enable flexible read-out of task-relevant information.

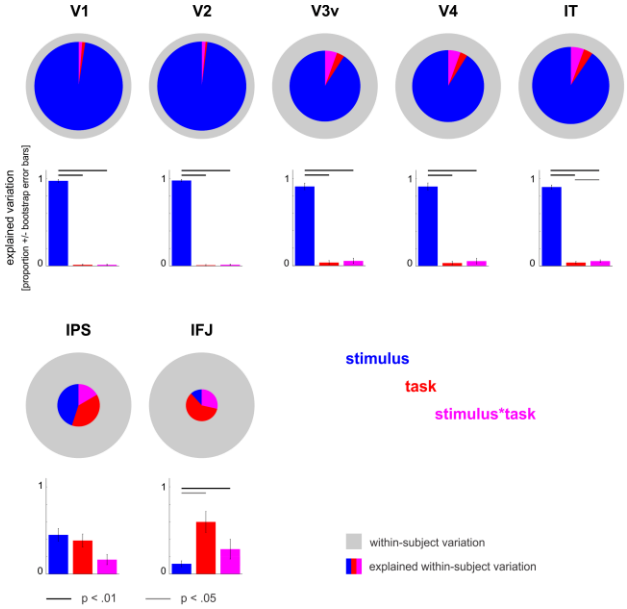

Figure 1 | Stimulus effects dwarf task effects in visual regions

Pie charts show the relative contributions of stimulus, task, and their interaction in explaining representational variance. The relative contributions were determined using repeated-measures ANOVA on activity-pattern dissimilarities. Stimulus-related variance was modelled as variance due to stimulus format (i.e. image or word) and stimulus category membership. Categories were based on visual, semantic, and verbal stimulus properties. Task-related variance was modelled as variance due to categorization rule. Subjects categorized stimuli based on their visual, semantic, or verbal properties. Subjects also performed a control categorization task at fixation, unrelated to the stimuli. Bar graphs replot the pie chart proportions, which sum to 1 for each region of interest, and indicate significant differences between proportions based on 1,000 bootstrap resamplings of the subjects. Results show that stimulus-related variance is significantly larger than task- and interaction-related variance in all visual regions. Cognitive-control regions either show no significant differences (IPS) or show the opposite pattern of results (IFJ). IT = inferior temporal cortex, IPS = intraparietal sulcus, IFJ = inferior frontal junction.

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Nanosymposium

277. Representation of Objects and Scenes

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Support: NSF award 1532591 and the McGovern Institute Neurotechnology Program (to A.O and D.P)

Title: Tracking the spatio-temporal neural trace of visual memorability

Authors: *Y. MOHSENZADEH[1], C. R. MULLIN[2], D. PANTAZIS[1], A. OLIVA[2]
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Abstract: *YM and CM equally contributed.
Some images stick in the mind while others quickly fade. Recent behavioral and computational studies have shown this image attribute, called memorability, is highly consistent and predictable across individuals (Isola et al., 2011; Bainbridge et al., 2013). But how does visual activity unfold in the brain when information is memorable? More specifically, which cortical regions are recruited, and when, to transfer information from initial perception to long term memory? The objective of this work is to trace the trajectory of neural signals processing perceptually memorable information. Here we employed the novel approach of MEG and fMRI data fusion (Cichy et al., 2014; 2016) based on representational similarity analysis (Kriegeskorte et al., 2008). We selected a set of 156 images from LaMem memorability image dataset (Khosla et al., 2015), half high memorable and half low memorable. The two subsets were balanced for low level visual features and high level semantic categories (faces, objects, scenes, animates). Participants (N=16) viewed these images during separate MEG and fMRI sessions while performing a vigilance task. Results revealed that high memorable images show a greater neural perceptual trace compared to less memorable images. Specifically, the high memorability condition resulted in a more robust and sustained representation beginning early in time (150ms after image onset) in high level brain regions (fusiform gyrus, lateral occipital and parahippocampal cortices). Taken together, our results indicate that viewing highly memorable images offers a perceptual boost (more robust and sustained brain signal in high level perception regions) allowing the details to stick in iconic memory and eventually encode in short and long term memory.
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Nanosymposium

277. Representation of Objects and Scenes

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Title: Defining the most probable location of the parahippocampal place area using cortex-based alignment and cross-validation

Authors: *K. S. WEINER[1], M. A. BARNETT[1], N. WITTHOFT[1], G. GOLARAI[1], A. STIGLIANI[1], K. N. KAY[2], J. GOMEZ[1], V. S. NATU[1], K. M. AMUNTS[3], K. ZILLES[3], K. GRILL-SPECTOR[1]
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Abstract: The parahippocampal place area (PPA) is a widely studied high-level visual region in the human brain involved in place and scene processing. The goal of the present study was to identify the most probable location of place-selective voxels in medial ventral temporal cortex. To achieve this goal, we first used cortex-based alignment (CBA) to create a probabilistic place-selective region of interest (ROI) from one group of 12 participants. We then tested how well this ROI could predict place selectivity in each hemisphere within a new group of 12 participants. Our results reveal that a probabilistic ROI (pROI) generated from one group of 12 participants accurately predicts the location and functional selectivity in individual brains from a new group of 12 participants, despite between subject variability in the exact location of place-selective voxels relative to the folding of parahippocampal cortex. Additionally, the prediction accuracy of our pROI is significantly higher than that achieved by volume-based Talairach alignment. Comparing the location of the pROI of the PPA relative to published data from over 500 participants, including data from the Human Connectome Project, shows a striking convergence of the predicted location of the PPA and the cortical location of voxels exhibiting the highest place selectivity across studies using various methods and stimuli. Specifically, the most predictive anatomical location of voxels exhibiting the highest place selectivity in medial ventral temporal cortex is the junction of the collateral and anterior lingual sulci. Methodologically, we make this pROI freely available (vpnl.stanford.edu/PlaceSelectivity), which provides a means to accurately identify this functional region when fMRI data are not available (for example, in patient populations). Theoretically, we consider different anatomical

and functional factors that may contribute to the consistent anatomical location of place selectivity relative to the folding of high-level visual cortex.

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Nanosymposium

277. Representation of Objects and Scenes

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Presentation Number: *277.06

Topic: *D.07. Vision

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Title: Computational mechanisms underlying the cortical analysis of affordance properties in visual scenes

Authors: ***M. F. BONNER**, R. A. EPSTEIN
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Abstract: A central component of spatial navigation is determining where one can and cannot go in the immediate environment. For example, in indoor environments, walls limit one's potential routes, while passageways facilitate movement. In a recent set of fMRI experiments, we found evidence that the human visual system solves this problem by automatically identifying the navigational affordances of the local scene (Bonner & Epstein, 2017). Specifically, we found that the occipital place area (OPA), a scene-selective region near the transverse occipital sulcus, appears to automatically encode the navigational layout of visual scenes, even when subjects are not engaged in a navigational task. Given the apparent automaticity of this process, we hypothesized that affordance identification could be rapidly achieved through a series of purely feedforward computations performed on retinal inputs. To test this idea, we examined visual scene processing in a biologically inspired deep convolutional neural network (CNN) with a feedforward architecture. This CNN was trained for scene categorization, but previous work has suggested that its internal representations are general-purpose and transfer well to other scene-related tasks (Zhou et al., 2014; Cichy et al., 2016). Using representational similarity analysis (RSA), we found that the CNN contained information relating to both the neural responses of the OPA and the navigational affordances of scenes. This information arose most prominently in higher convolutional layers, following several nonlinear feature transformations. By probing the

internal computations of the CNN, we found that the coding of navigational affordances relied heavily on visual features at high-spatial frequencies and cardinal orientations, both of which have previously been identified as low-level stimulus preferences of scene-selective visual cortex. These computations also exhibited a strong preference for information in the lower visual field, which is consistent with known retinotopic biases in the OPA. Visualizations of internal features from the CNN provide further insights into how affordance computation is achieved in the OPA. In summary, we used functional mapping of visual cortex to identify a previously unknown mechanism for encoding the navigational affordances of visual scenes, and we identified a biologically plausible implementation of this cortical process in a single forward pass through a hierarchical computational model.

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Nanosymposium

277. Representation of Objects and Scenes

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Support: ERC Grant ERC-StG-284101

Title: The influence of visual expertise upon the neural representational space of objects

Authors: F. MARTENS, C. TAS, *H. P. OP DE BEECK
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Abstract: When people become an expert in a particular domain, this expertise changes the way in which they process objects of expertise. Previous neuroimaging studies have demonstrated how this expertise alters the brain activity elicited during object perception (e.g., Gauthier et al., 2000, Nature Neuroscience; Harel et al., 2010, Cerebral Cortex). These studies have compared neural responses to objects of expertise with other objects. However, everyone knows whether an image depicts a bird or a car. In contrast, only a bird expert can tell apart a great-tailed from a boat-tailed grackle. Here we focus upon the neural basis of expertise at this level of detail by comparing the similarities and differences of the representational spaces of birds between 20 ornithologists and 20 control participants. We scanned subjects with functional magnetic resonance imaging while they were presented with images of 24 different types of birds. The image set was organized in 8 triplets, which each contained two birds that belonged to the same species but were visually different (e.g. male and female) and one bird that resembled one of the other two birds but that belonged to a different species. As such, the triplets dissociated species-

level semantics from visual similarity. Behavioral ratings by both subject groups revealed an overall correlation between semantic and visual differences, with both semantic-based and vision-based ratings being dominated by large-scale distinctions between songbirds, wading birds, and birds of prey. At the finer level of the triplets, only the ornithologists showed a sensitivity to the dissociation between species and visual appearance. A representational similarity analysis focused upon the neural activity patterns in low-level visual cortex (LVC), high-level visual cortex (HVC), and prefrontal cortex (PFC). In PFC, the neural patterns distinguished different bird types more reliably in ornithologists than in controls. In addition, the similarity structure of the neural patterns was more shared between ornithologists than between controls, in particular in HVC and in PFC. Overall, the findings suggest that expertise results in an overall expansion of the neural representational space of objects of expertise, but not in a qualitatively different organization.

Disclosures: F. Martens: None. **C. Tas:** None. **H.P. Op De Beeck:** None.

Nanosymposium

277. Representation of Objects and Scenes

Location: 150A

**Time: ***Monday, November 13, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***277.08

**Topic: ***D.07. Vision

Support: FWO [PEGASUS]2 Marie-Sklodowska-Curie Fellowship 12T9217N
ERC-2011-StG-284101

Title: Do neural representations of categories in visual cortex employ principles of abstraction?

Authors: *B. RITCHIE[1], H. P. OP DE BEECK[2]
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Abstract: Categorization is crucial to how we make sense of, and interact with, the visual world. Using fMRI coupled with multivariate pattern analysis (MVPA) researchers have investigated the structure of categorical representations in the human visual system. An open question is the role of abstraction in the structure of these representations. One possibility is complete abstraction across category members; that is, the representation of a prototype. Another is the representation of each individual exemplar. Between these extremes is a continuum of intermediary models varying in level of abstraction (Vanpaemel and Storms, 2008). We investigated whether these intermediary models might reflect a variable role of abstraction in the neural representation of novel visual categories.
Stimuli consisted of 16 annular square-wave gratings (1.5-8° eccentricity) varying in orientation

(45, 75, 105, 135°) and spatial frequency (.25, .5, 1, 2 cyc/deg). Representational similarity analysis (RSA) was used to construct neural dissimilarity matrices (DM) for each participant (N = 10) from V1 functional data. After testing for across subject reliability of neural DMs, multidimensional scaling was then used to construct a 2D neural space, which captured the relationship between the orientation and spatial frequency dimensions of the stimuli. Separate groups of subjects performed one of four categorization tasks (N = 4 x 20 = 80), and were trained to label (linearly and non-linearly separable) subsets of the stimuli, and generalize the learned categories to the remaining stimuli. The neural space served as input to different formal models of categorization in order to determine which best captured the choice behavior of observers in the categorization tasks.
Across the four categorization tasks models intermediary between prototype and exemplar models generally providing the best fit to the choice response data. Our results speaks against a dichotomous approach to abstraction in the neural representation of visual categories.

Disclosures: B. Ritchie: None. **H.P. Op De Beeck:** None.

Nanosymposium

277. Representation of Objects and Scenes

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**Topic: ***D.07. Vision

Support: NIH shared instrumentation grant S10OD020039

Title: Neural representation of layout and relational information among multiple objects

Authors: *R. WANG, Y. XU
Harvard Univ., Cambridge, MA

Abstract: In everyday visual environment, we are often confronted with multiple visual objects in a particular layout. Although the neural mechanisms underlying single object representation has been extensively studied, those supporting the representation of multiple objects have not been thoroughly investigated. Consider the layout of a pen, a mug and a notepad on a desktop. There are two levels of representations that can be characterized. At the first level, an object independent level, the general layout of the three objects may be analyzed, such as whether all three objects are equally distant from each other or whether two of the objects are closer to each other than they are to the third one. At the second level, an object specific level, the exact relationship between the objects may be analyzed, such as given a specific layout, which two objects are next to each other. Using fMRI MVPA, in the present study, we examined these two

levels of representations in the human brain. We measured fMRI response patterns in retinotopically defined early visual areas and object processing regions in lateral and ventral occipital regions. We used a donut-shape background and, by varying the locations of three objects on the donut, created displays of multiple objects with different spatial layouts. We additionally manipulated the pairing of the objects in a particular spatial layout. To avoid contextual priming effect from real world objects, we used two sets of artificial objects. Participants viewed the displays and detected an occasional size change of one of the objects. To investigate the effect of spatial layout in each brain region, we trained support vector machine classifiers to discriminate the multi-voxel patterns of the different layouts. To assess whether we could obtain an object-independent representation of the layout of the objects, we performed cross decoding by training the classifier on one type of objects and testing it on the other type. Within a given layout, we also tested whether the specific pairing of the objects could be decoded. Our results show that both an object-independent representation of layout and an object-specific representation of the pairing of the objects could be successfully decoded from the object processing region in ventral and lateral occipital cortex, but not in early visual areas. These results show that, in addition to encoding single objects, higher object processing region encodes the layout and relational information among multiple objects.

Disclosures: R. Wang: None. **Y. Xu:** None.

Nanosymposium

277. Representation of Objects and Scenes

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Support: NSF SMA-1640681
SL-CN: Collaborative Network on Individual Trajectories in Perceptual Expertise

Title: Time course for processing of real-world object size and contextual associations

Authors: *J. P. SHAFTO, R. KRISHNASAMY, M. J. TARR
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Abstract: Visual perception of scenes elicits robustly selective neural responses. Several ventral stream regions, including the parahippocampal place area (PPA), show greater activation for scenes compared with other categories of visual stimuli. However, the factors that contribute to the emergence of scene-selective responses have not been established.
Scenes may differ in content from other types of visual stimuli (e.g. objects, faces) along

multiple dimensions that could lead to selectivity. In particular, two factors that have been hypothesized to be be involved in scene perception are the image's real-world size, and the strength of its contextual associations. In addition, both of these properties have been found to influence the magnitude of PPA responses, as recorded with fMRI.
In the present study, we examined how the properties of real-world size and contextual associations influence neural responses when manipulated independently. Moreover, we aimed to identify the time course of the effects, to see how their emergence might compare to the emergence of category-selective responses.
Subjects viewed a series of pictures of objects that varied in size as well as in strength of contextual associations, while EEG was recorded. The size of the objects was matched between the levels of contextual association strength. Subjects performed a simple task that required no explicit judgement of category, size, or contextual associations. An ERP analysis revealed differences based on both real-world size, and strength of contextual associations during a later, scene-sensitive positivity. These results suggest that both real-world size and strength of contextual associations contribute to observed scene-selectivity during visual processing.

Disclosures: **J.P. Shafto:** None. **R. Krishnasamy:** None. **M.J. Tarr:** None.

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277. Representation of Objects and Scenes

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Topic: *D.07. Vision

Support: R01 NSO89069

Title: Abstract representations of object directed action in the left inferior parietal lobule

Authors: ***Q. CHEN**[1], F. E. GARCEA[1,2], R. A. JACOBS[1,2], B. Z. MAHON[1,2,3,4]
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Abstract: Prior neuroimaging and neuropsychological research indicates that the left inferior parietal lobule in the human brain is a critical substrate for representing object manipulation knowledge. In the present functional MRI study we used multivoxel pattern analyses to test whether action similarity among objects can be decoded in the inferior parietal lobule independent of the task applied to objects (identification or pantomime) and stimulus format in which stimuli are presented (pictures or printed words). Participants pantomimed the use of objects, cued by printed words, or identified pictures of objects. Classifiers were trained and

tested across task (e.g., training data: pantomime; testing data: identification), stimulus format (e.g., training data: word format; testing format: picture) and specific objects (e.g., training data: scissors vs corkscrew; testing data: pliers vs. screwdriver). The only brain region in which action relations among objects could be decoded across task, stimulus format and objects was the inferior parietal lobule. By contrast, medial aspects of the ventral surface of the left temporal lobe represented object function, albeit not at the same level of abstractness as actions in the inferior parietal lobule. These results suggest compulsory access to abstract action information in the inferior parietal lobe even when simply identifying objects.

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277. Representation of Objects and Scenes

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Title: Differential temporal patterns of object processing in the dorsal and ventral cortices

Authors: *E. COLLINS[1,4], E. FREUD[2], J. M. KAINERSTORFER[3], J. CAO[3], M. BEHRMANN[2]
[1]Dept. of Psychology, [3]Biomed. Engin., [2]Carnegie Mellon Univ., Pittsburgh, PA; [4]Sch. of Med., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Background. The visual cortex is widely considered to be functionally and anatomically segregated to the dorsal pathway that subserves visually guided action and to the ventral pathway that subserves object perception. However, recent findings have challenged this binary distinction and suggested that the dorsal pathway represents objects independently of the ventral pathway, and plays a functional role in object perception. Many questions remain concerning the nature of dorsal pathway representations and their contribution to object perception, including the temporal nature of these perceptual representations. Here we focus on the temporal evolvement of shape representations in the dorsal and ventral pathways. The extent to which representations in the dorsal pathway are temporally dissociable from those in the ventral pathway might reflect differences in input from the occipital cortex: dorsal and ventral cortices receive primarily magno (fast) and parvo (slow) cellular input, respectively. We

hypothesize that dorsal representations are computed independently from ventral pathway. The prediction that follows is that object sensitive activity in dorsal cortex will appear before that in ventral cortex. **Methods**. Participants viewed objects on a computer screen during 128 channel EEG recording. To parametrically manipulate shape information, objects were displayed as intact, or box-scrambled at 4 different levels (4, 16, 64, 256 pieces). Shape sensitivity, defined as the change in ERP amplitude as function of scrambling level, was measured across all time windows. **Results**. Linear regression analyses conducted in both sensor and source space, separately, revealed distinct patterns of temporal activity in dorsal and ventral cortex. Activity measured over the dorsal pathway shows the emergence of object sensitivity early in time, before ventral pathway. Yet, dorsal pathway sensitivity decreased over time, while ventral pathway sensitivity was more persistent across the 1 second post-stimulus epoch. **Conclusions.** Dorsal and ventral pathways exhibit temporally dissociable patterns of object representation. These temporal distinctions might reflect differences in cellular input from occipital cortex, namely, magno- and parvo-cellular input to dorsal and ventral streams respectively. Combined with evidence from fMRI and lesion studies, the evidence here implicates independent perceptual representations in the dorsal visual pathway.

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Nanosymposium

277. Representation of Objects and Scenes

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Support: The Israel Science Foundation (grant No. 65/15) to EF
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Title: The dorsal pathway contributes to the perception of three-dimensional (3D) structure - Evidence from continuous flash suppression

Authors: *E. FREUD, A. ROBINSON, M. BEHRMANN
Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The cortical visual system is almost universally thought to be segregated into two anatomically and functionally distinct pathways: a ventral occipito-temporal pathway that subserves object perception, and a dorsal occipito-parietal pathway that subserves object localization and visually-guided action. Accumulating evidence from both human and non-

human primate studies, however, challenges this binary distinction and suggests that regions in the dorsal pathway contain object representations that are independent of those in ventral cortex. Nevertheless, the extent to which these representations contribute to perceptual behaviors is not yet clear. To this end, we utilized the Continuous Flash Suppression (CFS) paradigm that abolishes object processing in the ventral pathway, but still allows largely intact processing in the dorsal pathway. Participants viewed pictures of 3D objects that were either structurally possible or impossible, and completed a depth classification task. To examine the contribution of the dorsal pathway to this task, unmasked target objects were primed by a suppressed object that was either the same or different from the target object. A priming effect was found only for possible objects: trials that were primed by the same object were classified faster compared to trials that were primed by a different object, suggesting that the dorsal pathway processes and contributes to depth classification task. Interestingly, no priming effect was found for impossible objects, indicating that the dorsal pathway is not only sensitive to 3D cues, but also to the legality of 3D structure. Together, these results provide novel evidence for a contribution of the dorsal pathway to perceptual behaviors and challenge the strict dichotomy between the visual functions subserved by the ventral and dorsal pathways.

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Nanosymposium

277. Representation of Objects and Scenes

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**Topic: ***D.07. Vision

Support: NSERC

Title: EEG-based visual word decoding, feature derivation and image reconstruction

Authors: *S. LING[1], A. C. H. LEE[1,2], B. C. ARMSTRONG[1,3], A. NESTOR[1]
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Abstract: Recent investigations into the neural basis of visual word processing have made substantial progress by exploiting the spatial structure of functional magnetic resonance imaging (fMRI) data. For instance, fMRI patterns in visual areas have been reliably used for the purpose of word form decoding and neural-based image reconstruction. Here, we capitalize on the spatiotemporal structure of electroencephalography (EEG) data to examine the neural signature

of visual word processing and its temporal dynamics. Specifically, we investigated the feasibility of EEG-based word decoding, visual feature derivation and image reconstruction as well as their corresponding time courses. To this aim, EEG data were collected from 10 participants who performed a one-back repetition detection task with 80 word stimuli, which consisted of three-letter high-frequency nouns with a consonant-vowel-consonant structure. Pattern analyses were then conducted across spatiotemporal signals recorded across 12 bilateral occipitotemporal electrodes separately for each participant. Our results show that: (i) pairwise word classification is well above chance (range: 69-78% accuracy across participants); (ii) visual word features can be synthesized directly from the structure of EEG data; (iii) image reconstruction can be achieved with a level of accuracy closely matching that of word classification, and (iv) the time course of classification/reconstruction peaks in the proximity of the N170 component, which prior research has associated with processing in the visual word form area (VWFA). Further, we find that reconstruction results are well explained by an ideal observer model that exploits objective orthographic and visual word similarity. Thus, our results illustrate the ability of EEG signals to support decoding, feature synthesis, and image reconstruction as applied to orthographic stimuli. More generally, the present findings provide a new window into visual word recognition and a detailed understanding of its mechanisms in terms of underlying features, temporal dynamics and neurocomputational principles.

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Nanosymposium

278. Neurobiology of Motivated Behavior

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Topic: *G.01. Appetitive and Aversive Learning

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Title: Two-photon calcium imaging of neurons in the paraventricular thalamus during Pavlovian conditioning

Authors: *J. M. OTIS, C. M. CATAVERO, A. M. MATAN, C. A. COOK, V. M. K. NAMBOODIRI, M. A. ROSSI, G. D. STUBER
Univ. of North Carolina At Chapel Hill, Carrboro, NC

Abstract: The paraventricular nucleus of the midline dorsal thalamus (PVT) is innervated by cortical and subcortical structures that underlie appetitive and aversive behaviors. In addition, recent studies suggest that activity in PVT contributes to both reward learning and fear learning, although how activity in overlapping or non-overlapping populations of PVT neurons might contribute to such disparate memory processes is unknown. Here we inject a virus to drive expression of the genetically-encoded calcium indicator GCaMP6s (AAVdj-CaMK2a-GCaMP6s) into the PVT of mice. Patch-clamp recordings reveal that GCaMP6s fluorescence directly tracks both elevations and reductions in action potential frequency, suggesting that visualization of PVT neurons *in vivo* would allow us to monitor the activity of these cells across learning. To this end, we next implanted chronic microendoscopic lenses above PVT, and used two-photon microscopy to visualize hundreds of GCaMP6s-expressing PVT neurons in each head-fixed, awake behaving mouse. Next, mice underwent Pavlovian conditioning wherein one conditioned stimulus predicts delivery of sucrose (CS^{S+}), a sweet and appetitive tastant, whereas another predicts delivery of quinine (CS^{Q+}), a bitter and aversive tastant. In this paradigm, mice acquire conditioned licking responses (anticipatory licks) to the CS^{S+}, but not CS^{Q+}, revealing that learning has taken place. In addition, data reveal that while some PVT neurons have excitatory responses to the CS^{S+} after learning, other PVT neurons have inhibitory CS^{S+} response profiles. In contrast, preliminary data suggest that PVT neurons do not develop excitatory or inhibitory responses to the CS^{Q+}. Ongoing experiments will determine whether projection-defined PVT neurons differentially encode reward predictive cues and whether such cue responses are specific to definable PVT output circuits.

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Nanosymposium

278. Neurobiology of Motivated Behavior

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**Topic: ***G.01. Appetitive and Aversive Learning

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NARSAD Foundation

Title: Choice-selective sequential activity in prelimbic cortical neurons that project to the nucleus accumbens

Authors: *N. F. PARKER[1], M. MURUGAN[2], I. B. WITTEN[3]
[1]Neurosci., [2]Princeton Neurosci. Inst., [3]Princeton Univ., Princeton, NJ

Abstract: How is the brain able to attribute reinforcement to a prior action appropriately, given that the action typically occurs before reinforcement is signaled? The nucleus accumbens (NAc), a structure in the ventral portion of the striatum, is involved in learning the relationship between a stimulus or action and its outcome. The prelimbic cortex (PL), a cortical region in the medial prefrontal cortex, provides a major source of glutamatergic innervation to the NAc, and the synaptic connection between PL neurons and the NAc output neurons are thought to be an important site of plasticity underlying reinforcement learning. However, given the heterogeneity of cell-types within both the PL and the NAc, it is not known what is encoded in the PL neurons that project to NAc (PL-NAc), and whether they may convey information to bridge the gap in time between actions and reinforcement signals. To address this question, we measured cellular-resolution activity in PL-NAc neurons in mice during a probabilistic reversal learning task, and discovered that (i) PL-NAc neurons display population-level sequential activations in relation to task events, (ii) PL-NAc neurons are more selective for actions as compared to sensory stimuli, and (iii) PL-NAc sequences are choice-specific and persist beyond the time of reward feedback. The existence of this choice-selective sequential activity provides a mechanism by which the identity of a choice could be paired with its resulting outcome. To test this idea, we disrupted the sequential activity of PL-NAc neurons on a subset of a trials using light-activated channelrhodopsin, and examined the effect on choice. We found that activation of this population disrupted the mouse's ability to use the outcome of prior trials to guide subsequent choices. Taken together, these data suggest that choice-selective sequential activity in PL-NAc neurons could be used to connect actions and outcomes separated in time.

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Nanosymposium

278. Neurobiology of Motivated Behavior

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Title: The role of the anterior cingulate cortex projection to the dorsomedial striatum in reinforcement learning

Authors: *J. M. COX, N. RANGARAJAN, I. B. WITTEN
Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Obtaining rewards in a complex and changing environment requires continual assessment of the relationship between our actions and their outcomes. The dorsomedial striatum (DMS) is thought to be crucially involved in reinforcement learning and decision-making, coordinating the selection of actions and evaluating their consequences. A major cortical input to the DMS is the anterior cingulate cortex (ACC), a region of the prefrontal cortex that encodes diverse decision-related information and is thought to be especially important for error evaluation. How these regions interact during decision-making and outcome evaluation is unclear, however. To address this, we trained mice in a probabilistic reversal task that requires them to use the history of their choices and their outcomes to guide decisions. We used a retrogradely transporting AAV to express the calcium indicator GCaMP6f or channelrhodopsin in the subset of ACC neurons projecting to the DMS (ACC-DMS neurons). We then monitored or manipulated the activity of these neurons as mice performed the probabilistic reversal task. The activity of ACC-DMS neurons was modulated by various task events, as well as the animal's recent history of rewards and choices. Additionally, most imaged ACC-DMS neurons encoded outcome, responding to an auditory stimulus signaling whether or not a reward was delivered. Interestingly, stimulating this projection during the outcome period specifically affected behavior following non-rewarded trials, making mice significantly more likely to repeat their previous choice. In contrast, stimulation during the outcome of rewarded trials had no effect on this measure. This data suggests that ACC-DMS neurons are involved in value-based decision-making, and may contribute preferentially in the processing of negative outcomes.

Disclosures: **J.M. Cox:** None. **N. Rangarajan:** None. **I.B. Witten:** None.

Nanosymposium

278. Neurobiology of Motivated Behavior

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**Topic: ***G.01. Appetitive and Aversive Learning

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MR/M023990/1

Title: Differential contributions of sub-regions of the dorsal anterior cingulate cortex (dACC) to the regulation of negative emotion in the common marmoset

Authors: *S. RAHMAN[1], A. M. SANTANGELO[1], N. K. HORST[2], G. COCKCROFT[1], A. C. ROBERTS[1]
[1]Physiology, Develop. and Neurosci., [2]Psychology, Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Neuroimaging studies in humans have implicated the dorsal anterior cingulate cortex (dACC) in a broad range of cognitive and emotional tasks, including negative emotion. Furthermore, abnormalities in dACC activity have been associated with disorders of negative emotion such as anxiety and depression. However, despite extensive study of this brain region there is no overall consensus of its role in negative emotion, Instead, there is mounting evidence that rather than being one functionally homogenous region, the dACC may have functionally dissociable roles which can be mapped on to distinct sub-regions. This evidence is largely correlational and there have been few causal studies in experimental animals designed to address this. The present study assesses the contributions of three distinct sub-regions of the dACC (rostral, mid and caudal) to the regulation of the behavioural and cardiovascular correlates of negative emotion in the common marmoset *(Callithrix jacchus)*. This New World primate has a highly developed prefrontal cortex, including dACC, with a similar cytoarchitecture to that of humans. This enabled us to precisely target these dACC sub-regions with indwelling cannulae to carry out pharmacological inactivation during two different tasks of negative emotion; (1) a task assessing behavioural anxiety in response to an unfamiliar human and (2) a Pavlovian fear extinction task. Results show that transient inactivation of the rostral dACC decreased anxiety while the same manipulation of the mid and caudal dACC increased anxiety in response to an unfamiliar human. Furthermore, inactivation of the rostral and caudal dACC blunted cardiovascular expression of fear during extinction of Pavlovian fear conditioning while inactivation of the mid dACC had no effect. This suggests that the dACC is indeed functionally heterogenous with regards to its role in negative emotion, with differences in both the regulation of anxiety and fear. These effects will be interpreted in light of the differential projection patterns of these regions evaluated by anterograde tracers. Further understanding of the precise roles of

these different sub-regions of the dACC in regulating negative emotion could give us a greater insight into the neurobiological mechanisms underlying anxiety and depression, disorders in which this function is impaired.

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278. Neurobiology of Motivated Behavior

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**Topic: ***G.02. Motivation

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Title: A dopaminergic signal coordinates the probabilities to initiate and sustain behavior

Authors: *X. ZHANG[1], D. ROGULJA[1], M. CRICKMORE[2]
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Abstract: A single motivational signal can alter many aspects of behavior. Using *Drosophila* courtship as a model, we examined how a dopamine tone acts on P1 courtship command neurons to generate a unified motivational state across behavioral transitions. An elevated dopamine tone promotes courtship by decreasing the sensitivity of P1 neurons to inhibition conveyed by the $GABA_A$ receptor subunit pHCl. A different $GABA_A$ receptor, Rdl, conveys inhibition to P1 regardless of satiety state if the courtship target is inappropriate. Receptor diversity is also employed in the reception of excitatory inputs at P1: initial stimulation by female pheromones is conveyed through the nicotinic acetylcholine receptor nAChRα3; but once courtship has been initiated, high dopamine levels maintain the courtship state by facilitating recurrent network stimulation of P1 through nAChRα6. This recurrent activity leads to persistent P1 activation that can endure for at least a minute in the absence of further pheromonal input. Here, excitatory and inhibitory receptor diversity in downstream circuitry allows a single motivational cue to adjust specific aspects of circuit function to coordinate the fundamental components of motivation: behavioral selection and persistence.

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278. Neurobiology of Motivated Behavior

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**Topic: ***G.02. Motivation

Support: NIDA R01 DA006214

Title: Orexin-1 receptors mediate oxycodone self-administration and cue-induced oxycodone seeking

Authors: *G. MARRONE, H. FARRUKH, G. ASTON-JONES
Brain Hlth. Inst., Rutgers University, RBHS-UBHC-GSBS, Piscataway, NJ

Abstract: Oxycodone is a mu opioid analgesic that is widely prescribed for the treatment of pain. However, like other prescription opioids, oxycodone has abuse liability contributing to the current opioid epidemic in the United States. The orexin/hypocretin system has multiple roles in reward and addiction. Our laboratory previously reported that the orexin-1 receptor antagonist SB334867 decreases heroin self-administration and cue-induced reinstatement of heroin and remifentanil seeking. In the present study, we found that intravenous oxycodone self-administration and cue-induced oxycodone seeking are also sensitive to orexin-1 receptor blockade. Fixed-ratio 1 responding was dose-dependently decreased and cued-reinstatement was blocked by SB334867. Current studies are underway to determine whether orexin-1 receptor antagonism can alter demand for oxycodone in a within-session behavioral economics paradigm. Taken together, our findings indicate that orexins might play an important role in opioid reward and seeking.

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278. Neurobiology of Motivated Behavior

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**Time: ***Monday, November 13, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***278.07

**Topic: ***G.02. Motivation

Support: JSPS KAKENHI Grant Number 15K01843
Ministry of ECSST of Japan

Title: Neural population network for information-seeking mechanism in monkey prefrontal cortex

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Abstract: The desire to obtain information is a powerful motivator in daily life. Previous literature indicates that information value is defined using probability distribution that represents current environmental state. Different brain areas are shown to be involved in coding information value and probability distribution. However, neural mechanism that computes information value from probability distribution remains unknown. This study shows that a neural population network of the monkey prefrontal cortex (PFC) computes information value using signals of probability distribution. Although responses of PFC neurons are highly diverse and change in time, previous studies have demonstrated that description of their activities at the population-level accounts for heterogeneous activity of single neurons. We recorded the activity of 1126 and 737 neurons from the PFC of two monkeys while they conducted information-seeking tasks. RESULTS: (1) We performed the principal component analysis on the obtained responses of neural populations and found that the first three principal components were adequate for the population responses to encode the value of information that monkeys expect to obtain while seeking information. (2) Using linear discriminant analysis, we identified minimal subpopulations whose neural responses respectively encode information value and probability distribution. (3) We preformed Granger-causality analysis and showed that activity of the former subpopulation was caused by that of the latter subpopulation, suggesting that a network of the two neural populations operated to compute information value. (4) Finally, we compared three information measures, Shannon information, probability gain, and impact, and found that Shannon information best accounts for the obtained population activity. CONCLUSION: Our results indicate that the neural population network of the PFC computes Shannon information from probability distribution to seek information.

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Title: Distinct processing of the effort cost and the food-patch information in socially foraging domestic chicks

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Abstract: To be adaptive, animals must decide how much cost to invest while foraging for a certain benefit. Several brain areas have been implicated in making foraging decisions in mammals, such as anterior cingulate cortex, orbitofrontal cortex, basolateral amygdala and nucleus accumbens (NAc). However, social contexts should also be considered for the cost-benefit computations, because (1) many animals forage socially and (2) the social interactions interfere with the individual benefit. Adaptive animals thus have to appropriately adjust their decisions to meet the social demand. Yet, few studies have addressed to what social factors are critical and which brain areas are involved in the underlying adjustments. Using domestic chicks as subjects, we have revealed that the limbic pallium (arcopallium, Arco) is responsible for effort investment for handling food (Aoki et al. 2006). Lesions in NAc, on the other hand, caused impulsive choices (Izawa et al. 2003) without effects on the cost-based choices (Aoki et al. 2006), despite that Arco is the major pallial source of the inputs to NAc in birds (Csillag et al. 2008). Furthermore, competition strongly enhances the choice impulsiveness (Amita et al. 2010) possibly through suppression of cue-associated representation of predicted reward (Amita and Matsushima 2014). The running cost for food is also socially facilitated (Ogura et al. 2011, 2015), and it is selectively suppressed by lesions of the lateral limbic area of Arco (Xin et al. 2017). The Arco and its projections to limbic areas may integrate the social contexts with foraging benefit/cost, although the responsible connections are yet unspecified. Here, we report how the patch-use behavior is controlled by the social context, the reinforcement rate and the travel time for food. In an I-shaped maze with two terminal feeders (patches), paired chicks showed a precise matching while it was considerably under-matching in single control chicks. When accompanied by own mirror image, single chicks showed a socially facilitated running, but the under-matching remained. Information on food availability must be publicly gained and shared among chicks, while the socially facilitated run (travel for food) does not contribute. The patch-use time may increase when the travel time is longer (Charnov 1976). Actually, experimentally enforced travel time caused a longer stay at gradually diminishing food patches, but the stay-time was consistently longer than that predicted, possibly due to the negative energy load by the travel. We must examine if the limbic Arco is involved in the adaptive patch-use behavior after integrating these diverse socio-economic factors.

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Title: Dissecting the functional network connecting the lateral preoptic area and the ventral tegmental area

Authors: *D. J. BARKER, C. MEJIAS-APONTE, R. JUZA, B. LIU, J. MIRANDA BARRIENTOS, S. MONGIA, S. ZHANG, M. MORALES
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Abstract: The Lateral preoptic area (LPO) is connected within limbic structures involved in physiological and behavioral responses to reward, stress, and aversion, including the ventral tegmental area (VTA). Both the LPO and VTA are heterogeneous structures, suggesting that the specific role of LPO glutamate or GABA neurons in reward and aversion may depend on the nature of their connection with the glutamatergic, GABAergic and dopaminergic neurons that comprise the VTA. Here, we examined the functional connectivity between the LPO and VTA. First, to determine the types of LPO neurons targeting the VTA, the retrograde tracer fluorogold was injected into discrete portions of the VTA. By *in situ* hybridization, we next established the phenotype of fluorogold-tagged neurons to determine if they expressed transcripts encoding vesicular GABA transporter mRNA (VGaT; a marker of GABAergic neurons) or vesicular glutamate transporter 2 mRNA (VGLuT2; a marker of glutamatergic neurons). In serial sections, we observed that 65.6 ± 3.9% of fluorogold positive neurons expressed VGaT mRNA, while 42.4 ± 2.4% expressed VGluT2 mRNA. Next, we used the psuedorabies monosynaptic tracing technique to determine whether LPO neurons synapse on dopamine, glutamate, or GABA neurons within the VTA. Our results indicate that LPO neurons provide inputs to all three cell types in the VTA, but that the proportions of input to each VTA cell type are not equal. Finally, we have observed that optogenetic stimulation of LPO glutamate fibers in the VTA results in aversion, while photostimulation of LPO GABAergic fibers results in reward. Based on our observations, we hypothesize that LPO GABAergic neurons participate in reward, possibly through the disinhibition of VTA dopamine neurons, while LPO glutamatergic neurons participate in aversion, possibly through the indirect inhibition of VTA dopamine neurons. To test this hypothesis, we are currently examining the specific types of LPO neurons that are synapsing onto VTA glutamate, GABA, or dopamine neurons using immuno-electron microscopy. This research was supported by the intramural research program at NIDA/NIH.

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Title: Persistently augmented lateral hypothalamic orexin/hypocretin function drives cocaine addiction behaviors after intermittent access

Authors: ***M. H. JAMES**[1], C. M. STOPPER[2], B. A. ZIMMER[2], N. E. KOLL[2], H. E. BOWREY[2], S. O'CONNOR[2], G. S. ASTON-JONES[2]
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Abstract: *Introduction*: A role for the hypothalamic orexin (hypocretin) system has been demonstrated in various reward behaviors, however a role for orexin in the expression of a multifaceted addiction phenotype has not been shown. Here we investigated whether the novel intermittent access (IntA) cocaine self-administration paradigm (Zimmer et al., 2012) is associated with the development of multiple addiction-like behaviors, and the extent to which the orexin system is important for their expression. *Methods*: Rats were given IntA to cocaine in daily sessions for two weeks, before being tested for economic demand for cocaine (Bentzley et al., 2012) and a range of other addiction-like behaviors. In a subgroup of animals, we quantified the numbers of orexin-expressing cells and the reactivity of these cells to a drug-associated context both immediately and 6 months after IntA training. To test the functional role of orexin in the expression of addiction-like behaviors following IntA, we either treated animals with the selective orexin-1 receptor antagonist SB-334867 (SB; 10mg, 30mg/kg, i.p.), or used an orexin-antisense morpholino to selectively reduce the expression in either the medial (perifornical/dorsomedial) or lateral orexin cell fields. *Results*: IntA produced a persistent increase in motivation for cocaine (decreased alpha) without affecting animals' hedonic set point for cocaine (Q_0). IntA also caused higher compulsive (punished) responding for cocaine, increased reinstatement of extinguished drug-seeking, and higher expression of depression- and anxiety-like behavior following protracted withdrawal from cocaine. We also found that IntA was associated with an increase in both the number and activity of orexin cells in LH. Further,

the IntA-induced addiction multi-phenotype was reversed by both SB treatment and LH-directed morpholino knockdown of orexin expression in LH. *Conclusions*: IntA to cocaine self-administration is associated with multiple addiction-like behaviors that persist for months. These behaviors are associated with persistent increases in the number and activation of LH orexin neurons. Moreover, reduction of orexin signaling with an antagonist reversed the IntA-induced addiction multi-phenotype. These data highlight the orexin system as a promising target for therapies designed to treat the multifaceted behavioral symptoms associated with psychostimulant addiction.

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Nanosymposium

279. Chemogenetics in Rodents and Primates

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Title: Developmental model of nonhuman primate DREADDs: hM4Di transfection in the amygdala of infant rhesus monkeys

Authors: *J. RAPER[1], C. PAYNE[2], W. R. JONES[2], J. BACHEVALIER[3]
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Abstract: Chemogenetics are powerful new tools for nonhuman primate behavioral studies, with several advantages over previous lesion and reversible inactivation techniques. Unlike permanent lesions, there is no opportunity for reorganization or compensation from other brain areas. Also, unlike previous reversible inactivation techniques, it does not require chambers and headpost, which are not feasible in infant animals with a rapidly developing body and brain. Therefore, chemogenetic tools, such as designer receptors exclusively activated by designer drugs (DREADDs) are ideally suited for developmental research questions. The current study used one male and one female infant rhesus monkeys to examine how transient inactivation of the amygdala impacted socioemotional behavior and cortisol stress reactivity. At 7 months of age infant monkeys underwent MRI-guided neurosurgery to inject AAV5-hSyn-HA-hM4D(Gi)-IRES-mCitrine bilaterally into the amygdala. We utilized the Human Intruder (HI) paradigm to

assess emotional behavior and cortisol stress reactivity in the monkeys. The HI paradigm was chosen because 1) it is robust task at assessing monkeys behavioral and stress response toward the presence and specific gaze direction of a novel human and 2) it has been previously shown to be sensitive to perturbation in amygdala activity. Prior to expression of the hM4Di receptors, animals were tested for sensitivity to clozapine-N-oxide (CNO) by administering 10mg/kg CNO prior to the HI task. Neither infant exhibited any sensitivity or side effect of CNO, and both expressed species-typical responses on the HI task. Four weeks after surgery, animals were tested again on the HI task either with 10mg/kg CNO or saline administered before the task to activate the hM4Di receptors and inhibit amygdala activity or not. Blood samples were collected immediately before and after each HI task for assay of cortisol, CNO, and metabolites (clozapine and n-desmethylclozapine) levels in plasma. CNO and metabolites were detectable in plasma samples collected during the HI task. These data will demonstrate whether activation of hM4Di receptors bilaterally in the amygdala can inhibit amygdala activity during an acute stressor leading to decreased cortisol stress response similar to previous data from adult monkeys with DREADDs or after permanent lesions of the amygdala. This study demonstrates proof-of-principle, that chemogenetics can be effectively used in infant monkeys and paves the way for future development studies using chemogenetic manipulation of neuronal activity.

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279. Chemogenetics in Rodents and Primates

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Presentation Number: *****279.02

Topic: *****H.01. Animal Cognition and Behavior

Title: Characterizing the action of DREADD activating ligands in monkey using PET and behavioral testing

Authors: ***M. A. ELDRIDGE**[1], S. S. SHRESTHA[2], S. TELU[2], J. M. FREDERICKS[1], R. L. GLADDING[2], W. LERCHNER[1], J. TURCHI[1], C. MORSE[2], Y. NAGAI[3], T. MINAMIMOTO[3], V. W. PIKE[2], R. B. INNIS[2], B. J. RICHMOND[1]
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Abstract: We have tested CNO and two alternative activators, compound 21 and clozapine, of the inhibitory DREADD (Designer Receptor Exclusively Activated by Designer Drug), hM_4Di in a PET imaging assay to measure receptor occupancy and in a behavioral assay. For behavioral testing, a monkey performed an association task in which stimuli predicting different reward

values were presented. In each trial, the monkey either accepted or rejected the offer presented by releasing a lever in one of two intervals.
Performance on this task before virus injection was unaffected by a systemic injection of 10 mg/kg CNO 1 hour before testing began. Six weeks after a unilateral injection of 10 µl of lentivirus, expressing hM_4Di under a synapsin promoter into right ventral striatum, CNO treatment caused the monkey to abort significantly more trials than vehicle injections. Compound 21 (10 mg/kg), also induced more aborted trials than in the control condition. Doses of 1 or 3 mg/kg of compound 21 did not influence behavior. Systemic administration of 0.1 mg/kg clozapine also produced more aborted trials.
Analysis of 10 mg/kg CNO injections in a group of 4 monkeys revealed an average peak CSF concentration of ~70 ng/mL of CNO 60 minutes after injection, and an approximately 70-fold lower concentration of clozapine at the same time point. Thus, there are two potentially active agents present in CSF during behavioral testing after CNO injection, CNO and clozapine.
In another monkey, we used PET imaging with [11C]-clozapine to visualize in vivo binding. We injected 150 µl of the same lentivirus used above into the right amygdala of a different monkey. After a 6-week delay for expression, PET imaging with [11C]-clozapine showed strong uptake in the right amygdala, but not the left, suggesting hM_4Di expression in the right amygdala. After pretreatment with 10 mg/kg of unlabeled CNO, binding of the radioligand was lower than seen without the CNO pretreatment in the right amygdala. It also appeared that signal at other clozapine binding sites was reduced. Pretreatment with compound 21, at 10 mg/kg, had the same effect on signal as pretreatment with CNO. Pretreatment with 1 mg/kg of compound 21, however, did not reduce the [11C]-clozapine signal in the right amygdala, or at other brain loci. The PET imaging also suggests that activating drugs might bind clozapine binding sites at other loci, even when the drug levels exhibit no effect on behavior. These preliminary results show that the hM_4Di DREADD can have a strong effect on behavior, and that can be mirrored and monitored using PET imaging.

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Title: Subcellular localization of mCherry proteins fused to hM4Di in monkeys

Authors: *A. GALVAN[1], X. HU[2], J.-F. PARE[2], J. RAPER[2], J. BACHEVALIER[3], T. WICHMANN[1], Y. SMITH[1]
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Abstract: Designer-receptors exclusively activated by designer drugs (DREADDs) have been used to modulate neuronal circuits in rodents, but the use of DREADD technology in primate studies has lagged behind. DREADDs can be selectively expressed in specific neuronal subpopulations through the use of transgenic animals or virus injections. In most studies, DREADD expression is confirmed through post-mortem immunohistochemical or fluorescence studies of tag proteins fused to the DREADDs. However, the neuronal localization of DREADDs has only been described at the regional or cellular level. In the present study, we used immunohistochemistry and electron microscopy to describe the subcellular localization of the tag protein mCherry fused to the Gi-coupled DREADD hM4Di, expressed in the subthalamic nucleus (STN) and basolateral amygdala (BLA) of rhesus monkeys after transduction with adeno-associated virus (AAV) solutions. Monkeys were injected with AAV5 or AAV8-hSyn-hM4Di-mCherry in the BLA (1 monkey) or STN (2 monkeys) using stereotaxic approaches and/or electrophysiological guidance. Two to 21 months after the injection, the animals were euthanized and perfused with Ringer solution, followed by 4% paraformaldehyde and 0.1% glutaraldehyde. The brains were collected and blocked in the coronal plane, and 60 μm-thick sections were obtained with a vibratome. Brain sections containing the BLA or STN were incubated with antibodies against mCherry. The antibodies were revealed with either immunoperoxidase or gold particles, and the sections observed under the electron microscope. Immunoperoxidase staining showed that, mCherry was localized in proximal and distal dendrites, as well as a subpopulation of axonal terminals in the BLA. In the STN, the protein was identified mostly in post-synaptic elements (proximal and distal dendrites). In sections from either target nucleus, the immunogold method revealed that ~90% of gold particles labeling for mCherry was localized in the cytoplasm, whereas ~10% were bound to the plasma membrane of immunoreactive elements. Our results suggest that, after viral solution injections in monkeys, hM4Di expression remains largely confined to the intracellular compartment. Only a small fraction of the tagged receptors is transported to the plasma membrane. This pattern of localization is likely to limit the effects of activation of these receptors by clozapine-n-oxide or other actuators after systemic administration. In agreement with the anatomical observations, we did not find significant behavioral or electrophysiological effects of CNO injections in these animals.

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Title: Stereological analysis of DREADD transduction in prefrontal cortex of rhesus monkeys

Authors: *N. UPRIGHT, C. G. DAMATAC, P. R. HOF, P. H. RUDEBECK, P. L. CROXSON, M. G. BAXTER
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Abstract: We used DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) to reversibly manipulate dorsolateral prefrontal cortex (dlPFC) function in macaque monkeys. An rAAV5/hsyn-hM4Di-mCherry viral vector construct was injected bilaterally into the dlPFC of four monkeys, to produce neuronal expression of the inhibitory (Gi-coupled) DREADD receptor. Monkeys were tested on a spatial delayed response task to assess working memory function after intramuscular injection of either clozapine-N-oxide (CNO) or vehicle. We subsequently performed immunohistochemistry for mCherry to quantify DREADD expression in the dlPFC. Neuronal bodies were determined by cresyl violet staining. We used unbiased stereological measures to quantify the level of DREADD transduction and compute the percentage of transduced cells. We found a greater number of immunolabeled neurons in monkeys that displayed behavioral impairment after CNO injection compared to those from monkeys that showed no behavioral effect after CNO. Even in monkeys that showed reliable effects of CNO on behavior after DREADD expression, the number of prefrontal neurons transduced with DREADD receptor was on the order of 3% of total prefrontal neuron number. This level of histological analysis facilitates our understanding of behavioral effects, or lack thereof, after DREADD vector injection in monkeys. It also implies that a functional silencing of a relatively small fraction of dlPFC neurons is sufficient to disrupt spatial working memory.

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Title: Chemogenetics revealed: DREADD occupancy and activation via converted clozapine

Authors: *M. MICHAELIDES[1,4], J. L. GOMEZ[1], J. BONAVENTURA[1], W. LESNIAK[4], W. B. MATHEWS[4], P. SYSA-SHAH[4], L. A. RODRIGUEZ[1], R. J. ELLIS[1], C. T. RICHIE[2], B. K. HARVEY[2], R. F. DANNALS[4], M. G. POMPER[4], A. BONCI[3,4]
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Abstract: The chemogenetic technology DREADD is a widely-used, translational approach for remote manipulation of neuronal activity in freely-moving animals. DREADD technology posits the use of "designer receptors" which are exclusively activated by the "designer drug" clozapine N-oxide (CNO). Nevertheless, the in vivo mechanism of action of CNO at DREADDs has never been confirmed. We found that CNO shows low affinity for DREADDs and does not enter the brain after systemic drug injections. Clozapine, to which CNO rapidly converts in vivo, shows high DREADD affinity and potency, and upon systemic CNO injections, converted clozapine readily enters the brain and occupies CNS-expressed DREADDs. Systemic subthreshold clozapine injections induce preferential DREADD-mediated behaviors, while pharmacological inhibition of CNO-to-clozapine conversion blocks behavioral responses observed after CNO injections. Our results demonstrate that metabolically-derived clozapine is the in vivo actuator of CNS-expressed DREADDs and reveal the in vivo mechanism of action of CNO at these sites.

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MH107563
MH100031

Title: Visualizing DREADDs receptor expression *in vivo* with ^{11}C-labeled clozapine PET imaging in the nonhuman primate

Authors: *J. A. OLER[1], P. H. ROSEBOOM[1], R. KOVNER[1], M. K. RIEDEL[1], E. M. FEKETE[1], M. R. RABSKA[1], V. R. ELAM[1], S. KULICK[1], P. J. LAO[2], M. D. ZAMMIT[2], B. T. CHRISTAIN[1,2], N. H. KALIN[1]
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Abstract: Despite current treatments, anxiety disorders remain a major public health concern. Molecular strategies aimed at selectively and reversibly altering the neural circuity underlying these disorders have the potential to provide new avenues for treatment. The nonhuman primate (NHP) is ideal for developing such treatments because of similarities between rhesus monkeys and humans in the development of socio-emotional behavior and its underlying neural substrates. DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) are ideal for examining anxiety-related circuits in NHPs because they allow for reversible and bi-directional control of brain cell function. The DREADDs technique involves infecting a brain region with a viral vector that drives the expression of a receptor that does not naturally occur in the brain, which is then combined with a pharmacological intervention, an otherwise "inert" drug that selectively activates DREADDs. Importantly, DREADDs can be used to chronically alter circuit function to model the long-term brain alterations associated with psychopathology as well as its treatment.
Here we describe a series of experiments that used ^{11}C-clozapine µPET imaging to detect DREADDs expression *in vivo*. First, we established methods for site-specific delivery of a vector driving expression of DREADDs in the NHP. Specifically, in one male rhesus monkey, we injected 40 µl of AAV5-hSyn-hM3D(Gq)-mCherry (3.4×10^{12} vg/ml) unilaterally into the left putamen. Six weeks after surgery the animal was anesthetized, placed in the µPET scanner, administered 5.0 mCi of ^{11}C-clozapine (I.V.), and scanned for 90 minutes. Clozapine binds to many receptors including dopamine and acetylcholine receptors, and has a very high affinity for

the DRAEDDs receptor. The results demonstrated a clear hemispheric asymmetry in putamen binding, confirming the ability to image DREADDs receptors in the primate brain. Subsequent scans were performed following pretreatment with DREADDs-activating designer drugs (either clozapine-N-oxide or Compound-21) to characterize the dose and timing of drug administration to optimally activate DREADDs receptors. These data will be useful for NHP studies and set the stage for translation to humans.

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Title: A novel PET ligand for visualising cellular and axonal DREADD expression in monkeys

Authors: ***Y. NAGAI**[1], B. JI[1], Y. XIONG[2], J. G. ENGLISH[3], J. LIU[2], Y. HORI[1], K.-I. INOUE[4], T. HIRABAYASHI[1], A. FUJIMOTO[1], C. SEKI[1], K. KUMATA[1], M.-R. ZHANG[1], T. SUHARA[1], M. TAKADA[4], M. HIGUCHI[1], B. L. ROTH[3], J. JIN[2], T. MINAMIMOTO[1]
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Abstract: The chemogenetic technology, Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) offers a means to temporally and remotely control activity of a target cell population expressing a "designer receptor" by systemic delivery of an agonist compound. Non-invasive visualization of the inhibitory designer receptor, hM4Di, by positron emission tomography (PET) (Nagai et al., 2016) now enables us to monitor the expression and the agonist dose–occupancy relationship that provides the critical information for successful chemogenetic silencing in long-term studies in monkeys as well as for future clinical therapeutics. However,

the current PET ligand, ^{11}C-clozapine, has low specificity for DREADDs, thereby the image suffers from a regional difference in "baseline noise". Here we developed a new ligand, a carbon-11-labeled derivative of DREADD agonists (Chen et al., 2015), to improve the sensitivity of DREADD-PET imaging. *In vitro* assay demonstrated that, unlike clozapine, the derivative did not display high potency for major endogenous G protein coupled receptors. We examined the new PET ligand in a monkey that received injections of an hM4Di-expressing viral vector into the unilateral putamen. As seen with ^{11}C-clozapine, PET imaging localized an increased uptake of the new ligand at the putative hM4Di-expressing site. Compared with ^{11}C-clozapine, the signal-to-noise ratio was largely improved; the ligand uptake at the putative hM4Di-expressing site was enhanced by about 10%, while the baseline uptakes in the striatum or other subcortical areas were reduced by about 30%. Pretreatment with an unlabeled ligand at a dose of 1 mg/kg almost completely diminished the uptake at the injection site, and therefore the ligand uptake appeared to reflect *in vivo* DREADD expression. Besides the injection site in the putamen, an increased uptake was also found in its projection areas, i.e., the globus pallidus and the substantia nigra, presumably reflecting hM4Di expression at the axon terminal. Two additional monkeys were scanned following bilateral injections of an AAV-hM4Di vector into the rostromedial caudate or the thalamus. *In vivo* hM4Di expressions in these two subcortical areas were also detected as high ligand uptakes. These results indicate that our new PET ligand provides a high DREADD selectivity in subcortical regions in monkeys, thus being beneficial for quantitative assessment and sensitive detection of DREADD expression even at the axon terminal.

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Nanosymposium

279. Chemogenetics in Rodents and Primates

Location: 144A

Time: *****Monday, November 13, 2017, 8:00 AM - 10:45 AM

Presentation Number: *****279.08

Topic: *****H.01. Animal Cognition and Behavior

Support: NIAAA Grant F31AA024660
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Title: Characterization of DREADD manipulation in rhesus monkeys trained to discriminate ethanol

Authors: D. C. ALLEN[1], V. C. CUZON CARLSON[2,1], C. D. KROENKE[2,1], Y. XIONG[3], J. JIN[3], *K. GRANT[2,1]
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Abstract: The nucleus accumbens (NAc) core is a primarily GABAergic brain nucleus that has been demonstrated to mediate the discriminative stimulus effects of ethanol in rodents. Additionally, self-report measures of intoxication directly correlate with BOLD signal within the NAc in human subjects, providing translational evidence of this brain nucleus in ethanol's interoceptive (subjective) effects. The goal of the current study is to characterize the role of the NAc in ethanol discrimination in rhesus monkeys utilizing a chemogenetic viral strategy (DREADDs). Five young adult male rhesus monkeys were trained on a two-choice food-reinforced ethanol (1.0 g/kg, 20% w/v in water, i.g.) vs. water discrimination with a 60-minute pretreatment interval (BEC: 70±5 mg%, n=5). All monkeys successful acquired the discrimination (≥90% accurate responding for 5 consecutive sessions) in 72 ± 19 sessions (*M*±*SD*), with an ED_{50} for ethanol substitution of 0.7 ± 0.1 g/kg. Substitution testing was conducted with ethanol, midazolam and pentobarbital. Upon completion of initial tests, monkeys were bilaterally injected into the NAc core with hM4D Gi-coupled DREADD receptors (plasmid: AAV1-hSyn-hM4Di-mCherry, 50 ul/injection, 1e12 vg/ml), with individually determined coordinates from the surface of the brain using an MRI-compatible stereotaxic frame. For DREADD testing, a water-soluble form of CNO was used (CNO-HCl) and administered 30 min prior to ethanol/water administration (i.m., 5.6 mg/kg, 30 mg/ml in saline). A separate pharmacokinetics study indicated that CNO concentrations at the time of ethanol administration (t=30 min post-injection) were 1052 ± 260, and rose to 1840 ± 877 ng/ml at the start of the behavioral test (t=90 min). Reverse metabolism to clozapine from CNO was between 1-1.5%, with plasma concentrations of 12 ± 4 (t=30 min) and 27 ± 8 (t=90 min). Administration of 5.6 mg/kg CNO with water resulted in partial ethanol-like discriminative stimulus effects in two subjects (24% and 50%, respectively). Pretreatment of 0.56 mg/kg CNO prior to 0.5 g/kg ethanol resulting in full substitution in one monkey. These preliminary data demonstrate that the rhesus monkeys has a ratio of clozapine:CNO of <2% following i.m. CNO administration, suggesting the effect of CNO activation is unlikely due to clozapine. Further, activation of the inhibitory hM4D receptor within the NAc enhances the potency of the ethanol discrimination in a subset of rhesus monkeys. Additional work is necessary to investigate extent of DREADD expression in the NAc across monkeys, as well as the extent of extra-NAc mediation of the ethanol cue in those monkeys that did not demonstrate changes with NAc inhibition.

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Nanosymposium

279. Chemogenetics in Rodents and Primates

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Title: Memory retention involves the ventrolateral orbitofrontal cortex: Comparison with the basolateral amygdala and dorsal striatum using DREADDs

Authors: *S. L. GOURLEY[1], K. S. ZIMMERMANN[2]
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Abstract: The orbitofrontal cortex (OFC) is thought to link stimuli and actions with anticipated outcomes in order to sustain flexible behavior in an ever-changing environment. How it retains these associations to guide future behavior is less well-defined. Here we utilized CaMKII-driven inhibitory Gi-coupled Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to understand the functions of one subregion, the ventrolateral orbital cortex (VLO). DREADDs were infused and activated by their ligand Clozapine-N-oxide (CNO) in conjunction with fear extinction training (a form of aversive conditioning) and response-outcome conditioning (a form of appetitive conditioning). Gi-DREADD-mediated inactivation during extinction conditioning interfered with fear extinction memory, resulting in sustained freezing when mice were later tested drug-free. Similarly, Gi-DREADD-mediated inactivation in conjunction with response-outcome conditioning caused a later decay in goal-directed responding - that is, mice were unable to select actions based on the likelihood that they would be rewarded in a sustainable fashion. By contrast, inhibitory Gi-DREADDs in the basolateral amygdala (BLA) impaired the acquisition of both conditioned fear extinction and response-outcome conditioning, as expected based on prior studies using other inactivation techniques. Meanwhile, DREADD-mediated inhibition of the dorsolateral striatum *enhanced* response-outcome conditioning, also in line with prior reports. Together, our findings suggest that learning-related neuroplasticity in the VLO may be necessary for memory retention in both appetitive and aversive domains and provide evidence for the utility of DREADDs approaches for dissecting brain function in mice.

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Nanosymposium

279. Chemogenetics in Rodents and Primates

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**Topic: ***H.01. Animal Cognition and Behavior

Support: HHMI Janelia

Title: Engineering ultra-potent ion channel and ligand interactions

Authors: *C. J. MAGNUS, P. H. LEE, M. H. RAMIREZ, S. M. STERNSON
HHMI, Janelia Farm, Ashburn, VA

Abstract: Ligand gated ion channels are powerful tools that control neuron activity. We have developed high potency ion channels and ligands for chemogenetic control of neurons. Our recent work has emphasized engineering ligand gated ion channels to be sensitive to both clinically approved drugs as well as to high potency chemical analogs with low endogenous receptor activity. This approach provides an avenue to new research reagents and the possibility of a chemogenetic toolbox for clinical therapies.

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Nanosymposium

279. Chemogenetics in Rodents and Primates

Location: 144A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***279.11

**Topic: ***H.01. Animal Cognition and Behavior

Title: Improving delivery of viral vectors to specific regions of the non-human primate brain

Authors: *J. M. FREDERICKS, M. A. G. ELDRIDGE, D. C. IDE, T. W. BENNETT, Jr., D. C. MILLER, W. LERCHNER, G. R. DOLD, B. J. RICHMOND
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Abstract: We wish to introduce viral vectors accurately into subcortical targets, and into substantial areas of the cortical sheet, with uniform penetrance in old world monkeys. Here we present three techniques that have proven helpful in our experiments with chemogenetic targeting.
1) When approaching deep subcortical structures (e.g., tail of caudate nucleus), small deflections at the point of entry can result in significant deviations from target. Typically, we insert a Hamilton gas-tight syringe into a Harvard Apparatus Pump 11 Elite Nanomite mounted on a micromanipulator to perform injections. To avoid needle deflection, we fitted the manipulator with a custom-made guide foot.
2) Targeting the ventral cortical surface (e.g., OFC area 12) can be done via visually guided hand-held injections. However, this method requires a great deal of skill to inject only the cortical grey matter, and might result in loss of virus from back-flow due to the quick bolus injections. We constructed an injector array, comprising a 3D-printed manifold, into which we insert four 31-gauge needles in 2 x 2 grid separated by 2 mm on each side.The injector array was attached with silicone tubing to an infusion pump, allowing for simultaneous infusions of desired volumes at a controlled rate of 0.5 ul/min.
3) On occasion we, and others, thought we had injected active virus, only to find later that there was no gene expression. One possible cause of this is that the material did not flow from the needle at the time of injection (blocked needle). To confirm that the material was injected successfully in the desired location, we infused a mixture of 0.1 mM manganese chloride tetrahydrate ($MnCl_2$) with our viral construct containing a DREADD-expressing sequence. The Mn-enhanced signal in the post-op MR scan provided good visualization of the target region, and persisted up to 8 hours after injection.

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Nanosymposium

280. Perception and Imagery: Semantic and Abstract Representation

Location: 152A

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**Topic: ***H.02. Human Cognition and Behavior

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Title: The hippocampus as a source of cross-modal predictions

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Abstract: Perception can be cast as a process of inference, in which bottom-up sensory signals are combined with top-down expectations. In line with this, neural activity in sensory cortex is strongly modulated by prior expectations. However, the source of such top-down expectations remains unknown. Here we focus on sensory expectations that arise from cross-modal associations, such as when an auditory sound (e.g., horn or bark) leads to an expectation of the visual appearance of the corresponding object (e.g., car or dog). These cross-modal expectations necessarily depend on a higher-order brain region that can learn statistical regularities from the world, retrieve them based on partial information (e.g., a sound), and reinstate missing information (e.g., the associated object) in sensory cortex. Based on these desiderata, we hypothesized that the hippocampus — known to be involved in learning arbitrary relationships and to have bidirectional connections with sensory cortices of all modalities — would be involved in such associative predictions. To test this hypothesis, we exposed human participants to complex auditory cues predicting the appearance of complex visual shapes, while measuring neural signals in both visual cortex and the hippocampus with high-resolution functional magnetic resonance imaging. Using multivariate pattern analysis to reconstruct shapes from neural activity after an auditory cue, we discovered a dissociation between these brain systems in terms of what visual information was represented. In particular, representations in visual cortex were dominated by the shape that was subsequently presented on the screen, whereas representations in the hippocampus only reflected which shape was predicted by the cue, regardless of what was actually presented. To investigate the circuitry underlying these expectation signals further, we applied an automated segmentation method to distinguish subfields of the hippocampus. Specifically, it has been suggested that the CA3 subfield is involved in “pattern completion” — i.e., retrieving previously encountered patterns from memory based on partial cues, such as the predictive cues presented in the current study — whereas CA1 compares such retrieved patterns to incoming sensory input to compute a match/mismatch signal. In line with this framework, we found that shape expectations were present in CA3 (combined with dentate gyrus), but not in CA1. Expectation signals were also present in the subiculum, known to be involved in relaying signals from the hippocampus back to sensory cortex. These findings suggest that the hippocampus may be a source of memory-based predictions in sensory systems.

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Nanosymposium

280. Perception and Imagery: Semantic and Abstract Representation

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Title: Neural representations of perceived and remembered spoken sentences

Authors: *K. MÜSCH[1], K. HIMBERGER[1], K. TAN[2], T. A. VALIANTE[3], C. J. HONEY[1]
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Abstract: How do we recall the sequence of words in a sentence that we have recently heard? There is an important role for fronto-parietal control processes, which order and rehearse basic phonological features of speech. However, when sequences of words possess a coherent structure, syntactic and semantic structure may be automatically extracted, which may later shape sentence recall. Here, we compared the neural processes involved in perceiving and subvocally rehearsing semantically coherent and incoherent sentences. We recorded electrocorticographic signals from the lateral surface of the human cerebral cortex in 17 patients with pharmacoresistant epilepsy. On each trial of a sentence repetition task two sentences were presented; participants silently rehearsed the second sentence and then repeated it aloud. Half of the sentences to be repeated were semantically coherent and half were incoherent. Broadband power (70-200 Hz) was modulated by sentence coherence in widespread cortical systems, both during sentence perception as well as subvocal rehearsal. During the perception and rehearsal of incoherent sentences, increased broadband power was observed in regions classically associated with language function and linguistic control: the left superior temporal and inferior frontal gyri. Conversely, perception and rehearsal of coherent sentences elicited greater activation in "semantic" regions such as the inferior and middle temporal gyri, the temporo-parietal junction and dorsal frontal regions. We employed a cross-validation approach to identify electrodes exhibiting stimulus-specific information (i.e. reproducible patterns specific to the presentation of a particular sentence). During perception of speech, we found very strong sentence-specific representation in classical language regions for both coherent and incoherent sentences. During the rehearsal of speech, however, these same regions exhibited sentence specific responses only for the incoherent sentences. In semantic regions, stimulus specific activity was marginal during the perception of speech, but the same sites exhibited clear sentence specific representation for both coherent and incoherent sentences during subvocal rehearsal. Sentence-specific patterns

were observed in many sites with below-baseline activation. Overall, these results are consistent with the notion that control and semantic systems support sentence recall in parallel: control systems operate on more sensory representations, and are especially critical for unfamiliar or incoherent patterns; semantic systems operate more diffusely and support recall of both coherent and incoherent sequences.

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Nanosymposium

280. Perception and Imagery: Semantic and Abstract Representation

Location: 152A

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**Presentation Number: ***280.03

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH DC012634

Title: The representations of lipread words in posterior temporal cortex studied using an fMRI-rapid adaptation paradigm and functional localizers

Authors: *L. E. BERNSTEIN[1], S. P. EBERHARDT[1], X. JIANG[2], M. RIESENHUBER[2], E. AUER, Jr.[1]
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Abstract: We have shown that a more anterior region of the left pSTS/pMTG responds preferentially to visual speech motion, and a more posterior pSTS/pMTG region responds to speech and non-speech face motion stimuli [Bernstein et al., 2011. Hum. Brain Mapp. 32, 1660-1676]. We dubbed the speech-selective area the "temporal visual speech area" (TVSA). Here, using an fMRI-RA (rapid-adaptation) paradigm, we investigated whether TVSA represents the visual patterns of spoken words. Regions of interest (ROIs), including the TVSA, the visual word form area (VWFA), and the fusiform face area (FFA), were individually localized using separate localizer scans. During fMRI-RA scanning, 19 young adults with good lipreading viewed visual spoken word pairs that were the same (but different videos), and near, near+, or far in perceptual distance. The TVSA localizer scan was used to define both TVSA and non-speech face motion area (NSFMA) ROIs. Left TVSA demonstrated the predicted pattern of release from adaptation: Far and near+ stimulus word-pairs both demonstrated release from adaptation that was not significantly different in signal level, suggesting that words that were perceptually far and words that were similar but discriminably different (demonstrated with behavioral

discrimination results) were represented as different words within TVSA. Release from adaptation was not statistically different across same and near pairs, and release from adaptation was significantly below that of far and near+ pairs. *D-prime* discrimination values across different stimulus pairs were, in order, *near* < (*near+*) < *far*. Left MT/V5 had high signal level, similar to TVSA signal levels, but it did not demonstrate release from adaptation as a function of stimulus dissimilarity condition. Left FFA signal levels were similar to TVSA levels, but same, nearplus, and far pairs resulted in similar signal levels, suggesting that left FFA does not represent visual spoken words. Left NSFMA demonstrated significantly lower signal levels than TVSA for all fMRI-RA pair types and did not demonstrate release from adaptation as a function of word-pair perceptual distance. The left VWFA signal levels were overall significantly lower but similar in pattern to those of left TVSA.

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Nanosymposium

280. Perception and Imagery: Semantic and Abstract Representation

Location: 152A

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**Topic: ***H.02. Human Cognition and Behavior

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Title: Perceptual adaptation to non-native sound contrasts: Electrophysiological evidence of neuroplasticity in the phonological system related to second language learning

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Abstract: Second language (L2) learners frequently encounter difficulty in perceiving specific non-native sound contrasts (Dupoux et al., 2008), i.e. a phenomenon called phonological deafness (Troubetzkoi, 1939). However, if the neurocognitive network underlying phonological processing is plastic to some extent, extensive L2 experience should lead to adaptive processes and eventually to a certain capacity to discriminate non-native phonemic contrasts even in late L2 learners (Best & Strange, 1992; Flege et al., 1997; Iverson et al., 2012). Here, our goal was to examine the extent to which neuroplastic changes take place in the phonological system as a

function of L2 experience. We designed an ERP experiment in which the capacity of listeners to discriminate second language phonemic contrasts mediated lexical access. A semantic violation paradigm was used in which the difference between semantically congruent and incongruent items was implemented by a phonemic contrast that was unique to the L2, English (e.g., /ɪ/ - /i/: *ship – sheep*). Nineteen young adult native speakers of French with intermediate proficiency in English participated in the ERP experiment. Participants listened to sentences that contained either a semantically congruent item (e.g., *The anchor of the **ship** was let down*) or an incongruent one (e.g., **The anchor of the **sheep** was let down*) and were asked to perform an acceptability judgement. The ERP data revealed a fronto-central incongruency effect, i.e. a larger negativity for incongruent than congruent words between 180-220 ms after critical word onset. Importantly, this early effect was larger in more proficient L2 learners. Moreover, a centro-parietal N400 incongruency effect was found, i.e. larger negativity for incongruent than congruent words between 350-650 ms. Within this time window, the effect peaked earlier in more proficient L2 learners. The present findings indicate that L2 learners were sensitive to semantic incongruencies mediated by non-native phonemic contrasts. The proficiency-related variations of ERP effects suggest that perceptual sensitivity to non-native sounds depends on the amount and type of sustained non-native language experience. However, the capacity to acquire non-native phonology has previously been found to show considerable inter-individual variability (Pruitt et al., 2006; Golestani & Zatorre, 2009). Thus, in the future it will be of importance to delimitate facilitating and limiting factors for neuroplastic changes in the phonological system. Amongst others, investigations should identify how targeted training can improve the sensitivity to second language phonemic contrasts.

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Nanosymposium

280. Perception and Imagery: Semantic and Abstract Representation

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Title: The evolution of braille letter representations in blind readers

Authors: *S. TENG[1], *R. CICHY[3], D. PANTAZIS[2], A. OLIVA[1]
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Abstract: The visual cortex in blind persons is functionally reorganized to respond to nonvisual inputs. A major model system to probe crossmodal plasticity is braille, a tactile reading modality known to activate visual cortical regions. However, the spatiotemporal dynamics of crossmodally reorganized cortical networks remain open question; in particular, the routing and functional dynamics of the braille-reading network are not well understood.
The goal of this study is to track the representational trajectory of tactile braille signals as they propagate through the cortical processing stream. To this end, we applied multivariate decoding and representational similarity analysis to magnetoencephalography (MEG) recordings of brain responses to braille letters. In previous work, braille letter identity emerged early in the MEG signal time course but was largely uncorrelated between individual subjects. Thus, to better capture the timing and content of subject-specific signals, we conducted repeated sessions in individuals. In each session, we presented single alphabetical braille letters in random order during MEG recording. Subjects performed a 1-back task in which they passively read presented letters and responded via button press to occasional repeated trials, which were then discarded. The recorded neuromagnetic activity was mapped onto left and right sensorimotor, early "visual" (EVC), and fusiform regions of interest (ROIs) using cortical models derived from individual MRI anatomical scans. We then used linear support vector machines to decode letter identity pairwise over time, constructing a representational dissimilarity matrix (RDM) of pairwise relationships between letter signals for each time point.
The ROI-based classification time courses demonstrate the earliest and strongest decoding signals in sensorimotor ROIs contralateral to the braille-stimulated finger. Fusiform and EVC ROIs showed later onsets and more sustained representations. Early representational patterns, as shown by RDMs, follow a scheme suggestive of sensitivity to letter complexity (e.g., number of dots), which correlates roughly with alphabetical letter position. Later representations in downstream ROIs exhibited weaker adherence to this scheme. These results elucidate the fine-grained representations of tactile braille signals as they are read out and transformed over time from sensory to more lexically and semantically complex representations.

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Nanosymposium

280. Perception and Imagery: Semantic and Abstract Representation

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Title: How do blind people represent rainbows? Disentangling sensory and semantic components in concept knowledge

Authors: *E. STRIEM-AMIT[1], X. WANG[3], Y. BI[4], A. CARAMAZZA[2,5]
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Abstract: How do we represent information that has no sensory features, and how are abstract concepts like "freedom", devoid of perceptible referents, represented in the brain? To address the role of sensory information in the neural representation of concepts, we investigated how people born blind process concepts whose referents are imperceptible to them because of their visual nature ("rainbow", "red"). We find that the left dorsal anterior temporal lobe (ATL) shows preference to concepts whose referents are not sensorily-available to the blind. Parts of inferior-lateral ATL and the temporal pole preferred abstract concepts devoid of any external referents ("freedom" vs "rainbow"). The medial ATL preferred concrete concepts and items (non-visually) perceptible to the blind ("snow" vs "rainbow"), suggesting a role in representing concepts with sensory referents, beyond vision. The findings point to a new division of labor among medial, dorsal and lateral aspects of ATL in representing different properties of concepts.

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Title: A modality-independent cortical organization of semantic knowledge

Authors: *E. RICCIARDI, G. HANDJARAS, A. LEO, L. CECCHETTI, P. PIETRINI
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Abstract: Sight has always been regarded as the most important sense for humans to interact with the surrounding world and acquire knowledge. Nonetheless, individuals who are visually-deprived since birth show perceptual and cognitive skills that are comparable to those of sighted individuals. Historically research focused mostly on the brain plastic reorganization that occurs in blind individuals. Only recently scientists from distinct labs, including our own, developed innovative strategies to understand how much vision is a mandatory prerequisite for the brain fine morphological architecture to develop and function. As a whole, studies in sighted and congenitally blind individuals have provided solid and novel evidence that most of the higher-level brain areas develop independently from any visual experience and are able to process also non-visual information in a task-specific manner: a property named *supramodality*.
The existence of a supramodal functional organization poses fundamental questions, including examining how unisensory information is integrated into a more abstract, 'conceptual' representation. In other words, at which level (e.g. region or network) and with which mechanism does the supramodal representation of information occur?
To address the importance of low-level sensory-based and high-level abstract features in conceptual representation, we recently combined linguistic studies and brain activity measures by fMRI in sighted and blind individuals during a property-generation task with concrete nouns from eight categories, presented through visual or auditory modalities. Patterns of neural activity within a large semantic cortical network correlated with linguistic production and were independent both from the modality of stimulus presentation and the (lack of) visual experience. In contrast, selected modality-dependent differences were observed only when the analysis was limited to the individual regions within the semantic network.
In addition, we recently moved from a category-based to a fine-grained representation of single items using computational models of semantic and shape information. Higher-level semantic and perceptual models led to significant encoding accuracies of single items in the left parietal cortex, a region involved in binding features and concepts across sensory modalities.
Altogether, these studies suggest that conceptual knowledge may rely on a distributed, modality-independent cortical representation that integrates the partial category and modality specific information retained at a regional level.

Disclosures: E. Ricciardi: None. **G. Handjaras:** None. **A. Leo:** None. **L. Cecchetti:** None. **P. Pietrini:** None.

Nanosymposium

280. Perception and Imagery: Semantic and Abstract Representation

Location: 152A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***280.08

**Topic: ***H.02. Human Cognition and Behavior

Support: National Basic Research Program of China Program 2013CB837300

Title: Fine-grained semantic representation in the white matter pathway

Authors: *Y. BI[1], ***Y. BI**[1], Y. FANG[2], X. WANG[2], S. ZHONG[2], G. GONG[2]
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Abstract: The neural basis of semantic representation has been localized to a distributed cortical network. A challenging question is how distributed regions that represent specific attributes are bound into a higher-order semantic space where concepts that do not necessarily share specific attributes are considered semantically similar. Herein, we tested a novel framework of representing semantic space in the pattern of white matter (WM) connections, representing higher-order semantic information by linking different lower-dimensional attributes in different cortical nodes. We extended representational similarity analysis to lesion data, computing the neural representational dissimilarity matrix (RDM) with a machine-learning model using the voxel-wise WM lesion patterns as features to predict item-specific naming performance in 80 patients with brain damage. Based on the rationale that naming accuracy would be similar between items that had similar neural bases, the relationship between the predicted naming score using the classifier trained with the naming performance of one item (e.g., "scissors") and the actual naming score of another item (e.g., "axe") was taken as the degree of neural similarity of these two items. We found that five WM tracts in left hemisphere, mainly connecting occipital/middle temporal regions and anterior temporal regions, had neural RDMs that were significantly associated with semantic space, such that the prediction of naming performance accuracy based on the lesion pattern was higher between semantically related items than between semantically distant items. Such semantic relatedness effects were not attributable to modality-specific attributes (shape, manipulation, color and motion) or to the organization properties of the cortical regions that they connected, which tended to represent multiple modality-specific attributes. In conclusion, we show that the semantic space could be formed through connection patterns across cortical regions representing modality-specific attributes. These results provide the first empirical evidence for the neural basis of the classical notion of representation by connection, and they mark a future avenue for studying the role of brain connections in representing higher-order information.

Disclosures: Y. Bi: None. **Y. Fang:** None. **X. Wang:** None. **S. Zhong:** None. **G. Gong:** None.

Nanosymposium

280. Perception and Imagery: Semantic and Abstract Representation

Location: 152A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***280.09

**Topic: ***H.02. Human Cognition and Behavior

Support: Natural Sciences and Engineering Research Council of Canada
Norman Anderson graduate student fund
National Science Foundation Fellowship

Title: Representations of belief concepts and the neural organization of abstract semantics

Authors: *A. LESHINSKAYA[1], J. CONTRERAS[2], A. CARAMAZZA[3], J. P. MITCHELL[4]
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Capital One, McLean, VA; [3]Dept. of Psychology, [4]Ctr. for Brain Sci., Harvard Univ., Cambridge, MA

Abstract: While the neural organization of sensory systems is relatively well understood, the principles guiding the cortical placement of non-sensory knowledge are much less known. Here, we identified neural regions that represent a class of concepts that are independent of any perceptual or sensory attributes: belief attributes. During functional magnetic resonance imaging scanning, human adult participants read names of social groups (e.g. Atheists, Evangelicals, and Economists) and performed a one-back similarity judgment according to 1 of 2 dimensions of belief attributes of those groups: political orientation (Liberal to Conservative) or spiritualism (Spiritualist to Materialist). By spanning a wide variety of social groups that possess these beliefs, belief attributes did not coincide with any specific sensory quality, allowing us to isolate conceptual representations from perceptual ones. We used whole-brain, multi-voxel pattern searchlight analysis to identify regions in which activation patterns distinguished the 2 ends of both belief dimensions: Conservative from Liberal social groups when participants focused on the political orientation dimension, and spiritual from Materialist groups when participants focused on the spiritualism dimension. A cluster in right precuneus exhibited such a pattern, indicating that it carries information about belief-attribute concepts and thus, possesses the capacity to represent at least one domain of non-sensory knowledge. This region was near to, but did not overlap with, the theory of mind network, which was localized with a standard task in the same participants and found to engage nearby, but distinct, parts of precuneus. Although the domain-selectivity of precuneus is not fully known, complementary findings from our group (and those of others) suggest that non-sensory concepts from other domains are represented in distinct areas. Taking those findings together, we suggest that specific domains of abstract concepts are localized in systematic relation to other neural systems computationally relevant to them.

Disclosures: **A. Leshinskaya:** None. **J. Contreras:** None. **A. Caramazza:** None. **J.P. Mitchell:** None.

Nanosymposium

280. Perception and Imagery: Semantic and Abstract Representation

Location: 152A

Time: *Monday, November 13, 2017, 8:00 AM - 10:45 AM

Presentation Number: *280.10

Topic: *H.02. Human Cognition and Behavior

Support: Templeton

Title: An asymmetrical relationship between verbal and visual thinking: Converging evidence from behavior and fMRI

Authors: ***E. AMIT**
Brown Univ., Providence, RI

Abstract: Humans rely on at least two modes of thought to ponder concepts, events and scenes: verbal (inner speech) and visual (imagery). Does engaging in one entail engaging in the other? We conducted an fMRI experiment to address this question. Specifically, using functional ROI approach, we measured the activation in visual and language brain regions while participants recalled sentences and images that they learned in advance. The results show that individuals had better control over their verbal thinking than visual imagery: verbal representations were invoked more when individuals deliberately attempted to think verbally, than when they engaged in visual imagery. However, they generated similarly robust visual representations regardless of whether they attempted to engage in visual imagery or verbal thinking. A possible interpretation of these findings is that visual thinking is somehow primary, given the relatively late emergence of verbal abilities during human development and in the evolution of our species.

Disclosures: **E. Amit:** None.

Nanosymposium

280. Perception and Imagery: Semantic and Abstract Representation

Location: 152A

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***280.11

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH Grant NS089609
NSF Grant 1349042

Title: Beyond Embodiment: Connectivity and dynamics in the conceptual system

Authors: *B. MAHON
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Abstract: The core idea behind embodied cognition is that sensorimotor processes play an instrumental role in the representation of common concepts. I argue that prior formulations of the embodied cognition hypothesis are undermined by causal evidence from neuropsychological studies of brain-damaged patients. Those prior studies indicate that sensorimotor processes can be impaired while conceptual processing is spared. More recent formulations of the embodied hypothesis that have been weakened so as to be compatible with the neuropsychological findings are not coherently distinct from the putative alternative hypothesis, that concepts are instantiated as amodal symbols. This suggests that we should move beyond questions of representational format and 'embodiment' to test hypotheses about the connectivity and processing dynamics in the conceptual system. I present a series of fMRI experiments, carried out in healthy participants and patients with lesions, that provide both correlative and causal evidence about how conceptually-related patterns of activity are modulated by processing in sensorimotor areas. These arguments and findings compel a reinterpretation of a large body of findings that have to date been considered within the context of the embodied cognition hypothesis. I suggest that the 'phenomena of embodiment' reflect the connectivity and dynamics of interactions between conceptual and sensorimotor representations.

Disclosures: B. Mahon: None.

Nanosymposium

281. Mechanisms of Working Memory

Location: 156

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***281.01

**Topic: ***H.02. Human Cognition and Behavior

Title: Decoding unattended working memory items: No evidence for activity-silent memory representations

Authors: *T. CHRISTOPHEL, P. IAMSHCHININA, C. YAN, C. ALLEFELD, J.-D. HAYNES
Bernstein Ctr. For Computat. Neurosci., Charité-Universitätsmedizin, Berlin, Germany

Abstract: Working memory enables retention of a limited number of stimuli differently prioritized depending on current goals. In prior work, attended memory items (AMIs) were found to be represented in a form of brain activity patterns which can be decoded using multivariate pattern analysis (MVPA). Unattended memory items (UMIs) that are less relevant during the task, however, could not be decoded even if they could be recalled. These findings lead some to postulate that working memory operates in an activity-silent state using short-term synaptic plasticity. We revisited this question using (a) a much larger sample size, (b) an experimental design cleanly separating AMIs and UMIs and (c) a more comprehensive set of brain regions. In each trial, participants memorized the orientation of two gratings. A first cue indicated that one of them should be used for a first orientation change discrimination task after a delay. Then, a second cue could select either the same or the other orientation for a second task. Such a double-cuing task forces participants to maintain the orientations of both gratings until the second cue, but directs attention to the cued item (AMI). We used multivariate pattern analyses (cvMANOVA MVPA) to measure the distinctness of brain activity patterns evoked by maintenance of AMIs and UMIs. Consistent with prior work, visual areas (V1-V4) carried information about AMIs, but not UMIs. However, more anterior regions (IPS and FEF) carried information about both AMIs and UMIs. These results demonstrate that UMIs are retained in an active (not an activity-silent) state.

Disclosures: T. Christophel: None. **P. Iamshchinina:** None. **C. Yan:** None. **C. Allefeld:** None. **J. Haynes:** None.

Nanosymposium

281. Mechanisms of Working Memory

Location: 156

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***281.02

**Topic: ***H.02. Human Cognition and Behavior

Support: Fyssen Foundation
Bettencourt-Schueller Foundation
Philipe Foundation

Title: Maintenance mechanisms of the content and the rule during visuomotor working memory

Authors: *R. QUENTIN[1], J. KING[2], E. SALLARD[1], N. FISHMAN[1], E. BUCH[1], R. THOMPSON[1], L. COHEN[1]
[1]NIH, Bethesda, MD; [2]New York Univ., New York, NY

Abstract: Working memory is our ability to temporarily hold information available for processing. It is required for learning, reasoning, updating information, and performing everyday visuomotor tasks. Intra-cortical recordings in nonhuman primates and functional MRI studies in humans demonstrated the involvement of an extended group of cortical and subcortical brain areas during working memory. However, the spatiotemporal neural mechanisms of memory content and recall rule maintenance are unknown.
In this experiment, we used magneto-encephalography (MEG) recordings and novel machine-learning algorithms to determine the spatiotemporal neural dynamics of memory content and recall rule maintenance. Two visual stimuli with different line orientations and spatial frequencies were briefly presented to the participant. After a short delay, a post-cue instruction indicated which visual feature (spatial frequency or orientation) of which stimulus (left or right) the participant had to remember in order to perform a motor action. We applied machine-learning algorithms to the MEG brain signal to decode i) the visual features of the stimuli immediately after their presentation; ii) the specific visual content maintained in memory (cued item) and iii) the maintenance of the rule that specify which visual feature has to be remembered. At the group level, we were able to decode i) visual perceptual features embedded in early stages of processing, ii) the working memory content and, weakly, the un-cued item (distractor) and iii) the working memory rule during several seconds after its presentation with a strong generalization across time.
We conclude that persistent and stable neural activity in a distributed brain network underlies working memory content and recall rule maintenance. Thus, our ability to act appropriately in our changing environment depends on the capacity of our neural networks to encode the task-relevant information via a persistent neural activity.

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Nanosymposium

281. Mechanisms of Working Memory

Location: 156

Time: *Monday, November 13, 2017, 8:00 AM - 10:00 AM

Presentation Number: *281.03

Topic: *H.02. Human Cognition and Behavior

Support: NIH Grand R21 AG047944

Title: COMT genotype, estradiol, and working memory after menopause

Authors: ***J. A. DUMAS**[1], J. MAKAREWICZ[1], J. Y. BUNN[2], J. NICKERSON[3], E. MCGEE[4]
[1]Psychiatry, [2]Med. Biostatistics, [3]Radiology, [4]Obstetrics, Gynecology, and Reproductive Services, Univ. of Vermont Larner Col. of Med., Burlington, VT

Abstract: The current study examined how a gene related to functioning of the dopaminergic system, catechol-*O*-methyltransferase (COMT) and estradiol interacted to affect brain functioning in healthy postmenopausal women. Participants were 110 healthy, cognitively normal postmenopausal women between the ages of 50-60. All women provided a blood sample for COMT and estradiol analyses and underwent an MRI scan. Working memory performance and related brain activation was measured with BOLD fMRI during the N-back task. Results were examined for COMT homozygotes, Met/Met (N=30) and Val/Val (N=31) women. A median split was performed on the circulating estradiol levels to create high and low estradiol groups. COMT genotype and estradiol level were hypothesized to be proxy measures for brain dopamine levels with the Met/Met and high estradiol group having the most dopamine and Val/Val and low estradiol group having the least dopamine. The results showed decreased activation in working memory-related brain regions as the hypothesized dopamine level increased. Specifically, women with a Met/Met genotype in the high estradiol group with the greatest amount of dopamine had the least activation in frontal lobe working memory regions and in the cuneus. Women with a Val/Val genotype in the low estradiol group had greater activation in these regions relative to the other groups. Performance on the N-back task did not show any group differences. These data highlight the continued influence of estradiol on brain functioning in women post menopause. They also indicate that the influence of estradiol on dopaminergically-driven cognition is decreased after menopause. This decrease may have implications for brain disorders associated with dopamine dysfunction in aging.

Disclosures: **J.A. Dumas:** None. **J. Makarewicz:** None. **J.Y. Bunn:** None. **J. Nickerson:** None. **E. McGee:** None.

Nanosymposium

281. Mechanisms of Working Memory

Location: 156

Time: *Monday, November 13, 2017, 8:00 AM - 10:00 AM

Presentation Number: *281.04

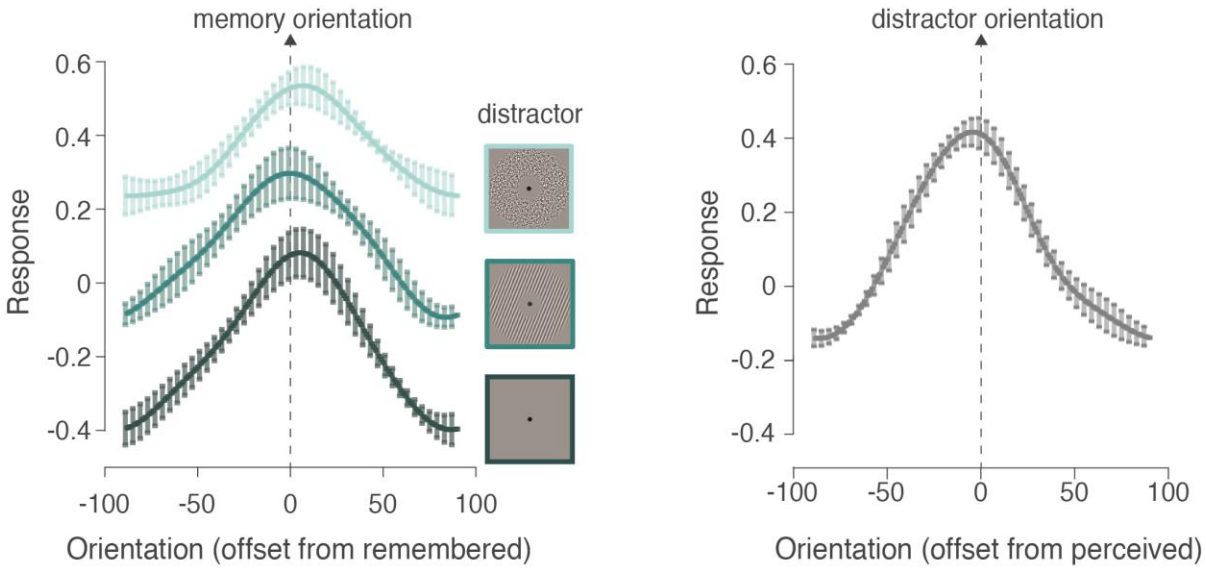
Topic: *H.02. Human Cognition and Behavior

Support: NIH R01-EY025872

Title: Visual working memory representations persist in visual cortex even in the presence of distracting visual inputs

Authors: ***R. L. RADEMAKER**, C. CHUNHARAS, J. T. SERENCES
Psychology, Univ. of California San Diego, La Jolla, CA

Abstract: When trying to attain behavioral goals, the ability to flexibly juggle thoughts is key. The mental workspace allowing visual information to be kept online for manipulation or future recall is known as Visual Working Memory (VWM). Notably, robust VWM maintenance can be achieved despite the continuous influx of new visual input from the eyes. Neuroimaging studies have firmly established that VWM contents can be decoded from occipital cortex, including primary visual area V1. Furthermore, the quality of information in these regions predicts behavioral performance, suggesting sensory cortical involvement in the representation of sensory memories. However, rarely have previous neuroimaging experiments mimicked the everyday reality of active visual distraction during memory maintenance. Recently, one study suggested that mnemonic representations migrate from visual cortex to a select patch of parietal cortex when people view predictable but irrelevant pictures during VWM. This study challenged the role of visual cortex during VWM, relegating previous findings to the realm of epiphenomena borne out of overly artificial tasks. In our experiment (N=6), people remembered a random visual orientation for 13 seconds while looking at either a blank screen or an 11-sec visual distractor. Distractors were a Fourier filtered white noise stimulus, or another visual orientation that could have any angular offset relative to the memory orientation. Distractors were predictable, but irrelevant to the task. Using a multivariate method (trained on independent data) we could reconstruct the orientation in memory from activity patterns in all areas along the visual hierarchy (V1-V4). Importantly, we were also able to reconstruct the distractor orientation that was physically present during the memory delay. In other words, visual cortex can concurrently represent incoming sensory information alongside mnemonic information that is no longer anchored to the outside world.



Disclosures: **R.L. Rademaker:** None. **C. Chunharas:** None. **J.T. Serences:** None.

Nanosymposium

281. Mechanisms of Working Memory

Location: 156

Time: *Monday, November 13, 2017, 8:00 AM - 10:00 AM

Presentation Number: *281.05

Topic: *H.02. Human Cognition and Behavior

Title: Neural correlates of an associative memory of elapsed time

Authors: ***V. G. VAN DE VEN**, J. LIFANOV, O. IOSIF, S. KOCHS, F. SMULDERS, P. DE WEERD
Fac. of Psychology and Neuroscience, Maastricht Univ., Maastricht, Netherlands

Abstract: The extent to which time duration is represented in associate memory remains under-investigated. We designed a time paired associate task (TPAT) in which participants implicitly learnt cue-time-target associations between cue-target pairs and specific cue-target intervals ranging from 500 to 2000 msec (van de Ven et al. 2017). Importantly, participants only judged whether a cue and probe item were part of the same pair, while making no explicit judgment about time. During learning, some cue-target pairs became associated to a short interval while others became associated to a long interval. During subsequent memory testing, cue-target pairs were shown with both the short and long intervals. Participants showed increased accuracy of identifying matching cue-target pairs if the time interval during testing matched the implicitly

learnt interval. A control experiment showed that participants had no explicit knowledge about the time associations. In subsequent neuroimaging experiments we investigated the neural correlates of TPAT memory performance. Using ultra-high field magnetic resonance imaging (UHF-MRI) study at 7 Tesla we found less hippocampal activity (in left Dentate Gyrus and CA1) when time intervals during test trials did not match the learnt interval, compared to when they did match. Further, in an electroencephalography (EEG) study we found decreased Theta oscillation power (centered at 6 Hz) at occipital/parietal scalp locations for the same comparison of trial types. These findings are in line with the role of hippocampus and Theta oscillations in associate memory (Buzsáki 2006) and suggest that the same mechanisms also play a role in representing time in memory (Ranganath and Hsieh 2016). Mismatch between presented and expected associate memory of time may change hippocampal activity and cortical Theta oscillations, possibly through a common neural source. We suggest that cue-dependent retrieval of time in associate memory could perhaps serve as a mechanism for prospective coding of expected visual spatiotemporal events.References: Buzsáki G. 2006. Rhythms of the brain. OUP; Ranganath C, Hsieh LT. 2016. Ann N Y Acad Sci 1369: 93-110; van de Ven V et al. 2017. Learn Mem 24: 158-162.

Disclosures: V.G. Van de Ven: None. **J. Lifanov:** None. **O. Iosif:** None. **S. Kochs:** None. **F. Smulders:** None. **P. De Weerd:** None.

Nanosymposium

281. Mechanisms of Working Memory

Location: 156

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***281.06

**Topic: ***H.02. Human Cognition and Behavior

Support: TTK1206211523

Title: A combined analysis of the neuroelectric and behavioral effects of racial/gender stereotype and mathematics anxiety on mathematics performance and accuracy

Authors: *E. T. MULUH
9 Cumnor Court, 292 Main Road Kenilworth, Cape Town, South Africa

Abstract: Aim: The neuroelectrical activity and behavioral response of highly mathematics anxious and self-stereotyping individuals is unknown. The aim of the current study was to establish the combined impact of math anxiety (MA) and racial/gender self-setereotyping (RGSS) threats mathematics. **Methods**: One hundred and thirteen first year university students participated in the study. They (1) completed a questionnaire containing the Abreviated

Mathematics Anxiety Rating Scale (AMARS) and Sarason's Test Anxiety Scale, (2) performed simple two-digit addition and multiplication mentally and (3) participated in first year university mathematics evaluations. High and low math anxious groups where formed and electroencephalography (EEG) collected from twelve from participants from each group. Analysis was carried out by ⋯ **Results**: A negative correlation between MA (RGSS) and mathematics performance was obtained. Mathematics performance differences as a function of mathematics anxiety was revealed in both mental and advanced mathematics. A positive correlation between MA and RGSS with a negative correlation between MA (RGSS) and mathematics performance was obtained. Event-related brain potentials revealed that compared to high-MA individuals, low-MA individuals generated high ERP amplitudes at fronto-central and centro-parietal electrode locations. **Conclusions**: Our results support the hypothesis that higher levels of self-reported MA and RGSS are associated with less cortical activation during the early stages of the processing of numeric information in a cognitive tasks. **Key words**: Event-related potentials; Stereotype threat; mathematics anxiety

Disclosures: E.T. Muluh: None.

Nanosymposium

281. Mechanisms of Working Memory

Location: 156

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***281.07

**Topic: ***H.02. Human Cognition and Behavior

Support: NMSS Grant PP2249
University at Buffalo Mark Diamond Graduate Research Grant

Title: Visual-verbal working memory training versus visual search training have overlapping and distinct transfer effects on tasks of spatial working memory and cognitive control: An event-related potential study

Authors: *T. J. COVEY, J. L. SHUCARD, X. WANG, K. SHERWOOD, J. NAKUCI, L. GOH, D. W. SHUCARD
Univ. At Buffalo, Buffalo, NY

Abstract: Cognitive training may improve aspects of cognitive performance. However, the findings in this literature have been mixed, and the unique impact of different forms of training on distinct cognitive abilities is still not fully understood. We examined the effects of two different forms of cognitive training on brain function and performance. Young adult participants were randomly assigned to one of two different training groups. Both groups underwent 20

sessions of adaptive cognitive training (30 minutes per session) over the course of approximately four weeks. One group trained on an n-back task of working memory (WM) with visual letter stimuli (n = 20); the other group trained on a visual search task of selective attention/perceptual discrimination, also with letter stimuli (n = 20). The two tasks were well-matched in terms of difficulty and participant engagement. Participants were administered a battery of tests before and after training (pre- and posttest), which included a Spatial 3-back task and a Go/Nogo Flanker task. The Spatial 3-back task measured transfer of training gains to spatial WM (note, a different domain than the visual-verbal n-back training task); the Go/Nogo Flanker task measured transfer of training gains to cognitive control processes such as response inhibition. Electroencephalographic (EEG) data were obtained during these tasks at pre- and posttest, and event-related potentials (ERPs) were derived for each task. The results indicated that both groups improved on their respective training tasks at a similar rate over the course of training. Only the n-back training group showed improved accuracy (and a greater decrease in RT than the visual search group) from pretest to posttest on the Spatial 3-back task. The n-back training group also exhibited enhancement of the N1 ERP component (within 150 msec after stimulus onset) and reduced latency of the N2 component at posttest on the spatial 3-back task, effects that were not observed for the visual search training group. For the Go/Nogo Flanker task, there was a significant reduction in RT at post- compared to pretest, regardless of group. ERP findings for this task indicated some overlap in training-related changes between the two groups. For example, both groups had reduced P3 latency for trials of the task that required response inhibition. The findings provide evidence that (1) training on a verbal-visual n-back WM task resulted in changes in brain function and cognitive gains on a spatial WM task, and (2) training on tasks that target aspects of attention, regardless of whether they explicitly engage WM, may result in performance gains and changes in brain function on tasks of cognitive control.

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Nanosymposium

281. Mechanisms of Working Memory

Location: 156

**Time: ***Monday, November 13, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***281.08

**Topic: ***H.02. Human Cognition and Behavior

Title: A novel mobile video game to assess the neural correlates of working and visual spatial memory for the brainstation wearable electroencephalography system

Authors: *R. GIL-DA-COSTA, M. LOPES, M. ZINNI, M. CASWELL
Neuroverse, Inc., San Diego, CA

Abstract: The measurement of the brain bases of cognition has long been restricted to laboratory environments with specialized equipment and staff, limiting the ability for applications at a large-scale and in real-world settings. With a rapidly growing number of persons affected by working and/or spatial memory deficits (prevalent in neurological and psychiatric disorders such as Alzheimer's and Parkinson's diseases or Depression), it is imperative to develop novel technologies with engaging assessments to enable monitoring of memory processes over time. To address this need, we used the Brainstation®, Neuroverse's fully integrated wearable electroencephalographic (EEG) system and software application for testing and analysis in mobile platforms (e.g. smartphones and tablets), to measure the neural correlates of working and visual spatial memory during performance of a novel memory game in healthy adults. Naturalistic images from a given semantic category (e.g. animals) were rapidly displayed on the screen, one at a time, at random locations in a grid of cards. Subjects were asked to detect and memorize the identity and location of matching pairs of cards, and subsequently tap the locations at which the matching cards had appeared. Subjects were given feedback on their performance after each trial and, using an adaptive algorithm based on the subject's performance, game parameters were adjusted in real-time to maintain engagement and promote potential training. Due to the nature of the game, subjects were not aware of the identity of the paired images until the presentation of the second image of the matching pair, thus requiring retention of the identity and location of every presented image until the paired image was detected.
A first-level analysis of the correct trials using event-related brain potentials (ERPs) suggests that successful memory use in this game is correlated with an attentional focus strategy. Subjects maintain visual attention until the matching card is detected, and withdraw it immediately after in order to aid memory retention of the location of the matching cards, as expressed by a statistically significant amplitude reduction of the P300 ERP for cards presented after the matching pair. This finding provides both an interesting insight into memory and attention compensation strategies, and a memory correlated neural measure that can be used, with this wearable EEG system, in healthy aging individuals and neurological and psychiatric patients for regular "at home" large-scale monitoring and assessment. Additionally, future and ongoing research is investigating the efficacy of this system and game for cognitive training and rehabilitation.

Disclosures: R. Gil-Da-Costa: A. Employment/Salary (full or part-time):; Neuroverse, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuroverse, Inc. **M. Lopes:** A. Employment/Salary (full or part-time):; Neuroverse, Inc. **M. Zinni:** A. Employment/Salary (full or part-time):; Neuroverse, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuroverse, Inc. **M. Caswell:** A. Employment/Salary (full or part-time):; Neuroverse, Inc..

Nanosymposium

355. Presynaptic Mechanisms

Location: 147B

**Time: ***Monday, November 13, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***355.01

**Topic: ***B.06. Neurotransmitter Release

Support: NIH Grant T32 GM007628 (J.A.)
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Louis V. Gerstner, Jr, Scholars Program (Z.F.)
Leon Levy Foundation (Z.F.)
NARSAD Young Investigator Award (C.S.K.)
K05 DA022413, (J.A.J.)
P01 DA12408 (J.A.J.)

Title: Neuronal depolarization drives increased dopamine synaptic vesicle loading via VGLUT

Authors: *Z. FREYBERG[1], J. AGUILAR[3], M. DUNN[4], S. MINGOTE[8], C. KARAM[5], Z. FARINO[2], M. SONDERS[5], Y. ZHANG[5], B. J. MCCABE[9], D. KRANTZ[10], J. A. JAVITCH[6], D. SULZER[5], D. SAMES[5], S. RAYPORT[7]
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Abstract: The ability of presynaptic dopamine terminals to tune neurotransmitter release to meet the demands of neuronal activity is critical to neurotransmission. Although vesicle content has been assumed to be static, *in vitro* data increasingly suggest that cell activity modulates vesicle content. Here we use a coordinated genetic, pharmacological and imaging approach in *Drosophila* to study the presynaptic machinery responsible for these vesicular processes *in vivo*. We show that cell depolarization increases synaptic vesicle dopamine content prior to release via vesicular hyperacidification. This depolarization-induced hyperacidification is mediated by the vesicular glutamate transporter (VGLUT). Remarkably, both depolarization-induced dopamine vesicle hyperacidification and its dependence on VGLUT2 are seen in ventral midbrain dopamine neurons in the mouse. Together, these data suggest that in response to depolarization, dopamine vesicles utilize a cascade of vesicular transporters to dynamically increase the vesicular pH gradient, thereby increasing dopamine vesicle content.

Disclosures: Z. Freyberg: None. **J. Aguilar:** None. **M. Dunn:** None. **S. Mingote:** None. **C. Karam:** None. **Z. Farino:** None. **M. Sonders:** None. **Y. Zhang:** None. **B.J. McCabe:** None. **D. Krantz:** None. **J.A. Javitch:** None. **D. Sulzer:** None. **D. Sames:** None. **S. Rayport:** None.

Nanosymposium

355. Presynaptic Mechanisms

Location: 147B

**Time: ***Monday, November 13, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***355.02

**Topic: ***B.06. Neurotransmitter Release

Support: HHMI

Title: The primed SNARE-complexin-synaptotagmin complex for neuronal exocytosis

Authors: *Q. ZHOU[1], P. ZHOU[2], T. C. SUDHOF[3], A. T. BRUNGER[3]
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Abstract: Synaptic transmission is essential for the process of communication between two neurons. It occurs upon fusion of synaptic vesicles with the plasma membrane, which is a fast and highly regulated process occurring in less than a millisecond. The minimal system consisting of synaptotagmin, complexin and neuronal SNARE proteins mediates evoked synchronous neurotransmitter release, but the molecular mechanisms and cooperation between these molecules remain unclear. Here, we determined crystal structures of the primed pre-fusion SNARE-complexin-synaptotagmin-1 complex that reveal an unexpected tripartite interface between synaptotagmin-1 and both the SNARE complex and complexin. Simultaneously, a second synaptotagmin-1 molecule interacted with the other side of the SNARE complex via the previously identified primary interface (Zhou *et al.*, Nature 2015). Mutations that disrupt either interface in solution also severely impaired evoked synchronous release in neurons, suggesting that both interfaces are essential for the primed pre-fusion state. Ca^{2+} binding to the synaptotagmin-1 molecules unlocks the complex, allows full zippering of the SNARE complex, and triggers membrane fusion. All complexes at a synaptic vesicle docking site have to be unlocked for triggered fusion to commence, explaining the cooperation between complexin and synaptotagmin-1 in synchronizing evoked release on the sub-millisecond timescale. Our studies also provide insights into the molecular mechanisms of asynchronous and spontaneous neurotransmitter releases.

Disclosures: Q. Zhou: None. **P. Zhou:** None. **T.C. Sudhof:** None. **A.T. Brunger:** None.

Nanosymposium

355. Presynaptic Mechanisms

Location: 147B

**Time: ***Monday, November 13, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***355.03

**Topic: ***B.06. Neurotransmitter Release

Support: Heart and Stroke
CIHR
NSERC
CIFAR

Title: Distinct functions of cGMP-dependent protein kinase in synaptic growth, synaptic vesicle exocytosis and endocytosis

Authors: *J. S. DASON[1,2], A. M. ALLEN[2,3], O. E. VASQUEZ[2], M. B. SOKOLOWSKI[2]
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Abstract: Balancing synaptic vesicle (SV) exocytosis and endocytosis is critical for sustained synaptic transmission. The NO/cGMP pathway has been implicated in the upregulation of SV endocytosis during periods of high synaptic activity, but whether it functions to repress SV exocytosis during periods of low synaptic activity is not clear. Pharmacological inhibition of cGMP-dependent protein kinase (PKG) blocks this upregulation of SV endocytosis. However, the contributions of presynaptic, postsynaptic and glial PKG are not known and separating the exocytic and endocytic functions of PKG are difficult. In *Drosophila*, the *foraging* gene encodes a PKG. Here, we used a *foraging* null mutant, tissue specific RNAi and acute photoinactivation of PKG using FlAsH-FALI to decipher the synaptic effects of PKG at the *Drosophila* larval neuromuscular junction. We found that glial PKG negatively regulates nerve terminal growth, presynaptic PKG inhibits neurotransmitter release in response to low frequency stimulation by inhibiting presynaptic Ca^{2+} entry and presynaptic PKG facilitates SV endocytosis during periods of high synaptic activity by regulating phosphatidylinositol 4,5-biphosphate levels. We found that PKG's effect on synaptic transmission was independent from its effect on synaptic growth. Using a temperature-sensitive *shibire* mutant in conjunction with acute photoinactivation of PKG, we show PKG's effects on SV endocytosis are distinct from its effects on SV exocytosis. We propose a model in which PKG functions to inhibit SV exocytosis during periods of low synaptic activity and facilitates SV endocytosis during periods of high synaptic activity.

Disclosures: J.S. Dason: None. **A.M. Allen:** None. **O.E. Vasquez:** None. **M.B. Sokolowski:** None.

Nanosymposium

355. Presynaptic Mechanisms

Location: 147B

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**Presentation Number: ***355.04

**Topic: ***B.06. Neurotransmitter Release

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ERC-ADG SYNPRIME
NIH/NIGMS R01GM095674
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CNMPB Goettingen
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EUROSPIN

Title: Munc13s - presynaptic regulators of short-term synaptic plasticity in physiology and pathology

Authors: *N. LIPSTEIN[1], B. COOPER[2], F. E. MICHELASSI[3], G. R. MONROE[4], O. JAHN[5], J. S. DITTMAN[7], T. SAKABA[8], J.-S. RHEE[9], H. TASCHENBERGER[6], J. J. JANS[4], N. BROSE[6]
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Abstract: Munc13 proteins are key regulators of neurotransmitter release. They mediate the priming step that renders synaptic vesicles fusion-competent, and their genetic elimination causes a complete block of the synaptic vesicle cycle at presynaptic active zones. Munc13 function is regulated by three Ca^{2+}-dependent pathways, and elevations of the presynaptic Ca^{2+} concentration during neuronal activity leads to a Munc13-dependent increase in the synaptic vesicle priming rate, and consequently to dynamic changes in the efficacy of neurotransmission. Here we show how the Ca^{2+}-dependent regulation of Munc13s affects synaptic signaling in intact circuits, and describe a synaptopathy caused by a *de-novo* variation in the UNC13A gene, characterized by a dyskinetic movement disorder, developmental delay, and autism spectrum disorder.

Disclosures: N. Lipstein: None. **B. Cooper:** None. **F.E. Michelassi:** None. **G.R. Monroe:** None. **O. Jahn:** None. **J.S. Dittman:** None. **T. Sakaba:** None. **J. Rhee:** None. **H. Taschenberger:** None. **J.J. Jans:** None. **N. Brose:** None.

Nanosymposium

355. Presynaptic Mechanisms

Location: 147B

**Time: ***Monday, November 13, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***355.05

**Topic: ***B.06. Neurotransmitter Release

Support: NIH Grant GM103554

Title: Presynaptic loss of dynamin-related protein 1 profoundly alters synaptic vesicle release and recycling at the calyx of Held

Authors: M. SINGH, H. DENNY, C. SMITH, J. GRANADOS, *R. B. RENDEN
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Abstract: Sustained transmitter release is essential for proper interneuronal communication. Impaired mitochondrial function is implicated in many neurodegenerative diseases, and likely affects neurotransmission prior to cellular loss. Synaptic transmission at glutamatergic synapses during repetitive trains of stimuli is affected when presynaptic mitochondrial function or localization is disrupted, but the underlying mechanism is poorly understood. In this study, we investigate the role of mitochondria in synaptic vesicle (SV) recycling, by eliminating Dynamin-Related Protein-1 (DRP1) selectively in the presynaptic terminal at the calyx of Held synapse. Floxed-DRP1 (DRP1fl/fl) mice were injected with AAV-cre-GFP at postnatal day 1(P1) to inhibit DRP-1 expression presynaptically, and used for the study at P16 - P18. Infected (GFP-positive) cell soma in the ventral cochlear nucleus, and their respective calyx of Held presynapses in the contralateral medial nucleus of the trapezoid body, showed loss of DRP1 protein via antibody staining, thus generating a presynaptic-specific DRP1-KO (DRP1-preKO). Conditional DRP1-KO was confirmed by Western Blot of DRP1 from AAV-cre-GFP infected neuronal cultures. Volumetric reconstruction of the VCN cell body and calyx terminal showed significant increase in mitochondrial particle size in DRP1-KO somata, and presynaptic calyx synapses. Using postsynaptic voltage-clamp recording from calyx synapses, we find that DRP1-preKO exhibited enhanced basal evoked response (response to 0.1Hz stimulation) and a 3-fold increase in spontaneous synaptic activity (mEPSC). Standing readily-releasable pool (RRP) size was significantly reduced in DRP1-preKO, suggesting an important role for mitochondria in maintenance of SV modality at presynaptic terminal. Additionally, DRP1-preKO synapses have profoundly altered kinetics of the RRP: faster depression, increased initial release probability, and slower recovery after pool depletion were all observed. DRP1-preKO also showed a significant reduction in synaptic transmission delay. These results indicate that the proper functioning of mitochondria is essential for the regulation of synaptic vesicle release during activity, and selectively affect vesicle release during a train of stimuli. Ongoing experiments aim to determine the specific mechanism underlying the presynaptic defect in SV release.

Disclosures: **M. Singh:** None. **H. Denny:** None. **C. Smith:** None. **J. Granados:** None. **R.B. Renden:** None.

Nanosymposium

355. Presynaptic Mechanisms

Location: 147B

Time: *Monday, November 13, 2017, 1:00 PM - 2:45 PM

Presentation Number: *355.06

Topic: *B.06. Neurotransmitter Release

Support: NIH grant MH086403.

Title: Synaptotagmin-7 mediated asynchronous release boostshigh-fidelity synchronous transmission at a central synapse

Authors: ***F. LUO**[1], T. C. SUDHOF[2]
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Abstract: Synchronous release triggered by Ca2+-binding to synaptotagmin-1 -2, or -9 is thought to drive fast synaptic transmission, whereas asynchronous release induced by Ca2+-binding to synaptotagmin-7 is thought to mediate delayed synaptic signaling, enabling prolonged synaptic computations. However, it is unknown whether synaptotagmin-7-dependent asynchronous release performs a physiological function at fast synapses lacking a prolonged signaling mode, such as the calyx of Held synapse. Here, we show at the calyx synapse that synaptotagmin-7-dependent asynchronous release indeed does not produce a prolonged synaptic signal after a stimulus train and does not contribute to short-term plasticity, but induces a steady-state asynchronous postsynaptic current during stimulus trains. This steady-state postsynaptic current does not increase overall synaptic transmission, but instead sustains reliable generation of postsynaptic spikes that are precisely time-locked to presynaptic spikes. Thus, asynchronous release surprisingly functions, at least at some synapses, to sustain high-fidelity neurotransmission driven by synchronous release during high-frequency stimulus trains.

Disclosures: **F. Luo:** None. **T.C. Sudhof:** None.

Nanosymposium

355. Presynaptic Mechanisms

Location: 147B

**Time: ***Monday, November 13, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***355.07

**Topic: ***B.06. Neurotransmitter Release

Support: KAKENHI 15K18349

Title: The pathological influences of excess α-synuclein and its mutants on synaptic transmission at calyx of Held synapses

Authors: *K. EGUCHI[1,2], Z. TAOUFIQ[2], T. TAKAHASHI[2]
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Abstract: A small neuronal protein α-Synuclein is highly localized in presynaptic terminals, and its abnormal abundance is associated with neuronal diseases called synucleinopathies including Parkinson's disease (PD), but the mechanism of its toxicity is not identified yet. To address how the elevation of α-synuclein can influence neurotransmission, we loaded recombinant wild-type (WT) human α-syunclein or its pathological mutants (A30P and A53T), related to familial PDs, directly into the calyx of Held presynaptic terminals in brainstem slices of rats using whole-cell patch-clamp method. Membrane capacitance measurements from presynaptic terminals revealed that α-synuclein loaded at 3.6 μM into calyceal terminals significantly slowed endocytosis of synaptic vesicles throughout postnatal development, before and after hearing onset. In contrast to wild-type α-synuclein, its A53T mutant slowed vesicle endocytosis only at immature calyces before hearing onset, while A30P mutant had no effect throughout development. The endocytic impairment by WT α-Synuclein was rescued by intraterminal co-loading of a microtubule (MT) depolymerizer nocodazole at both of immature and mature calyces. Furthermore, presynaptically loaded photostatin-1, a photoswitchable MT polymerization inhibitor, reversibly rescued vesicle endocytosis from the inhibitory effect of α-Synuclein in a light wavelength-dependent manner. However, the inhibition of endocytosis by the A53T mutant at immature calyces was not rescued by nocodazole. Functionally, WT α-Synuclein loaded into presynaptic terminals had no effect on basal synaptic transmission evoked at low frequency, but significantly slowed the recovery of EPSCs from synaptic depression induced by high-frequency stimulation, and impaired the fidelity of neurotransmission during continuous high-frequency stimulation. Co-loading with α-synuclein of nocodazole rescued the inhibitory effects of α-synuclein on recovery rate of EPSCs after synaptic depression and synaptic fidelity. We conclude that excess WT α-synuclein primarily targets vesicle endocytosis and impairs precision of fast neurotransmission via aberrant assembly of microtubules in the mammalian glutamatergic nerve terminals.

Disclosures: K. Eguchi: None. **Z. Taoufiq:** None. **T. Takahashi:** None.

Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.01

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

Support: JSPS KAKENHI 15K15438

Title: Roles of plexin-B3+ oligodendrocyte progenitor cells in the pathogenesis of Alzheimer's disease

Authors: *Y. TATEBAYASHI[1], N. KIKUCHI-NIHONMATSU[2], Y. MATSUDA[2], T. UCHIHARA[3], K. AOOI[2], M. WATANABE[2]
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Abstract: The roles of oligodendrocyte (OL) lineages cells in the Alzheimer's disease (AD) pathogenesis are still unclear. OL progenitor cells (OPCs) are widely distributed throughout the brain. OPCs culture from adult (> 2 months old) brains still remain challenging and often result in no or only low yield(s). The lack of technique to purify and culture OPCs from adult brain is one major disadvantage of studying for their functions. We have recently established a novel method to isolate and expand OPCs from adult rat brains (aOPC-culture). Using a combination of aOPC-culture and growth factor withdrawal, we found novel aOPCs expressing plexin-B3 (plexin-B3$^+$ aOPCs-culture) that were proliferative and positive for olig2, a marker for OL lineages cells. Immunohistochemical studies revealed that plexin-B3-expressing cells were distributed throughout the gray and white matters of the adult human and rat brains (plexin-B3$^+$ aOPCs). In the present study, we confirm that plexin-B3$^+$ aOPCs-culture releases the amyloid beta (Aβ), especially Aβx-42. FGF2 withdrawal from aOPC-culture increased the proportion of plexin-B3$^+$ aOPCs and the Aβ precursor protein expression. The β-secretase were highly expressed independently with FGF2 concentrations. Secreted Aβs in aOPCs-culture were immunoprecipitated from the conditioned media with antibodies specific for the carboxyl terminal of Aβx-40 and Aβx-42, respectively, and were analyzed by western blot. FGF2 withdrawal increased the secretion of both Aβx-40 and Aβx-42. In AD brains, plexin-B3$^+$ senile plaques distributed in the cortex and were coimmunolabeled with antibodies for Aβ. Taken together, these data suggest that plexin-B3$^+$ aOPCs plays an important role in Aβ secretion and senile plaques formation in AD brain.

Disclosures: Y. Tatebayashi: None. **N. Kikuchi-Nihonmatsu:** None. **Y. Matsuda:** None. **T. Uchihara:** None. **K. Aooi:** None. **M. Watanabe:** None.

Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.02

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

Support: NIGMS P5OGM08273
NINDS NS062184
NINDS NS046810

Title: Decoupling the effects of the amyloid precursor protein and plaque on neuronal transport in the mouse brain

Authors: *C. MEDINA[1], F. L. CHAVES[1], R. E. JACOBS[2], E. L. BEARER[3,4]
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Abstract: Amyloid precursor protein (APP) is the parent protein for amyloid plaques, the pathological hallmark of Alzheimer's disease (AD) with an abundance of plaque in the brain. Recent data from the Bearer lab show that transport is decreased and the distal location of accumulation also altered in transgenic mouse models expressing human APP with two mutations, Swedish and Indiana, in a transgene (APP^{SwInd})—mutations linked to Familial Alzheimer's Disease. Questions now arise about what role full-length mutated protein has on transport, independent of the presence of plaques, and what role can be attributed to plaques. To address this, we used the Tet-off system to control the expression of APP^{SwInd}. We studied transport in three experimental groups of these transgenic mice by altering the timing of expression of APP^{SwInd} with doxycycline. Group 'A' (no doxy, +plaques, + APP^{SwInd}); group 'B' (doxy at 8 days before sacrifice, +plaques, no APP^{SwInd}), and group 'C' (doxy prior to conception, and stopped 8 days before sacrifice, no plaques, + APP^{SwInd}). We used manganese-enhanced magnetic resonance imaging (MEMRI) to observe differences in axonal transport dynamics between the three groups, by performing MR imaging in a Bruker 11.7T scanner with T_1 weighted pulse sequences as previously described (Medina et al 2016). MR images were taken before and at successive time points after Mn^{2+} stereotactic intracerebral injection into CA3 of the hippocampus. Images were analyzed with our preprocessing technique (Medina et al. 2017). Histopathology revealed plaques in Groups A and B, but not in C, and Western blots showed APP^{SwInd} expressed 3.2-fold in Groups A and C, and Aβ in Groups A and B. Within group between timepoint intensity changes by statistical parametric mapping (SPM) indicate altered transport locations as well as diminished transport in Group C. ANOVA between group comparisons and ROI measurements are currently being performed, though preliminary analysis

supports the visual inspection of within group SPM maps that APP^{SwInd} expression alone may compromise transport. These results are surprising, as they indicate a role of the defective APP^{SwInd} protein that had previously been attributed entirely to the plaque that it forms. Cholinergic neurons in the medial septal nucleus were decreased as determined by anti-ChAT staining in Group C ($p=0.0006$ by one-way ANOVA, $n=15$), which further supports a toxic role of the APP^{SwInd} independent of plaques. Phospho-tau was present in dystrophic neurites surrounding plaques only in Group A and B. In conclusion, we observe separable effects between APP and plaque.

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Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.03

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

Title: Back translating human Alzheimer's Disease neuroimmune signatures to APP mouse models and high-content primary microglial screens

Authors: V. MAHADOMRONGKUL[1,4], K. Q. TANIS[2], S. ROTHMAN[3], P. GANDHI[4], C. WARE[4], J. GILLIAND[5], J. N. MARCUS[8], M. PEARSON[9], B. HOWELL[6], J. KLAPPENBACH[7], M. E. KENNEDY[1], *C. MIRESCU[10]
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Abstract: Alzheimer's Disease (AD) is pathologically marked by the formation of extracellular aggregates of amyloid beta (Aβ) and intracellular tau tangles. Coincident with the formation of Aβ plaques is recruitment and activation of microglia and astrocytes to the plaque contributing to the pathological niche in AD. Though multiple groups have tried to model aspects of this niche, results have been varied thereby reducing the chance of human translatability. Here we set out to create a cellular platform capable of reproducing key features found in the pathological niche from human AD brains. We used Genomic approaches which enabled comparisons of human disease profiles between different mouse models informing on their utility to evaluate secondary changes to triggers such as Aβ deposition. Here, we determined age-associated transcriptomic differences between two similar yet distinct APP transgenic mouse models known to differ in

proportional amyloidogenic species and plaque deposition rates, the Tg2576 Swedish APP (KM670/671NL) and TgCRND8 Swedish/Indiana APP (KM670/671NL+V717F) lines. In Tg2576, human AD genes signatures were not observed despite profiling mice out to 15 months of age. TgCRND8 mice however, show progressive and robust induction of lysomal, neuroimmune, and ITIM/ITAM-associated gene signatures overlapping with prior human AD brain transcriptomic studies. To confirm that these changes were associated with Aβ pathology and in order to support deeper transcriptional characterization, laser capture microscopy was used to isolate Thio-S positive plaques from distal non-plaque tissue. Data uncovered plaque-associated enrichment of microglia-related genes which likely converge on GWAS targets and pathways implicated in late-onset AD. In order to gain functional insights and prioritize plaque-associated 'hits', a high-content confocal imaging assay of fibrillar Aβ uptake by primary microglia was developed as a medium throughput platform. A small scale siRNA screen of plaque-associated microglia genes is presented to highlight this integrated platform view of identifying and validating novel modulators of Aβ pathology.

Disclosures: **V. Mahadomrongkul:** None. **K.Q. Tanis:** None. **S. Rothman:** None. **P. Gandhi:** None. **C. Ware:** None. **J. Gilliand:** None. **J.N. Marcus:** None. **M. Pearson:** None. **B. Howell:** None. **J. Klappenbach:** None. **M.E. Kennedy:** None. **C. Mirescu:** None.

Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

Time: *Monday, November 13, 2017, 1:00 PM - 4:30 PM

Presentation Number: *356.04

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

Support: CIHR
Brain Canada
CNPQ
FAPERJ

Title: Changes in cerebrospinal fluid and neuroimaging biomarkers in a non-human primate model of Alzheimer's Disease

Authors: ***S. E. BOEHNKE**[1], R. G. WITHER[1], J. Y. NASHED[1], D. J. COOK[2], R. LEVY[3], F. G. DE FELICE[4], D. P. MUNOZ[5]
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Abstract: We recently developed a non-human primate (NHP) model of AD that recapitulates key molecular aspects of human pathology (Forny-Germano et al., J.Neurosci, 2014). AD pathology was induced via intracerebroventricular (icv) injection of neurotoxic amyloid beta oligomers (AβOs). Here we describe changes in CSF and neuroimaging biomarkers in animals repeatedly injected to track disease progression *in vivo.* We tracked disease progression *in vivo* in male rhesus macaques receiving either 1) l icv injections of AβOs (100-400µg) approximately once per month for 12-18 months) and 2) a sequence of smaller (~80ug) icv injections 3x per week for 3 weeks and a control macaque receiving injections of vehicle. To track behavior, we used an activity tracker and 24/7 video. To measure cognition, we used a cage-side touch-screen device with cognitive tasks from the CANTAB AD battery. To track synaptic degradation, we analyzed structural and resting state functional connectivity via fMRI. To track molecular biomarkers in the CSF we quantified Aβ1-40, Aβ1-42, tTau, pTau and neurofilament light chain (NFL). A variety of blood biomarkers were also tracked. Here we describe changes in CSF and neuroimaging biomarkers caused by AβO injections. Aβ 1-42, pTau and NFL increased in the CSF of NHPs receiving ICV injections of soluble amyloid-beta oligomers. NFL levels at baseline for NHPs were similar to those published for aged human controls (Zetterberg et al., 2016) and markedly elevated after injections. AβO injections decreased functional connectivity across different brain networks measured by resting state fMRI, consistent with our previous neuropathological results showing loss of synapses in NHPs receiving AβO injections Ultimately, we will relate these *in vivo* metrics to each animal's post-mortem brain pathology. The long-term goal is to generate a viable NHP model presenting multiple facets of human AD for use in testing therapeutics. The platform presented to evaluate AD-like features in primates could easily be translated to track disease in other primate models of neurodegenerative diseases.

Disclosures: S.E. Boehnke: None. **R.G. Wither:** None. **J.Y. Nashed:** None. **D.J. Cook:** None. **R. Levy:** None. **F.G. De Felice:** None. **D.P. Munoz:** None.

Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.05

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

Support: NIH Grant R01 AG030142

Title: Calpain activation and ER stress in the 5XFAD mouse model of Alzheimer's disease

Authors: *K. R. SADLEIR, R. VASSAR
Cell and Mol. Biol., Northwestern Univ., Chicago, IL

Abstract: In the Alzheimer's disease (AD) field, the majority of mouse models rely on the overexpression of one or more transmembrane proteins in order to generate the amyloid β (Aβ) and plaques characteristic of AD pathology. Traditionally, it has been assumed that the altered signaling pathways, synapse loss, and neurodegeneration documented in these mouse models are caused by the elevated Aβ in the brain, but recently there have been assertions that some, or even a majority of, phenotypes are caused by the transgene overexpression itself. It is hypothesized that overexpression of the amyloid precursor protein (APP) and presenilin 1 (PS1) leads to chronic ER stress that elevates cytoplasmic calcium. Elevated calcium activates calpain to cleave p35 to the neurotoxic fragment p25, which is reported to be elevated in some AD mouse models with overexpression of APP and PS1.
To test whether any elevation of ER stress markers and calpain activation observed in the overexpression-based 5XFAD mouse model are artifacts of transgene expression, we make use of a critical control genotype, 5XFAD-transgene positive, BACE1 knockout (5XFAD+;BACE1-/-). Since BACE1 (β-amyloid cleaving enzyme) is required for the initial cleavage of APP in the generation of Aβ, 5XFAD+;BACE1-/- mice express the APP/PS1 transgene in the complete absence of Aβ. ER stress markers and calpain activation are compared in 5XFAD+;BACE1-/- mice, which have transgene expression but no Aβ, non-transgenic, BACE1 wild type (non-Tg;BACE1+/+) which have neither transgene expression nor Aβ, and 5XFAD-transgene positive, BACE1 wild type (5XFAD+;BACE1+/+) which have both transgene expression and Aβ, and have been reported to show ER stress and calpain activation compared to non-Tg;BACE1+/+. Any changes of ER stress markers or calpain activation observed in both 5XFAD+;BACE1+/+ and 5XFAD+;BACE1-/- relative to non-Tg;BACE1+/+ can be attributed to transgene expression, while any changes observed only in 5XFAD+;BACE1+/+ compared to non-Tg;BACE1+/+ can be attributed to Aβ.
Immunoblotting is used to measure relative levels of ER stress markers and measure p35 cleavage in the hemibrains of 10 mice (5 male, 5 female) per genotype at three timepoints (4 , 6 and 9 months). Preliminary analysis indicates no elevation of p35 cleavage or ER stress in the 5XFAD+;BACE1-/- mice compared to non-Tg;BACE1+/+, suggesting that any ER stress phenotypes in the 5XFAD mice are likely attributable to Aβ rather than transgene overexpression.

Disclosures: K.R. Sadleir: None. **R. Vassar:** None.

Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.06

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

Support: NIH Grant AG030142
BrightFocus Foundation

Title: Tau-independent effects of beta amyloid on primary neurons and in an Alzheimer's disease mouse model

Authors: *S. KEMAL, K. R. SADLEIR, R. VASSAR
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Abstract: The pathophysiological hallmarks of Alzheimer's disease (AD) include the presence of intra-cellular neurofibrillary tau tangles and extracellular beta amyloid (Aβ) plaques. In plaque regions, the neuronal response results in neurodegeneration, as evidenced by the formation of dystrophic neurites consisting of swollen dysfunctional axons and dendrites. Anti-amyloid strategies and inhibitors to Aβ production are currently in AD clinical trials; however, these have had varying efficacy. It is therefore crucial to drug development to explore alternative targets and elucidate the mechanism by which Aβ results in AD pathophysiology.
Previous studies suggest Aβ raises intra-cellular calcium and disrupts microtubules, which we hypothesize have a critical role in the development of presynaptic dystrophies. To investigate this further, here we have assessed the effects of neurotoxic Aβ on intra-cellular calcium levels and microtubules. Live-cell imaging of primary neurons revealed that exposure to Aβ oligomers caused varicose and beaded neurites with extensive microtubule disruption. As proof-of-concept experiments, we demonstrate that treatment with taxol, a microtubule stabilizing agent, is able to prevent Aβ-induced neuritic beading and microtubule breakdown.
Another hallmark pathology of AD is intra-neuronal deposits of tau, a microtubule associated protein that plays a role in microtubule stability. Data indicate that tau hyper-phosphorylation and tangle formation in AD are downstream of amyloid accumulation, and are the cause of neuronal death. For this reason we are investigating whether Aβ-induced microtubule disruption and toxicity are tau dependent or independent. We treated primary hippocampal neurons from tau knockout mice with Aβ oligomers, and using live cell imaging, observed microtubule beading equivalent to that seen in cultures from tau wild type mice. We also examined the formation of dystrophic neurites and plaque formation in a tau knockout AD mouse model (5XFAD). In preliminary analysis, we find that the absence of tau does not prevent plaque or dystrophy formation *in vivo*. These results indicate that some effects of Aβ, such as microtubule breakdown and dystrophic neurite formation, are not mediated by tau. An additional significant finding is that taxol treatment is able to prevent the observed Aβ effects even in the absence of tau, suggesting the possibility of microtubule stabilization as an AD therapy even before tau pathology is evident.

Disclosures: S. Kemal: None. **K.R. Sadleir:** None. **R. Vassar:** None.

Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.07

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

Support: Joint Lab IIT/CrestOptics
Sapienza Grant 2016
Sapienza Grant 2015

Title: The eye as a window on the brain: Alzheimer Disease-related protein aggregates in the retina

Authors: *S. DI ANGELANTONIO[1,2], A. GRIMALDI[1], C. BRIGHI[2], M. BOMBA[3], S. SENSI[4], G. RUOCCO[1]
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Abstract: Alzheimer Disease (AD) is the most common cause of dementia in the elderly. In the pathogenesis of AD a pivotal role is played by two neurotoxic proteins, that aggregate and accumulate in the brain: Amyloid Beta and p-tau. It is known that accumulation of these proteins and the consequent loss of neuronal cells begins 10-15 years before any cognitive impairment . Nowadays the election strategies for the diagnosis of AD require expensive and invasive techniques, like TAC, PET and MRI but, when first symptoms occurs, neurodegenerative processes are well advanced and therapies have a very low efficacy . So, the aim of this study is to find new approaches to anticipate and facilitate the diagnosis of AD. It has already been demonstrated that protein aggregation occurrs in the aging retina, so we analysed retinal tissue of triple transgenic AD mouse model (3xTg-AD) for the presence of Amyloid Beta and pTau by immunofluorescence; we found that 3xTg mice had Amyloid Beta and pTau aggregates in their retinal tissues (that were not present in wt mice) and that plaques dimension increased with age. Moreover, we are also trying to find new cellular and/or molecular targets to address drugs that could modulate AD-related neuroinflammation; in particular, we are evaluating morphologic differences in retinal microglia during the progression of the disease. Here we propose a less invasive and cheaper method to detect Amyloid Beta and pTau aggregates based on the analysis of retinal tissue, that could anticipate the diagnosis and the beginning of treatment.

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Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.08

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

Support: NIH Grant AG051179
NIH Grant NS37853
BrightFocus Foundation

Title: Modulation of voltage gated L-type calcium channels in hypothalamic NPY/AgRP neurons as a molecular mechanism for body weight dysregulation in Alzheimer's disease and neuropsychiatric disorders

Authors: *M. ISHII[1], G. WANG[1], L. PHAM[1], R. HART[1,2], C. IADECOLA[1]
[1]Feil Family Brain and Mind Res. Inst., Weill Cornell Med., New York, NY; [2]Univ. of Exeter, Exeter, United Kingdom

Abstract: Weight loss is an early clinical manifestation of Alzheimer's disease (AD), but the underlying molecular mechanisms remain unclear (*Cell Metabolism* 2015, 22, 761). Body weight is regulated by the adipocyte hormone leptin, which inhibits hypothalamic neurons in the arcuate nucleus co-expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP) leading to decreased appetite, increased metabolism, and decreased body weight (*Mol. Endocrinol.* 2016, 30: 3). We previously found that amyloid-beta (Aβ), a key pathogenic factor in AD, could disrupt NPY/AgRP neuronal function (*J. Neurosci.* 2104, 34: 9096). In this study, we sought to identify the underlying cellular mechanisms leading to the NPY/AgRP neuronal dysfunction and determine if this would cause alterations in body weight. In Ca^{2+} imaging studies with fura-2AM, exogenous Aβ dose-dependently increased cytosolic-free Ca^{2+} levels in GFP-labeled NPY/AgRP neurons from wild-type (WT) mice, which was reversed by the voltage gated L-type Ca^{2+} channel (LTCC) antagonist nimodipine, suggesting that Aβ causes dysfunction in these neurons by inducing Ca^{2+} overload via LTCC. Furthermore, leptin (100nM) decreased cytosolic-free Ca^{2+} levels in GFP-labeled NPY/AgRP neurons from WT mice (340/380nm: -33.8±3.4%, n=35, $p<0.05$). In whole-cell voltage-clamp electrophysiology studies, leptin (100nM) decreased the amplitude of L-type Ca^{2+} currents (-37.8±5.1%, n=4, $p<0.05$). These data suggest that altering intracellular Ca^{2+} levels by LTCC could modulate NPY/AgRP neuronal function. We next evaluated if NPY/AgRP neurons express $Ca_v1.2$, the most abundant LTCC isoform in the forebrain (*J. Physiol. 2016,* 594, 5823), and found $Ca_v1.2$ antibody staining on the soma of GFP+ neurons in the arcuate nucleus of NPY-GFP mice. To study the in vivo role of Cav1.2 in NPY/AgRP neurons, we used cre-lox recombination to delete $Ca_v1.2$ in NPY/AgRP neurons of mice (AgRP-$Ca_v1.2$-/- mice). AgRP-$Ca_v1.2$-/- mice were viable, appeared grossly normal, but

had lower body weight compared to cre- littermates at age 8 weeks (cre-: 19.6±0.3g, AgRP-Cav1.2-/-: 18.6±0.2g, n=7-20, $p<0.05$). These studies are consistent with LTCC in particular $Ca_v1.2$ playing a key role in regulating NPY/AgRP neuronal function and possibly body weight. Since human genetic studies have found the gene encoding the α_{1c} subunit of $Ca_v1.2$ is a risk factor or cause of various neuropsychiatric disorders (*J. Physiol. 2016,* 594, 5823), $Ca_v1.2$ could be part of a shared molecular pathway that is vulnerable in diverse neuropsychiatric conditions, which may explain the high prevalence of eating and body weight disorders in anxiety, depression, and AD.

Disclosures: M. Ishii: None. **G. Wang:** None. **L. Pham:** None. **R. Hart:** None. **C. Iadecola:** None.

Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.09

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

Support: APRI201500002/G00002795
NSERC Discovery Grant #40352

Title: Single App knock-in mouse model of Alzheimer's disease: Behavioral and neurochemical characterization

Authors: *J. MEHLA[1], S. LACOURSIERE[1], E. STUART[1], S. SINGH[1], S. INAYAT[1], H. PATEL[1], T. SAITO[2], R. J. MCDONALD[1], M. H. MOHAJERANI[1]
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Abstract: A single amyloid precursor protein (APP^{NL-G-F}) knock-in mouse model for Alzheimer's disease (AD) has been developed by the Saito research group to overcome the problem of over expression of APP in transgenic mouse models for AD. To date this mouse model has not been well characterized with respect to behavioral and neurochemical functions. Therefore, the present study was designed to evaluate the memory functions of this mouse model at different age in various behavioral paradigms and correlate these changes with biochemical brain alterations. Three months old male C57BL/6 (n=5) and APP^{NL-G-F} (n=10) mice were used in the present study. Various behavioral models (Morris water maze, fear conditioning, object recognition and balance beam tests) were used to assess the cognitive and motor functions of mice. All behavioral tests were performed at the age of 3, 6, 9 and 12 months. After behavioral

tests, voltage sensitive dye imaging was used to examine cortical dynamics in response to sensory stimulation and during brain resting state. Lastly, immunostaining for cholinergic function (ChAT), tyrosine hydroxylase (TH), norepinephrine transporter (NET), inflammatory markers (GFAP and IBA-1) and amyloid plaque was performed in brain slices from 12 months old mice. AD control mice showed normal learning and memory functions in all behavioral tests at the age of 3 months similar to C57 mice. However, results from water maze showed the impairment of spatial learning and memory functions of AD control mice at the age of 6, 9 and 12 months as compared to age match C57 mice. In the object recognition test also, AD mice spent significantly less time to explore the novel object at the age of 6, 9 and 12 months in comparison to C57 mice indicating an impairment of object associated memory. The percentage of freezing in a fear test was also reduced significantly at the age of 6, 9 and 12 months AD control mice when compared to C57 mice. However, results from balance beam test showed no impairment of motor function at different test points. The spontaneous activity was less synchronized over cortical space in AD mice than in C57 mice. The immunostaining result showed the increased amyloid plaque burden and neuro-inflammation and reduced number of ChAT positive cells in basal forebrain, TH and NET positive cells in locus coeruleus of AD mice's brain as compared to C57 mice. APP^{NL-G-F} mice showed and accelerated age dependent learning and memory impairment which may be due to amyloid plaque induced cholinergic and norepinephrine dysfunctions and neuro-inflammation. The findings support the use of this novel mouse model to study AD pathology and to screen the treatment options for AD.

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Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.10

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

Support: DZNE
MPG
Metlife Fnd

Title: Neurogenic effect of the anti-aggregant Tau repeat domain in the hippocampus

Authors: *M. JOSEPH[1,2], M. ANGLADA-HUGUET[1,2], K. PAESLER[2], E. M. MANDELKOW[1,2,3]

[1]DZNE, German Ctr. for Neurodegenerative Dis., Bonn, Germany; [2]Max-Planck Inst. for Metabolism Research, Hamburg Outstation, Hamburg, Germany; [3]CAESAR Res. Ctr., Bonn, Germany

Abstract: The microtubule-associated protein Tau is known to play an important role in neurodegeneration, but is also important for neurogenesis. Previous work from our laboratory has shown that the expression of the pro-aggregation mutant Tau (TauRDΔK) caused robust Tau aggregation and neurodegeneration in the hippocampus. By contrast, the anti-aggregant Tau containing two additional proline mutations (TauRDΔK-PP) had no deleterious effects. We used organotypic hippocampal slice cultures (OHSCs) from TauRDΔK-PP expressing transgenic mice. The transgene expression in the hippocampus was monitored via a sensitive bioluminescence reporter gene assay. Using immunohistochemistry and western blot analysis we found that the expression of TauRDΔK-PP leads to an increase in mature neurons and enhanced neurogenesis in OHSC's. Interestingly there were no signs of activation of microglia and astrocytes, indicating the absence of an inflammatory reaction. Investigation of signaling pathways showed that Wnt-5a was strongly decreased whereas Wnt3 was enhanced. Significant increase in hippocampal stem cell proliferation by BrdU was observed as early as P8, specifically in the CA3 region, leading to a larger volume of the hippocampus in adulthood due to neurogenesis. This increase in neuronal number in the CA3 region was consistent even at 16 months of age. In summary, the data suggest that the expression of TauRDΔK-PP enhances hippocampal neurogenesis mediated by the canonical Wnt signaling pathway, without any inflammatory reaction. The post-natal and adult neurogenesis in the CA3 region can be increased by a fragment of non-aggregating Tau. The mouse model is also interesting for the study of neurogenesis with the potential of translation into a therapeutic approach.

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Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.11

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

Support: NIH Grant T32 AG 21890-14

Title: Consequences of nucleoplasmic reticulum expansion in tauopathy: A possible role for aberrant nuclear RNA export in tau pathogenesis

Authors: *G. L. CORNELISON[1], *G. L. CORNELISON[1], B. FROST[2]
[1]Barshop Inst. for Longevity and Aging Studies, [2]Barshop Inst. for Longevity and Aging Studies, Dept. of Cell Systems and Anat., UT Hlth. Sci. Ctr. At San Antonio, San Antonio, TX

Abstract: The nuclear lamina is a filamentous protein network that lines the interior of the inner nuclear membrane. It provides mechanical support to the nucleus and serves as a scaffold for a number of proteins involved in regulating the three-dimensional structure and transcriptional activity of the genome. Laminopathies, a group of rare hereditary degenerative disorders, are characterized by aberrant nuclear architecture and genetic dysregulation that lead to progeroid or "advanced aging" and dystrophic phenotypes. Using a *Drosophila melanogaster* model of tauopathy and postmortem brain tissue from patients with Alzheimer's disease, we have recently established a novel mechanism of acquired neuronal lamin dysfunction caused by pathological tau. We found that tau-induced over-stabilization of filamentous actin, which interacts with the nuclear lamina through the linker of nucleoskeleton and cytoskeleton (LINC) complex, causes nuclear envelope invagination, heterochromatin relaxation and subsequent cell death. Interestingly, increased nuclear invagination has also been reported to occur in normal physiological aging, suggesting that exacerbation of this process by tau may underlie the association between aging and an increased risk of developing Alzheimer's disease and related tauopathies. These nuclear invaginations, referred to as the "nucleoplasmic reticulum," are thought to bring functions of the nuclear periphery, such as nucleocytoplasmic transport of macromolecules, into the nuclear interior. We have found that the nuclear invaginations observed in patients with Alzheimer's disease are lined with nuclear pores and previous studies have reported that nuclear invaginations often terminate at nucleoli, areas of high transcriptional activity. Based on these observations, together with our previous findings of heterochromatin relaxation in tauopathies, we hypothesize that increased transcription and nucleocytoplasmic export of RNA via nuclear invaginations may underlie tau-mediated neuronal death. Preliminary studies support this hypothesis, as both genetic knockdown and pharmacological inhibition of nuclear RNA-export machinery ameliorate tau-induced neurodegeneration *in vivo*. Further, FISH/IF experiments have revealed a strong association of poly(A) RNAs within and adjacent to lamin invaginations in a *Drosophila* model of tauopathy. We are currently working on methods of quantifying tau-induced changes in RNA export and using *Drosophila* models of tauopathy to investigate the ability of pharmacological inhibitors of nucleocytoplasmic transport to prevent tau-induced neurodegeneration *in vivo*.

Disclosures: G.L. Cornelison: None. **B. Frost:** None.

Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.12

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

Support: NIH

Title: Knock-down of endogenous mouse tau by intracranial delivery of zinc-finger protein transcription factors *In vivo*

Authors: *S. WEGMANN[1], B. ZEITLER[2], S. DEVOS[3], K. MARLEN[2], D. MACKENZIE[1], Q. YU[2], C. COMMINS[1], H.-O. NGUYEN[2], A. B. ROBBINS[1], M. C. HOLMES[2], B. RILEY[2], S. ZHANG[2], B. T. HYMAN, MD,PhD[3]
[1]Neurol., Mass Gen. Hosp. / Harvard Med. Sch., Charlestown, MA; [2]Sangamo Therapeutics, Inc., Richmond, CA; [3]Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Reduction of the neuronal microtubule associated protein tau (MAPT) in the brain has been shown to be protective against different pathological conditions, including A-beta induced neurotoxicity, neuronal death in frontotemporal dementia (FTD)-tau transgenic mice, and neuronal loss and lethality in mouse seizure models. In these studies, reduction of mouse tau protein in the brain was achieved either via permanent genetic ablation, or by transient knock-down of tau expression using antisense oligonucleotides. Here we use a novel approach, administration of adeno-associated virus (AAV) into the mouse brain to deliver gene-silencing zinc-finger protein transcription factors (ZFP-TFs) that are highly specific for murine *MAPT*. After stereotactic injection of the AAV (AAV ZFP-TF) into the hippocampus of wild type mice, potent (>85%) reduction of tau mRNA and protein was achieved compared to control (PBS, GFP, or scrambled ZFP-TF) injected hippocampi after 6 weeks, with sustained knock-down out to 11 months. We observed only minimal elevation of neuroinflammatory markers and no evidence for compensation of tau loss by other microtubule associated proteins (MAPs). Using different neuronal-specific promotors (synapsin-1, CamK2alpha, MeCP2), we were able to eliminate ZFP expression in astrocytes compared to the ubiquitous CMV promotor. To evaluate the protective effect of a ZFP-TF tau knock-down approach, we injected AAV synapsin-1 ZFP-TF into the cortex of adult amyloid precursor protein (APP) transgenic mice (APP/PS1 line). After 10 weeks, we found a reduced number of neuritic dystrophies around amyloid plaques (a pathologic hallmark in these mice), suggesting a protective effect of endogenous tau reduction in this model. These results support the further study of sustained knock-down of endogenous tau expression following administration of an AAV ZFP-TF to the adult brain.

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drug study, report that research relationship even if those funds come to an institution.; Sangamo Therapeutics. **B. Zeitler:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics. **S. DeVos:** 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.; Sangamo Therapeutics. **K. Marlen:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics. **D. MacKenzie:** None. **Q. Yu:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics. **C. Commins:** None. **H. Nguyen:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics. **A.B. Robbins:** None. **M.C. Holmes:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics. **B. Riley:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics. **S. Zhang:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics. **B.T. Hyman:** None.

Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.13

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

Title: Receptor mediated prion-like propagation of PH-tau

Authors: V. MOROZOVA[1], *A. ALONSO[2,1]
[1]Ctr. for Developmental Neurosci., Col. of Staten Island, Staten Island, NY; [2]Deaprtment of Biol., Col. of Staten Island, CUNY, Staten Island, NY

Abstract: Neurofibrillary tangles are the hallmark of Alzheimer disease (AD) and associated tauopathies. They result from an accumulation of hyperphosphorylated tau that polymerized into helical filaments inside the neuron and cause neuronal degeneration. It has been shown that hyperphosphorylation of tau at Ser199, Thr212, Thr231 and Ser262 (PH-Tau) is sufficient to induce a tau pathological conformation, a structural change similar to that found in AD. AD starts in the hippocampus and progresses in a well-defined pattern - a mechanism of cellular transmission has been proposed. To investigate if PH-Tau can be an agent responsible for disease transmission we used two different strategies: 1) addition of the purified recombinant tau and/or PH-Tau to a cell culture medium; and 2) co-culture cells transfected with RFP-tau or GFP-PH-Tau. When recombinant protein was added to the media, we observed that both tau and PH-Tau are readily incorporated into HEK cells. The same results were found in primary neuronal culture. In neurons, PH-Tau uptake induced retrograde neurodegeneration: disrupted the neuritic processes and accumulated in the somatodendritic compartment. Additionally, we found that pretreatment of cells and primary neurons with the broad muscarinic receptor antagonist

Atropine led to a great reduction of extracellular tau uptake. During co-culture, we observed that GFP-PH-Tau but no RFP-tau was released from the cells and taken up by neighboring cells, disrupting their cytoskeleton. These experiments suggest that PH-tau can be secreted from cells and transferred to normal cells, transmitting the disease in a "prion-like" fashion through muscarinic receptors that may mediate the endocytotic mechanism.

Disclosures: V. Morozova: None. **A. Alonso:** None.

Nanosymposium

356. APP and Tau: Animal and Cellular Models

Location: 147A

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***356.14

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

Support: NIH HL123331
NIH HL124576
NIH AG054104

Title: Chronic sleep loss degeneration of locus coeruleus neurons is tau-dependent

Authors: *S. C. VEASEY[1], Y. ZHU[2], P. FENIK[2], G. ZHAN[2], P. BELL[2]
[1]Ctr. for Sleep and Circadian Neurobio., Univ. of Pennsylvania, Perelman Sch. of Med., Philadelphia, PA; [2]Ctr. for Sleep and Circadian Neurobio., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Whether insufficient sleep shapes the temporal progression or development of Alzheimer's disease (AD) is not known. We recently found that chronic short sleep (CSS) in young adult mice up regulates locus coeruleus neuron (LCn) $A\beta_{42}$ that, in turn, prompts pathogenic tau modifications, P202 and Ac280 in LCn. Here we report that these alterations continue to progress beyond CSS in the LCn and that while no CSS effect on P202 was observed immediately after CSS in the hippocampus, 9 months into recovery, P202 was substantially increased in the hippocampus. Hippocampal p-tau was associated with spatial memory consolidation impairment. A strikingly similar phenotype of increased $A\beta_{42}$ and tau modifications was observed in LCn of amyloid precursor protein knock-in mice (both NL and NLGF), well before the development of amyloid plaques. These Aβ and tau changes in the APPKI mice were most pronounced in the LC, suggesting that the LC has heightened susceptibility to intraneuronal $A\beta_{42}$ and AD-associated tau post-translational modifications. We find that LCn in rested wild type and APPKI young adult mice have heightened levels of PSEN2 and total tau, and we are now determining the role these LCn findings have on the development

of $A\beta_{42}$ and toxic tau modifications in both wild type mice exposed to sleep loss and APPKI rested mice. Mice with transgenic absence of tau confer resistance to CSS LCn degeneration and axonopathy. Moreover, mice with SiRNA tau injected into the LC prior to sleep loss maintained LCn counts. Therefore, CSS in early adulthood increases toxic acetylated and phosphorylated tau within LCn, and tau plays a critical role in CSS degeneration of LCn. Studies are underway now to explore whether early suppression of LC tau prevents later hippocampal tau phosphorylation and memory impairments from young adult exposure to CSS.

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Nanosymposium

357. Amyloid-Beta Tau Interaction

Location: 152A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***357.01

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

Support: Australian Research Council DP13300101932
National Health and Medical Research Council of Australia GNT1037746
National Health and Medical Research Council of Australia GNT1003150

Title: Somatodendritic accumulation of Tau is promoted by local protein translation

Authors: *J. GOETZ[1], G. LEINENGA[1], C. LI[2]
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Abstract: Background: Protein accumulation is a defining feature of neurodegenerative diseases but what causes this accumulation is only incompletely understood. This also holds true for Alzheimer's disease (AD), a disease in which the axonally enriched protein Tau forms hyperphosphorylated aggregates in the somatodendritic domain. It is generally assumed that this accumulation is because Tau becomes hyperphosphorylated in the axon and detaches from the microtubules, passing through the axon initial segment that serves as a diffusion barrier for physiologically phosphorylated Tau before accumulating in the cell body and dendrites. This process is partly mediated by Abeta. However, whether Abeta employs a mechanism other than relocalization of Tau to account for the massive accumulation of Tau remains unclear. Methods: The data were obtained in vitro using HEK293 cells and primary neurons (grown as dispersed cultures or in microfluidics systems), and in vivo in both aged transgenic mice with Abeta accumulation and wild-type mice that were stereotaxically injected with Abeta. Results: We identified an alternative mechanism of *de novo* protein synthesis of Tau in the somatodendritic

domain, induced by Abeta and mediated through a novel signaling pathway. Conclusions: Our findings identify a novel mechanism that in part accounts for the somatodendritic accumulation of Tau in AD.
Relevant references: (1) Hatch R, Wei Y, Xia D, Götz J (2017) Hyperphosphorylated tau causes reduced hippocampal CA1 excitability by relocating the axon initial segment, Acta Neuropathol 133: 717-730(2) Xia D, Gutmann JM, Götz J (2016) (2) Mobility and subcellular localization of endogenous, gene-edited Tau differs from that of over-expressed human wild-type and P301L mutant Tau, Scientific Reports 6:29074 (3) Ittner LM, Götz J (2011) Amyloid-β and tau--a toxic pas de deux in Alzheimer's disease, Nature Reviews Neurosci 12: 65-72

Disclosures: J. Goetz: None. **G. Leinenga:** None. **C. Li:** None.

Nanosymposium

357. Amyloid-Beta Tau Interaction

Location: 152A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***357.02

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

Support: NIA Grant R01AG050425
AARFD-17-504409

Title: Investigation of Aβ-driven hyperexcitability and tau spread *In vivo*

Authors: *G. A. RODRIGUEZ[1], S. A. HUSSAINI[2], K. E. DUFF[3]
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Abstract: Alzheimer’s disease (AD) is characterized by two hallmark pathologies in the brain: extracellular plaques composed primarily of amyloid beta (Aβ) and intracellular tangles of the abnormally misfolded protein tau. Tau pathology leads to significant neurodegeneration in the entorhinal cortex (EC) and spreads from the EC to downstream, synaptically connected regions of the hippocampus in a stereotypical manner. We, and others, have proposed that heightened neuronal activity can exacerbate tauopathy either by promoting tau release from EC neurons or facilitating its uptake in synaptically connected neurons. In these studies, we examine whether Aβ-driven hyperexcitability in the EC acts as an accelerant of pathological tau spread from this region into the hippocampus. hAPP/J20 mice that overexpress human amyloid precursor protein (hAPP) with Swedish/Indiana mutations were crossed to EC-Tau mice that overexpress human mutant tau predominantly in the EC, resulting in the EC-Tau/J20 line. Immunohistochemical

detection of hAPP/Aβ (6E10), abnormally folded tau (MC1), and total human tau (CP27) was performed in EC-Tau/J20 mice and their controls at three time-points: 10-, 16-, and 23-months of age. Plaque load was considerably increased in the EC and hippocampus of hAPP-expressing mice at 16-mo and 23-mo compared to 10-mo mice. Abnormally misfolded tau was appreciably elevated in EC neurons of 16-mo and 23-mo EC-Tau/J20 mice compared to age-matched EC-Tau controls. Notably, 16-mo EC-Tau/J20 mice showed early signs of tau propagation into the hippocampus compared to age-matched EC-Tau mice lacking hAPP-expression, demonstrating an age-dependent effect of increased Aβ on accelerated tau spread. To determine the effects of increased Aβ on EC neuronal activity immediately prior to tau spread, we collected extracellular, single-unit recordings and local field potential (LFP) data in the EC of 12- to 14-mo hAPP/J20 controls *in vivo*. We found a significant increase in single-unit firing rates in EC of hAPP-expressing mice compared to non-hAPP-expressing controls, as well as a reduction in the percentage of theta oscillations in the power spectrum. Characterization of neuronal activity patterns in EC-Tau/J20 mice and their controls in this age-range are ongoing, with the goal of applying chemogenetics (DREADDs: designer receptors exclusively activated by designer drugs) to resolve Aβ-driven hyperexcitability in this mouse model. By attenuating Aβ-driven EC hyperactivity, we aim to prevent or slow down the spread of tau pathology.

Disclosures: G.A. Rodriguez: None. **S.A. Hussaini:** None. **K.E. Duff:** None.

Nanosymposium

357. Amyloid-Beta Tau Interaction

Location: 152A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***357.03

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

Support: NHMRC grant 1081916
NHMRC grant 1037746
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ARC grant DP130102027
ARC grant DE130101591
Alzheimer’s Association grant NIRG000070035
AADRF grant DGP14-39

Title: Site-specific phosphorylation of tau inhibits amyloid-beta toxicity in Alzheimer's mice

Authors: *A. ITTNER[1], S. CHUA[1], J. BERTZ[1], A. VOLKERLING[1], J. VAN DER HOVEN[1], A. GLADBACH[1], M. PRZYBYLA[1], M. BI[1], A. VAN HUMMEL[1], C. H. STEVENS[1], S. IPPATI[1], L. S. SUH[1], A. MACMILLAN[4], G. SUTHERLAND[5], J. J. KRIL[5], A. P. G. SILVA[6], J.

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Abstract: Amyloid-β (Aβ) toxicity in Alzheimer's disease (AD) is considered to be mediated by phosphorylated tau protein. In contrast to previous assumptions on tau phosphorylation, we found that, at least in early disease, site-specific phosphorylation of tau inhibited Aβ toxicity. This specific tau phosphorylation was mediated by the neuronal p38 mitogen-activated protein kinase p38γ and interfered with postsynaptic excitotoxic signaling complexes engaged by Aβ. Accordingly, depletion of p38γ exacerbated neuronal circuit aberrations, cognitive deficits, and premature lethality in a mouse model of AD, whereas increasing the activity of p38γ abolished these deficits. Furthermore, mimicking site-specific tau phosphorylation alleviated Aβ-induced neuronal death and offered protection from excitotoxicity. Consistently, newly generated CRISPR-engineered mice expressing phospho-mimicking tau were protected from acute excitotoxicity. Our work provides insights into postsynaptic processes in AD pathogenesis and challenges a purely pathogenic role of tau phosphorylation in neuronal toxicity.

Disclosures: **A. Ittner:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **S. Chua:** None. **J. Bertz:** None. **A. Volkerling:** None. **J. van der Hoven:** None. **A. Gladbach:** None. **M. Przybyla:** None. **M. Bi:** None. **A. van Hummel:** None. **C.H. Stevens:** None. **S. Ippati:** None. **L.S. Suh:** None. **A. Macmillan:** None. **G. Sutherland:** None. **J.J. Kril:** None. **A.P.G. Silva:** None. **J.P. Mackay:** None. **A. Poljak:** None. **F. Delerue:** None. **Y.D. Ke:** None. **L.M. Ittner:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder.

Nanosymposium

357. Amyloid-Beta Tau Interaction

Location: 152A

Time: *Monday, November 13, 2017, 1:00 PM - 3:00 PM

Presentation Number: *357.04

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

Support: UK Medical Research Council (MC_UP_A025_1012
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Joint Programme-Neurodegeneration Research
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Title: Cryo-EM structures of Tau filaments from Alzheimer disease brain

Authors: *B. GHETTI[1], A. W. FITZPATRICK[2], B. FALCON[2], S. HE[2], A. G. MURZIN[2], G. MURSHUDOV[2], H. J. GARRINGER[1], R. CROWTHER[2], M. GOEDERT[2], S. H. W. SCHERES[2]
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Abstract: Alzheimer disease (AD) is the most common neurodegenerative disease, and there are no mechanism-based therapies. Abundant neurofibrillary lesions and neuritic plaques are the defining pathological characteristics of AD. In AD, neurofibrillary lesions have the tinctorial and biophysical characteristics of amyloid and are made of paired helical and straight Tau filaments (PHFs and SFs). Different Tau filaments characterize other neurodegenerative diseases, suggesting that molecular conformers of aggregated Tau underlie human tauopathies. No high-resolution structures of Tau filaments are available. The structures of PHFs and SFs extracted from AD brain was determined by single-particle cryo-electron microscopy. The study was carried out using tissue from the frontal and temporal cortex of a 74 year-old patient, who had a neuropathologically confirmed diagnosis of AD (Braak stage VI; Consortium to establish a registry for Alzheimer disease, age-related plaque score: C; National Institute on Aging/Reagan Institute of the Alzheimer Association: high likelihood of AD). The interval between clinical diagnosis and death was 10 years. The patient's *Apolipoprotein-E* genotype was ε3/ε4. Exons 16 and 17 of the *Amyloid precursor protein* gene, exons 3-13 of the *Presenilin-1* gene, as well as exons 4, 5, 7 and 12 of the *Presenilin-2* gene (including adjacent intronic sequences) were sequenced and no disease-causing mutations were found. The patient's mother had died aged 86 with a 16 year history of AD. Thioflavin S stainin showed the presence of abundant neurofibrillary tangles and neuritic plaques in cerebral cortex. We show that PHFs and SFs form ultrastructural polymorphs, where the C shaped subunit of each protofilament of Tau is arranged in a base-to-base or back-to-back manner, respectively. Details of the atomic structures of PHFs and SFs will be presented, yielding insights into the self-assembly, polymorphisms and propagation of tau aggregates in AD and other Tauopathies. The findings also demonstrate that cryo-EM allows atomic characterization of amyloid filaments from patient derived material, and pave the way to study a range of neurodegenerative diseases.

Disclosures: B. Ghetti: A. Employment/Salary (full or part-time):; Full time. 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.; Indiana University. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NIA. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); NA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

rights/patent holder, excluding diversified mutual funds); NA. F. Consulting Fees (e.g., advisory boards); NA. Other; NA. **A.W. Fitzpatrick:** A. Employment/Salary (full or part-time):; Full time. 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.; NA. **B. Falcon:** A. Employment/Salary (full or part-time):; Full time. 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.; NA. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NA. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); NA. **S. He:** A. Employment/Salary (full or part-time):; Full time. 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.; NA. **A.G. Murzin:** A. Employment/Salary (full or part-time):; Full time. **G. Murshudov:** None. **H.J. Garringer:** None. **R. Crowther:** None. **M. Goedert:** None. **S.H.W. Scheres:** None.

Nanosymposium

357. Amyloid-Beta Tau Interaction

Location: 152A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***357.05

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

Title: Neuronal excitation enhances tau release *In vitro* and the spread to distal anatomically connected regions *In vivo*

Authors: *M. K. SCHULTZ, JR[1], R. C. GENTZEL[2], S. PARMENTIER-BATTEUR[3], J. SCHACHTER[2], H. A. ZARIWALA[2]
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Abstract: Tau pathology in the brains of AD patients progresses in a spatiotemporally distinct pattern along anatomically connected brain regions. Previous work has indicated that neuronal stimulation promotes synaptic tau release. We hypothesized that tau spread to anatomically connected brain regions is dependent on constitutive neural activity and synaptic release. To test this hypothesis, we intracellularly seeded neurons using AAV (adeno-associated viral vector) to express human tau and provided an exogenous stimulation to these neurons using the excitatory DREADD hM3D(Designer Receptors Exclusively Activated by Designer Drugs, modified

human M3 muscarinic receptor) both in vitro and in vivo.
We tested the prediction that neuronal stimulation would promote extracellular tau release in mouse primary hippocampal cultures. We determined that AAV-tau-seeded neuronal cultures released tau into the supernatant, and treatment with DREADD stimulating ligand clozapine N oxide (CNO) increased tau release compared to vehicle treatment (300% increase from vehicle at 1 h, $p<0.05$). We determined that NMDA receptor antagonism with APV was sufficient to suppress tau release below baseline, confirming the role of neuronal activity (60% decrease from vehicle at 1 h, $p<0.05$)
We translated this model of tau release to an in vivo framework using wild type mice. We seeded the right ventral hippocampus with AAV tau and AAV hM3D, and treated with CNO 5 mg/kg or vehicle s.c. 2 times daily from 2^{nd} to the 8^{th} week after infusion. Brains were examined with IHC for viral products, markers of tauopathy, neuroinflammation, and neurodegeneration. Viral tau and hM3D were expressed in AAV-infected neurons in the subiculum and dentate gyrus. Viral tau spread to neurons in the ipsilateral entorhinal cortex, dorsal CA1, and contralateral polymorph layer of the dentate gyrus. DREADD signaling significantly increased the spread of tau to the entorhinal cortex and dentate gyrus (percent increases: EC 140% $p<0.05$, DG 140% $p<0.05$, CA1 120% ns) indicating that increasing neural activity facilitated the trans-synaptic spread of tau. Taken together with findings of increased DREADD-induced tau release in culture, the combined results suggest that DREADD signaling promoted distal pre-synaptic tau release and spread to post-synaptic cells. The results also highlight the negative impact of hyperexcitability (as observed in certain mouse models of AD) on the spread of the disease. This model can be used to test other modes of tau transmission and efficacy of treatment mechanisms that target tau.

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Nanosymposium

357. Amyloid-Beta Tau Interaction

Location: 152A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***357.06

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

Support: UTMB NIEHS Center in Environmental Toxicology
UTMB Mitchell Center for Neurodegenerative Disease

Title: Ozone exposure induces tau pathology and cognitive deficits in wildtype and amyloidogenic mice

Authors: *K. T. DINELEY[1], I. CORTEZ[3], E. ISHIMWE[1], L. DENNER[2], L. M. HALLBERG[2], R. KAYED[1], B. T. AMEREDES[2]
[1]Neurol., [2]Intrnl. Med., Univ. of Texas Med. Br. Dept. of Neurol., Galveston, TX; [3]Univ. of Texas Med. Br., Galveston, TX

Abstract: LOAD (late onset Alzheimer's disease) emerges from a combination of genetic risk factors and environmental influences. Notwithstanding the role for aging in AD, environmental risk factors have long been suspected but untested. Identification of causative agents will be extremely informative not just from a risk assessment standpoint, but also in understanding AD etiology. We tested the hypothesis that exposure to a key component of outdoor air pollution, ozone, exacerbates AD-like cognitive deficits and pathology in a preclinical animal model for Aβ amyloidosis (Tg2576) as well as inducing AD-like pathology and cognitive deficits in wildtype littermates. Ours and others' work shows that an early target of β-amyloid toxicity is loss of integrity within the entorhinal cortex (EC), dentate gyrus, and Cornu Ammonis 3 (EC/DG/CA3) synaptic network. This temporal cortex circuit underlies pattern separation; the ability to process overlapping environmental cues into unique representations to distinguish similar, yet non-identical contexts. The fear conditioning context discrimination behavioral paradigm is a way to evaluate this circuitry, which is dependent on adult neurogenesis within the subgranular zone of the DG. Wildtype and Tg2576 AD mice were exposed to ozone for one month (from 2-3 months of age) using an exposure paradigm of 8 hours per day, 5 days per week. Six months later, context discrimination fear conditioning in combination with *post hoc* analyses revealed putative mechanism underlying ozone toxicity. We found that ozone exposure significantly compromised context discrimination performance in both wildtype and Tg2576 mice. *Post hoc* analysis of neuroinflammation six months after ozone exposure revealed differences in neuroimmune responses between wildtype and Tg2576 mice. Further, analysis of toxic tau and Aβ species suggests that ozone exposure exacerbates and induces AD-like pathology in Tg2576 and wildtype littermates, respectively. In summary, ozone exposure compromises cognitive performance through effects on neurogenesis in aged mice and Tg2576 mouse model for AD amyloidosis. Further, these findings suggest that ozone exposure injures the brain in a manner consistent with increased risk for AD.

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Nanosymposium

357. Amyloid-Beta Tau Interaction

Location: 152A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***357.07

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

Title: Bilateral and intermittent infusions of Aβ oligomers into the brain parenchyma induces Aβ deposits, tau aggregation, extraneuronal neurofibrillary tangle formation and cognitive impairment in older cynomolgus monkeys

Authors: *Z. ZHANG[1,3], F. YUE[4], Y. AI[2,3], R. GRONDIN[2,3], C. LU[4], G. QUINTERO[2,3], G. GERHARDT[2,3], D. GASH[2]
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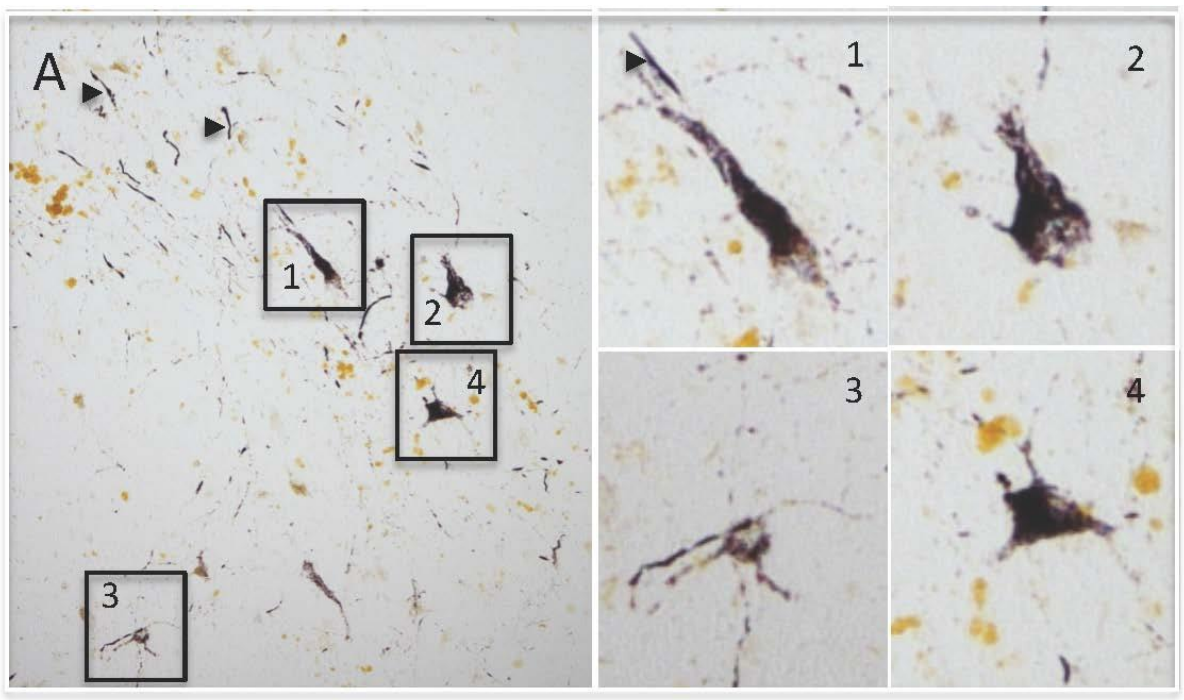
Abstract: A nonhuman primate model of human Alzheimer's disease (AD) with high predictive value should mimic key features seen in human AD, including progressive Aβ deposits, tau aggregation, neuronal cell death and cognitive impairments. Clinical data indicate that tau aggregation in particular is a slow process that progresses from the pre-tangle to the ghost tangle stage in tauopathies. A model should, therefore, avoid inducing rapid tau aggregation since it is not encountered in sporadic tauopathies in human AD. The development of a progressive model in late middle-aged nonhuman primates may help to decipher pathophysiological mechanisms leading to neurofibrillary degeneration and test pharmacological approaches to slow down the pathological progression in AD. In the present study, we have developed a unique nonhuman primate model of human AD that displayed Aβ deposits, tau aggregation and late stage of neurofibrillary tangles (NFTs) formation and cognitive impairments from intermittent infusions of soluble Aβ oligomers (AβO) bilaterally administered directly into the ventral temporal lobes near the hippocampal regions of 12 later-middle aged (age ranging from 18-21 years old) cynomolgus monkeys (N=7 AβO recipients and N=5 vehicle controls) using MRI-guided convection enhanced delivery (CED) methods. Profound cognitive declines were observed in AβO recipients 12 months after the initial injection of AβO along with significant increases of Aβ plaque depositions, and late stages of NFTs formations. It is well established that NFT burden in human AD brain is tightly correlated with cognitive decline while significant cognitive impairments and extraneuronal NFTs (eNFTs) were found relatively at the same time indicating a slowly occurring process in the AβO recipients' brains. Overall, our data suggest that bilateral and intermittent infusions of AβO into the brain parenchyma can reproduce key features of human AD in older cynomolgus monkeys and that this model could be used for testing new therapeutic strategies, tau-based treatments in particular.



Disclosures: **Z. Zhang:** None. **F. Yue:** None. **Y. Ai:** None. **R. Grondin:** None. **C. Lu:** None. **G. Quintero:** None. **G. Gerhardt:** None. **D. Gash:** None.

Nanosymposium

357. Amyloid-Beta Tau Interaction

Location: 152A

Time: *Monday, November 13, 2017, 1:00 PM - 3:00 PM

Presentation Number: *357.08

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

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Brigham Young University, School of Family Life, Gerontology Program
righam Young University, Dr. Sarah M. McGinty Neuroscience Graduate Student Research Fellowship
Neurodar, LLC
Limitless Worldwide, LLC

Title: Effects of oxidative stress on transgenic mice: An Alzheimer's disease behavioral model

Authors: *K. S. STEED[1], K. BARKDULL[1], T. HANCOCK[1], J. J. WISCO[1,2]
[1]Physiol. and Developmental Biol., Brigham Young Univ., Provo, UT; [2]Dept. of Neurobio. and Anat., Univ. of Utah Sch. of Med., Salt Lake City, UT

Abstract: Introduction: Alzheimer's Disease (AD) is the 6th leading cause of death in the US, but while prevalence of other diseases is dropping or leveling, AD continues to rise, in particular within the female population. We propose that the disease progression is largely caused by excess reactive oxygen species or free radicals created by iron dysregulation. An AD brain is struggling with damage control and creates harmful tau tangles and amyloid plaques to deal with the iron. We hypothesized that female murine transgenic APP/PS1 and Tau mice would exhibit decreased behavioral performance in a radial arm maze task. Methods: We bred three strains of mice: APP/PS1, tau, and wild-type. Mice received a diet of either regular or methionine rich chow as an oxidative stressor. Sub-groups received a rescue treatment of either zinc, metformin or clioquinol chow. Data collection time points were: baseline (2 months), 3, 6 and 9 months. Behavioral data was collected using a radial arm maze (RAM) for 2 weeks at each point. Mice "completed" the task if they entered the baited arm three times in a row, and were then moved to a reversal task. Trials were recorded and analyzed using ANY-Maze, and statistics were analyzed using SPSS. Results: We multiplied the behavioral metrics by a factor to reward mice for reaching criterion or reversal. We performed a multi-variate ANOVA and corrected for multiple comparisons using a Bonferroni correction. There was a statistically significant main effect of genotype [$F(2,25)=13.505$, $P=0.000$] and a trend toward significance for genotype and treatment interaction [$F(11,23)=1.900$, $P=0.094$] in the mean time mice spent in the RAM. Post hoc analysis showed significant increase in the mean time a mouse spent in the RAM between APP/PS1 and Tau cohorts ($P=0.000$), Tau and Wild Type ($P=0.003$) cohorts, and mean errors made in the RAM between APP/PS1 and Tau cohorts ($P=.024$), and WT and Tau cohorts ($P=.015$). Pairwise comparison showed a significant difference between the male and female mice, and the time they spent in the RAM ($P=.002$). There were no significant differences seen between genotype or sex on distance run while in the RAM. There was a trend toward significance for genotype [$F(2,10)=3.377$, $P=0.074$], and the difference between male and female mice ($P=.064$) in the number of errors made while in the RAM. Conclusions: We conclude that behavior, specifically short-term spatial memory, is impaired in the presence of the protein Tau, and this affects females more than males. We did not see any significance between treatments as we had expected.

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Nanosymposium

358. Synaptic Signaling Deficits in Alzheimer's Disease I

Location: 150B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***358.01

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

Support: NIA 1R01AG050658-01A1

Title: Monitoring microtubule dynamics at synaptic contacts in hippocampal neurons challenged with oligomeric $A\beta_{1-42}$

Authors: *X. QU, F. BARTOLINI
Columbia Univ., New York, NY

Abstract: Growing evidence indicates that fine control of microtubule dynamics in axons, dendrites and at synaptic contacts is critical for neuronal viability and normal synaptic function. Despite the significance of these observations, virtually nothing is known about whether anomalies in microtubule dynamics in axons, dendrites and at synaptic contacts is a primary activity of oligomeric $A\beta_{1-42}$ that initiates synaptotoxicity. We have compelling data that mDia1-mediated acute stabilization of dynamic microtubules in dendrites and axons is necessary for oligomeric $A\beta_{1-42}$synaptotoxicity through tau (Qu et al., under revision in JCB). To test whether these changes further occur at synapses and are directly responsible for synapse loss, we have developed microscopy assays that measure microtubule invasions into dendritic spines and microtubule contacts with single pre-synaptic boutons of hippocampal neurons in culture. Our preliminary results indicate that oligomeric $A\beta_{1-42}$ acutely perturbs both pre-synaptic and post-synaptic microtubule behaviors prior to loss of synapses. We are currently examining the role of mDia1 in mediating these changes, and optimizing means to record microtubule dynamics at pre- and post-synaptic terminals simultaneously to investigate the temporal and spatial nature of these changes in the intact synapse upon modulation of synaptic activity and exposure to oligomeric $A\beta_{1-42}$.

Disclosures: X. Qu: None. **F. Bartolini:** None.

Nanosymposium

358. Synaptic Signaling Deficits in Alzheimer's Disease I

Location: 150B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***358.02

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

Support: ADC Pilot Grant

Title: Deficiencies in basal forebrain cholinergic neurons from Alzheimer's disease patients

Authors: *T. ZANG, M.-L. LIU, C. REN, C.-L. ZHANG
Mol. Biol., UT South Med. Ctr., Dallas, TX

Abstract: Neurodegeneration in basal forebrain is the first hallmark for Alzheimer’s disease (AD) and cholinergic hypothesis has been proposed for AD treatment. The basal forebrain is located to the front of and below the striatum to project cholinergic innervations to cortex, hippocampus, and thalamus. Acetylcholine released by basal forebrain cholinergic neurons (BFCNs) modulates targeted neurons to exercise attention and cognitive control. Remarkable deficiency and atrophy have been documented from AD patients indicting the cognitive impairment because the cholinergic circuitry went awry. Neuronal reprogramming is a novel tool to study disease mechanism in neurodegenerative disease. We have successfully reprogrammed somatic cells, fibroblasts in particular, into neurons to study human diseases *in vitro*. We are able to induce the conversion from adult skin fibroblasts into human BFCNs. We hypothesize the functional neuronal deficiency proceeds neurodegeneration in AD. We studied the intrinsic excitability, synaptic properties, and connectivity of these reprogrammed AD BFCNs comparing to their age and gender matched controls, we found that they have severe deficient in excitability to stably contribute to the cholinergic network. Furthermore, we have reconstructed anterior and posterior cholinergic circuitry to investigate BFCN circuitry dysfunction. These findings suggest that BFCN dysfunction has a crucial effect in the cognitive failure in AD patients.

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Nanosymposium

358. Synaptic Signaling Deficits in Alzheimer's Disease I

Location: 150B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***358.03

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

Support: P01 HD29787
R01 NS086890
DP1 DA041722
P30 NS076411

Title: Increased electrical activity in alzheimer patient hiPSC-derived cortical neurons with presenilin 1 mutation vs. isogenic controls

Authors: S. GHATAK[1], N. DOLATABADI[1], D. TRUDLER[1], A. SULTAN[2], M. V. TALANTOVA[3], R. AMBASUDHAN[1], *S. A. LIPTON[4,5]
[1]Neurodegenerative Dis. Ctr., Scintillon Inst., San Diego, CA; [2]Scintillon Inst., Neurodegenerative Disease Center, CA; [3]Neurosci., Scintillon Inst., San Diego, CA; [4]Scintillon Inst. & UC San Diego, San Diego, CA; [5]Mol. Med., The Scripps Res. Inst., La Jolla, CA

Abstract: Mutations in the presenilin 1 (PSEN1) gene have been implicated in familial Alzheimer's disease (AD). Here, we performed patch-clamp electrophysiology and Ca^{2+} imaging experiments on hiPSC-derived cortical neurons bearing the ΔE9 PSEN1 mutation vs. isogenic controls. After 5-6 weeks in culture on a bed of mouse astrocytes, we found increased activity in heterozygous (WT/ΔE9) neurons compared to wild-type (WT/WT) controls by both electrophysiology and calcium imaging criteria. Whole-cell patch clamp studies showed that WT/ΔE9 neurons fired bursts of evoked action potentials and manifest greater sodium current density than their WT/WT counterparts, whereas resting membrane potential, cell capacitance, and potassium current density were not significantly different. As monitored with Fluo-4 AM imaging, basal Ca^{2+} levels and responses to 100 μM glutamate were also significantly greater in WT/ΔE9 than WT/WT neurons. The increased intracellular calcium level and spontaneous activity of WT/ΔE9 neurons were abrogated by application of 5 μM of the NMDAR receptor antagonist memantine and to an even greater extent by the improved version of the drug, NitroSynapsin (aka NitroMemantine YQW-036). To our knowledge, this is the first report showing increased electrophysiological/Ca^{2+} activity in hiPSC-derived AD neurons vs. isogenic controls, and confirm similar conclusions previously made in transgenic mice and inferred from human patient data. Moreover, this aberrant electrical activity can be normalized with the new drug, NitroSynapsin.

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(stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Harvard University: S.A.L. named inventor on patents for memantine (Namenda®) and NitroSynapsin for treatment of neurodegenerative diseases, royalty sharing agreement, Forest Laboratories/Actavis/Allergan: licensed memantine and NitroSynapsin patents from S.A.L and Harvard Medical School/Boston Children's Hospital, Adams Pharmaceuticals, Inc.: S.A.L. Scientific Co-Founder of Adamas Pharmaceuticals, Inc. for developing long-lasting formulations of memantine and combination with donepezil.

Nanosymposium

358. Synaptic Signaling Deficits in Alzheimer's Disease I

Location: 150B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***358.04

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

Support: Department of Biotechnology, India
Tata Program Grant
University Grants Commission

Title: Nanoscale distribution of APP at an excitatory synapse

Authors: *D. KUMARAN NAIR[1], S. KEDIA[1], V. RAVINDRANATH[1,2]
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Abstract: The transient composition of the postsynaptic membrane of synapses is controlled by passive diffusion of molecules on the synaptic membrane as well as active processes like endo- and exocytosis. The alteration in number and lateral organization of transmembrane molecules in postsynapse is considered as a crucial factor in health and diseases like Alzheimer's Disease (AD). AD is the most prevalent form of dementia in the elderly. In the last decade a paradigm shift was observed towards understanding the molecular and biochemical pathways implicated in AD where the onset of the disease was proposed to be an altered function of synapses. This resulted in a careful evaluation of the biochemical pathways which regulate the Amyloid Precursor Protein (APP) as well as the development of mouse models for AD. Despite the enormous efforts, the finer mechanisms involved in the early onset of disease still remains unclear. This is partly due to the lack of in-depth evaluation of the mechanisms governing the spatial and temporal evolution of molecular machineries involved in the regulation, retention and recycling of APP. It is already known that genetic alterations of the APP is one of the major causes of Familial Alzheimer's Disease (FAD). Here we try to combine single particle tracking and super resolution imaging to compare the organization and trafficking of wild type APP (APP_{wt}) and a genetic variant of APP (APP_{swe}) identified in FAD. We combined high density

single particle tracking techniques like Photo Activation Localization Microscopy (sptPALM) and Direct Stochastic Optical Reconstruction Microscopy (dSTORM) to map trajectories of individual APP molecules on the plasma membrane. Additionally, we illustrate diffusional behaviour from thousands of spatially discrete single molecule trajectories from live neuronal cells with which it is possible to appreciate finer details of versatile molecular mechanisms pertinent in the organization and recycling of APP molecules at the membrane.

Disclosures: D. Kumaran Nair: None. **S. Kedia:** None. **V. Ravindranath:** None.

Nanosymposium

358. Synaptic Signaling Deficits in Alzheimer's Disease I

Location: 150B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***358.05

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

Support: NIH 1R01AG042890
Mitchell Center for Neurodegenerative Diseases
Amon Carter Foundation

Title: The synaptic binding and dysfunctional impact of amyloid beta and tau oligomers is modulated by near infrared light treatment

Authors: *M. M. COMEROTA, G. TAGLIALATELA
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Abstract: Alzheimer’s disease (AD) is the most prevalent age related neurodegenerative dementia for which there is currently no cure. Cognitive decline in early stages of AD is attributed to the synaptic dysfunction initiated by the binding of small oligomeric amyloid beta (Aβo), which further promote the production of toxic tau oligomers (tau-o). Emerging evidence suggests that the co-presence of Aβo and tau-o exacerbate synaptic dysfunction accelerating disease progression. Thus, identifying interventions that target both proteins may be the most effective way to slow the progression of AD. In the present study, we focused on near infrared (NIR) light treatment (600-1000nm), a novel noninvasive therapeutic originally used for pain relief. Notably, it has been reported that NIR light treatment on APP/PS-1 transgenic mice induced a reduction of Aβ plaque load and improved memory function. However, the impact of NIR light on synaptic health and neuroprotection against Aβo and tau-o induced toxicity is unknown. In the present study, we investigated the presence of Aβo and tau-o at synapses and the susceptibility of synapses to oligomeric Aβ and tau binding after NIR light treatment at 670 nm (90 sec a day for 4 weeks). We further examined the changes in long term potentiation (LTP)

after such NIR light treatments. We found that after NIR light treatment, the amount of $A\beta_{1-42}$ was significantly reduced at synapses of 6-month-old APP transgenic mice (Tg2576). These results extend to tau oligomers at the synapses in 3x Tg-AD mice receiving the same NIR light treatment. We further found that the synapses of wild type mice treated with NIR light showed a reduction in *ex vivo* Aβo binding. The resulting depressed LTP induced by Aβo is reversed in NIR light treated animals, however, no changes are observed against tau-o induced depressed LTP. Collectively these results indicate that NIR light, in addition to reducing levels of Aβ oligomers, further promotes synaptic resistance to Aβ oligomer binding thus alleviating the ensuing synaptic impairments, thus fostering further development of NIR light as a possible novel therapeutic approach in AD.

Disclosures: M.M. Comerota: None. **G. Taglialatela:** None.

Nanosymposium

358. Synaptic Signaling Deficits in Alzheimer's Disease I

Location: 150B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***358.06

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

Support: NIA PO1 AG02250
NIA PO1 AG027956

Title: Amyloid plaques accumulation in the entorhinal cortex mechanistically links defective mitochondrial structure with working memory dysfunction in mito-CFP-3xTg-AD mice

Authors: *S. N. SARKAR, J. Z. CAVENDISH, D. QUINTANA, S. JUN, E. ENGLER-CHIURAZZI, J. W. SIMPKINS
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Abstract: Alzheimer’s disease (AD) is characterized by an early region-specific decline in glucose utilization and mitochondrial dysfunction, particularly in the entorhinal cortex (EC). This reduce energy utilization is associate with impairs spatial working memory. Ionic homeostatis in neurons rely on mitochodnrially generated ATP. In order to determine whether mitochondrial dysfunction in EC-hippocampal neural networks correlates with memory impairments, we generated a transgenic mice named Cyano Fluorescent Protein (CFP)-mito-3xTgAD mice by crossing JB6.Cg-Tg(Thy1-CFP/COX8A)S2Lich/J mice with B6;129-*Psen1*^{tm1Mpm} Tg(APPSwe,tauP301L)1Lfa/Mmjax mice from Jackson laboratory. Presence of CFP in the mitochondria of these mice allowed us to determine structural defects using laser scanning

confocal microscopy (LSM). In a delayed nonmatching-to-place (DNMP) T-maze task that assays EC-Hippocampal netwoks dependendent working memory, male aged CFP-mito-3xTgAD mice (20-24 months) compared to age matched male CFP-mito mice showed severe impairment of learning as well as formation and use of working memory for successful DNMP task. Brain sections encompassing EC and CA1 regions from memory impaired as well as wild type CFP mice were visualized by LSM and respective confocal micrographs were analyzed using fully automated software for quantitative measurements of mitochondrial morphology. Mitochondrial length measurement analysis showed that higher number of smaller size or fragmented (0.5-1.2μm) mitochondria present in EC of AD mice compared to age-matched wild type, and the number of greater than 1.8 μm in length mitochondria was reduced in EC of AD mice compared to wild type. Amyloid antibody staining of the same EC section showed presence of high density amyloid plaques as well as amyloid β-oligomers whereas in case of wild type it was almost undetectable. At present it is not known whether fragmented mitochondria in EC region are also defective in oxidative phosphorylation. Our results raise the possibilities that mitochondrial fragmentation in EC region may be linked working memory impairment in (CFP)-mito-3xTgAD mice.

Disclosures: S.N. Sarkar: None. **J.Z. Cavendish:** None. **D. Quintana:** None. **S. Jun:** None. **E. Engler-Chiurazzi:** None. **J.W. Simpkins:** None.

Nanosymposium

358. Synaptic Signaling Deficits in Alzheimer's Disease I

Location: 150B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***358.07

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

Support: MRC PhD studentship

Title: CYFIP2: Altered local protein synthesis regulates Alzheimer's disease pathology

Authors: *A. GHOSH, S. TIWARI, K. MIZUNO, K. P. GIESE
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Abstract: Alzheimer’s disease (AD) is histopathologically characterised by the presence of plaques made of amyloid-β (Aβ) peptide and tangles comprising hyperphosphorylated tau. However synaptic degeneration in fact precedes neuronal loss and correlates best with impaired memory in both AD and its prodrome Mild Cognitive Impairment (MCI). Therefore, early changes in the AD brain may involve alterations at synaptic sites.
Normally, synaptic function involves the requirement for rapid access to specific

macromolecules. An attractive hypothesis is that several proteins required for synaptic function are locally synthesised within dendrites or spines, and are regulated by RNA-binding proteins and related molecules. A likely candidate for such a local protein synthesis is the *Cy*toplasmic *F*MRP-*I*nteracting *P*rotein 2 (CYFIP2), a highly conserved protein that is abundant in synapses, developmentally expressed and may itself be locally translated. While not much is known about the precise physiological role of CYFIP2 in the brain, it has been proposed to have functions in regulating protein synthesis of FMRP-regulated mRNAs, as well as in modulating cytoskeletal dynamics via a Rac-dependent pathway.
We have previously found that CYFIP2 protein expression is reduced by about 50% in severe AD post mortem hippocampus when normalised for the number of synapses, suggesting it is an early event that precedes synapse loss (Tiwari et al. 2016). We also reported that adult CYFIP2 heterozygous knockout mice, which model the reduced expression, have increased levels of FMRP-regulated proteins such as Amyloid Precursor Protein (APP) and the α subunit of the calcium/calmodulin-dependent kinase II (αCaMKII) at hippocampal synapses. These changes result in elevated $A\beta_{1\text{-}42}$ in whole hippocampi and increased tau phosphorylation in hippocampal synapses at Ser214, a site that is phosphorylated by αCaMKII in the AD brain and known to result in dissociation of tau from microtubules in vitro (Tiwari et al. 2016). Reduced CYFIP2 expression also results in altered dendritic spine morphology of pyramidal neurons in the hippocampal CA1 region, and interestingly, a deficit in memory retention in the Morris water maze (Tiwari et al. 2016). Taken together, reducing CYFIP2 in the mouse brain is sufficient to recapitulate key aspects of the disease and therefore may be a key mediator of early changes in the AD brain. We now address the questions of how ageing can affect the phenotypes previously observed in the CYFIP2 +/- mouse model, and additionally how CYFIP2 may be downregulated in AD using a primary neuronal model.

Disclosures: **A. Ghosh:** None. **S. Tiwari:** None. **K. Mizuno:** None. **K.P. Giese:** None.

Nanosymposium

358. Synaptic Signaling Deficits in Alzheimer's Disease I

Location: 150B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***358.08

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

Title: Interactions between epilepsy and Alzheimer's disease: novel therapeutic strategies

Authors: *S. GOURMAUD[1], D. TALOS[1], L. JACOBS[1], M. HANDY[1], R. J. VASSAR[2], F. E. JENSEN[1]

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Abstract: Clinical and experimental data suggest a potential interaction between epilepsy and Alzheimer's disease (AD), with seizures occurring in at least 20% of AD patients. Also, chronic epilepsy syndromes such as temporal lobe epilepsy (TLE) exhibit alterations in amyloid and tau AD neuropathology, supporting the hypothesis that chronic excitability may promote neurodegeneration. We hypothesize that AD pathophysiology includes altered epilepsy-associated factors that enhance network excitability, and that hyperexcitability can further exacerbate AD neuropathology. We used the 5XFAD mouse model of AD that exhibits EEG seizures at 6 months of age (mo) prior to major behavior deficit and neurodegeneration later at 8-9 mo. We examined AD and epilepsy markers to determine whether increases in the latter were associated with the EEG seizure prodrome. Next, we tested whether seizure induction with pentylenetetrazol (PTZ) at 3 mo accelerated alterations in epilepsy markers and AD neuropathology at a later age.

5XFAD mice exhibited early changes in epilepsy-associated markers, including glutamate receptor (NMDAR and AMPAR) expression and mTOR-dependent signaling prior to the onset of neurodegeneration. Compared to wildtype, 5XFAD mice (n=6/group) exhibited a progressive increase of NR2A (+71%, $p<0.01$), NR2B (+116%, $p<0.0001$), and GluA1 (+117%, $p<0.05$) from 4 to 6mo (coinciding with a period of EEG seizures) before a subsequent decrease at 9mo (-48% NR2A, -42% NR2B, $p<0.001$). mTOR activity progressively increased from 4 to 9mo (+49% S6 activation). These data suggest that epilepsy-associated alterations in glutamate receptors and mTOR activation may occur in the prodromic stages of AD pathology in this mouse model. We next determined seizure threshold using PTZ (50mg/kg i.p.) at the presymptomatic stage of 3 mo. 5XFAD mice exhibited significantly more cumulative seizure activity *vs* WT age-matched controls (+177%, $p<0.001$). Furthermore, these mice showed increase AD markers as well as mTOR activation at 4 mo compared with seizure-free 5XFAD mice, with an increase of pAPP (+63%) and $A\beta_{42}$ hexamers (+270%) compared to saline-treated 5XFAD (n=3-6/group).

These results suggest that epilepsy-associated changes in glutamate receptors and mTOR activity are coincident with the EEG seizure prodromal stage of AD in 5XFAD mice. Furthermore, these mice are more susceptible to seizure induction, and seizures in the prodromal stage appear to enhance AD neuropathology. Epilepsy associated factors like glutamate receptors and mTOR pathway may represent therapeutic targets in the prodromal stages to attenuate AD neuropathologic progression.

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Nanosymposium

358. Synaptic Signaling Deficits in Alzheimer's Disease I

Location: 150B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***358.09

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

Support: NIH grants R01AG049402
Italian FFO
Canadian Institute of Health Research TAD-117950
Catholic University intramural funds

Title: Oligomers of Amyloi-beta and Tau impair synaptic plasticity and memory in an APP dependent fashion

Authors: *D. PUZZO[1], R. PIACENTINI[3], M. FA[5], W. GULISANO[2], D. D. LI PUMA[3], A. STANISZEWSKI[6], H. ZHANG[6], M. TROPEA[1], S. COCCO[4], A. PALMERI[1], P. FRASER[8], L. D'ADAMIO[9], O. ARANCIO[7]
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Abstract: Background – Extracellular oligomers of amyloid-beta (oAβ) and Tau (oTau) are likely to play a key role in Alzheimer's disease (AD). They have been shown to enter neurons and lead to an impairment of synaptic plasticity and memory. Interestingly, we have recently demonstrated that the concurrent application of subtoxic doses of oAβ and oTau impairs memory and its electrophysiological surrogate long-term potentiation (LTP). These findings prompted us to hypothesize that oAβ and oTau share a common mechanism in their detrimental effect against memory and synaptic plasticity. Specifically, we have tested whether Amyloid Precursor Protein (APP) is a key protein involved in a common mechanism by which extracellular oAβ and oTau interfere with second messenger cascades relevant to memory formation. Methods – We have first performed far-WB and co-immunoprecipitation studies to investigate whether oTau binds APP. To establish whether oAβ and oTau act in an APP-dependent fashion, we used APP knock-out (APP-KO) mice. In particular, we examined whether suppression of APP function blocks: i) the intra-neuronal uptake of oAβ and oTau in primary hippocampal neuronal cultures; ii) spatial and associative memory, tested through the Radial Arm Water Maze and Fear Conditioning; and iii) LTP at CA3/CA1 hippocampal synapses. Results – We found that, similar to oAβ, oTau is able to bind APP. Moreover, WT neurons internalized much more Aβ and Tau than APP-KO cells, suggesting that the expression of APP is required for intra-neuronal uptake of the two

proteins. Finally, the deleterious effect of extracellular oAβ and oTau depended upon the presence of endogenous APP, since oAβ and oTau did not impair memory and LTP in APP KO mice. Conclusions – Both oAβ and oTau need APP to impair synaptic plasticity and memory, thus suggesting that the two proteins act through a key molecular common target. Despite the prevailing hypothesis in the AD field is that Aβ triggers Tau pathology, our data suggest that extracellular oAβ and oTau act in parallel, both through APP. Thus, APP represents an interesting therapeutic target against AD and other neurodegenerative diseases characterized by abnormal levels of Aβ and/or Tau.

Disclosures: **D. Puzzo:** None. **R. Piacentini:** None. **M. Fa:** None. **W. Gulisano:** None. **D.D. Li Puma:** None. **A. Staniszewski:** None. **H. Zhang:** None. **M. Tropea:** None. **S. Cocco:** None. **A. Palmeri:** None. **P. Fraser:** None. **L. D'Adamio:** None. **O. Arancio:** None.

Nanosymposium

358. Synaptic Signaling Deficits in Alzheimer's Disease I

Location: 150B

Time: *Monday, November 13, 2017, 1:00 PM - 3:45 PM

Presentation Number: *358.10

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

Support: NIH grant R01AG049402 to OA
Università Cattolica Intramural Funds to CG

Title: Reduced gliotransmitter release from astrocytes mediates tau-induced synaptic dysfunction in cultured hippocampal neurons

Authors: ***R. PIACENTINI**[1], D. D. LI PUMA[1], M. MAINARDI[1], G. LAZZARINO[2], B. TAVAZZI[2], O. ARANCIO[3], C. GRASSI[1]
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Abstract: Tau is a microtubule-associated protein exerting several physiological functions in neurons. In Alzheimer's disease misfolded Tau accumulates intraneuronally and disrupts axons. However, it has also been found in the extracellular medium, and we recently demonstrated that extracellular Tau oligomers (ex-oTau) negatively affect synaptic function. Aim of the present study was to identify the role of astrocytes in ex-oTau synaptotoxicity. Following 1-h application of 100 nM fluorescent ex-oTau to co-cultures of mouse hippocampal neurons and astrocytes we found that Tau accumulated more abundantly and rapidly in astrocytes (11.3±1.0 spots/cell) than in neurons (2.5±0.3 spots/cell). Exposure to Tau also affected intracellular Ca^{2+} signals in cultured astrocytes, decreasing the amplitude of ATP-induced Ca^{2+} transients (from 14.3±1.2 to

8.0±0.7 ΔF/F; P<0.001) as well as the frequency and amplitude of Ca^{2+} waves (from 22.5±0.7 to 15.7±0.9 oscillations/10 min and from 1.9±0.3 to 1.1±0.2 ΔF/F; P<0.001). Accordingly, gliotransmitter release from astrocytes, measured by HPLC, was reduced by Tau treatment: ATP levels decreased from 93±27 to 28±13 nM (-73±7%; P<0.01) whereas glutamate, glutamine and serine were reduced by about 50% (P<0.05). One-hour ex-oTau treatment (100 nM) also depressed basal synaptic transmission in hippocampal neurons co-cultured with astrocytes. The frequency and the amplitude of miniature excitatory postsynaptic currents dropped from 5.9±0.6 Hz and 12.8±1.6 pA in controls to 3.2±0.5 Hz and 7.2±0.8 pA in Tau-treated cultures (P<0.005). Moreover the expression of synapsin-1, synaptophysin and GluR1 was reduced by 59±7%, 45±7% and 27±1%, respectively (P<0.05). Application of 10 μM ATP to the culture medium completely reverted the synaptotoxic effects of ex-oTau, thus indicating that the Tau-induced reduction in gliotransmitter release, especially ATP, significantly contributed to synaptic dysfunction in neurons. We also found that amyloid precursor protein (APP) null astrocytes did not upload and accumulate ex-oTau. Correlation among Tau accumulation in astrocytes, altered gliotransmitter release and synaptic dysfunction was further supported by the results of experiments in which 1-h ex-oTau treatment did not exert any synaptotoxic effects in WT hippocampal neurons grown on APP-KO astrocytes that are unable to internalize Tau and do not exhibit Tau-induced reduction of gliotransmitter release. Collectively, our findings suggest that astrocytes significantly contribute to the synaptotoxic effects of Tau via reduced gliotransmitter availability, and they are major determinants of Tau pathology.

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Nanosymposium

358. Synaptic Signaling Deficits in Alzheimer's Disease I

Location: 150B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***358.11

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

Support: PRIN- PRIN2015W729WH

Title: Recurrent Herpes Simplex type-1 (HSV-1) infections trigger progressive Alzheimer’s disease-related neuropathology in mice

Authors: *G. DE CHIARA[1], M. FABIANI[2], R. PIACENTINI[3], A. MASTRODONATO[3], M. E. MARCOCCI[2], D. LIMONGI[4], I. CELESTINO[4], C. GRASSI[3], A. T. PALAMARA[2,5,4]
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Med. Sch., Rome, Italy; [4]San Raffaele Pisana, IRCCS, Telematic Univ., Rome, Italy; [5]Pasteur Inst. – Cenci-Bolognetti Foundation, Sapienza Univ. of Rome, Rome, Italy

Abstract: Accumulating data suggest a potential link between HSV-1 infection and Alzheimer's disease (AD). Our previous in vitro studies showed that HSV-1infection in neurons triggers i) the amyloidogenic processing of amyloid precursor protein (APP) causing intra-and extra-neuronal accumulation of beta amyloid peptides (Aβs), and of C-Terminal APP-fragments (CTFs) (Piacentini et al, 2011; De Chiara et al, 2010); ii) CTFs nuclear translocation which modulates the transcription of GSK-3β and Neprilysin (Civitelli et al, 2015); iii) synaptic dysfunction via GSK-3-dependent intraneuronal accumulation of Aβs (Piacentini et al, 2015); accumulation of DNA lesions (De Chiara et al, 2016). Herein we performed in vivo studies to investigate whether recurrent HSV-1 infections may result in an AD-like phenotype during ageing. To this aim, 6-8 week-old female BALB/c mice were infected by labial HSV-1 inoculation, mimicking common HSV-1 infection in humans, and subjected to multiple thermal stress (TSs) every 6 weeks over the next 10 months to induce repeated virus reactivations, spreading and active replication into the brain. These events were checked by detection of viral TK gene and ICP4 mRNA/protein expression in brain tissues. Immunohistochemistry and western blot analysis on mouse cerebral tissues revealed the occurrence of APP amyloidogenic processing in cortex and hippocampus from HSV-1 infected mice (HSV1-M) with consequent intraneuronal Aβ accumulation and extraneuronal amyloid plaque deposition, that increased with TS number and mouse ageing. Moreover, altered tau phosphorylation, aggregation and cleavage, together with signs of neuroinflammation were significantly increased in the brain of HSV1-M undergone several TSs as compared to matched control mice (CONTROL-M). Behavioral studies -performed 1 week before and after TSs- showed that each virus reactivation results in significant cognitive deficits in mice, especially when assessed by the Novel object recognition (NOR) test ($p<0.05$ after the 1^{st} and -3^{rd} TSs; $p<0.001$ after the 6^{th} TS vs CONTROL-M). On the contrary, no significant difference was found when NOR performance was assessed before the 3^{rd} TS, suggesting that damages caused by few virus reactivations may be promptly recovered during latency. Conversely a significant impairment in NOR performance was observed before the 6^{th} TS ($p<0.01$), suggesting a virus-related progressive and irreversible accumulation of damages, likely mediated by Aβs and phospho-tau. Altogether these data strongly indicate recurrent HSV-1 infections as a potential risk factor for AD.

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Nanosymposium

359. LRRK2 Mechanisms, Targets, and Pathways

Location: 152B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***359.01

**Topic: ***C.03. Parkinson's Disease

Support: Van Andel Institute Graduate School
Van Andel Research Institute
Reta Lila Weston Trust

Title: Role of the retromer complex in mediating neurotoxicity induced by Parkinson's disease-linked LRRK2

Authors: *L. A. CUNNINGHAM[1,2], A. PODHAJSKA[3], A. TRAN NGUYEN[2], R. BANDOPADHYAY[4], D. J. MOORE[2,3]
[1]Van Andel Inst. Grad. Sch., [2]Ctr. for Neurodegenerative Sci., Van Andel Res. Inst., Grand Rapids, MI; [3]Brain Mind Inst., Swiss Federal Inst. of Technol. (EPFL), Lausanne, Switzerland; [4]Reta Lila Weston Inst. of Neurolog. Studies, Univ. Col. of London Inst. of Neurol., London, United Kingdom

Abstract: Parkinson's disease (PD) is the most common neurodegenerative movement disorder and mutations in at least twelve genes cause familial forms of PD. Mutations in the *leucine-rich repeat kinase 2* (*LRRK2*) gene are the most common cause of autosomal dominant PD, whereas common genetic variation at the *LRRK2* locus is associated with increased PD risk. At present, the downstream cellular pathways critical for mediating LRRK2-induced neurodegeneration remain poorly defined. We have identified a novel interaction of LRRK2 with the dominant PD-linked gene product, VPS35. VPS35 functions as a key component of the retromer complex which mediates retrograde transport of protein cargo from endosomes to the *trans*-Golgi network or plasma membrane. Previous studies suggest that familial LRRK2 mutants induce a retromer deficiency in mammalian cells and mouse brain, with VPS35 overexpression rescuing neurotoxicity induced by mutant LRRK2 in primary neuronal and *Drosophila* models. A critical validation of this potential mechanism is currently lacking in neuronal and rodent LRRK2 models. To extend these prior studies, we have evaluated the functional interaction of LRRK2 and VPS35 using a variety of approaches. We observe the robust interaction and colocalization of FLAG-tagged LRRK2 and V5-tagged VPS35 in human cells. Familial PD mutations in either protein have a limited effect on their interaction whereas functional mutations support a stronger interaction of VPS35 with kinase-inactive LRRK2. Domain mapping suggests that the N- and C-terminal regions of LRRK2 can support the interaction with VPS35. We find that VPS35 does not serve as a substrate of LRRK2 kinase activity *in vitro,* and familial VPS35 mutations fail to alter LRRK2 kinase activity in cells. We demonstrate that familial mutations in LRRK2 fail to

alter the steady-state levels of endogenous retromer subunits when overexpressed in human cell lines or rat primary cortical neurons. Furthermore, we find no evidence for altered retromer protein levels in distinct brain regions of human G2019S LRRK2 transgenic mice or in G2019S mutant and idiopathic PD brains relative to control brains. Finally, we show that *VPS35* heterozygosity in mice does not increase the susceptibility of dopaminergic neurons to degeneration induced by the adenoviral-mediated expression of human G2019S LRRK2 in the nigrostriatal pathway. We are currently exploring the impact of LRRK2 mutations on retromer cargo sorting and protein interactions in neuronal and rodent models. Our data reveal an interaction of LRRK2 with VPS35 but so far fail to provide clear evidence for a retromer deficiency induced by mutant LRRK2 in PD-relevant models.

Disclosures: L.A. Cunningham: None. **A. Podhajska:** None. **A. Tran Nguyen:** None. **R. Bandopadhyay:** None. **D.J. Moore:** None.

Nanosymposium

359. LRRK2 Mechanisms, Targets, and Pathways

Location: 152B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***359.02

**Topic: ***C.03. Parkinson’s Disease

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Title: Progressive dopamine transporter dysfunction and Serine129 phospho-α-synuclein overload in G2019S LRRK2 mice

Authors: *S. NOVELLO[1], D. MERCATELLI[1], F. LONGO[1,2], F. VINCENZI[1], I. RUSSO[3], G. BERTI[3], O. S. MABROUK[4], L. BUBACCO[3], E. GREGGIO[3], K. VARANI[1], M. MORARI[1]
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Abstract: Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most common genetic cause of Parkinson’s disease. Since defects in cytosolic dopamine handling have been associated with dopamine neuron degeneration, we investigated whether G2019S LRRK2 affects the function of dopamine transporters, namely membrane dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2). To this aim we used G2019S knock-in mice in comparison with age-matched wild-type controls. Twelve-month-old G2019S knock-in mice

showed an increase in DAT levels and activity, in particular maximal dopamine transport rate (V_{max}), not paralleled by changes in dopamine affinity. This was associated with a blunted neurochemical and motor response to systemic administration of the DAT blocker GBR-12783. Time-course analysis revealed that the difference in DAT activity between genotypes emerged at 9 months of age but not earlier time-points (3 and 6 months), indicating the progressive nature of DAT dysfunction. Interestingly, G2019S knock-in mice showed a reduction of VMAT2 levels at 12-month-old but not earlier time points (9, 6 or 3 months). In 12-month-old mice, the reduction of VMAT2 levels was associated with an enhancement of vesicular dopamine uptake (maximal transport rate but not affinity), and a greater resistance to the hypolocomotion induced by systemic reserpine. These changes in dopamine transporter activity were not associated with overt neurodegeneration, as evaluated by changes of striatal dopamine release (in vivo and in vitro) or nigro-striatal dopamine neuron integrity, or synaptic toxicity as determined by levels of DOPAL-bound a-synuclein,in striatum. Nonetheless, they were paralleled by an elevation of Serine129-phosphorylated α-synuclein levels in striatum, evaluated both via Western blot analysis and immunohistochemistry. We conclude that the G2019S mutation causes progressive and temporally-spaced dysfunctions of DAT and VMAT2 levels and activity, along with Serine129-phosphorylated α-synuclein overload, in striatum that might contribute to intrinsic dopaminergic terminal vulnerability leading to Parkinson's disease.

Disclosures: **S. Novello:** None. **D. Mercatelli:** None. **F. Longo:** None. **F. Vincenzi:** None. **I. Russo:** None. **G. Berti:** None. **O.S. Mabrouk:** None. **L. Bubacco:** None. **E. Greggio:** None. **K. Varani:** None. **M. Morari:** None.

Nanosymposium

359. LRRK2 Mechanisms, Targets, and Pathways

Location: 152B

Time: *Monday, November 13, 2017, 1:00 PM - 3:00 PM

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Topic: *C.03. Parkinson's Disease

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Title: Implications for LRRK2 and auxilin in Parkinson's disease pathogenesis

Authors: ***M. NGUYEN**, L. ALI, J. SAVAS, D. KRAINC
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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by the dramatic loss of dopaminergic (DA) neurons in the substantia nigra pars compacta. The majority of patient cases described arise sporadically. However, several monogenic forms of the disease have been identified within the past two decades. Through functional studies, genetic implications for PD pathogenesis have been linked to lysosomal, mitochondrial, and more recently synaptic dysfunction. Mutations in clathrin-mediated synaptic vesicle recycling genes leading to early-onset Parkinsonism, such as the recently identified synaptic PD gene DNAJC6 (auxilin), are rare. However, there is growing interest to study the regulation of synaptic function by more common PD genes such as LRRK2, the most commonly mutated gene in PD. In this study, we investigate the cellular consequences resulting from LRRK2 regulation of auxilin in clathrin-mediated synaptic vesicle recycling using PD patient-derived human DA induced pluripotent stem cells (iPSCs). Our results show that LRRK2 is able to interact with and phosphorylate auxilin at novel a site. As mutations in LRRK2 have been shown to increase its kinase activity, our data further suggests that misregulated phosphorylation of auxilin by LRRK2 results in deficient synaptic vesicle recycling. Taken together, our results propose a new role for LRRK2 at the synapse through modulation of auxilin and a potential mechanism by which dopaminergic neurodegeneration is mediated by synaptic dysfunction. The work from this project expands the range of proteins for therapeutic intervention to those located at the synapse, potentially leading to the development of targeted treatments for patients with Parkinson's' disease.

Disclosures: M. Nguyen: None. **L. Ali:** None. **J. Savas:** None. **D. Krainc:** None.

Nanosymposium

359. LRRK2 Mechanisms, Targets, and Pathways

Location: 152B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***359.04

**Topic: ***C.03. Parkinson's Disease

Support: NIH Grant NS098393

Title: Lrrk2-r1441g mutation increases oxidative stress in substantia nigra dopamine neurons

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Abstract: Emerging evidence suggests that synaptic dysfunction of dopamine (DA) neurons is an early event in the pathogenesis of Parkinson disease (PD) occurring prior to the onset of

symptoms. Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most prevalent causes of familial and sporadic PD, demonstrating an unprecedented significant role in PD pathogenesis. Recently a transgenic mouse model with over-expression of human LRRK2-R1441G has been shown to recapitulate motor behavioral, neurochemical and pathological features of PD, and we have found age-dependent deficits in DA release in the dorsal striatum (dSTR) in this model. Both genetic and environmental causes of PD have highlighted the importance of mitochondrial dysfunction in the pathogenesis of PD. LRRK2 has been shown to localize to mitochondria and influence its function. Increased oxidative stress has been shown in cell cultures of pathogenic LRRK2 mutations and iPSC-derived neural cells from PD patients with LRRK2 mutations as well as *Drosophila* with LRRK2 mutations. However, whether this is true *in vivo* in vertebrates is not known. Here we use a 2PLSM (Two-Photon Laser Scanning Microscope): mitochondrial roEGFP imaging in DA neurons in living brain slices to investigate whether there is a higher basal oxidation level in the hLRRK2-R1441G transgenic mice and whether this is age dependent. LRRK2-R1441G mice were crossed with tyrosine hydroxylase (TH)-mito-roGFP mice expressing a redox-sensitive variant of green fluorescent protein (roGFP) with a mitochondrial-matrix targeting sequence under the control of the TH promoter to generate LRRK2-R1441G/TH-mito-roGFP mice. We have successfully conducted the experiments in these mice up to 10 month old and the preliminary results show that there is an increased oxidative stress in SNc DA neurons and DA terminals in dSTR from transgenic mice. Importantly, this alteration is age dependent and occurs prior to the DA release deficits. While the data support the conclusion that R1441G mutation leads to elevated oxidation level *in vivo*, further investigations of the underlying mechanisms, and how R1441G mutation leads to mitochondrial dysfunction are ongoing.

Disclosures: H. Zhang: None. **Y.X. Chen:** None. **L.T. Zhi:** None. **B. Gou:** None.

Nanosymposium

359. LRRK2 Mechanisms, Targets, and Pathways

Location: 152B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***359.05

**Topic: ***C.03. Parkinson’s Disease

Support: MJFF Grant 11604

Title: In silico simulation of LRRK2 related Pathways: A search for druggable targets

Authors: *B. BEHROUZ, J. W. RYAN, D. A. DODDS, L. E. VINCENT, A. D. LEE
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Abstract: Genetic mutations, such as those in LRRK2, offer an exciting opportunity to unravel the molecular mechanisms that underlie disease etiology. Here we used computer simulation to model pathways directly connected to LRRK2 and compared WT vs. G2019S mutated LRRK2 in order to observe downstream molecular abnormalities that result from this pathogenic mutation. Unbiased analysis of the results revealed abnormalities in multiple pathways including but not limited to cytoskeleton, tau, and MAPK pathways. We were further able to show partial rescue some of these abnormalities by manipulating other proteins within these pathways.

Disclosures: **B. Behrouz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuroinitiative. **J.W. Ryan:** A. Employment/Salary (full or part-time):; Neuroinitiative. **D.A. Dodds:** A. Employment/Salary (full or part-time):; Neuroinitiative. **L.E. Vincent:** None. **A.D. Lee:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuroinitiative.

Nanosymposium

359. LRRK2 Mechanisms, Targets, and Pathways

Location: 152B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***359.06

**Topic: ***C.03. Parkinson's Disease

Support: NIH Grant U01NS097028

Title: Autophosphorylated LRRK2 in cerebral spinal fluid as a biomarker for Parkinson Disease

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Abstract: Parkinson's disease (PD) is one of the most common neurodegenerative disorders and affects more than one million people in the U.S. alone. Biomarkers that reliably predict early disease and progression, treatment efficacy, and engagement of a therapeutic target are sought for successful clinical trials for neuroprotection. Mutations in the *leucine-rich repeat kinase 2* (*LRRK2*) gene are the most common known genetic cause of late-onset of PD. Pathogenic mutations in different domains of the LRRK2 protein cause an upregulation of the pSer1292-autophosphorylation site in model systems. Previously, we demonstrated that measurements of autophosphorylated LRRK2 in exosomes from urine could predict with some efficacy the presence of a heterozygous LRRK2 mutation and PD diagnosis with a receiver operating characteristic curve of 0.844. Here, in a new cohort of subjects collected in Trondheim, Norway,

we analyze exosomes from both cerebral spinal fluid (CSF) and urine, collected at the same clinic visit, for the abundance of autophosphorylated LRRK2. While the *G2019S*-LRRK2 mutation upregulated pSer1292-LRRK2 levels in urinary exosomes, the levels between groups were not different in CSF exosomes. Moreover, there was no significant correlation between the abundance of LRRK2 in CSF compared to urine. While these results establish the feasibility of measuring phospho-LRRK2 in CSF and baseline characteristics in patient populations for utility in therapeutic targeting of LRRK2 for neuroprotection, CSF LRRK2 may be unlikely as a successful biomarker for the diagnosis or prediction of PD.

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Nanosymposium

359. LRRK2 Mechanisms, Targets, and Pathways

Location: 152B

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**Presentation Number: ***359.07

**Topic: ***C.03. Parkinson's Disease

Support: MR/M00676X/1 to KH
WT095010MA to KH

Title: Signalling pathway changes in LRRK2 G2019S knock-in mouse model

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Abstract: Objectives
Examination of the influence of leucine-rich repeat kinase 2 (LRRK2) on Wnt and Ca^{2+} signalling changes in Parkinson's disease (PD).
Background: Wnt and Ca^{2+} signalling changes are some of the most reproducible reported observations in LRRK2 signalling activity to date. LRRK2 was shown to modulate Ca^{2+}-dependent immune responses, autophagy and mitochondrial function. In addition, LRRK2 protective and pathogenic genetic PD variants affect canonical Wnt signalling in opposite directions showing a clear correlation between Wnt signalling activity and neurodegenerative disease susceptibility.
Methods
Functional signalling assays in LRRK2 knockout and G2019S knock-in models using delivery of

lentiviral biosensors containing a luciferase reporter. We transduced mice with biosensors to record Wnt and Ca^{2+} cell signalling changes in the brains of live animals from one week to six months of age using IVIS imaging. This allows quantification of cell signalling activity in the brain over the lifetime of an animal.
Results
We present the analysis of Wnt and Ca^{2+} signalling activity in live mice. Wild type mice were compared to *LRRK2* knockout mice and mice harbouring the most prevalent familial *LRRK2 G2019S* mutation. Our data collectively support the idea of LRRK2 as a modulator of Wnt and Ca^{2+} signalling. In addition, we show impairments of Wnt and Ca^{2+} signalling activity in LRRK2 G2019S knock-in mice.
Conclusions
Decrease in Wnt signalling activity has previously been linked to neurodegeneration and provides a plausible mechanism in the pathogenesis of Parkinson's disease. Increasing our understanding of the role of LRRK2 in Wnt and Ca^{2+} signalling pathways might contribute to the generation of novel PD treatments targeting early events in the disease pathogenesis.

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Nanosymposium

359. LRRK2 Mechanisms, Targets, and Pathways

Location: 152B

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***359.08

**Topic: ***C.03. Parkinson's Disease

Title: Chronic in diet administration of the selective LRRK2 inhibitors, MLi-2 and PFE-360, produces a mild and reversible effect on lung morphology in mice

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Abstract: Inhibiting the kinase activity of leucine-rich repeat kinase 2 (LRRK2) is one of the most promising targets for the treatment of Parkinson's disease; however, morphological

changes in lungs of non-human primates following treatment with LRRK2 kinase inhibitors, which are similar to those observed in the lungs of LRRK2 knockout rodents, have brought the safety of this mechanism into question. Recently we demonstrated that in-diet dosing with the highly potent and selective LRRK2 kinase inhibitor MLi-2, induces similar pulmonary changes in mice and provides a rodent model by which we can study the effects of LRRK2 kinase inhibition on lung morphology (Fell et al., 2016). Here, we treated wild-type (C57Bl/6) or LRRK2 G2019S KI mice with the selective LRRK2 inhibitor MLi-2 (3, 10, 30, 60, and 120 mg/kg/day) in diet for 7 days. Following treatment, the lungs were harvested and assessed for histomorphological changes. Enlargement of scattered individual epithelial cells, consistent with type II pneumocytes was observed in both the wild-type and LRRK2 G2019S mice following 7 days treatment with MLi-2 at 60 or 120 mg/kg/day. No morphological changes were noted at the lower doses tested in either genotype. Similar morphological changes in the lung were observed following in-diet dosing with a structurally differentiated, potent and selective inhibitor of LRRK2 kinase activity, PFE-360 in wild-type mice (the effect of PFE-360 in G2019S KI mice was not evaluated). In a subsequent study we determined the effects of intermittent MLi-2 (60 mg/kg/day) dosing with and without washout (drug holiday) periods on lung histomorphology. Consistent with previous findings, morphological changes in the lung were observed in mice that received a one week drug treatment immediately preceding the lung harvest. However, no morphological changes were observed in the lungs of mice that had a one week drug washout immediately prior to lung harvest. Similarly no morphological changes in the lung were noted in mice that underwent intermittent (one week on, one week off, one week on) MLi-2 treatment followed by a one week washout demonstrating that the lung morphological changes are rapidly reversed even after multiple treatments with MLi-2. Collectively the data described here support previous work by our group in which we demonstrated a rodent model for the study LRRK2 inhibitor-induced changes in lung, allowing for elucidation of safety concerns surrounding LRRK2 kinase inhibitors in PD. Further studies assessing the efficacy of chronic treatment in mice will allow for the establishment of a therapeutic index for LRRK2 inhibitors.

Disclosures: **R. Hodgson:** A. Employment/Salary (full or part-time):; Charles River Laboratories. **T. Parkkari:** A. Employment/Salary (full or part-time):; Charles River Discovery. **A. Bradley:** A. Employment/Salary (full or part-time):; Charles River Laboratories Edinburgh Ltd. **D.K. Bryce:** A. Employment/Salary (full or part-time):; Merck. **P. Galatsis:** A. Employment/Salary (full or part-time):; Pfizer Inc. **T. Heikkinen:** A. Employment/Salary (full or part-time):; Charles River Discovery. **C. Houle:** A. Employment/Salary (full or part-time):; Pfizer Inc. **L.A. Hyde:** A. Employment/Salary (full or part-time):; Merck. **S. Kuruvilla:** A. Employment/Salary (full or part-time):; Merck. **T.N. Martinez:** None. **A.J. Nurmi:** A. Employment/Salary (full or part-time):; Charles River Discovery. **A. Stepan:** A. Employment/Salary (full or part-time):; Pfizer Inc. **M.J. Fell:** A. Employment/Salary (full or part-time):; Merck. **M.A. Baptista:** None.

Nanosymposium

360. Neuro-Immune Interactions in Pain, Migraine, and Itch

Location: 146C

Time: *Monday, November 13, 2017, 1:00 PM - 3:45 PM

Presentation Number: *360.01

Topic: *D.03. Somatosensation: Pain

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Title: Intercellular redox signaling between macrophage AT2R and sensory neuron TRPA1 in neuropathic pain

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Abstract: The Angiotensin II (Ang II) type-2 receptor (AT2R) is thought to be expressed in sensory neurons, where it couples to Gαs- or Gαi-subunits, and accordingly their activation results in pro- and anti-nociceptive effects, respectively. Furthermore, recent success of an AT2R antagonist EMA401 in phase-IIa clinical trial for the relief of neuropathic pain has suggested a new mechanism-based therapeutic approach for chronic pain. However, we were unable to detect any direct effects of Ang II on cultured mouse and human DRG neurons. Evoked action potential firing and membrane excitable properties of DRG neurons were unaffected by Ang II exposure, as was TRPV1/TRPA1-mediated Ca^{2+} flux. Furthermore, no Ang II-induced activation of ERK1/2 or p38 MAPK was detected in DRG neurons. This is supported by the absence of AT2R gene (*Agtr2*) expression in mouse and human DRG neurons, as well as no detectable GFP signal in DRG neurons of the *Agtr2*^{GFP} reporter mouse. Deep RNAseq of mouse and human DRGs show no detectable *Agtr2* mRNA expression. However, macrophages, which infiltrate injured

nerves in neuropathic pain states, express *Agtr2,* and demonstrate Ang II/AT2R-induced ERK1/2 activation, as well as production of reactive oxygen/nitrogen species (ROS/RNS). Using co-cultures of mouse DRG neurons and macrophages, we show that Ang II exposure evokes a slow and sustained increase in DRG $[Ca^{2+}]_i$, but only when co-cultured with macrophages. This effect can be blocked by antagonists of AT2R and TRPA1, as well as the antioxidant n-acetylcysteine. Co-culture of wild-type mouse DRG neurons alongside macrophages derived from AT2R-null mice failed to show such increases in DRG $[Ca^{2+}]_i$. Human DRG neurons exhibit a similar macrophage/AT2R/TRPA1-dependent $[Ca^{2+}]_i$ response to Ang II exposure, and experiments using a mutant TRPA1 construct in HEK cells indicate that previously-identified N-terminal Cys residues are crucial for TRPA1 activation in this context. In line with this, inhibition of TRPA1 by pharmacological or genetic manipulations result in attenuation of Ang II-induced pain hypersensitivity in mice. Collectively, our findings indicate that inhibition of macrophage-AT2R ROS/RNS production in the vicinity of injured nerves blocks pathological, constitutive activation of TRPA1 and reduces sensory neuron excitation. This may constitute a mechanism underlying the effectiveness of AT2R and TRPA1 antagonists in providing relief for neuropathic pain.

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Nanosymposium

360. Neuro-Immune Interactions in Pain, Migraine, and Itch

Location: 146C

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***360.02

**Topic: ***D.03. Somatosensation: Pain

Support: Washington University Start-up

Title: Macrophage angiotensin II Type-2 receptor is critical for neuropathic pain

Authors: *A. J. SHEPHERD[1], A. D. MICKLE[2], P. KARLSSON[4], J. P. GOLDEN[3], M. R. MACK[5], S. HAROUTOUNIAN[6], V. K. SAMINENI[3], Y. M. USACHEV[8], B. S. KIM[5], R. W. GEREAU, IV[9], D. P. MOHAPATRA[7]
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Abstract: The recent success of an AT2R antagonist EMA401 both in pre-clinical and in phase-IIa clinical trials for the relief of neuropathic pain suggests angiotensin signaling plays a critical role in the etiology of neuropathic pain. We sought to delineate the mechanism underlying this analgesic effect. Angiotensin II (Ang II) levels are elevated in mouse sciatic nerve after spared nerve injury (SNI). Accordingly, systemic or peri-sciatic (but not intrathecal) delivery of an AT2R antagonist dose-dependently reduced mechanical and cold hypersensitivity in male and female SNI mice. SNI-induced mechanical and cold hypersensitivity were also reversed by a TRPA1 antagonist. Both AT2R and TRPA1 antagonists attenuated non-reflexive behavioral measures of tactile and cold hypersensitivity in SNI mice. Macrophages are present in large numbers at sites of nerve injury, both in SNI mice and human skin biopsies from patients with neuropathy. We report AT2R expression in macrophages that are present in the vicinity of injured nerves, which exhibit Ang II/AT2R-induced production of reactive oxygen/nitrogen species (ROS/RNS). Since ROS/RNS are known to activate TRPA1, we explored whether macrophages are required for mechanical and cold hypersensitivity in nerve injury/neuropathy. Following SNI, specific chemogenetic depletion of peripheral macrophages in the MaFIA mouse model was associated with a progressive loss of mechanical and cold hypersensitivity in male and female mice, which was restored upon macrophage re-population. Furthermore, transplantation of bone marrow hematopoietic progenitors from AT2R-null mice into wild-type mice drastically attenuated mechanical and cold hypersensitivity in response to subsequent SNI. In control experiments, transplantation of bone marrow hematopoietic progenitors from wild-type mice into wild-type mice led to the development of SNI-induced mechanical and cold hypersensitivity, as observed in non-transplanted wild-type mice. Taken together, our findings suggest that macrophages in the vicinity of nerve injury produce ROS/RNS in response to Ang II/AT2R signaling, which in turn activates TRPA1 on sensory neurons to elicit neuropathic pain.

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Nanosymposium

360. Neuro-Immune Interactions in Pain, Migraine, and Itch

Location: 146C

Time: *****Monday, November 13, 2017, 1:00 PM - 3:45 PM

Presentation Number: *****360.03

Topic: *****D.03. Somatosensation: Pain

Support: NS072432
NS092851
PhRMA Foundation Predoctoral fellowship

Title: Mechanisms of thermal and mechanical hyperalgesia induced by the complement system component C5a: The role of macrophages and TRPV1

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Abstract: The complement system is a principal component of innate immunity. Recent studies have highlighted the involvement of C5a and other complement system components in inflammatory and neuropathic pain, although the mechanisms are largely unknown. In particular, it is unclear how the complement system communicates with nociceptors and which ion channels and receptors are involved. Here we propose that C5a triggers macrophage-to-neuron signaling which involves TRPV1 sensitization and ultimately leads to thermal and mechanical sensitization. The inflammatory thermal and mechanical hyperalgesia induced by intraplantar injection of complete Freund's adjuvant (CFA) was accompanied by upregulation of C5a in the hindpaw and was markedly reduced by C5a receptor (C5aR1) knock-out or treatment with the C5aR1 antagonist PMX53. C5aR1 KO mice were also protected from spared nerve injury induced neuropathic pain. Administration of C5a into the mouse hindpaw produced mechanical and thermal hyperalgesia with C5aR1 KO mice showing no effect. Immunohistochemistry of mouse plantar skin revealed that C5aR1 was expressed primarily in resident skin macrophages. Additionally, C5a evoked strong Ca^{2+} mobilization in cultured macrophages dependent upon C5aR1 activation of Gβγ-phospholipase Cβ signaling and Ca^{2+} mobilization from ER calcium stores. Drug-induced macrophage depletion in transgenic macrophage Fas-induced apoptosis (MAFIA) mice abolished C5a-induced thermal and mechanical hyperalgesia. Examination of inflammatory mediators following C5a injection revealed a rapid upregulation of numerous factors including NGF, a mediator known to sensitize TRPV1. Preinjection of an NGF-neutralizing antibody significantly decreased C5a-induced thermal and mechanical hyperalgesia. Interestingly, both thermal and mechanical hyperalgesia produced by C5a were absent in TRPV1 knock-out mice, and were blocked by coadministration of TRPV1 antagonist AMG9810. Blockade of TRPV1 after induction of C5a-induced mechanical hyperalgesia showed slow reversal of mechanical hyperalgesia suggesting a signaling intermediary. Consistent with this hypothesis, blockade of calcitonin gene-related peptide prevented C5a induced mechanical hyperalgesia. This suggests that C5a produces heat hyperalgesia by directly sensitizing TRPV1 to heat stimuli while mechanical hyperalgesia is potentially dependent upon neurogenic inflammation originating from TRPV1 containing fibers. Collectively, our findings highlight the importance of macrophage-to-neuron signaling in pain processing and identify C5a, NGF, and TRPV1 as key players in this cross-cellular communication.

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Nanosymposium

360. Neuro-Immune Interactions in Pain, Migraine, and Itch

Location: 146C

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**Presentation Number: ***360.04

**Topic: ***D.03. Somatosensation: Pain

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Title: Paclitaxel-induced neuropathic pain relies on TLR4 on macrophages in males only

Authors: *M. D. BURTON, I. CRUZ, T. A. SZABO-PARDI, S. MEGAT, P. BARRAGAN-IGLESIAS, J. K. MOY, T. J. PRICE
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Abstract: Uncovering how particular cell-types recognize and respond to chemotherapy drugs will lead to an improvement in therapeutic opportunities and increase our understanding of the mechanisms in pain plasticity. Chemotherapy-induced peripheral neuropathy (CIPN) persists in over a third of the population exposed to chemotherapy and is linked to the generation of pain and pain plasticity underlying chronic pain long after cessation of treatment. It has been previously shown that paclitaxel activates toll-like receptor-4 (TLR4) on macrophages. In light of recent findings, we were interested in sex differences in neuroimmune interactions during the development of CIPN. We employed a transgenic model allowing for cre-mediated deletion of a floxed TLR4 allele, utilizing the Lysozyme M promoter to drive cre expression in macrophages. Interestingly, we observed a reversal of mechanical hypersensitivity when TLR4 is removed from macrophages in males. Conversely, macrophage TLR4 knock-out females develop mechanical hypersensitivity similar to their wild-type littermates. We then assessed whether paclitaxel-induced nuclear trans-location of NFκB in isolated wild-type peritoneal macrophages was similar in males and females. Fittingly, we observed a decrease in the trans-location of NFκB to the nucleus after treatment of 200nM paclitaxel in females when compared to males. This work demonstrates a sex-specific effect on macrophage TLR4 in paclitaxel-induced neuropathic pain; pointing to the need to delve into uncovering mechanisms behind sex-differences observed in the promotion of pain states.

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Nanosymposium

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Title: Sex-dependent mechanisms of ischemia/reperfusion-induced peripheral sensitization

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Abstract: Musculoskeletal pain is a highly prevalent clinical problem with a variety of causes. Recent evidence has suggested that the myalgia associated with a number of clinical conditions, such as sickle cell anemia and fibromyalgia, originates from deficits in peripheral perfusion. We have previously characterized a model of transient ischemia and reperfusion injury of the muscles (I/R) in male Swiss Webster mice. After I/R, increased paw guarding and decreased mechanical thresholds, grip strength, and voluntary activity were correlated with the dynamic upregulation of acid-sensing ion channel 3 (ASIC3) in the affected dorsal root ganglia (DRGs). Using an *ex vivo* muscle-nerve-DRG-spinal cord recording preparation, we also found I/R-induced alterations in the chemosensitivity and mechanical thresholds of individual group III and IV muscle afferents. Neurochemical analysis of functionally identified afferents substantiated a role for *de novo* ASIC3 expression in the induction of the myalgia-like phenotype following I/R. Upregulation of ASIC3 was likely originating from a specific increase in interleukin 1β (IL1β) in the injured muscles acting at the upregulated interleukin 1 receptor (IL1r1) within the DRGs. Here, we also confirm the role of IL1β in I/R-induced changes in behavior and physiology in males by systemic inhibition with IL1 receptor antagonist (IL1RA). However, as men and women have been shown to experience differences in pain sensitivity, discrete expression patterns of pain-related genes, and differing susceptibility to chronic pain conditions (including fibromyalgia), we also investigated the effects of I/R in female mice. We found that female naïve and I/R injured mice did not differ in ASIC3 or IL1r1 mRNA expression within the affected DRGs, nor IL1β in the injured muscle. Rather, I/R induced a robust increase in the proton-sensing heat transducer, TRPV1, in females. Furthermore, both naïve and I/R females displayed significantly more mechanically sensitive muscle afferents than naïve/sham males. We however observed similar behavioral responses to I/R in females as we have previously documented in males. Altogether, this data strengthens the evidence for a role of IL1β in the I/R-induced

sensitization of primary group III and IV muscle afferents in males, but suggests that the underlying peripheral mechanisms evoking a similar ischemic myalgia-like phenotype in females may be distinct. These results may have implications for the future development of specific pain therapeutics for ischemic muscle pain for both males and females.

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Nanosymposium

360. Neuro-Immune Interactions in Pain, Migraine, and Itch

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Topic: *****D.03. Somatosensation: Pain

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Title: Educated $CD8^+$ t cells prevent chemotherapy-induced peripheral neuropathy (CIPN)

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Abstract: Many chemotherapeutic agents, including paclitaxel and cisplatin, cause chemotherapy-induced peripheral neuropathy (CIPN). CIPN negatively affects the quality of life of an increasing number of cancer survivors. In 30% of cancer survivors disabling CIPN persist long after treatment cessation. The reason for this are unknown. We propose that persistent CIPN is a consequence of a dysregulation of endogenous resolution pathways. T cells are essential for nervous system homeostasis. We recently showed that CD8+ T cells are necessary for resolution of paclitaxel-induced mechanical allodynia (Krukowski et al., J Neurosci 2016). Here we investigated in another model of CIPN whether T cells need to recognize an antigen to induce CIPN resolution and/or can be educated to resolve CIPN more efficiently. **Materials and methods:** CIPN was induced by cisplatin (3 injections of 2 mg/kg) in male and female wild-type (WT) and T cell-deficient (*Rag2*$^{-/-}$) mice. CD8+ T cells were isolated from spleen of WT mice and intravenously injected into *Rag2*$^{-/-}$ mice. Two symptoms of CIPN were assessed; mechanical allodynia (von Frey test) and ongoing pain (conditioned place preference (CPP) test). **Results:** Cisplatin induced similar onset and intensity of mechanical allodynia in WT and T cell-deficient (*Rag2*$^{-/-}$) mice. After 21 days, WT mice had recovered from CIPN, while T cell-deficient mice displayed persistent CIPN. Reconstitution of *Rag2*$^{-/-}$ mice with CD8+ T cells from WT mice normalized CIPN resolution in both males and females. CIPN resolution was similar in *Rag2*$^{-/-}$

mice reconstituted with CD8+ T cells expressing only T cell receptors (TCR) specific to an irrelevant antigen (chicken ovalbumin) or WT CD8+ T cells. These data indicate that T cell dependent resolution of CIPN does not require recognition of a specific (auto-) antigen by the CD8+ T cells. We next investigated whether CD8+ T cells can be educated to improve endogenous resolution of CIPN. We compared the resolution of CIPN in *Rag2*$^{-/-}$ mice reconstituted with CD8+ T cells from cisplatin-treated mice that had recovered from CIPN or from naïve PBS-treated mice Interestingly, T cells isolated from cisplatin-treated WT mice prevented the development of CIPN in reconstituted *Rag2*$^{-/-}$ mice. **Conclusion:** Our data demonstrate that CD8+ T cells are required for CIPN resolution and prevent the transition to chronic neuropathic pain. CD8+ T cells induced CIPN resolution via an antigen-independent pathway. Nevertheless, T cells can be educated to prevent CIPN. Taken together our data open the possibility to educate the CD8+ T cells *ex vivo* to prevent or reverse CIPN. **Funding:** NIH R01NS073939

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Nanosymposium

360. Neuro-Immune Interactions in Pain, Migraine, and Itch

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Title: Altered glial glutamate transporter expression in descending circuitry and the emergence of pain chronicity

Authors: *W. GUO[1], S. IMAI[1,2], S. ZOU[1], J. YANG[1], M. WATANABE[1,3], J. WANG[1,4], F. WEI[1], R. DUBNER[1], K. REN[1]
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diseases of Gansu province, Inst. of Orthopedics, the Second Hosp. of Lanzhou Univ., Lanzhou, China

Abstract: The glutamate type 1 transporter (GLT1), mainly expressed in astroglia, plays a major role in glutamate homeostasis in the brain. Although alterations of glutamate transporter activity have been linked to persistent pain, the significance of these changes is poorly understood. Focusing on the rostral ventromedial medulla (RVM), a key site in pain modulation, we systematically examined the expression and function of GLT1 and related transcription factor kappa B-binding protein (KBBP) in rats after complete Freund's adjuvant-induced hind paw inflammation and hyperalgesia. After inflammation, GLT1/KBBP showed an early upregulation at 30 min and gradual transition to downregulation that lasted throughout the 8-week observation period. It has been shown that reduced GLT1 activity is associated with its nitration by peroxynitrite. Utilizing GLT1 immunoprecipitation and an anti-nitrotyrosine antibody, nitration of GLT1 was reduced at 30 min and increased at 8 w after inflammation, suggesting an initial increase and later decrease in transporter activity. In contrast to GLT1, the astroglial marker glial fibrillary acidic protein expression in the RVM was constantly upregulated during the 8-week observation period after inflammation. Evaluation of adjuvant-induced behavioral hyperalgesia revealed that mechanical hyperalgesia was characterized by an initial developing phase (≈ one day), a later attenuating phase (≈2 weeks), and a long-lasting persistent phase (>13 weeks). The paw edema followed a similar course to mechanical hyperalgesia. Thermal hyperalgesia showed similar developing and attenuating phases, but was resolved at 4-5 weeks. Importantly, the transition to persistent mechanical hyperalgesia occurred at a time when glutamate transporter expression started to decrease. In the RVM, pharmacological block with dihydrokainic acid and RNAi of GLT1 and KBBP expression facilitated nociception and overexpression of GLT1 reversed persistent hyperalgesia. Further, the initial upregulation of GLT1 and KBBP was associated with activation/phosphorylation of the extracellular signal-regulated kinase and blocked by peripheral local anesthetic block. Pretreatment with dihydrokainic acid facilitated the development of hyperalgesia at 30 minutes after inflammation. These results suggest that the initial increased GLT1 activity depends on injury input and serves to dampen the development of hyperalgesia. However, later downregulation of GLT1 fosters the net descending facilitation as injury persists, leading to the emergence of lasting pain.

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Nanosymposium

360. Neuro-Immune Interactions in Pain, Migraine, and Itch

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**Topic: ***D.03. Somatosensation: Pain

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NS16541
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AR062236-02

Title: Contribution at the spinal level of innate and adaptive immunity to the development of persistent post-inflammatory mechanical allodynia in arthritic mice

Authors: S. A. WOLLER[1], *J. JIMENEZ-ANDRADE[3], T. L. YAKSH[4], M. CORR[2]
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Abstract: Pain persisting beyond the resolution or control of clinical signs of rheumatoid arthritis (RA) decreases quality of life for millions of people. Unfortunately, this pain does not respond well to typical analgesics, and **t**here is a need to better understand the mechanisms underlying pain occurring with arthritis. We have previously shown that Toll-like receptor 4 (TLR4) mediates the transition from acute to chronic pain in a murine model of arthritis. Rather than developing persistent tactile allodynia (TA), animals deficient in TLR4 showed an attenuation of the late phase TA. This receptor is unique in signaling through both MyD88-dependent and independent pathways. To further understand the role of TLR signaling, we examined the development of arthritis and persistent TA in mice deficient in these adaptor proteins.

Adult arthritic K/BxN mice were bled and the sera pooled. 100µl of pooled sera was injected into recipient mice on Days 0 and 2. Clinical arthritis scores and TA were assessed over a period of 28 days in male C57Bl/6, *Tlr4*$^{-/-}$, *Trif*^{lps2}, *Myd88*$^{-/-}$, *Tnf*$^{-/-}$, *Rag1*$^{-/-}$, and *Ifnar1*$^{-/-}$ mice. Spinal cords were collected from WT and *Tlr4*$^{-/-}$ arthritic mice and changes in gene expression were measured.

WT mice developed a persistent TA that outlasted the period of inflammation; the 50% withdrawal thresholds dropped from 1.66g at baseline to 0.74g on day 28. *Tlr4*$^{-/-}$ mice developed an initial increase in reactivity, which resolved concurrent with inflammation (WT AUC 13.2 and TLR4 AUC 9.7, $p<0.05$). MyD88 and TRIF played distinct roles in the development of TA: mice lacking MyD88 do not develop swelling or TA (AUC 2.6, $p<0.01$), while those deficient in TRIF develop a *prolonged* TA (AUC 12.2) outlasting the period of inflammation. Analysis of genes in the spinal cords of WT and *Tlr4*$^{-/-}$ mice harvested on Day 10 of arthritis showed differences in expression levels of IL2, RANKL, IFNβ, and TNF transcripts. Therefore, we also examined the development of TA resulting from arthritis in *Rag1*$^{-/-}$, *Ifnar1*$^{-/-}$, and *Tnf*$^{-/-}$ mice. In the *Tnf*$^{-/-}$ mice there was an attenuated development of pain (AUC 8.0, $p<0.001$), the *Rag1*$^{-/-}$ (10.0, $p<0.05$) mice developed pain, which resolved with the resolution of inflammation similar to *Tlr4*$^{-/-}$ mice, and *Ifnar1*$^{-/-}$ mice developed pain that was not different than the WT mice (AUC 12.2). Male WT mice were treated with IT anti-TNF antibody or IT IFNβ with no effect on TA. However, when *Tnf*$^{-/-}$ male mice were given IT IFNβ, we saw a sustained reversal in TA. Together, the combination of genetic and pharmacological manipulations suggest that co-modulation of TNF and IFNβ is be necessary to prevent or reverse persistent TA.

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Nanosymposium

360. Neuro-Immune Interactions in Pain, Migraine, and Itch

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Presentation Number: *360.09

Topic: *F.05. Neuroimmunology

Support: Wellcome Trust PhD fellowship

Title: Disruption of the nociceptive system alters resolution of sterile cutaneous inflammation *In vivo*

Authors: ***F. LA RUSSA**[1], D. H. L. BENNETT[2], S. B. MCMAHON[1]
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Abstract: Inflammation is a physiological response aimed to protect the host from potential or actual damage and initiate tissue repair. There is growing consensus that the sensory system, along with the immune system, forms an integral component of the inflammatory response. An extensive body of work has described the ways by which immune cells can affect properties of nociceptive neurons. On the contrary, the role of nociceptors as immune modulators has only begun to attract attention. In particular, it has been suggested that nociceptors may acquire immunomodulatory properties in a variety of tissues including the skin, a prototypical neuroimmune organ. Notwithstanding, the underlying mechanisms of such properties are still far from being elucidated.
To deeper investigate the immunomodulation mediated by sensory fibers *in vivo*, we asked how an inflammatory response would change in a skin depleted from sensory fibres. UVB irradiation causes dramatic alterations of both neuronal and immune cell biology, and was therefore employed as a model system to study neuroimmune interactions in the skin.
Depletion of sensory fibers modulated resolution of UVB-induced inflammation causing significant increase of immune cells in the plantar skin compared to controls. Further studies confirmed that this effect might be driven by the disruption of neuronal signalling. Indeed, mice lacking the Transient Receptor Potential A1 receptor, a neuronal sensor of inflammatory mediators, showed a very similar phenotype to denervated mice; and so did the mice knockout of the Calcitonin Gene-Related Peptide, a neurotransmitter with immunomodulatory activities.
Finally, preliminary studies suggest that such an alteration may result from a combination of mechanisms including increased extravasation and changes in trascription of distinctive genes,

thus involving several cells types.
In conclusion, sensory innervations may play a protective role in skin immunity being essential for complete resolution of sterile cutaneous inflammation.

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Nanosymposium

360. Neuro-Immune Interactions in Pain, Migraine, and Itch

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**Time: ***Monday, November 13, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***360.10

**Topic: ***D.03. Somatosensation: Pain

Support: NSERC Grant RGPIN418299-2012

Title: Genetic deletion of microglial pannexin-1 attenuates morphine withdrawal, but not analgesic tolerance or hyperalgesia

Authors: *N. E. BURMA, H. LEDUC-PESSAH, T. TRANG
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Abstract: Opioids are among the most powerful analgesics for managing pain. The number of opioids prescriptions continues to skyrocket across North America, with a concomitant increase in accidental opioid related deaths and hospital visits. Repeated opioid use is associated with adverse effects such as physical dependence (characterized by a withdrawal syndrome upon drug cessation), analgesic tolerance (loss of the pain relieving effects) and opioid-induced hyperalgesia (a paradoxical increase in pain with repeated opioid use). The increase in opioid use and associated adverse effects has led to a strong urgency to help individuals stop taking their opioid medication when their pain has subsided or if they no longer require opioid analgesics. The adverse effects of opioids are associated with increased microglial reactivity, and within the spinal dorsal horn (a key site of opioid action) we have identified the microglial pannexin-1 (Panx1) channel as a novel therapeutic target in opioid withdrawal. We next tested whether blocking microglial Panx1 alleviates morphine analgesic tolerance and hyperalgesia.
Opioid analgesic tolerance was established by daily injection of morphine (10 mg/kg) for 7 days, and was characterized by a progressive decline in morphine antinociception, as well as a loss in morphine analgesic potency. To assess the role of microglial Panx1, we used a transgenic mouse strain with a targeted deletion of Panx1 from microglia ($Cx3cr1\text{-}Cre^{ERT2}::Panx1^{flxflx}$). Genetic deletion of microglial Panx1 had no effect on acute response to morphine or development of analgesic tolerance. The development of morphine tolerance correlated with increased CD11b immunoreactivity in the spinal dorsal horn. However, flow cytometric analysis revealed no

significant change in microglial Panx1 expression in morphine tolerant mice.
Opioid-induced hyperalgesia is characterized by pain hypersensitivity with repeated opioid administration. Mice were treated with escalating doses of morphine twice a day for 5 days, and tail withdrawal latency to a thermal stimulus was recorded immediately prior to morning injections of morphine. Tail withdrawal latencies of wild-type mice progressively decreased over the 5 day treatment period, and genetic deletion of microglial Panx1 had no effect on this decline in response.
Together, our findings suggest that genetic deletion of microglial Panx1 preferentially alleviates symptoms of opioid withdrawal without attenuating the development of morphine analgesic tolerance or morphine-induced hyperalgesia.

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Nanosymposium

360. Neuro-Immune Interactions in Pain, Migraine, and Itch

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**Presentation Number: ***360.11

**Topic: ***D.03. Somatosensation: Pain

Title: Novel rat monoclonal antibody against P2RY12 for specific detection and isolation of microglia

Authors: *A. CARTIER[1], L. DISSING-OLESEN[3], H. ZHANG[1], K. COHANE[2], M. A. TAM[1], B. A. STEVENS[3], M. TAYLOR[2]
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Abstract: Microglia are the brain and spinal cord-resident macrophages that function as sentinels in maintaining CNS homeostasis. Dysregulation of these sentinels 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 novel, microglia-specific tool, we have generated a rat monoclonal antibody against murine Purinergic Receptor P2Y12 (P2RY12), a highly selective marker for microglial cells that enables immunostaining in histological sections as well as isolation of these cells by FACS and magnetic nanobeads. The specificity of the P2RY12 antibody was validated in single cell homogenates from various organs including the brain, spinal cord, spleen, liver, and lungs which were analyzed by flow cytometry. Phenotype of corresponding tissue resident macrophages i.e. microglia, splenic macrophages, Kupffer cells, and alveolar macrophages, was confirmed by

their CD11b and CD45 expression. Additionally, immunohistochemistry was used to further validate the antibody in tissue sections from these organs. Furthermore, we validated the utility of the P2RY12 antibody for use in combination with BioLegend's MojoSort™ magnetic cell separation system, to isolate microglia with high purity and yield. Cells were isolated from 7-day old C57BL/6 mouse brains using biotinylated P2RY12 antibody, followed by incubation with streptavidin nanobeads. Isolated cells were co-stained with CX3CR1 and CD11b as general markers for microglia and flow cytometric quantification demonstrated a purity of microglia above 99%. On-going experiments address LPS-induced alterations in microglial morphology, an inflammatory stimulus known to downregulate P2RY12 and to induce amoeboid morphology in microglia. With our studies we demonstrate the specificity, versatility, and utility of a novel and unique rat anti-mouse P2RY12 antibody that will facilitate research in microglia and their role in the CNS.

Disclosures: **A. Cartier:** None. **L. Dissing-Olesen:** None. **H. Zhang:** None. **K. Cohane:** None. **M.A. Tam:** None. **B.A. Stevens:** None. **M. Taylor:** None.

Nanosymposium

361. Gating Olfactory Information

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Presentation Number: *361.01

Topic: *D.05. Olfaction and Taste

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Title: Stimulus induced LFP oscillations in the accessory olfactory bulb

Authors: ***Y. BEN-SHAUL**[1], A. KAHAN[2], M. YOLES-FRENKEL[2], N. HORESH[2], Q. CHENG[2]
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Abstract: One of the notable features of the vomeronasal system (VNS), distinguishing it from the main olfactory system (MOS), is the mode of stimulus delivery. In the MOS, stimulus exposure is coupled to breathing, and thus, the breathing cycle defines a natural temporal scale to which neuronal responses can be referred. The ongoing breathing cycle is prominently reflected by the olfactory bulb theta rhythm (2-12 Hz), manifest as both intracellular voltage fluctuations, and in population level local field potentials. Importantly, the activity of many main olfactory bulb neurons is coupled to particular phases of the theta rhythm in a stimulus specific manner.

Thus, consideration of neuronal activity with respect to the respiration cycle (e.g. to inhalation onset) is informative with regard to stimulus features. The situation is very different in the accessory olfactory bulb (AOB), which receives its inputs from vomeronasal sensory neurons, located in the vomeronasal organ. Although AOB neuronal activity is not coupled to the breathing rhythm, previous studies have demonstrated the existence of local field potential fluctuations in the AOB across various frequency bands. Yet, unlike the case in the MOB, clear oscillatory events which are locked to stimulus uptake, have not been reported in the AOB. Here, we describe a novel type of AOB oscillatory pattern: a prominent local field potential oscillation, lasting several seconds and sweeping across the classically defined theta and beta frequency ranges. Importantly, stimulus coupled AOB oscillations do not occur spontaneously, but are rather locked to stimulus delivery to the vomeronasal organ. Furthermore, these oscillatory events are correlated with increases in the firing rates of individual AOB mitral-tufted cells. We speculate that like theta oscillations in the main olfactory bulb, these AOB oscillations can provide a temporal framework for downstream processing regions that decode AOB neuronal activity.

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Nanosymposium

361. Gating Olfactory Information

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Topic: *****D.05. Olfaction and Taste

Support: NIH Brain Initiative Grant U01NS090498
NIH NRSA T90DA043219

Title: Behavioral readout of spatiotemporal codes dissected by holographic optogenetics

Authors: ***J. V. GILL**[1], G. M. LERMAN[3], S. SHOHAM[4], D. RINBERG[2]
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Abstract: A fundamental goal of neuroscience is to understand how the activity of specific neuronal circuits supports behavior. Determining which aspects of neural activity are used by downstream circuits to guide behavior requires simultaneously manipulating activity while monitoring behavioral readout. The mouse olfactory system is emerging as an ideal model for investigating spatiotemporal coding, given its ease of access for recording and manipulation, as

well as its behavioral relevance for the animal. Recent studies have revealed that fine temporal scales are essential to olfactory information processing, but it is unknown which precise features of this code are behaviorally accessible. Recently, we developed a system for simultaneous large-scale 2-photon calcium imaging and holographic stimulation in the olfactory bulb of awake, behaving mice, permitting recording and manipulation of groups of neurons with high spatiotemporal resolution. With this system we have measured odor-evoked activity in broad populations of mitral and tufted cells (MTCs), the projection neurons of the olfactory bulb, and demonstrated the use of this system for closed-loop optogenetic feedback, mimicking natural, stimulus-evoked activity temporally patterned across an intrinsic biological rhythm (respiration). This resolution permits a series of theory-driven experiments to establish the basic rules of MTC code readability by higher brain areas. Specifically, we ask what features of spatiotemporal neuronal activity in the olfactory bulb are *detectable* and *discriminable* by downstream circuits to guide behavior. Initial results of these experiments indicated that mice can detect synchronous optogenetic activation of <20 neurons with high accuracy, suggesting exquisite sensitivity. Further experiments explore how this sensitivity changes as a function of timing, cell type and the odor tuning of targeted neurons.

Disclosures: **J.V. Gill:** None. **G.M. Lerman:** None. **S. Shoham:** None. **D. Rinberg:** None.

Nanosymposium

361. Gating Olfactory Information

Location: 140A

Time: *Monday, November 13, 2017, 1:00 PM - 3:30 PM

Presentation Number: *361.03

Topic: *D.05. Olfaction and Taste

Support: HFSP

Title: Neuronal representation of social information in the medial amygdala of awake behaving mice

Authors: ***Y. LI**[1], A. MATHIS[2], B. F. GREWE[4], M. J. SCHNITZER[5], V. N. MURTHY[3], C. G. DULAC[3]
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Abstract: The medial amygdala (MeA) has been shown to play a critical role in processing species- and sex-specific signals that trigger instinctive social and defensive behaviors. However, the principles by which this deep brain structure encodes social information have remained elusive. By using a miniature microscope to image the dynamics of large neural ensembles in

awake behaving male and female mice, we tracked the responses of MeA neurons to conspecific and predator cues over several months. These recordings revealed spatially intermingled subsets of MeA neurons with distinct temporal dynamics of inhibition or excitation to one or several animal cues. We show that the encoding of sex-specific social information by MeA ensembles is sexually dimorphic, and that it relies on neural population codes, rather than signaling by individual cells. Moreover, long-term imaging in different social contexts reveals that sexual experience triggers lasting and sexually dimorphic changes in how the MeA represents social information, which, in sexually experienced males, involves signaling by the neuropeptide oxytocin. These findings uncover basic principles underlying the representation of social information and its modulation by intrinsic and extrinsic factors.

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**Presentation Number: ***361.04

**Topic: ***D.05. Olfaction and Taste

Support: NIH grant: DC014453

Title: Diverse roles of the serotonergic system on olfactory behavior in mice

Authors: *V. KAPOOR[1,2], L. D. GUARNIERI[3], V. N. MURTHY[1,2]
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Abstract: The serotonergic system modulates a wide range of perceptual and cognitive functions. It affects a wide variety of learned behaviors such as decision-making and reward prediction, as well as innate behaviors (*e.g.*, novelty exploration). One critical limitation of existing research has been the use of system-wide non-specific manipulation of serotonergic populations. Since the serotonergic raphe neurons project widely in the vertebrate brain, broad manipulations could lead to confounding results. In this study, we used virally-targeted, chemogenetic inhibition (Gi-DREADDs) in mice to test the effects of serotonergic modulation on different olfactory behaviors. We could then selectively block activity of serotonergic projections to the olfactory bulb by local injection of clozapine-N-oxide (CNO) or cause system wide inhibition of serotonergic neuron activity systemic injection. We found that targeted block of serotonergic projections to the olfactory bulb during olfactory figure-ground segregation task

impaired the animals' ability to detect single components embedded in an odor mixture. This impairment was highly correlated with the complexity of the task. The performance of mice was unaffected at lower difficulties (*i.e*, low number of components in background mixture ~ four), but deteriorated rapidly with increasing difficulty (~ number of components in the background mixture). In addition, impairment was highly dependent upon the identity of target odors. We found similar impairment in animals' performance during a two-alternate force choice task in presence of variable background mixtures, where targeted block of serotonergic projections to the bulb resulted in odor identity-dependent and task complexity-dependent impairment of performance. In contrast to local manipulation, system wide inhibition of serotonergic modulation resulted in qualitatively distinct and more severe behavior deficits. Systemic manipulations resulted in nonspecific impairment that was neither dependent upon the complexity of the task nor on the identity of target odors to be detected. To further compare the targeted versus system-wide effects of serotonergic modulation, we tested mice in an open field arena. We found that the systemic manipulations resulted in increased mobility, decreased patience and impaired animals' ability to correctly identify attractive and repulsive olfactory stimuli. By contrast, targeted manipulation of serotonergic projections had no effects on these tasks. Together, these results point to a specific role of serotonergic projections to the olfactory bulb in complex, but not simple, olfactory behaviors.

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**Presentation Number: ***361.05

**Topic: ***D.05. Olfaction and Taste

Title: Context dependent olfactory generalization depends on anterior olfactory nucleus

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Abstract: We describe a novel functional role for the anterior olfactory nucleus (AON), a small two-layer cortex located between the olfactory bulb (OB) and piriform cortex. Despite its location and its intense interconnectivity with other olfactory structures, research into AON function has been lacking. Anatomical evidence indicates that the AON *pars medialis* serves as a bridge between the ventral hippocampus (vHC) and the OB, suggesting a role in contextual processing of odor signals. To investigate whether contextual information, represented within vHC, can regulate olfactory learning via this pathway, we measured context-dependent odor

generalization using an established contextually-cued odor discrimination task. Rats exhibited distinct and parallel generalization patterns for the same odorants learned in two distinct contexts, demonstrating that context can modulate generalization between odorants. Moreover, the expression of contextually dependent generalization depends on AON processing, whereas noncontextual generalization does not. Briefly, rats were trained on a contextually cued odor discrimination task in which they were presented with two cups of digging medium containing two similar odorants (a 4- and a 5-carbon straight-chain aliphatic odorant) presented together in two visually distinct environmental contexts. In one context, the 4-carbon odor was rewarded, whereas in the other context the 5-carbon odor was rewarded. After rats reached criterion on this task, we tested their generalization to closely related odorants in each context using an established testing paradigm, measuring digging times in response to non-rewarded odorants with aliphatic chains ranging from 2 to 7 carbons. Rats displayed different asymmetric generalization curves in the two different contexts. We then bilaterally infused muscimol into the AON after training but prior to generalization testing; this disruption of AON function eliminated contextually modulated generalization. In contrast, non-contextual odor learning was not affected by AON inhibition. These results demonstrate a novel role for the AON in the integration of non-olfactory contextual information onto early olfactory processing, which we further investigate using computational modeling.

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Topic: ***D.05. Olfaction and Taste

Support: NIH Grant 1R01DC014487-01A1

Title: Implementation of a robust odor identification algorithm using olfactory cortical feedback

Authors: ***G. H. OTAZU**, P. MASSET, D. ALBEANU
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Abstract: Mammals use olfaction to identify food sources and mates, and to avoid predators. This is notable given that natural olfactory scenes are composed of mixtures of tens of volatile molecules out of a large pool of known odorants. Nevertheless, despite the complexity of this inference problem, rodents can detect a target odor in the presence of large number of distractor odors.

A framework to solve this problem is to use constructive algorithms. These algorithms create an estimate of the observed olfactory scene by choosing a set of odors from a large dictionary of known odors such as the estimate matches the scene. This approach works well when the olfactory scenes are composed of only known odors, but it fails to identify known odors in the presence of strong novel odors.
We propose that the nervous system overcomes the problem of novel odors by using a sparse representation algorithm called Corrected Projections Algorithm (CPA). CPA does not directly estimate the odor concentrations, but estimates a binary variable that indicates if an odor is present or not.
The size of the dictionary of possible odors that CPA can identify increases with the dimensionality of the olfactory space similar to other reconstruction algorithms. We estimated lower bounds for the dimensionality of olfactory neural response using data from glomeruli, mitral, and tufted cells in awake and anesthetized mice. We found that an extrapolated dimensionality lower bound (~50) limited the size of this dictionary to a few thousand odors precluding a dictionary size that could contains all possible odors that might appear in a mouse natural environment. Nevertheless, CPA was more effective than other algorithms in identifying known odors in simulated natural environment because of its resilience to novel distractor odors that are not part of the dictionary.
CPA can be implemented using the cortical feedback from the piriform cortex (PC) back into the olfactory bulb (OB). Within this framework, the OB broadcasts to downstream cortical areas, in parallel two information channels: the sensory input (carried by the tufted cells), as well as an error signal of the current sensory input (carried by the mitral cells). The latter is further re-casted and minimized by predictive cortical feedback into an error signal on the identity of olfactory objects present. Our computational framework necessitates specific feedback signals (enhanced and suppressed) from the olfactory cortex (piriform cortex and anterior olfactory, nucleus, AON) to the bulb, assigns distinct and falsifiable roles to mitral and tufted (M/T) cells, and is consistent with recent experimental reports on feedforward and feedback processing in the OB.

Disclosures: **G.H. Otazu:** None. **P. Masset:** None. **D. Albeanu:** None.

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Topic: * D.05. Olfaction and Taste

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R01DC011554

Title: Nasal breathing modulates rhythmic activity in the prefrontal cortex and fear behavior

Authors: *A. H. MOBERLY, M. MA
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Abstract: Voluntary control of respiration, especially via rhythmic nasal breathing, alleviates negative feelings such as fear and has been used clinically to manage certain types of panic attacks. Although respiration-coupled olfactory inputs entrain the rhythmic activity in widespread brain regions beyond the olfactory pathway, the neural substrates that link nasal breathing to fear circuits remain largely unknown. Here we show that during conditioned fear induced freezing behavior, mice breathe at a steady rate (~ 4 Hz), which is strongly correlated with a 4 Hz oscillation observed in the olfactory bulb (OB), the first relay station in the olfactory pathway, as well as in the prelimbic, medial prefrontal cortex (mPFC), a structure critical for expression of conditioned fear behaviors. We use circuit tracing to reveal inputs to the mPFC from the taenia tecta and anterior olfactory nucleus, both of which receive direct projections from the OB. Optogenetic activation of olfactory sensory neurons entrains rhythmic activity in the OB and mPFC, whereas removal of olfactory sensory inputs reduces the correlation between the OB and mPFC activity during conditioned fear behavior. We further demonstrate that olfactory inputs are not required for the expression of fear induced freezing behavior, but disruption of olfactory inputs leads to prolonged freezing periods. Collectively, our results indicate that olfactory inputs can modulate rhythmic activity in fear circuits and suggest a neural pathway that underlies the behavioral benefits of nasal breathing.

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**Topic: ***D.05. Olfaction and Taste

Support: NIH Grant DC003906 to DAW
Profutura Scientia Fellowship to JO

Title: State-dependent competition between bottom-up and top-down inputs to olfactory cortex

Authors: *D. A. WILSON[1,2], M. JUVENTIN[3], M. ILINA[3], B. EAST[3,4], J. OLOFSSON[3,4,5]
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Abstract: Sensory cortices process afferent input in the context of activity from a wide variety of other inter-cortical inputs. These top-down inputs provide information about expectation, recent history and multisensory inputs that modulate the processing of bottom-up sensory input. Importantly the balance between bottom-up and top-down inputs in driving sensory cortical neurons is state- and behavior-dependent. Such shifts can, for example, be important for sleep-dependent memory consolidation during periods of reduced responsiveness to ongoing sensory input. Most analyses of changes in network connectivity rely on indirect correlational measures of activity, such as local field potential coherence. Here, we used optogenetic stimulation to assay the strength of extracellular evoked potentials in identified pathways into the rat piriform cortex (PCX) over a variety of behavioral states as a direct measure of state-dependent network connectivity. Rats received AAV5-ChR (AAV5-CaMKIIa-ChR2(E123T/T159C)-eYFP) infections targeting CAMKII neurons in the OB, LEC or BLA, and were implanted with an optotrode into the anterior or posterior PCX. EMG was recorded in some animals from the nuchal muscle. Infected fibers were stimulated with 1ms flashes (473nm, 5-15mW), once every 20 sec and evoked potentials and/or single-unit activity monitored. Evoked potentials were measured on the initial slope to avoid polysynaptic contributions to the response, including those induced by antidromic effects. NREM sleep was associated with an enhancement of LEC->pPCX synaptic strength. Switches to either REM or waking were associated with reduced LEC->pPCX synaptic strength. Systemic ACh muscarinic receptor antagonist scopolamine significantly reduced this state-dependent change, largely by enhancing responses during waking, thus reducing the difference between NREM and fast-wave states. Similar results were observed for BLA->PCX evoked responses. In contrast to these top-down inputs to layer Ib/III, input from the OB to layer Ia, showed state-dependent changes which were in the opposite direction. Thus, during slow-wave activity, OB afferent synapses depressed compared to waking. The results suggest that during periods of low ACh, such as NREM sleep, inter-cortical association fibers are released from pre-synaptic inhibition, effectively enhancing the influence of top-down inputs on PCX activity, while at the same time input from the OB is reduced. During periods of high ACh, such as waking and especially during arousal or alertness, the efficacy of these top-down inputs is diminished, shifting the cortical driver towards the OB.

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**Presentation Number: ***361.09

**Topic: ***D.05. Olfaction and Taste

Title: Mental whisking - Concurrent respiratory phase shapes Human task performance and its neural underpinning

Authors: *O. PERL, A. EISEN, T. WEISS, T. SOROKA, S. LUBLINSKY, L. SECUNDO, N. SOBEL
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Terrestrial mammals rely on chemosensory sampling through rhythmic nasal inhalation, namely sniffing. Olfaction, however, is not the only sense orchestrated by the respiratory cycle, and respiratory phase-locking of diverse active sensing mechanisms is common across species. We set out to ask whether respiratory phase impacts human cognition. We measured nasal airflow during a lexical decision task (n=18, 7F). We observed that individuals had their own highly consistent pattern of phase-locking nasal respiration to task performance, such that mentation was always either at inhale or exhale within an individual (ANOVA intra-subject corr. Fisher-corrected: ISI vs Preparation vs Task: $F(2,34)=10.7$, $p<0.001$).
To probe this implicit respiratory preference we designed two follow-up experiments using EEG-ERP (n=16, 5F) and event-related fMRI (n=22, 8F). Unbeknownst to participants, we used their respiratory trace to trigger trials phase-locked to either inhale or exhale onset. In addition to the lexical decision task we applied a spatial task in the EEG experiment and a face-memory task in the fMRI experiment.
Using fMRI, a VOI analysis applied to trials presented during inhale and exhale revealed a significant increase in BOLD signal associated with nasal inhalation in the left IFG, left thalamus and putamen (ANOVA on BOLD AUC: VOI x Respiration: $F(8,192)=3.89$, $p<0.001$).
Preliminary results from EEG-ERP indicate that significantly better performance during inhale in the spatial task (accuracy: IN=77.9±6.2, EX=74.3±4.9, paired t-test ($t(15)=2.22$, $p<0.05$) was associated with decreased amplitude in a frontal N1 component (amplitude: post-hoc ANOVA A+F cluster IN=-2.55μV±3.3, EX=-4.25μV±3.7, paired t-test $t(14)=-2.6$, $p<0.05$).
Taken together, our results suggest that human cognition is impacted by respiratory phase, and that inhalation may be associated with improved acquisition and processing of information.

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**Topic: ***D.05. Olfaction and Taste

Support: NIH 2T32HL007909-17

Title: Sleep-deprivation enhances processing of food odors in olfactory cortex

Authors: *S. BHUTANI, J. D. HOWARD, J. A. GOTTFRIED, T. KAHNT
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Abstract: Excessive caloric intake and weight gain have been associated with reduced sleep (<6 h/night) in controlled experimental trials as well as large population-based studies. This enhanced food intake has been linked to alteration of appetite-regulating hormones. However, the central brain mechanisms mediating sleep-related increases in food craving and intake have remained unclear. Here we tested the hypothesis that sleep-deprivation alters the neural processing of food odors in olfactory cortex. We report preliminary data (N=14) from a counterbalanced crossover olfactory fMRI experiment in healthy weight humans. After 1-week of sleep stabilization (7-9h sleep/night), participants were randomly assigned to a night of non-deprived sleep (ND, sleep from 11:00 pm to 7:00 am) or deprived sleep (DS, sleep from 1:00 am to 5:00 am). Each subject completed both conditions, and the two sessions were separated by a 4-week washout. Participants' sleep and wakeup times were verified using a wrist actigraph. Caloric intake was controlled for all participants on both days of the experiment. On the evening following the night of sleep manipulation, participants were scanned while they rated the pleasantness and intensity of calorie-dense sweet and savory food odors and non-food control odors. We used searchlight-based multi-voxel pattern analysis (MVPA) to identify brain regions encoding food vs non-food odors in each of the two sleep conditions. No differences in food odor ratings for pleasantness and intensity were observed between the SD and ND condition. However, in the imaging data, decoding of food vs non-food odors in the posterior piriform cortex was enhanced in SD compared to the ND condition. These preliminary results suggest that sleep deprivation enhances processing of food stimuli in early olfactory regions.

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Nanosymposium

362. Cerebellum: Circuitry to Function

Location: 144A

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**Presentation Number: ***362.01

**Topic: ***E.02. Cerebellum

Support: NIH Grant U54HD090257

Title: Adaptive cerebellar learning deficits and abnormal *In vivo* Purkinje cell physiology in a mouse model of premature birth injury

Authors: *A. SATHYANESAN, S. KUNDU, V. GALLO
Ctr. for Neurosci. Res., Children's Natl. Med. Ctr., Washington, DC

Abstract: Premature infants born earlier than 32 weeks with very low birth weight (<1500 g) are highly vulnerable to developmental delay in locomotor function. Perinatal insults such as hypoxia (low O_2) affect the developmental program of specific neuronal populations resulting in defined behavioral deficits. It has only recently been recognized that the developing cerebellum is especially vulnerable to neonatal injury, since the third trimester is a period of rapid growth and expansion of the cerebellar cortex. In a chronic perinatal hypoxia (Hx) mouse model of premature brain injury, we recently demonstrated the presence of cellular and physiological changes in the cerebellar white matter. We also observed an Hx-induced delay in Purkinje cell (PC) dendritic arborization. However, the behavioral consequences of Hx-induced disruption in PC development and associated physiological abnormalities have not been systematically determined. Using an automated behavioral system - the Erasmus Ladder - to comprehensively probe cerebellar behavior, we report the presence of locomotor malperformance and long-term adaptive cerebellar learning deficits in Hx mice. Juvenile (P25) Hx mice commit a dramatically higher percentage of missteps on the horizontally-oriented Erasmus Ladder compared to age-matched normoxia (Nx) controls. Importantly, in an adaptive, conditioned-learning, cerebellar-dependent task on the Erasmus Ladder, juvenile Hx mice show increased steptimes to avoid an obstacle (unconditioned stimulus; US) paired with a preceding warning tone (conditioning stimulus; CS). Adaptive cerebellar learning deficits persist in naïve adult Hx mice. Locomotor stepping pattern analysis shows a differential change in percentage of short-steps between Hx and Nx mice across age groups. Next, to identify potential pathophysiological features of PC firing in Hx mice underlying abnormal cerebellar behavior, we used *in vivo* optogenetics and multielectrode array recordings. Our results indicate a profound reduction in spontaneous and optostimulated PC firing frequency as well as deficits in regularity and rhythmicity of spontaneous PC firing (altered CV and CV2) in juvenile Hx mice. Finally, treatment with a GABA-reuptake inhibitor partially rescues Hx-induced deficits in locomotor performance and improves some aspects of PC firing. Our results demonstrate a long-term miscoordination

phenotype characterized by locomotor malperformance and adaptive cerebellar learning deficits in a mouse model of premature brain injury. Our findings also implicate the developmental GABA system as a potential therapeutic target for prematurity-related locomotor deficits.

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Nanosymposium

362. Cerebellum: Circuitry to Function

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**Topic: ***E.02. Cerebellum

Support: JSPS 2543007
JSPS 26120005
JSPS 16K12476

Title: Neural evidence of the cerebellum as a state predictor

Authors: *H. TANAKA[1], T. ISHIKAWA[2], S. KAKEI[3]
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Abstract: We here provide neural evidence that the cerebellar circuit can predict future inputs from present outputs, a hallmark of an internal forward model. Evidence from clinical observations and psychophysical experiments indicates that impairments of the cerebellum lead to motor ataxia characterized by incoordination and dysmetria in multi-joint movements. Still, the precise mechanisms by which the cerebellum coordinates body movements are not yet understood. Recent computational studies hypothesize that the cerebellum performs state prediction known as a forward model. We analyzed firing rates of 94 mossy fibers (inputs to the cerebellar cortex), 83 Purkinje cells (output from the cerebellar cortex to dentate nucleus), and 73 dentate nucleus cells (cerebellar output), all recorded from a monkey performing step-tracking movements of the right wrist. Consistent with the feedforward anatomical structure of the cerebellum we were able to reconstruct the firing rates of one population as a weighted linear sum of those of preceding populations. Given that the Purkinje cells receive projections from the mossy fibers (via granule cells and interneurons), the firing rates of Purkinje cells were well reconstructed as a weighted linear sum of those of mossy fibers. Similarly, given that the dentate cells receive projections from the mossy fibers and the Purkinje cells, the firing rates of dentate cells were well reconstructed from those of mossy fibers and Purkinje cells.
To test the forward-model hypothesis, we then investigated if the current outputs of the

cerebellum (dentate cells) could predict the future inputs of the cerebellum (mossy fibers). We found that the firing rates of mossy fibers at time $t+t_1$ were well reconstructed from a weighted sum of firing rates of dentate cells at time t, thereby proving that the dentate activities contained predictive information about the future inputs. The average goodness-of-fit (R^2) decreased moderately from 0.89 to 0.86 when t_1 was increased from 20 to 100 ms, hence indicating that the prediction was able to compensate the latency of sensory feedback. The linear equations derived from the firing rates resembled those of a predictor known as Kalman filter composed of prediction and filtering steps. In the prediction step, a next state is predicted from a current estimate by a state equation, and in the filtering step, the prediction is corrected by a measurement. This analogy leads to a speculation that the Purkinje and the dentate cells perform the prediction and the filtering steps, respectively. In summary, our analysis of cerebellar activities supports the forward-model hypothesis of the cerebellum.

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362. Cerebellum: Circuitry to Function

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**Topic: ***E.02. Cerebellum

Support: NMRC/CBRG/0075/2014

Title: Diverging projection patterns of glutamatergic neuron in the interposed anterior nucleus

Authors: *A. Y. LOW[1], J. KIM[3], G. J. AUGUSTINE[4], A. I. CHEN[2]
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Abstract: The deep cerebellar nuclei (DCN) represent the major output channel of the cerebellum, but how they transmit integrated sensory and motor signals to the various brain regions is not clear. Therodent, DCN consist of the lateral, interposed and medial nuclei, and each nucleus provides a source of input in the cerebellar cortex and extra-cerebellar regions. To date, only six neuronal subpopulations have been identified in the DCN comprising of glutamatergic, GABAergic and/or glycinergic interneurons and projection neurons. Apart from nucleocortical neurons and neurons that project to the vestibular nuclei, the molecular identity and neurotransmitter profile of neurons connecting the DCN to cerebral targets are not well-defined. Additionally, details of the exact target regions and topographical organization are lacking because of the challenges to study DCN neurons as isolated subpopulations. To define

the connectivity of neurons in the DCN, we used a combination of genetic, molecular and viral tracing strategies to examine a subset of genetically tractable neurons in the mouse interposed anterior nucleus (IntA). We show that IntA neurons gives rise to mossy fibers in the cerebellar cortex, and divergentprojections to distinct subregions of the red nucleus and thalamus. Tract tracing analysis also indicates different subpopulations of neurons in the IntA differentially project to ascending targets. Furthermore, molecular and electrophysiological profiling indicate the subpopulation of IntA neurons are glutamatergic. Together, our findings describe the neurotransmitter properties and anatomical organization of a novel subpopulation of glutamatergic DCN neurons.

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362. Cerebellum: Circuitry to Function

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**Topic: ***E.02. Cerebellum

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Title: Glutamatergic projection neutrons of the Interposed anterior nucleus facilitate accurate of skilled reaching

Authors: *A. R. THANAWALLA[1], A. CHEN[2]
[1]Sch. of biological Sci., [2]Nanyang Technological Univ., Singapore, Singapore

Abstract: The deep cerebellar nuclei are an important output channel relaying processed information in the cerebellum to extracerebellar target regions. Neurons of the cerebellar nuclei represent a site of convergence within the cerebellum and play a specific role in control over motor behavior. To characterize the role of the cerebellum in mediating motor function, we specifically target glutamatergic neurons in the interposed anterior nucleus for chemical genetic ablation. We use virally expressed diphtheria toxin receptor and subsequent administration of diphtheria toxin to selectively ablate IntA neurons. Mice lacking Int A glutamatergic neurons are deficient in a task of skilled reaching while general motor ability is left intact. Mice are specifically deficient in their ability to accurately reach towards a food reward while other aspects of prehension; grasping and retrieving, are unaffected. Furthermore, the deficit in accuracy shows a tendency towards hypermetria. Together our results point to a specific role of Interposed anterior neurons in controlling the accuracy of goal directed arm movements.

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Title: The cerebellar double/triple representation hypothesis: An fMRI study using the Human Connectome Project dataset

Authors: ***X. GUELL**[1,2], J. D. E. GABRIELI[1], J. D. SCHMAHMANN[2]
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Abstract: There is a sizeable body of evidence indicating that the cerebellum is engaged in cognition and affect as well as motor control; however, the contribution of the cerebellum to such functions is incompletely understood. One central question is whether functional subregions exist in the cerebellum and, if so, how they are arranged. Double representation of motor activity in the cerebellum was described in classical electrical stimulation studies, and later confirmed by PET, fMRI and clinical studies. Tract tracing studies have demonstrated labeling of the cerebellum in two different locations after injecting viral tracers in both motor and nonmotor cerebral cortical areas; resting-state functional connectivity studies suggest that resting-state networks are represented two or possibly three times in the cerebellum; and volumetric studies of cerebellar grey matter in neuropsychiatric disorders seem to obey a similar distribution. We used data provided by the Human Connectome Project (n=787) to analyze cerebellar fMRI task activity (motor, working memory, language, social and emotion processing) and resting-state functional connectivity. The latter was calculated using cerebral cortical seeds corresponding to the peak Cohen's d of each task contrast. We observed a consistent pattern of double motor representation of both task-activity and seed-based resting-state functional connectivity (first = lobules IV/V/VI, second = lobule VIII). Further, within the nonmotor domains of cognition and affect, we observed a pattern of triple representation of both task-activity and seed-based resting-state functional connectivity (first = lobules VI/Crus I; second = lobules Crus II /VIIB; third = lobules IX/X). These findings are consistent with classical electrophysiology, tract tracing, grey

matter volumetric and resting-state networks studies. The observation that double/triple representation is consistent across multiple dimensions of cerebellar functional topography (i.e., task activity and seed-based resting-state functional connectivity) raises the possibility that other dimensions of cerebellar topography including anatomy, physiology and pathology obey a similar organizing principle. This hypothesis is consistent with current trends in neuroscience indicating a close relationship between task activity, functional connectivity and neural degeneration patterns. In this way, the double/triple representation hypothesis might be relevant for understanding not only cerebellar function, but also cerebellar structural and functional abnormalities in diseases such as autism, ADHD, dyslexia, depression and schizophrenia.

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Nanosymposium

362. Cerebellum: Circuitry to Function

Location: 144A

**Time: ***Monday, November 13, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***362.06

**Topic: ***E.02. Cerebellum

Support: NIH NIGMS P20 GM103446
UDRF grant 16A01402.

Title: The effect of split-belt treadmill training on functional connectivity within the cortico-thalamic-cerebellar network

Authors: *A. J. FARRENS[1], S. M. MORTON[2], J. E. GALGIANI[2], F. SERGI[1]
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Abstract: Stroke is a leading cause of disability that frequently results in gait asymmetry and impaired walking function. Split-belt treadmill training is a rehabilitation strategy that utilizes motor adaptation to induce change in an individual's gait pattern. Previous studies in stroke have shown that split-belt locomotor adaptation training results in short-term increases in gait symmetry and walking speed, making it a promising tool for post-stroke rehabilitation. However, there is considerable variability in individuals' responsiveness to split-belt therapy. Predictors of responsiveness may be identified by understanding the neural correlates of split-belt locomotor adaptation.
This pilot study investigated the neural correlates of split-belt locomotor adaption using resting state fMRI in three chronic stroke patients and two healthy controls. We hypothesized that locomotor adaptation would affect the resting state functional connectivity (rsFC) of the cortico-thalamic-cerebellar network of both the fast and slow legs (Fig. 1). Treadmill training had

participants walk on a split-belt treadmill that drove the non-dominant (or non-paretic) leg at twice the speed of the other leg, requiring subjects to adapt their inter- and intra-limb coordination. Adaptation was measured as the change between initial and end-session gait symmetry, calculated throughout training as the normalized difference between the fast and slow leg's respective step lengths. Resting state fMRI scans were performed immediately before (pre) and after (post) training.

ROI-ROI connectivity analysis showed an increase in rsFC after training between M1 and the Cerebellum, and between M1 and the Thalamus in both leg networks. Unexpectedly, split-belt training decreased M1 interhemispheric connectivity, a result previously seen in unilateral motor learning studies. Initial CL Thalamus to IL Cerebellum rsFC was also found to be anti-correlated with adaptation rate ($r = -0.76$, $p=0.13$), consistent with previous findings that less synchronization between these regions may increase ability to adapt.

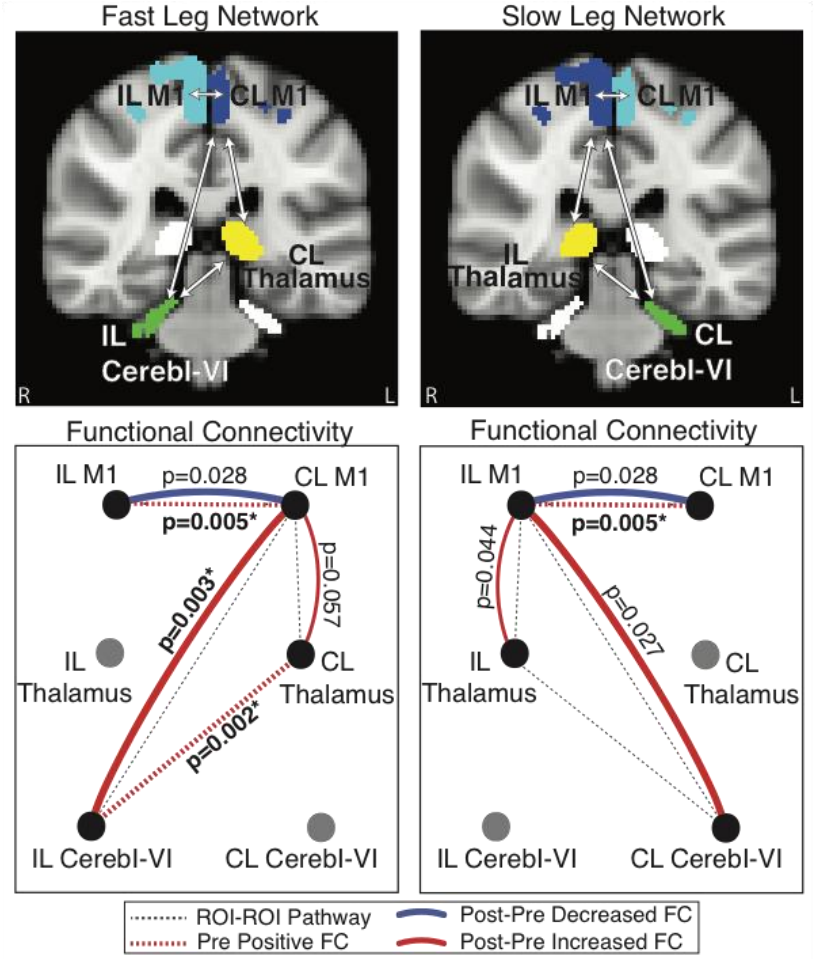

Figure 1: Top: Fast and slow leg cortico-thalamic-cerebellar networks. CL and IL defined by the leg on the fast belt. M1 ROI: Jeulich atlas BA4a and BA4p. Thalamus ROI: Harvard Atlas. Cerebellum ROI: FSL Cerebellum 1-6. Bottom: ROI-ROI Pre FC and ΔFC after training. Reported p-values are uncorrected, starred p-values remained significant after Bonferroni correction was applied.

Disclosures: **A.J. Farrens:** None. **S.M. Morton:** None. **J.E. Galgiani:** None. **F. Sergi:** None.

Nanosymposium

362. Cerebellum: Circuitry to Function

Location: 144A

**Time: ***Monday, November 13, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***362.07

**Topic: ***E.02. Cerebellum

Support: Grants-in-Aid for Young Scientists (B) (16k21649)

Title: Tandem internal model predicts two types of cerebellar patients

Authors: *T. HONDA
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Abstract: Information represented as internal models is stored in the brain in advance, so that we precisely control our movements without visual feedback information. There are two hypotheses of Internal models: the forward model representing where to move and the inverse model representing how to move. I have experimentally explored hand-reaching movements while wearing a prism plate causing the image to be deviated rightward. When the healthy subjects repeated alternation between 10 trials in offline feedback mode when they were allowed to see the target and their finger after each blindfolded attempt to touch the target, and 5 trials in non-feedback mode when they were not allowed to see the target and their finger after each blindfolded attempt to touch it, up to 210 trials, they rapidly became able to touch the target in offline feedback mode correctly (fast adaptation), whereas they spent many more trials to correctly touch the target in non-feedback mode (slow adaptation). These observations suggest that two types of adaptation, fast and slow, represent different internal model mechanisms of prism adaptation in the cerebellum. What is the relationship between fast/slow adaptations and forward/inverse models? I built a tandem system of forward and inverse models. As a result, I formulated and simplified the system. This experimental formulation shows that the forward model is quickly updating with trials, whereas the inverse model is gradually updating with trials. In the case that the inverse model is not able to update, the formulation also predicts that the slow adaptation will disappear, whereas the fast adaptation will appear. This lets us know that the forward model compensates for the inverse model. On the other hand, in the case that the forward model is not able to update, the formulation predicts that both the fast and slow adaptations will disappear. This shows that the inverse model does not compensate for the forward model. Therefore, it is possible to predict that there are three types in the distribution: (i) both the fast and slow adaptations appear in healthy subjects, (ii) the fast adaptation appears and the slow adaptation disappears in some cerebellar patients whose inverse models are impaired, (iii) both fast and slow adaptations disappear in the other cerebellar patients whose forward model are impaired. It is suggested that precise motor controls are achieved by the forward and

inverse models stored in the cerebellum. The formulation will contribute to provide rehabilitation conforming to cerebellar patients.

Disclosures: T. Honda: None.

Nanosymposium

363. Corticolimbic Circuits in Emotion and Psychiatric Disorders

Location: 150A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***363.01

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: MEXT 24116005
AMED

Title: Immunohistochemical analyses of paraventricular thalamic nucleus in human postmortem brains

Authors: *M. KUBOTA-SAKASHITA[1], N. MECHAWAR[2], T. SHIMOGORI[3], G. TURECKI[4], T. KATO[1]
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Abstract: The paraventricular thalamic nucleus (PVT) is a part of epithalamus and receives afferents from serotonergic neurons and hypothalamic CRH neurons. PVT sends output to amygdala, nucleus accumbens, and anterior cingulate cortex. These connections suggest the role in mood disorders including depression and bipolar disorder. Based on clinical evidence that patients with mitochondrial diseases frequently accompany mood disorders, we generated transgenic mice of mutant Polg (mitochondrial DNA polymerase) with CAMKIIα promoter (mPolg Tg mice) and found that the mice show depression-like episodes satisfying the DSM-5 criteria of major depressive episode. Escitalopram reduced the frequency of the depression like episodes. The mice showed hyperphagia and hypersomnia during the episodes, showed manic-like symptoms in response to a tricyclic antidepressant, and showed increased episodes after lithium withdrawal, suggesting that the phenotypes of the mice resemble bipolar depression. mtDNA deletions were most accumulated in paraventricular thalamic nucleus (PVT) in the Tg mice. The cells lacking COX (cytochrome c oxidase) (COX negative cells), carrying high level of mtDNA deletion, are accumulated in the PVT of the Tg mice. We generated the mice in which synaptic transmission of PVT neurons were inhibited by tetanus toxin expression using injection of AAV expressing Cre into PVT. The mice expressing tetanus toxin in PVT showed significantly higher number of depression-like episodes than controls. We also examined two

cases with a mitochondrial disease and mood symptoms and found that COX negative cells are accumulated in paraventricular thalamus (Kasahara et al, 2016). These findings implicate that PVT plays a role in mood regulation and is a strong candidate brain region of recurrent mood disorders. To search for whether some of patients with bipolar disorder or recurrent depression have pathology in PVT, it is crucial to identify the location of PVT in human postmortem brains. A previous study showed that immunostaining by anti-calretinin can delineate the PVT (Uroz et al. Synapse 2004). We performed anti-calretinin immunostaining or in situ hybridization of CALB2 or other candidate genes in mice, marmoset, and human brains to delineate the PVT in the human brain.

Disclosures: M. Kubota-Sakashita: None. **N. Mechawar:** None. **T. Shimogori:** None. **G. Turecki:** None. **T. Kato:** None.

Nanosymposium

363. Corticolimbic Circuits in Emotion and Psychiatric Disorders

Location: 150A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***363.02

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Reliability of reward processing and prediction error neural correlates in young ages

Authors: *H. KEREN[1], G. CHEN[2], B. BENSON[3], M. ERNST[4], E. LEIBENLUFT[5], N. A. FOX[6], D. S. PINE[3], A. STRINGARIS[1]
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Abstract: Reward processing is key for our interaction with the environment, affecting mood and behavior and its alterations are thought to underlie depression. An important component of reward processing is the prediction error (PE) - the difference between the expected value and the outcome, which is the basis of reinforcement models. PE is represented by phasic firing of dopaminergic neurons, and its encoding appears to be changed in the brain of those with depression. However, an important question remains unanswered: whether the encoding of the PE signal is stable across time. Answering this question is important because a stably encoded PE could prove a valuable parameter for assessing reward processing alterations in mood disorders. Moreover, it concerns the study of changes in PE during adolescent development, the

time of maximum incidence of depression, yet with no understanding of PE encoding in that age group.To answer these questions, we analyzed the reliability of prediction error activations in a modified child-friendly monetary-incentive-delay task, the Pinata. PE was defined as: PE=R-EV*S, R being the outcome value, EV the expected value (presented to the subject by a preceding cue) and S - the success rate of receiving the reward - here 66%. In this paradigm, positive reward values are either won or lost, hence negative PEs are more pronounced (absolute sum of possible negative PEs is ~32% larger). Subjects performed the task during fMRI scanning, being 10 years old at Visit 1. We used both a short 3 months ($Visit_{1,2}$) and a long 3 years ($Visit_{1,3}$) test-retest time intervals. We estimated the Intraclass Correlation Coefficient (ICC) and assessed reliability of behavioral findings and then quantified the whole brain level reliability of PEs neural representation, as well as of the underlying anticipation and feedback phases activations.Behaviorally, reaction times were found to be reliable across all time points ($ICC_{1,2}$=0.84, $ICC_{1,3}$=0.75). We show that PE modulation is most reliable at the insula ($ICC_{1,2}$ =0.8, $ICC_{1,3}$=0.82), while striatal regions did not encode stably PEs across time. Reliability of activity during anticipation and feedback phases, was highly reliable in striatal regions, across all three time points ($ICC_{1,2,3}$=0.74, $ICC_{1,2,3}$=0.89 respectively). Overall, PE signal is stable across time in children and into adolescence. Encoding in the insula is consistent with previous studies of negative outcomes activation, also supporting the separate encoding of positive versus negative outcomes. A stable PE is encouraging to its usage as an output parameter in longitudinal, including treatment trials, as well as being a treatment target in its own right.

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Nanosymposium

363. Corticolimbic Circuits in Emotion and Psychiatric Disorders

Location: 150A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***363.03

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Hypothalamic pituitary adrenal axis genetic polymorphism & limbic functional connectivity patterns in depression

Authors: *K. D. SUDHEIMER[1], J. KELLER[2], R. O'HARA[2], N. HANTKE[2], R. KARNA[2], D. DUVIO[2], S. BEAUDREAU[2], E. HEINEMEYER[2], G. MURPHY[2], R. GOMEZ[3], A. GARRETT[4], L. TENNAKOON[2], A. SCHATZBERG[2]
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Abstract: Dysregulation of limbic brain networks and dysregulation of the HPA-axis are both considered likely contributing factors to the development and maintenance of emotional symptoms in depression. This study used resting state functional connectivity patterns to characterize limbic connectivity patterns. It also used an array of naturally occurring single nucleotide polymorphisms (SNPs) of HPA-axis genes (corticotropin releasing hormone, corticotropin releasing hormone receptors 1 & 2, glucocorticoid receptor, and mineralcorticoid receptor), age, gender, and severity of depressive symptoms to predict patterns of resting state limbic functional connectivity.
We characterized the limbic functional connectivity patterns in a study sample comprised of healthy participants (N=41), depressed patients without psychotic symptoms (N=45), and depressed patients with psychotic symptoms (N=27). We analyzed whole-brain connectivity patterns of 33 limbic brain regions for each participant using a modified seed-based approach. The modification of the seed-based approach involved the use of a hierarchical clustering algorithm to detect the largest (in terms of voxels), homogenous time courses within each of the 33 limbic brain regions. We then constructed a series of simple regressions to test the whole-brain for the strength of the connectivity with each of these time courses. Next, we extracted the average connectivity value from each of the limbic brain regions for each of the regressions (33 regions of interest X 33 regressions = 1,089), yielding a limbic functional connectivity matrix. This limbic connectivity matrix was used to test for omnibus patterns of differences between groups via a single multivariate analysis of variance (MANOVA). We also investigated whether depressive symptoms, psychotic symptoms, age, and a variety of HPA-axis single nucleotide polymorphisms could be used to predict large-scale patterns of limbic connectivity. These analyses used step-wise regression models with Bonferroni correction for multiple comparisons. Significant differences between groups were detected using the omnibus test of limbic functional connectivity. These results were driven by a number of group differences in pairwise connectivity. Some of the largest group differences in limbic connectivity were between involved connectivity amongst BA25, brainstem, insula, uncus, parahippocampal gyrus, thalamus, amygdala, and the hypothalamus. Depressive symptoms, age, and a variety of HPA-axis SNPs were also able to predict large scale patterns of limbic connectivity with the subgenual cingulate (Brodmann Area 25), the putamen and the thalamus.

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Nanosymposium

363. Corticolimbic Circuits in Emotion and Psychiatric Disorders

Location: 150A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***363.04

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NARSAD YI Grant 25465

Title: Induced neuronal cells as a model system to study complex psychiatric disorder

Authors: *R. SRIVASTAVA[1], K. ISHIZUKA[2], A. SAWA[3]
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Abstract: Research on the major mental disorder like the Bipolar Disorder (BP) has been challenging due to their multifactorial etiology, which could include multiple genetic factors and possible interaction with the environmental factors. Utilization of patient-derived neuronal cells (like direct skin fibroblast conversion to neuronal cells, the induced neuronal (iN) cells) could serve as an important model system for understanding the molecular aspects of disorders at the cellular level at a scalable level. We have utilized iN model system to compare the calcium homeostasis in control versus BP patient samples including the rapid cyclers. Our results have indicated altered spontaneous and depolarization-evoked calcium transients in the BP iN cells. We further found correlations between calcium homeostasis data in iN cells and the clinical phenotypes in the BP group.

Disclosures: R. Srivastava: None. **K. ishizuka:** None. **A. Sawa:** None.

Nanosymposium

363. Corticolimbic Circuits in Emotion and Psychiatric Disorders

Location: 150A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***363.05

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH
HDRF
CIHR

Title: Sex-specific transcriptional signature in human depression

Authors: *B. LABONTÉ[1,2], O. ENGMAN[2], I. PURUSHOTHAMAN[2], C. MÉNARD[2], J. WANG[4], C. TAN[6], J. R. SCARPA[3], G. MOY[2], E. LOH[2], M. E. CAHILL[2], Z. S. LORSCH[2], P. J. HAMILTON[2], E. S. CALIPARI[2], G. E. HODES[7], O. ISSLER[2], H. KRONMAN[2], M. L. PFAU[2], A. OBRADOVIC[2], Y. DONG[5], R. L. NEVE[8], S. J. RUSSO[2], A. KAZARSKIS[3], C. A. TAMMINGA[9], N. MECHAWAR[10], G. TURECKI[10], B. ZHANG[3], L. SHEN[2], E. J. NESTLER[2]
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Abstract: Besides being 2-3 times more susceptible to major depressive disorder (MDD) than males, females also exhibit different symptomatic profiles, antidepressants responses, and biological adaptations to stress. These sex-specific differences are believed to be accompanied by different transcriptional signatures across brain regions. This study aims at defining the sex-specific transcriptional signatures and gene expression networks in the brain associated with MDD and characterizing their mechanistic implications. RNAseq was performed on brain regions from postmortem brains of humans with MDD and controls. Transcriptional profiles of NAc and PFC from male and female mice after chronic variable stress (CVS) were also analyzed. For both humans and mice, differential analysis was performed with voom Limma and gene expression networks were constructed and analyzed through weighted gene co-expression network analysis (WGCNA). Viral-mediated gene transfer in mice was used to assess the functional relevance of our findings. Males and females with MDD exhibit drastically distinct transcriptional signatures. Several hundreds of genes were differentially expressed across every brain region in depressed males and depressed females but with a strikingly small overlap, results that were also found in mice after CVS. We identified both common and divergent gene networks between depressed males and depressed females associated with a gain or loss of connectivity in MDD and enriched for differentially expressed genes in males or females. By virally manipulating genes within these networks, we induced stress susceptibility in a sex-specific fashion in mice. Viral knockdown of Dusp6 (downregulated in female MDD and stressed mice) in PFC increased stress susceptibility in females only. Consistent with Dusp6's action as an ERK phosphatase, we found higher levels of phospho-ERK, but not total ERK, in PFC of both females with MDD and female mice after CVS. IHC confirmed these findings in mice and showed that these effects are specific to a cell subpopulation in layer 5 of PFC. Dusp6 knockdown also increased the frequency but not amplitude of sEPCS in PFC of female but not male mice. RNAseq performed on PFC tissue after Dusp6 knockdown highlighted its impact on the gene network's structure and identified several potential gene targets interacting with Dusp6

to mediate its molecular, physiological, and behavioral effects. Our findings suggest that males and females with MDD show largely distinct transcriptional signatures in brain, which control the activity of molecular cascades and consequent behaviors in a sex-specific fashion.

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Nanosymposium

363. Corticolimbic Circuits in Emotion and Psychiatric Disorders

Location: 150A

Time: *Monday, November 13, 2017, 1:00 PM - 3:15 PM

Presentation Number: *363.06

Topic: *G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NARSAD Young Investigator Award (S.A.A.)
NSF Graduate Research Fellowship (J.R.P.)
NIH Grant P50 GM076547 (L.H.)

Title: Transcriptional regulatory network analysis reveals a role for POU3F2 in bipolar disorder and schizophrenia

Authors: *S. A. AMENT[1], J. R. PEARL[3,4], D. E. BERGEY[4], C. FUNK[4], B. BASU[4], L. HOOD[4], C. COLANTUONI[5,2], N. D. PRICE[4]
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Abstract: Genetic and genomic studies suggest that psychiatric disorders involve changes in brain gene regulation, but roles for specific transcription factors and regulatory elements remain largely uncharacterized. We reconstructed a transcriptional regulatory network (TRN) model for the human brain by integrating DNase-seq of 15 brain regions with gene co-expression between TF-gene pairs across 2,748 gene expression profiles from human brain tissue. Our model predicts 1,121,670 binding sites for 741 transcription factors (TFs), as well as 201,218 interactions linking these TFs to 11,093 target genes. We used our brain TRN model to predict master regulators of gene expression changes in the prefrontal cortex of schizophrenia (SCZ) and bipolar disorder (BD) cases vs. controls. We also annotated functional non-coding SNPs on risk

haplotypes for SCZ. We identified 19 TFs whose predicted target genes were consistently over-represented among differentially expressed genes across five independent cohorts. Notably, the gene encoding one of these 19 TFs, *POU3F2*, is located at a genome-wide significant risk locus for BD, and a second, *SREBF1*, is located at a risk locus for SCZ. We over-expressed POU3F2 in primary human neural stem cells to validate our network predictions and characterize its biological functions. POU3F2 over-expression repressed a SCZ- and BD-related transcriptional module that is highly expressed in an early subset of dividing neural stem cells in the developing brain, as well as in adult astrocytes. POU3F2 up-regulated a transcriptional module that emerges in newborn neurons and increases further in mature neurons of the adult cortex. In addition, we found that a BD- and SCZ-associated SNP in the promoter of *VRK2* disrupts a putative POU3F2 binding site and alters the activity of the *VRK2* promoter. These results provide convergent evidence that *POU3F2* influences BD- and SCZ-related gene expression through cis- and trans-acting mechanisms in the human brain.

Disclosures: S.A. Ament: None. **J.R. Pearl:** None. **D.E. Bergey:** None. **C. Funk:** None. **B. Basu:** None. **L. Hood:** None. **C. Colantuoni:** None. **N.D. Price:** None.

Nanosymposium

363. Corticolimbic Circuits in Emotion and Psychiatric Disorders

Location: 150A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***363.07

**Topic: ***I.05. Biomarker and Drug Discovery

Title: Molecular profiling in olfactory neurons at single-cell resolution: Neural markers associated with state changes in brain disorders

Authors: *K. ISHIZUKA, Y. CHUNG, Y. C. WU, N. GAMO, S. NARAYAN, J. LAVOIE, A. SAWA
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Abstract: “Precision Medicine” is a growing approach for detecting, treating, and managing disease based on patient-specific features. However, techniques that are sensitive and specific enough to robustly monitor pathophysiological dynamics associated with phenotypic “state” changes during the course of disease are still in their infancy. Monitoring “state” changes is especially challenging for diseases of the central nervous system (CNS) due to the lack of access to human brain tissue *in vivo*. Here, we demonstrate a novel, non-invasive system that can be used to track CNS disease-associated dynamic “state” changes in neurons.
In an effort to find tissues that may reflect changes in the brain, the olfactory epithelium (OE) has been proposed as a good candidate. The capacity of the OE to regenerate olfactory receptor

neurons allows us to conduct repeated biopsies over time. However, insufficient purity of neurons in biopsied tissue has been a problem. Thus, we first established the nasal punch biopsy coupled with laser-capture microdissection (LCM) to exclude submucosa and enrich neural layers from biopsied tissue. By using the LCM method, we detected molecular changes associated with lithium treatment in olfactory neurons obtained from patients with bipolar disorder. Specifically, mRNA levels of *GSK3β* were significantly higher in the patients at baseline (before lithium treatment) than in controls. The increased *GSK3β* levels were normalized after lithium treatment (Narayan et al, J Vis Exp, 2014). Encouraged by this promising data, we next optimized the nasal brush cell collection followed by single-cell analysis to further improve neural purity. This new platform is quick and non-invasive, and can be applied to children and unstable subjects. We found that about half of the cells collected by a nasal brush were mature olfactory neurons, indicating that the number of captured neurons was sufficient for downstream single-cell molecular profiling in an unbiased manner. Finally, we have established a protocol to detect protein levels of GSK3β and phosphorylated GSK3β at Ser9 in olfactory neurons at single-cell resolution.

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Nanosymposium

363. Corticolimbic Circuits in Emotion and Psychiatric Disorders

Location: 150A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***363.08

**Topic: ***I.05. Biomarker and Drug Discovery

Support: VA SPiRE l21 RX001731-01A1
Brain and Behavior Research Foundation NARSAD YIA
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NIH R01MH105461

Title: 1-norm support vector machine on single-trial EEG and ECG data to identify neural oscillatory features in the ketamine model for schizophrenia: Using your head and following your heart

Authors: X. YANG[1], A. PALMER[2], L. S. KEGELES[3], C. RODRIGUEZ[4], J. BI[2], J. K. JOHANNESEN[5], *C.-M. A. CHEN[1]

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Abstract: Objective: Ketamine provides a useful model for studying the physiopathology of schizophrenia as it induces and exacerbates schizophrenic symptoms in healthy individuals and patients, respectively. However, it remains unclear how ketamine affects neural oscillations across frequency bands and the extent to which changes in cortical firing are independent from ketamine's cardiovascular effects. The present study used 1-norm support vector machine (SVM) learning as a classification approach to determine sources of psychophysiological signal, considering both EEG and ECG, characterizing primary effects of ketamine administration. Methods: EEG and ECG recordings of 11 participants were collected before (saline) and after the ketamine (0.5 mg/kg) intravenous infusion. For each session, second-by-second single-trial amplitudes of EEG electrodes from frontal, central, and occipital regions of left and right hemispheres (i.e., F3, F4, C3, C4, O3, and O4) and those of the ECG electrode were extracted by Morlet wavelet decomposition (98 scales from 0.5 to 100 Hz) and subjected to the outlier analyses (a criterion of 2 SD). Single-trial amplitudes of 5 frequency features (i.e., delta: 0.5 - 4 Hz, theta: 4 - 8 Hz, alpha, 8 - 12 Hz, beta: 14 - 28 Hz, gamma: 30 - 58 Hz) were extracted from each time sample and electrode (numbers of single trails in the SVM models: left hemisphere in saline and ketamine sessions, mean (SE) = 300 (26) and 312 (19) trials per participant; right hemisphere, 293 (24) and 310 (20)). 1-norm SVM built classifiers of the two sessions (before and after ketamine) based on EEG and ECG alone and in combination. The C value in 1-norm SVM was optimized. By performing a 10-fold cross-validation for each C, the optimal C was chosen with the highest AUC. Results: The SVM models successfully differentiated two sessions based on single-trial EEG and ECG frequency features (F3 and ECG, AUC = 0.820; F4 and ECG, AUC = 0.860; C3 and ECG, AUC = 0.830; C4 and ECG, AUC = 0.865; O3 and ECG, AUC = 0.849; O4 and ECG, AUC = 0.828). Oscillatory activities of delta and beta frequency bands were consistently identified across SVM models. However, SVM models based on EEG (F3, AUC = 0.523; F4, AUC = 0.546; C3, AUC = 0.545; C4, AUC = 0.558; O3, AUC = 0.554; O4, AUC = 0.499) or ECG (AUC = 0.589), taken alone, performed only slightly above chance. Conclusion: 1-norm SVM models suggest that machine learning methods could successfully distinguish saline and ketamine sessions, but only when both EEG and ECG single-trial data were considered. Our findings show concurrent cardiac and brain effects of ketamine that may resemble alterations in the prodromal phase of schizophrenia.

Disclosures: X. Yang: None. **A. Palmer:** None. **L.S. Kegeles:** None. **C. Rodriguez:** None. **J. Bi:** None. **J.K. Johannesen:** None. **C.A. Chen:** None.

Nanosymposium

363. Corticolimbic Circuits in Emotion and Psychiatric Disorders

Location: 150A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***363.09

**Topic: ***I.05. Biomarker and Drug Discovery

Title: Waking the sleeping beauty: An improved high-throughput method for studying NMDAR receptors with sensitivity to stimulation with glutamate and glycine

Authors: *F. YEBOAH, H. GUO, M. E. DIGAN, H. NIU, Y. PAN, S. REILING, G. SOLER-LLAVINA, W. A. WEIHOFEN, H.-R. WANG, G. SHANKER, T. STAMS, L. M. CAMARGO, A. BILL
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Abstract: N-methyl-D-aspartate-receptors (NMDARs) are ionotropic glutamate receptors that function in synaptic transmission, plasticity and cognition. Malfunction of NMDARs has been implicated in a variety of nervous system disorders, including schizophrenia, epilepsy and pain, making them attractive therapeutic targets. NMDARs require membrane depolarization as well as binding of glycine/D-serine and glutamate for their activation. Overexpression of functional receptor in non-neuronal cells results in cell death by excitotoxicity, hindering the development of flexible, robust, and high throughput cell-based assays for NMDAR drug discovery. Here we report a novel, plate-based, high-throughput approach to study NMDAR function that overcomes many limitations of previously available approaches.
Our assay enables the functional study of NMDARs with different subunit composition after activation by glycine/D-serine or glutamate and hence presents the first plate-based, high throughput assay that allows for the measurement of NMDAR function in glycine/D-serine and/or glutamate sensitive modes. Our approach leverages the use of weak antagonists to mitigate cellular toxicity and – after antagonist wash out – to free up glycine/D-serine and glutamate binding sites. This allows to assay the effect of small molecule modulators on the activation of NMDARs at different concentrations or combinations of the co-ligands. The reported assay system faithfully replicates the pharmacology of the receptor in response to known agonists, antagonists, positive and negative allosteric modulators, as well as the receptor's sensitivity to magnesium and zinc. We believe that the ability to study the biology of NMDARs rapidly and in large scale screens will enable the identification of novel therapeutics whose discovery has otherwise been hindered by the limitations of existing cell based approaches.

Disclosures: F. Yeboah: None. **H. Guo:** None. **M.E. Digan:** None. **H. Niu:** None. **Y. Pan:** None. **S. Reiling:** None. **G. Soler-Llavina:** None. **W.A. Weihofen:** None. **H. Wang:** None. **G. Shanker:** None. **T. Stams:** None. **L.M. Camargo:** None. **A. Bill:** None.

Nanosymposium

364. Network, Synaptic, and Molecular Mechanisms of Learning and Memory

Location: 143A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***364.01

**Topic: ***H.01. Animal Cognition and Behavior

Support: HHMI
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Title: An *Aplysia* neurotrophin acts cooperatively in the pre- and postsynaptic neurons through both anterograde and retrograde signaling during the induction of learning-related intermediate-term facilitation

Authors: *I. JIN[1], H. UDO[2], H. ZHU[1], E. R. KANDEL[1], R. R. HAWKINS[1]
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Abstract: In most systems short-term plasticity is initiated on one side of the synapse but long-term plasticity involves changes on both sides. However, the extracellular signaling involved is not well understood. We have been investigating that question during the transition from short- to intermediate- and long-term facilitation produced by 5HT at *Aplysia* sensorimotor neuron synapses (Jin et al., Soc. Neurosci. Abstr. 2015, 2016). We have previously found that an *Aplysia* neurotrophin (ApNT) and its Trk receptors act through autocrine signaling to form a presynaptic positive feedback loop during the induction of ITF. In addition, ApNT acts through both anterograde and retrograde signaling to form a transynaptic feedback loop that may coordinate pre- and postsynaptic mechanisms of facilitation. We have now explored that idea in two additional ways. First, the postsynaptic neuron regulates protein synthesis in the presynaptic neuron during the induction of LTF (Wang et al., 2009). To examine whether that process first begins during ITF we performed quantitative immunocytochemistry on phospho-eukaryotic translation initiation factor 4E (p-eIF4E), the rate-limiting component of the eukaryotic translation apparatus, in isolated sensory neurons or sensorimotor neuron cocultures. Selective activation of ApTrk receptor signaling in the sensory neuron with the ApTrkmem/BB system produced a gradual increase in p-elF4E in that neuron over 30 min, consistent with positive feedback, and the increase was significantly greater in cocultures than in isolated sensory neurons. There were significant main effects of coculture ($p<0.01$), time ($p<0.001$), and the coculture x time interaction ($p<0.05$) in a two-way ANOVA. These results suggest that ApNT from the postsynaptic neuron may also play a role in regulation of protein synthesis in the presynaptic neuron during the induction of ITF. Second, activation of both pre- and postsynaptic kinases and protein synthesis is required for ITF of the eEPSP at these synapses (Jin et al., 2011). Similarly, activation of ApTrk receptor signaling in either the presynaptic or postsynaptic neuron alone enhanced mEPSC frequency ($p < 0.001$ and $p < 0.01$, respectively), but did not produce

facilitation in eEPSP ($p > 0.05$ for both). However, simultaneous activation of ApTrk receptor signaling in both the pre- and postsynaptic neurons produced facilitation of the eEPSP as well as mEPSC frequency ($p < 0.01$). Collectively, these results suggest that cooperative back and forth communication between the pre- and postsynaptic neurons by ApNT plays essential roles during the induction of learning-related intermediate-term facilitation in *Aplysia*.

Disclosures: I. Jin: None. **H. Udo:** None. **H. Zhu:** None. **E.R. Kandel:** None. **R.R. Hawkins:** None.

Nanosymposium

364. Network, Synaptic, and Molecular Mechanisms of Learning and Memory

Location: 143A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***364.02

**Topic: ***H.01. Animal Cognition and Behavior

Title: Ras is a memory suppressor affecting multiple types of consolidated memory in *Drosophila*

Authors: *N. NOYES
Neurosci., The Scripps Res. Inst., Jupiter, FL

Abstract: The requirement for Ras/ERK signaling in mammalian memory formation is well established. Surprisingly, we discovered that Ras activity acts as a memory suppressor in *Drosophila*. Knocking down Ras in the mushroom body, a brain structure necessary for olfactory memory, enhanced memory without affecting acquisition. Memory was reduced in flies expressing an ERK pathway-specific constitutively active mutant of Ras but not in flies expressing an AKT pathway-specific version. Our deeper analysis, which focused on the types of memory formed after olfactory conditioning, showed that Ras knockdown produced an enhancement of the protein synthesis-independent and anesthesia-resistant memory forms of memory but decreased protein synthesis-dependent memory. Overall, these results indicate that Ras acts as a memory suppressor in *Drosophila* with effects on specific types of memory. Memory suppressor genes, like Ras, offer unique insights into the constraints that the brain has on memory formation.

Disclosures: N. Noyes: None.

Nanosymposium

364. Network, Synaptic, and Molecular Mechanisms of Learning and Memory

Location: 143A

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**Presentation Number: ***364.03

**Topic: ***H.01. Animal Cognition and Behavior

Support: NINDS T32-NS061764 (JA)
NIH NIMH R01MH106623 (MJ)
NINDS P30 NS047243 (to FRJ)

Title: A novel role for APC in modulating the translation of mRNA's required for synaptic plasticity

Authors: *J. ALEXANDER[1], S.-X. JIN[2], L. A. FEIG[3], M. H. JACOB[4]
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Abstract: Intellectual disabilities (ID, IQ<70) occur in 2-3% of the general population. Treatments are lacking because these disorders are molecularly ill-defined. Recent advances suggest that the hundreds of ID-linked human genes converge on a few key biological processes in neurons that predispose to disease. Our studies focus on one of these- the β-catenin (β-cat), adenomatous polyposis coli (APC), canonical Wnt signal transduction pathway. We are elucidating how malfunction of this pathway alters the brain and thereby leads to cognitive impairments. β-cat functions in both cadherin synaptic adhesion complexes and canonical Wnt target gene expression; these pathways modulate synaptic density, maturation, and plasticity, and are essential for proper brain function. APC is the major negative regulator of β-cat in the canonical Wnt pathway. Additionally, APC is a large scaffold protein that is enriched at excitatory postsynaptic sites, and binds to multiple proteins, as well as selected mRNAs, implicated in synaptic maturation and plasticity. However, direct tests that malfunction of APC or β-cat can cause cognitive impairments, and knowledge of the underlying pathophysiological changes, are largely lacking. Our recent studies show that targeted deletion of APC (APC cKO) in neurons of the mouse brain leads to elevated levels of β-cat and Wnt target gene expression, altered synaptic density and function, and moderate cognitive deficits, relative to wild-type littermates (Mohn et al., 2014). To test the hypothesis that elevated β-cat is major cause of these phenotypes, we have created a new mouse model with targeted deletion of the degradation domain of β-cat, resulting in a stabilized protein product, even in the presence of APC. Our new β-cat conditional overexpressor mouse (β-cat cOE) displays elevated levels of β-cat and Wnt target genes in the brain, comparable to that of APC cKOs. However, β-cat cOEs exhibit more severe cognitive deficits, drastically reduced synaptic plasticity (both LTP and LTD), dramatic reductions in AMPAR and NMDAR receptor surface levels, and an unanticipated hyperphosphorylation of APC. ComparingAPC functions between APC cKOs with β-cat cOEs,

we find differential changes at the protein level, but not the mRNA level, of selected APC mRNA targets that function at synapses. APC targets that show altered levels, in opposite directions, in APC cKOs versus β-cat cOEs, include SynCAM, CDC42, and Fodrin. Our findings identify a novel role for APC, and its phosphorylation state, in modulating the expression levels of several proteins important for synaptic stability, plasticity and cognition.

Disclosures: J. Alexander: None. **S. Jin:** None. **L.A. Feig:** None. **M.H. Jacob:** None.

Nanosymposium

364. Network, Synaptic, and Molecular Mechanisms of Learning and Memory

Location: 143A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***364.04

**Topic: ***H.01. Animal Cognition and Behavior

Support: NIH Grant R01 MH109498 02
NIH Fellowship F32 MH107139 02S1

Title: Behavioral genetics reveals an unexpected role for channel palmitoylation in regulating learning

Authors: *J. C. NELSON, E. S. WITZE, K. C. MARSDEN, K. E. HAYER, M. GRANATO
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Habituation is a basic learning process disrupted in several neuropsychiatric disorders. To better understand this fundamental learning process, we conducted a forward genetic screen in the larval zebrafish (Wolman et al 2015, Neuron). Here we report on a mutant identified in this screen, which arises from a premature stop in the *hip14* (*Huntingtin-Interacting Protein 14*) gene. *Hip14* encodes a palmitoyl transferase best known in the context of *Huntingtin* mediated pathology. We find that restoration of *hip14* expression in the nervous system during development is sufficient to restore habituation learning, suggesting that *hip14* is required for the establishment of the relevant circuits. Moreover, we provide compelling evidence that *hip14* promotes habituation learning through a previously unidentified Hip14 substrate, the Shaker channel subunit Kcna1, and that like *hip14* mutants, *kcna1* mutants display deficits in habituation learning. Finally, whole brain neural activity mapping reveals changes in distinct brain areas of *hip14* mutants as they fail to habituate. Together, these results uncover an unexpected role for posttranslational modification in promoting habituation learning, and demonstrate that the Huntington's Disease associated *hip14* functions through *kcna1* to promote a fundamental form of learning *in vivo*.

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Nanosymposium

364. Network, Synaptic, and Molecular Mechanisms of Learning and Memory

Location: 143A

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Presentation Number: *364.05

Topic: *H.01. Animal Cognition and Behavior

Support: R37 NS019904-33
R01 NS052351-09

Title: Dopamine neurons mediate learning and forgetting through bidirectional modulation of output neuron synapses in *Drosophila*

Authors: ***J. A. BERRY**, R. L. DAVIS, Prof
The Scripps Res. Institute, Neurosci. Dept, Jupiter, FL

Abstract: Memory systems, faced with dynamic environments and finite memory resources, must be elegantly flexible, allowing not only efficient memory formation, but also the ability to forget, or update memories. Recent work from our lab and others, has demonstrated that dopamine neurons (DANs) are critical for both forming and removing memories. However, it remains unclear how dopamine, a single neurotransmitter, can bi-directionally affect behavior at the circuit level. Focusing on specific circuits important for both learning and forgetting, we present evidence that association of electric shock and odor causes a complete and immediate block of the learned odor's ability to drive downstream MB output neurons (ONs), previously shown to drive approach behavior in the fly. These data suggest that aversive memory is, in part, represented in the brain as a decreased approach drive. Intriguingly, after odor shock learning, subsequent shocks unpaired with learned odor, or paired with a counter odor, *re-potentiate* the initial learned odor's ability to drive ONs, essentially removing the learned associative plasticity. Furthermore, optogenetic activation of specific DANs with axon terminals localized to the ON dendrites, is sufficient to drive the paired depression, when coupled with an odor, and the subsequent un-paired re-potentiation. Thus our data indicates that aversive memories are likely stored and forgotten in the same memory circuit via bidirectional connectivity to memory output neurons. The directionality of the plasticity, whether a depressed functional connectivity during learning or a re-potentiated connectivity during forgetting, is dependent on odor pairing or un-pairing rules, respectively. These results help to reveal the rules of storing and removing information using a single neurotransmitter in a simple memory system.

Disclosures: **J.A. Berry:** None. **R.L. Davis:** None.

Nanosymposium

364. Network, Synaptic, and Molecular Mechanisms of Learning and Memory

Location: 143A

Time: *Monday, November 13, 2017, 1:00 PM - 3:00 PM

Presentation Number: *364.06

Topic: *H.01. Animal Cognition and Behavior

Support: HHMI

Title: Parallel memory units in the mushroom body

Authors: ***Y. ASO**, G. M. RUBIN
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Abstract: Sparse activity in the 2,000 Kenyon cells of the MB represents the identity of sensory stimuli. Along the parallel axonal fibers of Kenyon cells, we have shown that dopaminergic neurons and MB output neurons form 16 matched compartmental units. These anatomically defined units are also units of associative learning. Our latest optogenetic activation experiments demonstrate that individual dopaminergic neurons independently write and update memories in each unit with cell-type-specific rules. We find extensive differences in the rate of memory formation, decay dynamics, storage capacity and flexibility to learn new associations across different units. Thus individual memory units within the mushroom body store different information about the same learning event. To understand molecules and cell biological features that enable dopamine neurons to produce diverse forms and kinetics of synaptic plasticity in different compartments, we are analyzing gene expressions using RNAseq. the functions of four different dopamine receptors, putative co-transmitters of dopaminergic neurons and other known memory-related genes in distinct compartments.

Disclosures: **Y. Aso:** None. **G.M. Rubin:** None.

Nanosymposium

364. Network, Synaptic, and Molecular Mechanisms of Learning and Memory

Location: 143A

**Time: ***Monday, November 13, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***364.07

**Topic: ***H.01. Animal Cognition and Behavior

Title: Connectome-driven study of the associative learning circuit in *Drosophila* larva

Authors: *C. ESCHBACH[1], A. FUSHIKI[1], B. COCANOUGHER[1], B. AFONSO[1], G. SI[2], J. VALDES ALEMAN[1], M. GERSHOW[3], A. D. SAMUEL[2], J. TRUMAN[1], A. CARDONA[1], M. ZLATIC[1]
[1]Janelia Res. Campus, Ashburn, VA; [2]Harvard Univ., Cambridge, MA; [3]Dept of Physics, NYU, New York, NY

Abstract: For adaptive decisions to be made in an ever-changing environment, animals must be able to update expectations about stimulus valences, and implement the behavior accordingly. How is the predicted valence about a cue integrated with the innate circuits that drive the behavior towards this cue by default?
Associative memories in Drosophila are formed at the output synapses of the parallel Kenyon Cells of the Mushroom Body that signal conditioned stimuli (CS). The CS-driven memory signal is relayed by the Mushroom Body Output Neurons (MBONs), which encode it at population level to skew behavior towards e.g. attraction vs. aversion of the CS. Understanding how memory drives behavior thus requires characterizing the connection of MBONs population with the innate circuits.
We tackled this question in Drosophila larva, an animal with a smaller brain, allowing large-scale electron microscopy circuit mapping, but capable of learning and memory. Using optogenetic activation, we characterized which individual MBON biases the larval turning behavior, a reliable proxy for attraction or aversion. We found that MBONs inducing attraction are downstream of sites of aversive memory, and vice versa, suggesting synaptic depression as a result of associative learning, similar to adult Drosophila.
We then used EM reconstruction to identify “convergence neurons” downstream of MBONs that receive convergent inputs from MBONs and from Lateral Horn output neurons that drive innate attraction. Using optogenetic activation and inactivation we showed “convergence neurons” drive approach to increase in their activity and drive avoidance to a decrease in their activity. These neurons are excited by innately attractive odors via the Lateral Horn and by attraction-driving MBONs and they are inhibited by avoidance-driving MBONs. We found that aversive olfactory learning alters the balance of excitatory and inhibitory input onto convergence neurons and results in inhibition of the neuron by the CS+, which in turn drives avoidance. Our study identifies a crucial layer of neurons downstream of the MB that integrate learnt and innate

pathways and provides a detailed mechanistic understanding of the way in which innate attraction can be switched to learnt avoidance.

Disclosures: **C. Eschbach:** None. **A. Fushiki:** None. **B. Cocanougher:** None. **B. Afonso:** None. **G. Si:** None. **J. Valdes Aleman:** None. **M. Gershow:** None. **A.D. Samuel:** None. **J. Truman:** None. **A. Cardona:** None. **M. Zlatic:** None.

Nanosymposium

364. Network, Synaptic, and Molecular Mechanisms of Learning and Memory

Location: 143A

Time: *Monday, November 13, 2017, 1:00 PM - 3:00 PM

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Topic: *H.01. Animal Cognition and Behavior

Support: NIH Grant 1R15MH107892-01

Title: Transcriptional correlates of savings memory for long-term sensitization in *Aplysia* californica

Authors: L. PEREZ[1], U. PATEL[2], I. E. CALIN-JAGEMAN[1], *R. CALIN-JAGEMAN[3]
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Abstract: Most long-term memories fade, becoming progressively less likely to be recalled. Still, it can be easier to re-learn “forgotten” information, a phenomenon known as savings memory (Ebbinghaus, 1885). Even though savings memory occurs across the animal kingdom, the mechanisms mediating savings remain shrouded in mystery. Here we describe the first molecular correlates of savings memory using the long-term sensitization paradigm in the marine mollusk *Aplysia calinfornica*.
First, we confirmed savings memory in this paradigm. *Aplysia* received long-term sensitization training (a series of noxious shocks to one side of the body). This produced long-term sensitization memory, expressed as a long-lasting increase in reflex responsiveness on the side of training. One week after training, sensitization memory seemed to have faded, as reflex responsiveness had returned to within 1% of baseline. A weak reminder shock, however, revealed savings memory, producing a much stronger change in reflex duration on the previously trained side.
To identify the molecular correlates of savings memory we conducted microarray analysis on CNS samples harvested 1 and 7 days after training, time points associated with strong memory and apparent forgetting. We found over 1,000 strongly-regulated transcripts 1 day after training. One week later, most of these changes had relapsed to baseline. Notably, however, we identified a small set of transcripts which remain strongly regulated after apparent forgetting. We

confirmed several of these with pPCR in independent samples.
Our results show that transcriptional regulation persists beyond the decay of memory recall; these long-lasting molecular changes could play a role in active forgetting and/or the rapid re-expression of a memory that occurs during savings.

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Nanosymposium

365. Perception and Imagery: Visual Awareness

Location: 156

Time: *****Monday, November 13, 2017, 1:00 PM - 4:00 PM

Presentation Number: *****365.01

Topic: *****H.02. Human Cognition and Behavior

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Title: Human single unit activity in middle temporal and frontal lobes precedes the reported emergence of a visual percept

Authors: ***H. GELBARD-SAGIV**[1,2,5,6], L. MUDRIK[3,2,6], C. KOCH[7,6], I. FRIED[5,4]
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Abstract: Firing of neurons in the human medial temporal lobe (MTL) correlates with conscious perception during both flash suppression and backward masking tasks. However, their causal role in the processes that gives rise to conscious perception is unclear, as in these paradigms perception is externally manipulated rather than internally driven. Here we used binocular rivalry, where perceptual switches are internally driven, in nine epilepsy patients implanted with depth electrodes (for clinical purposes). Pairs of images that elicited selective responses in MTL neurons were presented binocularly, while patients reported the emergence and disappearance of each of the rivaling images. These reports were used to create a matched-duration replay condition, in which the perceptual switches were externally driven by an actual stimulus change. Comparing the instantaneous firing rate to baseline firing rate using a cluster-based permutation analysis, we found that about a half of MTL selective neurons (n=40) responded prior to the report of the emergence of their preferred image. Importantly, the neuronal response was significantly earlier when the emergence of the image was internally generated in the rivalry

condition (~1100ms; $p<0.001$) as compared to when it was externally driven in the replay condition (~450ms; $p<0.001$). Such a latency difference between rivalry and replay implies that MTL neurons might not merely reflect the content of consciousness, but could rather have an active role in the process that shapes it. In frontal areas, 30% of the neurons in anterior cingulate cortex (ACC; n=29) and pre supplementary motor area (preSMA; n=10) responded during rivalry but not during replay. This neuronal response started as early as 2000ms ($p<0.001$) before the report of the emergence of an image and significantly preceded MTL response, suggesting that these areas are involved in resolving perceptual conflicts during rivalry. Taken together, our findings suggest that internal changes in the content of perception may be induced by early activity in a cortical network that includes the ACC and preSMA. This early activity is followed by MTL activity that presumably leads to the perceptual change.

Disclosures: H. Gelbard-Sagiv: None. **L. Mudrik:** None. **C. Koch:** None. **I. Fried:** None.

Nanosymposium

365. Perception and Imagery: Visual Awareness

Location: 156

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**Presentation Number: ***365.02

**Topic: ***D.07. Vision

Support: Natural Science Foundation of China Grants S.K. (31571160)
Natural Social Science Foundation of China Grants to S.K. (15ZDB016)

Title: Effect of internal reference on angle perception: Computational models and human psychophysics

Authors: *Z.-X. XU[1,2], Y. CHEN[1,2], S.-G. KUAI[1,2]
[1]The Sch. of Psychology and Cognitive Sci., East China Normal Univ., Shanghai, China; [2]Key Lab. of Brain Functional Genomics, Ministry of Education, Shanghai Key Lab. of Brain Functional Genomics, Inst. of Cognitive Neurosci., Shanghai, China

Abstract: An angle is determined by two lines and the difference between them (angle size). Previous studies showed either the combination of two bounding lines or Weber's law of angle size failed to predict discrimination thresholds (Fig.1 A). Angle discrimination threshold is not a strictly increasing function of angle size but has several inflection points. To explain the phenomena, we proposed an internal reference frame (IRF) model, by which the visual system establishes an internal orthogonal reference frame to represent an angle feature (Fig.1 B). The model included three stages: 1) Orientation Encoding: encode orientations of two lines; 2) Axis Alignment: align one bounding line with its nearest coordinate axis; 3) Angle Calculation:

calculate an orientation difference between the other bounding line and its nearest axis. Our IRF model solved problems which earlier theories failed to do and fitted the data of previous two studies well (Fig.1 A). We further conducted a series of experiments to verify the necessity of three stages and explore the underlying mechanisms of IRF. We used a 2AFC paradigm with a staircase method to measure angle discrimination thresholds across conditions. We found that the discrimination thresholds varied when the same angle was tilted to different directions, suggesting orientation sensitivity of bounding lines contributes to angle perception. Second, participants' response time was longer when a bounding line was not aligned with coordinate axes, supporting the essential role of the alignment stage. Third, the discrimination thresholds increased as the bounding line was far from coordinate axes, supporting the third step in our model. Further, we found human IRF was altered when participants performed angle discrimination tasks in a tilted visual environment, suggesting IRF may gain from our visual experience of the natural world. We present for the first time a theory that the human visual system represents an angle feature in an internal orthogonal reference frame and provide empirical evidence to support the three-stage model in angle perception.

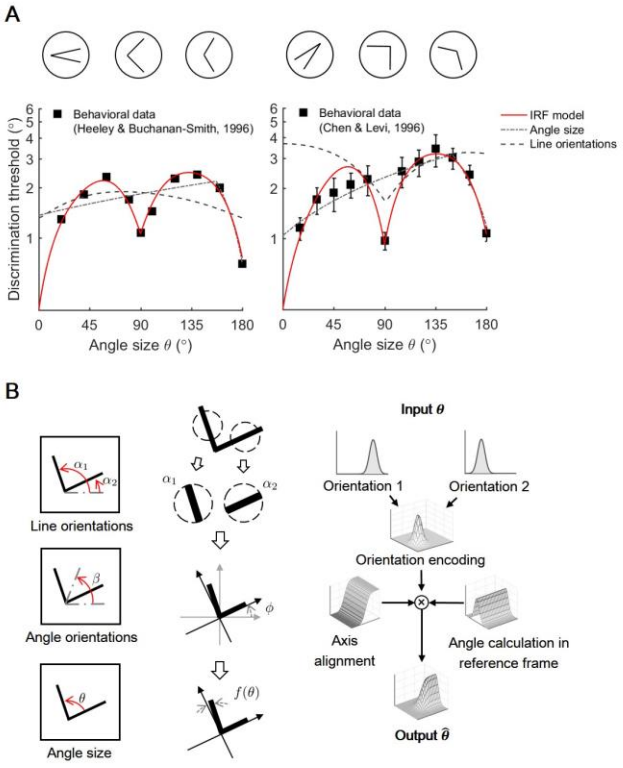

Figure 1. Internal Reference Frame Model and Data Fitting.

A. The Data of angle discrimination performance adapted from Heeley & Buchanan-Smith (1996), Chen & Levi (1996). The data were fitted by the IRF model, a combination of two bounding lines and Weber's law of angle size.

B. Three-stage model in angle perception: orientation encoding, axis alignment and angle calculation.

Disclosures: Z. Xu: None. **Y. Chen:** None. **S. Kuai:** None.

Nanosymposium

365. Perception and Imagery: Visual Awareness

Location: 156

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***365.03

**Topic: ***H.02. Human Cognition and Behavior

Support: Israel Science Foundation (ISF)

Title: The "eyes wide shut" illusion

Authors: *S. HOCHSTEIN
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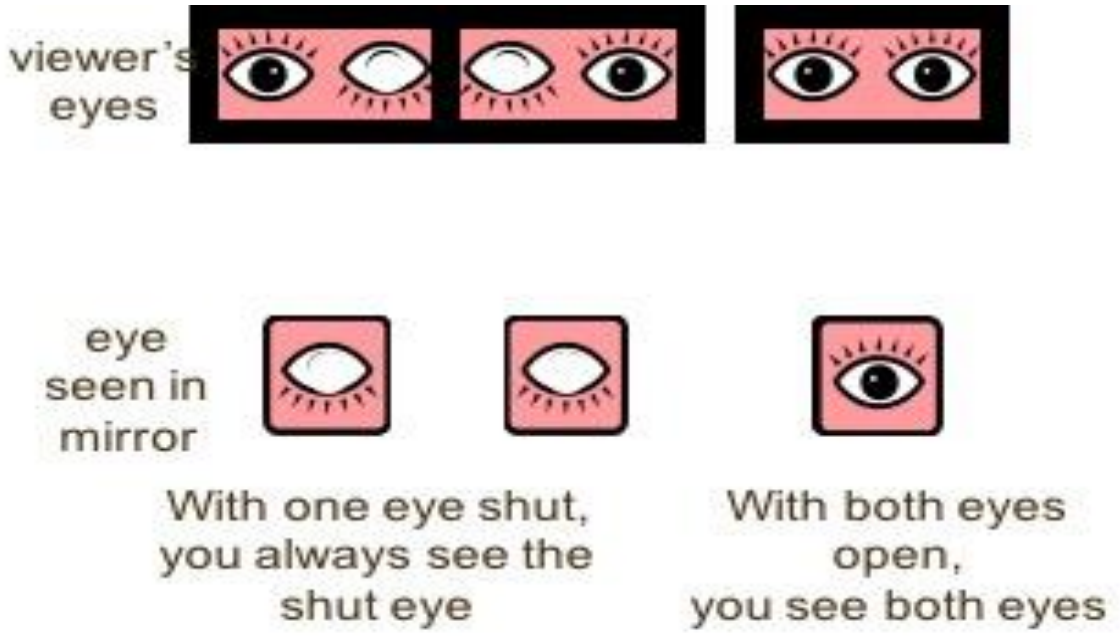
Abstract: Vision often needs to resolve interpretation ambiguities of incoming information, including ambiguous figures, ambiguous motions and ambiguous figure-ground segregations, as well as binocular differences leading to rivalry or integration. Rivalry produces relatively slow alternation between possible percepts and integration may disregard inconsistencies. The site and algorithm of disambiguating mechanism/s are under long-standing debate. Reverse Hierarchy Theory proposes implicit rapid hierarchical processing leading to early high-level representation of scene gist, followed by return to lower cortical areas retrieving details with scrutiny. We proposed a similar reverse hierarchy process for scene interpretation disambiguation: Initial perception is integrative, a "best-possible" high-level interpretation using relevant bottom-up information. Later perception selects among low-level processes avoiding logically incompatible integration. The Eyes Wide Shut illusion utilizes a standard enlarging (shaving/make up) mirror. Close one eye and look at the closed eye in the mirror; the eye should take up most of the mirror. Switch eyes. Surprisingly, you now see the other closed eye! Switch back-and-forth a few times, then open both eyes. You see an open eye. Which eye is it? To find out, close one eye. Whichever you close, that's the eye you see! How can this be possible? The eye seen with both eyes open has a hazy quality to it, due to the mirror curvature, but also to the core of the illusion: In fact, the brain is fusing two images of the two eyes! The illusion depends on: 1- Binocular fusion: the two eyes see different pictures, which the brain combines into a single percept; 2- Mirrors: do not affect appearance of left-right symmetric objects; 3- Symmetry: The eyes are sufficiently left-right symmetric for the brain to combine them; (with both eyes open, where is the nose?); 4- Reverse Hierarchy Theory: Our first conscious percept is a high-level conceptual representation allowing us to accept non-perfectly symmetric overlaid eyes as one symmetric eye.



Disclosures: **S. Hochstein:** A. Employment/Salary (full or part-time):; Hebrew University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Israel Science Foundation (ISF).

Nanosymposium

365. Perception and Imagery: Visual Awareness

Location: 156

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Presentation Number: *365.04

Topic: *H.02. Human Cognition and Behavior

Support: Supported by the Israel Science Foundation (ISF).

Title: Statistical averaging and deviant detection may share mechanisms

Authors: ***M. B. PAVLOVSKAYA**[1], N. SOROKER[2], Y. BONNEH[3], S. HOCHSTEIN[4]
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Abstract: Global scene properties are associated with early rapid gist perception, including set mean statistics and presence of an element with properties that strongly deviate from others (pop-

out). These scene features are associated with broad global attention and higher-level cortical processes, in contrast to slower processing of scene/object details requiring focused attention perhaps with lower-level neural elements. There is long-lasting interest in rapid parallel feature-search compared to slower serial-search and growing interest in set summary statistics, analyzing which properties can be averaged, and the relative precision of mean perception. We now ask if there is a relationship between these two rapid gist percepts, set mean discrimination and deviant detection? While most studies of pop-out used homogeneous backgrounds, we join the few using heterogeneous backgrounds to relate pop-out to set mean perception. We tested observers' mean orientation discrimination and deviant orientation pop-out detection using the same paradigm. They viewed two fields of dark bars of heterogeneous orientations, with one field either with a mean orientation rotated clockwise, or containing an orientation-deviant pop-out target. Variable parameters were field orientation variance and the orientation difference between the left and right field means or between the target and the field mean. We find that pop-out detection and mean orientation discrimination have similar dependences on background variance with strong correlation between them. In both cases, detection is reduced by 25% when variance is increased fourfold. Nevertheless, mean orientation comparison supports much larger orientation variance. Furthermore, we found that pop-out performance depends on target distance from the edge of the distribution. This shift reflects precise statistical mean computation and the ease of comparing means, even for large variance, versus pop-out dependence on target distance not from the mean but from the distribution edge. We conclude that pop-out detection is inherently related to set statistics perception: Only by knowing the mean and variance of a set can one know if an outlier is indeed a deviant, or just the cusp of the set.

Disclosures: **M.B. Pavlovskaya:** A. Employment/Salary (full or part-time):; Loewenstein Rehabilitation Hospital, Tel Aviv University. **N. Soroker:** A. Employment/Salary (full or part-time):; Loewenstein Rehabilitation Hospital. **Y. Bonneh:** A. Employment/Salary (full or part-time):; Bar-Ilan University. **S. Hochstein:** A. Employment/Salary (full or part-time):; Hebrew University.

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365. Perception and Imagery: Visual Awareness

Location: 156

Time: *****Monday, November 13, 2017, 1:00 PM - 4:00 PM

Presentation Number: *****365.05

Topic: *****H.02. Human Cognition and Behavior

Support: OGS
NSERC

Title: Efficient encoding of ensemble statistics in the visual periphery

Authors: *M. X. LOWE[1,2], J. RAJSIC[1], J. S. CANT[2], S. FERBER[1,3]
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Abstract: The human visual system constructs an efficient representation of the visual world by encoding similar items as a statistical summary. This ability is remarkably accurate, affording the opportunity to compensate for finite limitations in visual processing capacity. In contrast to detailed central vision, however, visual signals from the periphery are of much lower spatial resolution. How does the human visual system efficiently encode summary statistics in the face of these limitations in visual acuity? To understand the cognitive mechanisms underlying ensemble encoding, it is essential to explore the individual roles of central and peripheral vision in ensemble perception. Since the neural mechanisms underlying ensemble encoding have been shown to overlap with the neural substrates of scene recognition, this exploration could elucidate how we rapidly encode the visual world in only an instant. Here, we use traditional analyses combined with a Bayesian approach to investigate ensemble extraction in central and peripheral vision across seven experiments exploring multiple dimensions of ensemble encoding: perceptual biases, perceptual grouping, estimates of mean size, and estimates of mean orientation. Additionally, we explore whether ensemble encoding is weighted more heavily towards items in central or peripheral vision. Our findings reveal that ensemble statistics bias perception of individual object features equivalently in the fovea and periphery, that objects in the periphery and fovea contribute equally to ensemble statistics, and that ensemble information is encoded more accurately in the visual periphery despite limited access to local detail. Critically, this provides evidence that peripheral vision may afford greater efficacy for the extraction of ensemble information compared with central vision, consistent with research suggesting the visual periphery may be more useful for rapid scene recognition. Together, our results support a model of ensemble encoding wherein high-resolution information is not required to encode accurate summary statistics, and rapidly pooling information across low-resolution input may aid in the efficiency of encoding scene statistics. These findings contribute to our understanding of the neural substrates of scene recognition by suggesting a mechanism wherein peripheral information facilitates rapid scene understanding.

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365. Perception and Imagery: Visual Awareness

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**Topic: ***H.02. Human Cognition and Behavior

Support: IBS-R015-D1

Title: Neural representations of ensemble coding for visual features in the early visual and frontoparietal cortex

Authors: *K. TARK[1], M.-S. KANG[1,2], S. CHONG[4,5], W. SHIM[1,3]
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Abstract: The human brain is endowed with an ability to summarize properties of similar objects to efficiently represent a complex visual environment. Although previous behavioral studies have demonstrated that we can extract the mean orientation, size and speed from sets of items (Ariely, 2001; Chong & Treisman, 2003; Dakin & Watt, 1997; Watamaniuk & Duchon, 1992), the underlying neural mechanism remains poorly understood. Here, using fMRI and encoding methods, we examined whether the mean orientation is represented in population-level orientation tuning responses in early visual areas as well as high-level frontoparietal regions. On each trial, 30 small Gabor patches varying in orientation briefly appeared at random locations within an imaginary circle, and participants reported their mean orientation. Robust increases in mean BOLD responses were found during the task in parietal and dorsolateral prefrontal cortices including intraparietal sulcus (IPS), superior parietal lobule (SPL), and frontal eye fields (FEF). Crucially, in these regions as well as early retinotopic visual areas (V1/V2/V3), we found that population-level orientation tuning functions peak at the mean orientation and the tuning strength was progressively increased from early visual cortex to higher-order frontoparietal areas. To confirm that such tuning responses were derived from the representation of the mean orientation, rather than motor responses or stimulus differences associated with each mean orientation, we conducted a binary decision task for the mean orientation and a luminance averaging task using the same sets of stimuli. We found similar orientation-selective responses for each mean orientation in frontoparietal regions during the binary decision of the mean orientation, but not in the luminance averaging task, indicating that the tuning responses indeed reflect the statistical summary representation. Our findings suggest that higher-order frontoparietal regions as well as early visual cortex serve to extract summary statistics of visual stimuli.

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Nanosymposium

365. Perception and Imagery: Visual Awareness

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**Presentation Number: ***365.07

**Topic: ***H.02. Human Cognition and Behavior

Support: National Science Foundation Graduate Research Fellowship
NIH Shared Instrumentation Grant S10OD020039

Title: To bind or not to bind? Neural coding of color and shape

Authors: *J. TAYLOR[1], Y. XU[2]
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Abstract: How does the brain combine color and shape information into integrated percepts of whole objects? On the one hand, the existence of illusory conjunctions, slower visual search for feature conjunctions, and neuropsychological dissociations between color and shape processing suggest some independence between color and shape processing, therefore requiring a subsequent binding step. On the other hand, rapid feature conjunction detection with the flicker paradigm and the intermingling of color and shape selective neurons in early visual areas suggest that color and shape information may be integrated at early stages of visual processing, thereby dissolving this binding problem. Indeed, a previous fMRI MVPA study by Seymour et al. (2010) reported successful conjunction decoding in human early visual areas. To reconcile these two seemingly disparate sets of findings, as well as to examine the response properties of higher ventral object processing regions (LO and pFs) and a series of ventral stream color patches, we conducted an fMRI MVPA study using the methodology developed by Seymour et al. (2010). Specifically, we examined the decoding of color, shape, and their conjunction in a set of early visual and higher ventral visual areas. We presented participants with colored spirals that varied in color (red or green) and orientation (clockwise or counterclockwise). Progressing up the ventral visual hierarchy, nearly every region we examined contained both color and shape information, including early visual areas V1 to V4, LO, pFs and posterior color patches. However, one ventral region we examined, a set of mid-temporal color patches, appeared to code for color but not shape. This may account for the existence of pure forms of achromatopsia. Meanwhile, consistent with the early-binding theory, we also found that color and shape were coded in a conjoined fashion in early visual cortex, but not in later object processing regions despite the presence of color and shape representations in these regions. Overall, these findings indicate an early binding of color and shape as well as a separation of these two types of features during later stages of visual processing.

Seymour, K., Clifford, C. W., Logothetis, N. K., & Bartels, A. (2010). Coding and binding of color and form in visual cortex. *Cerebral cortex*, *20*(8), 1946-1954.

Disclosures: **J. Taylor:** None. **Y. Xu:** None.

Nanosymposium

365. Perception and Imagery: Visual Awareness

Location: 156

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Presentation Number: *****365.08

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Support: National Eye Institute grant EY020484
NSF award 1532591
McGovern Institute Neurotechnology Program

Title: The spatiotemporal deconvolution of natural images: Distinct neural trajectories for objects and scenes

Authors: ***S.-M. KHALIGH-RAZAVI**[1], C. MULLIN[2], D. PANTAZIS[3], A. OLIVA[4]
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Abstract: Visual scene and object recognition is a rapid process characterized by considerably more complex neural dynamics than a stimulus-evoked feedforward wave of activity. Understanding these dynamics can help us describe how information from multiple brain regions is synthesized over the course of a second to construct a unified percept of the whole image. Behavioral and neurological evidence suggest a division of object and scene background processing into distinct neural pathways. Despite extensive investigation, whether these pathways function sequentially or in parallel remains unknown. Here, we investigated the spatiotemporal representational dynamics of scene and object perception, from the deconvolution of a singular natural image into separate object and background information to their recombination into a unified percept. There has been little effort in developing techniques that allow for such investigations in humans. Here, using representational similarity analysis, we integrated high spatial resolution and high temporal resolution brain data to reveal 'when' information about objects and/or scenes ('what') becomes explicitly represented 'where' in the brain. During individual MEG and fMRI sessions, eighteen participants viewed a series of natural images containing objects orthogonally paired with different backgrounds. Outside the scanner, participants arranged these stimuli based on the similarity of their object and background content separately. We then correlated these behavioral judgement similarity

representations of the object and scene background with the brain representations over space (fMRI) and time (MEG). Results from MEG analysis support the parallel processing pathways of object and background information with both signal onsets occurring simultaneously at ~100ms. These signals deviate after onset with scene backgrounds showing a transient response while objects were more sustained over time. fMRI searchlight analysis revealed distinct as well as overlapping regions corresponding to the representational similarity of both object and background. Regions such as lateral occipital and parahippocampal place area were correlated with object and background representations respectively. While some regions parse the visual input into background and object others treat the image in its entirety. These findings shed light on how the higher-order properties of images are separated and converge in specific brain regions at different stages of processing to enable our unified visual experience.

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**Topic: ***H.02. Human Cognition and Behavior

Support: NWO Vidi Grant 452-13-016
ERC Starting Grant 678286, 'Contextvision'

Title: The neural dynamics of category-based attention

Authors: *E. J. WARD[1], F. P. DE LANGE[2]
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Abstract: Attention classically has been conceptualized as a "spotlight," a metaphor that fits spatial attention well, but fails to capture more sophisticated forms of attention such as feature- and object-based attention. However, attention goes beyond even these more sophisticated forms: we can attend to categories, such as "cars" or "garages," which consist of complex combinations of spatial, featural, and object-based elements. This hints that attentional tuning may extend to categorical information. In this study, we investigated the neural dynamics of visual category information as a way to explore category-based attention.
We used magnetoencephalography (MEG) while participants (n=16) viewed rapid serial visual presentation (RSVP) streams consisting of six images from eight categories. Each image was presented for 100 ms. Participants reported the presence or absence of a specific target category.

On each trial, the target category was 1) cued before the RSVP [precue], 2) cued after the RSVP [postcue], or 3) not cued [no cue]. Cues were a visually presented word corresponding to one of the categories. Consistent with previous research (e.g. Potter & Hagman, 2015), participants detected targets above chance for both pre- and post-cued trials, with a strong advantage for precues vs. postcues: participants were more accurate ($p<0.001$) and faster ($p<0.001$) to detect targets when they had seen a cue before the RSVP. This suggests that while some category information is processed automatically, a cue to attend to a particular category facilitates its processing at some level.

To explore the neural dynamics of category and cue processing, we used pattern classification to measure information content across the timecourse of each trial. We used trial-by-trial amplitude in 41 occipital MEG channels as features for classification and found significant decoding of category for both pre-cued trials (accuracy = 74%, $p<0.001$) and post-cued trials (71%, $p<0.001$). During the RSVP, not only could we decode the category of the target (17% [chance = 12.5%], $p<0.001$), but we could also decode the category of each individual distractor image (16%, $p<0.01$). Of these measures, target category decoding was greater for correct than incorrect trials ($p=0.007$), but target classification based on MEG signals was not influenced by the presence of a cue.

These results show that early visual responses contain categorical information about both relevant and irrelevant images, and that the fidelity of target category information is related to task performance. However, as assessed by classification accuracy, the categorical information in early visual processing is not affected by cueing.

Disclosures: E.J. Ward: None. **F.P. de Lange:** None.

Nanosymposium

365. Perception and Imagery: Visual Awareness

Location: 156

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**Presentation Number: ***365.10

**Topic: ***D.07. Vision

Support: Wellcome Trust Grant 098433
UK Economic and Social Research Council (ESRC) Grant ES/I02395X/1

Title: Prestimulus EEG power predicts visual awareness but not discrimination sensitivity, whilst prestimulus phase predicts neither

Authors: *C. S. BENWELL[1], C. F. TAGLIABUE[2], D. VENIERO[1], R. CECERE[1], S. SAVAZZI[3], G. THUT[1]
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Ctr. for Mind/Brain Sci., Univ. degli Studi di Trento, Trento, Italy; [3]Dept. of Neuroscience, Biomedicine and Movement Sci., Univ. of Verona, Verona, Italy

Abstract: Prestimulus oscillatory neural activity has been linked to perceptual outcomes during performance of psychophysical detection and discrimination tasks. Specifically, the power and phase of low frequency oscillations have been found to predict whether an upcoming weak visual target will be detected or not. Yet, the mechanisms by which baseline oscillatory activity influence perception remain unclear. Recent studies suggest that the negative relationship between alpha power and stimulus detection may be explained by changes in detection criterion (i.e. increased target present responses regardless of whether the target was present/absent) driven by the state of neural excitability rather than changes in visual sensitivity (i.e. more veridical percepts). We recorded EEG whilst participants performed a luminance discrimination task with perithreshold stimuli in combination with single-trial ratings of perceptual awareness. Our aim was to investigate whether the power and/or phase of prestimulus oscillatory activity predict discrimination accuracy and/or perceptual awareness on a trial-by-trial basis. Prestimulus alpha power was inversely related to perceptual awareness ratings (i.e. higher ratings in states of low prestimulus alpha/high excitability) but did not predict discrimination accuracy. In contrast, prestimulus oscillatory phase did not predict awareness ratings or accuracy in any frequency band. These results provide evidence that prestimulus alpha power influences the level of subjective awareness of a threshold visual stimuli but does not influence visual sensitivity when a decision has to be made regarding stimulus features. Hence, we find a clear dissociation between the influence of ongoing neural activity on conscious awareness and objective performance.

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Nanosymposium

365. Perception and Imagery: Visual Awareness

Location: 156

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***365.11

**Topic: ***D.07. Vision

Support: NIMH-DIRP

Title: Visual awareness: the gradual build-up and sharp stabilization of visual percepts

Authors: *M. VERNET, S. JAPEE, V. ZACHARIOU, S. AHMED, S. LOKEY, L. G. UNGERLEIDER
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Abstract: Does subjective visual awareness, i.e., the feeling of perceiving, arise from enhanced activity within the ventral stream (mediating object recognition), from information reaching the fronto-parietal network (mediating visuospatial processes and attention), or from monitoring performed by other areas, such as the superior temporal sulcus (STS) or the temporo-parietal junction (TPJ)? In most studies tackling this issue, visual awareness has been manipulated in an all-or-nothing fashion (i.e., seen vs. unseen). However, such a dichotomous measure would mainly reflect attentional mechanisms related to the stabilization of percepts. By contrast, a gradual build-up [e.g., not seeing anything (rating 1), seeing something that cannot be categorized (rating 2), categorizing with low (rating 3) or high certainty (rating 4)], is more closely related to awareness.
In our fMRI study, 25 healthy participants used such a scale after seeing noisy images of faces and avocados. We hypothesized that some cortical areas would display a dichotomous pattern of activity (i.e., ratings 1 & 2 < 3 & 4), reflecting a stabilization mechanism once an image is categorized, whereas other areas would display a gradual pattern of activity (i.e., ratings 1 < 2 < 3 < 4), reflecting a build-up of awareness. Finally, a U-shaped pattern of activity (i.e., ratings 1 & 4 > 2 & 3) should be observed for areas evaluating certainty, as participants, in addition to report being sure of seeing something (rating 4), often report being sure of not seeing anything (rating 1).
Dichotomous activity was found in fronto-parietal and early visual areas, in line with a stabilization mechanism mediated by the attentional fronto-parietal network modulating early visual areas. Gradual activity, related to visual awareness, was found in a subset of fronto-parietal and higher-order visual areas. Finally, a U-shaped pattern, most likely related to certainty evaluation, was found in STS/TPJ. In conclusion, our methodology enables the dissociation between closely related mechanisms of attention, awareness and certainty. Fronto-parietal and higher-order visual areas seem to jointly contribute to the build-up of awareness, which appears to be more gradual than previously assumed.

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Nanosymposium

365. Perception and Imagery: Visual Awareness

Location: 156

**Time: ***Monday, November 13, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***365.12

**Topic: ***H.02. Human Cognition and Behavior

Title: What do we continue liking: Gauging sustained human interest using explicit and implicit measures

Authors: *B. R. SHETH[1], K. H. FUNG[2], M. H. ISMAIL[3]
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Abstract: Gauging interest of a person in a scene, and before the person even signals it consciously, is of critical import to a number of fields of human endeavor including billboard advertising, web design, business, economics, and, of course, basic science, i.e. the study of human behavior. What triggers interest in people, what sustains it, and how can an external observer reliably gauge said interest through measures other than explicit communication which is not always truthful?
Here, we address these questions. Subjects (Ss) viewed images of different categories while we measuring their viewing time, recorded their eye scan patterns and asked them to rate their interest in each image on an analog scale. On separate sessions on separate days, Ss (n=17) viewed a series of images, one by one, all of which were of the same general category, but were otherwise different in other respects. There were five categories of images: *aerials*, *cityscapes*, *indoors*, *landscapes*, and *people* and a combined mix of all five. *Aerials* are aerial perspectives of the environment; *cityscapes* are scenes of city infrastructures, *indoors* are interiors of buildings, *landscapes* are scenes of nature, and *people* contain one or more humans. There were 25 images per category. Ss viewed images in a self-paced manner, while we monitored their eyes with an eye tracker (Eyelink II, SR Research). We recorded viewing time per image and variables related to eye movements, i.e. number of saccades, fixation duration, saccade length etc. In particular, we measured viewing time as a function of image order. We expected that i) as one views increasingly more images, the time duration devoted to viewing each successive image declines, due to emerging tedium or a gradually developing lack of interest; ii) however, the decline in interest is category dependent. A linear regression summarized the change in viewing duration with image number. There was a negative correlation between viewing duration vs. image number for *aerials* (r =-0.56; p=0.004), *cityscapes* (r =-0.03; p=0.88), *indoors* (r =-0.41; p=0.04), *landscapes* (r =-0.24; p=0.25), and the combination (r =-0.36; p=0.08). In contrast to the above, there was a positive correlation for *people* (r =+0.59; p=0.002). The dynamic change in viewing time was mirrored to some extent by change in the number of saccades - a negative correlation with image number was found for *aerials*, *indoors*, *landscapes* and the mix, but a positive correlation for cityscapes and people. Fixation duration, saccade length, or number of fixations all did not show similar category based division. Thus, sustained interest is dependent on image class. Future studies will further address the above questions.

Disclosures: B.R. Sheth: None. **K.H. Fung:** None. **M.H. Ismail:** None.

Nanosymposium

448. Neuronal Differentiation Mechanisms

Location: 156

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***448.01

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: Volkswagen Foundation Freigeist fellowship A110720
ERC starting grant 678071—ProNeurons

Title: A systems level view on miR-124 function during neuronal differentiation from human iPS cells

Authors: *L. K. KUTSCHE[1], D. M. GYSI[2], R. PETRI[3], K. LENK[1], K. NOWICK[2], J. JAKOBSSON[3], V. BUSSKAMP[1]
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Abstract: The human brain comprises various neuronal cell types, whose underlying developmental programs are still widely unclear. miRNAs, such as miR-124, have been identified as key players of neurogenesis. However, we lack a coherent understanding of miR-124 functions at the systems level.
To reveal which pathways are targeted by miR-124, we have established a complete miR-124 knockout in an easy-to-manipulate cellular system. The model is based on human induced pluripotent stem cells and enables the generation of a homogenous population of neurons within four days. For an extensive analysis we characterized the phenotype, sequenced the RNA over the time course of differentiation and performed RNA immunoprecipitation (RIP-Seq).
Phenotypically, miR-124 knockout cells still differentiate into neurons, express neuronal markers and are electrically active. However, the neurite outgrowth capacity is reduced and the differentiation is altered leading to a partly non-bipolar shape. In long-term cultures the neurons are more vulnerable suggesting impaired maturation or survival.
Using systems biology and an unbiased consideration of all transcripts under miR-124 control in the RISC complex (via RIP-Seq) we could identify key gene regulatory pathways and targets of miR-124 present in human neurons and monitor their behavior during differentiation. Besides that, we examined which miRNA are controlling the cell in the absence of miR-124. The up-regulation of the proliferative miR-200 cluster in the knockout indicates a shift in the differentiation time frame.
The data suggests that miR-124 has a modulating role during human neurogenesis. Transcription factors still exert a greater influence on neurogenesis. Nevertheless, miR-124 is extremely important for maturation and optimal development of the cells. A systems level view on

modulators of neurogenesis and the resulting knowledge about tuners of differentiation can facilitate subtype specification and maturation of neuronal cells from human stem cells.

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Nanosymposium

448. Neuronal Differentiation Mechanisms

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**Presentation Number: ***448.02

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: KAKENHI
Takeda Science Foundation
Uehara Memorial Foundation

Title: Investigation of the mechanisms underlying gyrification of the cerebral cortex using ferrets

Authors: *H. KAWASAKI, Y. SHINMYO, T. TODA
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Abstract: Gyrencephalic mammals such as ferrets have folds on the cerebral cortex (i.e. the gyrus and the sulcus), whereas mice do not have. To investigate the molecular mechanisms underlying the formation of cortical folds, we recently developed a genetic manipulation technique for the cerebral cortex of ferrets using *in utero* electroporation. Genes-of-interest can be expressed in the ferret cortex rapidly and efficiently. Using our technique, we examined the mechanisms of cortical folding. We focused on the role of the Tbr2 transcription factor, which is expressed in neural progenitors of the subventricular zone (SVZ). When Tbr2 was suppressed, we found that the number of SVZ progenitors was markedly reduced and that cortical folding was impaired. Interestingly, upper layers were more reduced than lower layers, suggesting the ratio between upper layers and lower layers is important for cortical folding. Our findings provide *in vivo* data about the mechanisms of cortical folding in gyrencephalic mammals. Our technique for the ferret cerebral cortex is useful for investigating the mechanisms underlying the formation and malformation of brain structures unique to higher mammals.

Disclosures: H. Kawasaki: None. **Y. Shinmyo:** None. **T. Toda:** None.

Nanosymposium

448. Neuronal Differentiation Mechanisms

Location: 156

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***448.03

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: NUS startup grant R-181-000-155-133
NUS startup grant R-181-000-155-733

Title: PIWI protein regulates retinoic acid-mediated neuronal differentiation of human embryonic carcinoma cells

Authors: *C. S. SUBHRAMANYAM[1], Q. HU[2]
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Abstract: In regenerative medicine, stem cell therapy is one of the most appreciated revolutionary strategy to re-establish neural circuits for neurodegenerative diseases. Though 90% of the eukaryotic genome is transcribed, only 1-2% of the transcripts encodes for protein. Majority of the remaining gets transcribed into numerous classes of non-coding RNA. In particular, piRNAs are ~26-32 nucleotide small non-coding RNAs that bind specifically to the PIWI subfamily of argonaute proteins. Some pilot work has suggested that PIWI has a vital role not only in germline stem cells but also in somatic stem cells. Recent evidences have revealed the presence of PIWI/piRNA in brain but the exact role of PIWI/piRNA complex in the nervous system is still unknown. Hence we aim to investigate the role of PIWI/piRNA complex in neuronal differentiation of human pluripotent stem cells. The human NT2 cells (pluripotent human embryonal carcinoma cells) are a well characterized cell line that resembles human embryonic stem cells (hESC) and is able to differentiate into mature neurons in the presence of retinoic acid (RA) with the loss of tumorigenicity. We studied the expression profile of individual PIWI homolog proteins in RA-mediated differentiation of human NT2 cells to neurons. During the course of differentiation, we found that a particular PIWI homolog is gradually increasing. With the knockdown of this homolog, we found that the embryonic stem cell markers were upregulated and neuronal differentiation markers were suppressed in the presence of RA. Interestingly, since the PIWI/piRNA complex has been suggested to epigenetically regulate tumor growth and memory, we investigated and observed that during RA-mediated neuronal differentiation, the PIWI homolog could potentially interact with epigenetic regulators to modulate the expression of various developmental genes such as HOXA1, CYP26A1 and NeuroD1.
Thus by understanding the role of small RNAs and their associated proteins in neuronal

development, we will be able to devise new ways of enhancing neuronal differentiation of stem cells and greatly benefit patients suffering from neurodegenerative diseases.

Disclosures: C.S. Subhramanyam: None. **Q. Hu:** None.

Nanosymposium

448. Neuronal Differentiation Mechanisms

Location: 156

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***448.04

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: Grant-in-Aid for Scientific Research (C) (16K11305) from Japan Society for the Promotion of Science (JSPS).

Title: Bicistronic 2A-peptide-based co-expression reporter knock-in hiPSC lines revealed gene expression profiles during human photoreceptor differentiation

Authors: *K. HOMMA
Dept. of Ophtalmology, Keio Univ. Sch. of Med., Tokyo, Japan

Abstract: Fluorescent cell labeling with fluorescent reporter genes have been utilized to visualize specific cell lineages and to investigate cell specific morphologies, motilities, gene expressions, neural activities, intracellular signaling, etc. However, in human cells, transgenes are often silenced during cell differentiation, and so knock-in technology was adopted to label the specific human cell lineages. We applied the genome editing, and the bicistronic 2A-peptide-based co-expression (B2AC) system to the knock-in for the fluorescent cell labeling. By using these technologies, knock-in hPSC lines were established, and the co-expression of target gene, *Crx* (a photoreceptor marker), and the fluorescent protein was observed during three-dimensional retinal organoid culture. The *Crx* expression and fluorescent intensity in the cells were positively correlated, suggesting that the B2AC reporter system functioned during human retinal development. The immunohistochemistry of Crx and the maturation of fluorescent reporter cells after long-term differentiation culture indicated that knock-in of the reporter gene did not affect the function of the target *Crx* gene. B2AC reporter cells successfully represented *Crx* upregulation by DAPT, a Notch signal inhibitor, during retinal differentiation from hPSC. These results validated the B2AC reporter knock-in system which could be used to investigate cell transplantation, developmental mechanisms, disease signaling, drug screening, and intracellular signaling.

Disclosures: K. Homma: None.

Nanosymposium

448. Neuronal Differentiation Mechanisms

Location: 156

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***448.05

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: NIH Grant U01 MH105989

Title: Cellular diversity in the developing human brain

Authors: *A. BHADURI, T. NOWAKOWKSI, A. POLLEN, B. ALVARADO, C. SANDOVAL-ESPINOSA, A. KRIEGSTEIN
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Abstract: The astonishing diversity of human cortical cell types emerges from radial glia cells distributed along an initially uniform forebrain neuroepithelium. Single cell sequencing provides the opportunity to discover molecular features related to the origin of laminar and areal differences. However, continuous gradients of gene expression, and orthogonal sources of variation such as cell cycle, neuronal differentiation, and stem cell maturation make the interpretation of single cell data in developing tissues challenging. Here, we survey cell type-specific gene expression trajectories from human cortex and medial ganglionic eminence. We describe a molecular signature of radial glia maturation and relate it to the lineage bifurcation of classically defined ventricular radial glia into outer and truncated radial glia half-way through human cortical neurogenesis. Across cortical areas, we find that a small number of transcriptional differences among radial glia, that are independent of differential maturation, cascade during neuronal differentiation into robust distinctions between prefrontal and occipital cortex neurons. Together, our results provide a methodology for interpreting single cell data in the development of heterogeneous tissue, a resource for determining the cellular targets of disease, and a standard to measure the fidelity of human in vitro derived cortical neurons.

Disclosures: A. Bhaduri: None. **T. Nowakowksi:** None. **A. Pollen:** None. **B. Alvarado:** None. **C. Sandoval-Espinosa:** None. **A. Kriegstein:** None.

Nanosymposium

448. Neuronal Differentiation Mechanisms

Location: 156

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***448.06

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: John S. Dunn Foundation
4T32DA007287-20

Title: Combined substance use on adult endogenous neural stem cell differentiation and metabolic enzyme expression

Authors: *E. L. MCGRATH[1], C. SCHLAGAL[3], J. GAO[3], T. DUNN[3], R. FOX[3], S. STUTZ[3], K. T. DINELEY[4], B. KAPHALIA[5], K. A. CUNNINGHAM[6], P. WU[2]
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Abstract: Cocaine use disorder (CUD) and alcohol use disorder (AUD) are two of the most prevalent substance use disorders in the United States affecting roughly 12 million. Efforts in drug addiction research primarily focus on preventing or stopping abuse, however little work is being done to reverse brain damage incurred by chronic drug abuse. Individual use of these substances cause neurodegeneration; however little is known about the combined effects of these substances on neurogenesis or the neural stem cell (NSC) population. Additionally, sex differences in NSC behavior following chronic drug abuse have yet to be evaluated. NSCs are a population of cells in the brain maintained throughout life that are characterized by their ability to self-renew and give rise to new neurons and astrocytes. Neurogenesis is broadly defined as the proliferation and differentiation of NSCs into neurons. This is the first study to evaluate regional and sex differences of endogenous adult neural stem cells to chronic treatment with alcohol and cocaine. We sought to elucidate the response of adult endogenous NSCs to chronic alcohol and cocaine treatment using an inducible lineage tracing mouse model. Adult mice were randomly divided into 1 of 4 groups: control, cocaine, ethanol, or combination treatment. Daily i.p. injections of cocaine were administered and ethanol was provided in a complete nutrient liquid diet to appropriate groups. Brain tissue was analyzed for markers of NSC survival and differentiation. The subventricular zone of lateral ventricle (SVZ) subgranular zone of dentate gyrus (SGZ) were evaluated. The hippocampus was evaluated for changes in metabolic enzymes associated with ethanol and cocaine metabolism. KEY FINDINGS: We found that NSCs have a unique response to drug depending on the regional location and sex of the animal. Females had more robust decreases in neural stem cell (NSC) survival in SVZ compared to males. SGZ

neurogenesis was reduced in combination group. Changes in metabolic enzymes in response to drug treatment were observed in the hippocampus, with differences between sexes.

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Nanosymposium

448. Neuronal Differentiation Mechanisms

Location: 156

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***448.07

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: NIH MH070596
NYSTEM Einstein Training Program in Stem Cell Research
NS088943

Title: FGFR activity regulates adult hippocampal neurogenesis through two intracellular mediators

Authors: *M. GRONSKA, J. M. HEBERT
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Abstract: Adult born hippocampal neural stem cells are critical to proper functioning of our hippocampus. Loss of adult neurogenesis has been implicated in multiple memory deficits. Thus, identification of the molecular pathways that control the generation, maturation, and integration of newborn neurons has the potential to identify therapeutic targets for age-related memory decline. We previously showed that loss of Fibroblast Growth Factor Receptors (FGFRs)1-3 leads to decreased stem cell maintenance, progenitor cell proliferation, and dendrite elaboration. However, the identities of the ligands and intracellular signal transducers for these FGFR-dependent processes are unknown. To address this gap, we are examining stem/progenitor cell proliferation and dendritic elaboration in the dentate gyrus (DG) of FGFR1-3 conditional mutant mice in which FGFR1 lack binding sites for the downstream mediators Phospholipase-C gamma (PLCγ) and Fgf Receptor Substrate (FRS) proteins. Surprisingly, our data thus far suggest that not only FRS, which was previously implicated in FGFR-mediated proliferation in other contexts, but also PLC-γ, which was not previously implicated in FGFR-mediated cell proliferation, are together non-redundantly required to transmit FGFR activity in promoting adult neural stem cell expansion. The potential roles of FRS and PLC-γ in dendrite elaboration are currently being addressed using AAV-Cre and Cre^{ER} transgene drivers that target newborn

neurons and bypass the requirements for FGFRs in stem and progenitor cells. Using multiple Cre and Cre^{ER} drivers, we are also determining whether L1CAM, a non-canonical FGFR ligand implicated in dendritogenesis, acts in a cell-type autonomous or non-autonomous manner to promote FGFR-mediated dendritogenesis in the DG. Determining which intra- and extracellular pathways differentially affect adult stem cell expansion and the generation and integration of new neurons will provide a better understanding of potential therapeutic targets for reversing deficiencies that lead to age-related memory decline.

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

Nanosymposium

448. Neuronal Differentiation Mechanisms

Location: 156

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***448.08

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and [Institute of Psychiatry, Psychology & Neuroscience] King's College London

Title: Inter-individual variation in genes governing human hippocampal progenitor differentiation is associated with hippocampal volume in adulthood

Authors: *T. POWELL, T. MURPHY, S. H. LEE, R. R. DUARTE, H. LEE, D. SMEETH, J. PRICE, G. BREEN, S. THURET
Inst. of Psychiatry, Psychology & Neurosci., King's Col. London, London, United Kingdom

Abstract: Neurogenesis is the process by which neural stem cells differentiate into neurons. The hippocampus is a brain structure important in regulating learning, memory and mood. No study to-date has characterised genome-wide expression changes associated with human hippocampal neurogenesis. Here we use a unique multipotent human cell line to assay genome-wide expression changes when hippocampal progenitor cells differentiate into young neurons (doublecortin-positive cells), mature neurons (MAP2-positive cells) and astrocytes (S100β-positive cells) after a seven-day differentiation protocol. RNA was extracted from proliferating cells versus differentiated neural cells and applied to Illumina Human HT-12 v4 Expression BeadChips. Data was then normalised and linear regressions were used to determine the effect of differentiation on probe expression. GoriLLa was used to assess enrichment for gene ontology terms, and genetic pathway analysis (MAGMA) was used to evaluate the relationship between hippocampal progenitor cell differentiation and adult hippocampal volume, using results from

the imaging genomics consortium, ENIGMA. We found extensive expression changes, and from our data we constructed a 'neural progenitor differentiation gene set' (1,142 probes). Downregulated transcripts were enriched for mitotic processes and upregulated transcripts were enriched for cell differentiation. These upregulated (differentiation) transcripts were predictive of adult hippocampal volume, but not the downregulated transcripts (mitosis). In conclusion, our results reveal extensive transcriptional reprogramming of cells during hippocampal neural progenitor differentiation, with genes governing differentiation, rather than mitosis, having a pervasive impact on adult hippocampal volume.

Disclosures: **T. Powell:** None. **T. Murphy:** None. **S.H. Lee:** None. **R.R. Duarte:** None. **H. Lee:** None. **D. Smeeth:** None. **J. Price:** F. Consulting Fees (e.g., advisory boards); ReNeuron. **G. Breen:** 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.; Eli Lilly. **S. Thuret:** None.

Nanosymposium

448. Neuronal Differentiation Mechanisms

Location: 156

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***448.09

**Topic: ***A.01. Neurogenesis and Gliogenesis

Title: Human foetal cholinergic neurons isolated from nucleus basalis of Meynert express functional cholinergic receptors whose activation modulates neuronal excitability

Authors: *E. COPPI[1], I. FUSCO[2], F. PEDATA[2], A. MORELLI[3], A. M. PUGLIESE[2], G. VANNELLI[3]
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Abstract: The degeneration of cholinergic neurons in the nucleus basalis of Meynert (NBM) is responsible for the gradual cognitive decline in Alzheimer's disease (AD). To date no resolutive therapies exist. Understanding the mechanisms driving human neuroblast differentiation towards the cholinergic phenotype could help identifying efficient therapies aimed at preventing neuronal loss in neurodegenerative pathologies. Here we isolated and characterized human foetal NBM (hfNBM) neurons in 12-week old foetuses by using electrophysiological and biochemical techniques. Flow cytometry showed that almost all cells in the primary culture were positive for the neuronal marker MAP2 (97.2±3%) and for choline acetyltransferase (ChAT; 97.1±2%). Patch-clamp experiments demonstrated that these cells express tetrodotoxin-sensitive fast inward

voltage-gated Na+ currents (INa), delayed rectifier IK currents and, in some cases, also inwardly rectifying Kir channels and transiently activated K+ IA currents. The expression of functional nicotinic and muscarinic receptors was found on hfNMB neurons. In fact, nicotine concentration-dependently (1-100 µM) evoked a depolarizing inward current prevented by the nicotinic antagonist mecamilamine (100 nM). Furthermore, acetylcholine or carbachol application enhanced outward IK currents evoked by a voltage ramp protocol (+80/-120 mV, 800 ms) and hyperpolarized cell membrane. These effects were concentration-dependent (0.1-100 nM), atropine-sensitive and prevented by the unselective K+ channel blocker tetraethylammonium (10 mM). The adenylate cyclase activator forskolin (1 µM) did not modify ramp currents, ruling out the involvement of cAMP in acetilcoline- or carbachol-mediate enhancement of IK. Finally, acetilcholine or carbachol application concentration-dependently (0.1-100 nM) inhibited inward Na+ currents activated by a 0 mV step. Both effects were blocked by ATR. This is the first study in which human NBM cells are isolated and fully characterized as programmed to become functional cholinergic neurons expressing nicotinic and muscarinic receptors. Nicotinic receptor activation excites hfNBM neurons by depolarizing cell membrane and approaching them to firing threshold, whereas mAchRs proved to be inhibitory by opening hyperpolarizing outward IK currents in a cAMP-independent manner, and by inhibiting INa and, presumably, action potential initiation and neurotransmitter release. The study provide a useful model to investigate ontogenetic mechanisms of human cholinergic system development in order to assess disease modelling and drug screening in neurodegenerative disorders.

Disclosures: **E. Coppi:** None. **I. Fusco:** None. **F. Pedata:** None. **A. Morelli:** None. **A.M. Pugliese:** None. **G. Vannelli:** None.

Nanosymposium

448. Neuronal Differentiation Mechanisms

Location: 156

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***448.10

**Topic: ***A.01. Neurogenesis and Gliogenesis

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Generalitat Valenciana Prometeo Excellence Program PROMETEO2013/069
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Research Support Funds Paracelsus Medical University PMU-FFF (R-14/04/063-KÖN)

Title: Functional maturation of tangled cells into glutamatergic neurons within the adult mouse piriform cortex

Authors: D. DANNEHL[1,2,3], M. BELLES[5], P. ROTHENEICHNER[3,2], R. KÖNIG[4,2], B. BENEDETTI[3,2], C. KREUTZER[3,2], P. ZAUNER[3,2], L. AIGNER[4,2], J. NACHER[5], M. ENGELHARDT[1], *S. COUILLARD-DESPRES[2,3]
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Abstract: Tangled cells (TCs) are post-mitotic immature cortical neurons characterized by their expression of doublecortin (DCX) and polysialylated neuronal cell adhesion molecule (PSA-NCAM). TCs arise during embryonic corticogenesis and remain predominantly detectable in higher order cortical areas in adult mammals, e.g. the piriform cortex of mice. Previous studies have shown that the number of TCs decreases over the lifespan, although no signs of TCs apoptosis have been reported. Using a DCX-CreER^{T2}::STOPfloxed-GFP transgenic mouse line, we followed a population of GFP-labeled TCs in the piriform cortex and observed that their number remained constant over time and that numerous TCs developed into morphologically mature neurons. Virtually all of the latter subgroup integrated into the local network as glutamatergic neurons (TBR1$^+$, CaMKII$^+$), whereas scarce inhibitory neurons and no dopaminergic or cholinergic neurons could be detected.
It remains to be determined to which extent TCs get functionally integrated in the surrounding neuronal network, i.e. processing of synaptic input and actively firing action potentials (AP). The structural requirement for AP generation is the establishment of an electrogenic microdomain, the so-called axon initial segment (AIS). The AIS is equipped with a dense cluster of voltage-gated ion channels, tethered in place by specific membrane scaffolding and anchor proteins, such as ankyrin-G and βIV-spectrin. Here, we used the AIS as a surrogate marker for functional maturation of TCs into neurons. We observed the emergence of an AIS on GFP-labeled TCs concomitant with the development of a complex neuron-like morphology and the increase of synaptic inputs. However, the length of the AIS in maturing TCs was significantly shorter than the AIS of surrounding principal neurons in the piriform cortex.
Our data indicate that a population of post-mitotic immature neurons residing within adult cortical structures have the capacity to structurally and functionally integrate as glutamatergic neurons within the local networks. Further studies will address the process of functional integration of TCs in piriform cortex circuits, and in particular the relationship between AIS features and neuronal activity.

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Nanosymposium

448. Neuronal Differentiation Mechanisms

Location: 156

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***448.11

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: Ministerio de Economía y Competitividad, Spain
ISCIII-Subdirección General de Evaluación and European Regional Development Fund (ERDF) [RETICS and CIBERNED]
Catalonia Trade and Investment, Generalitat de Catalunya and ERDF [ADVANCE(CAT)], Spain
CHDI Foundation Inc., USA

Title: Using single neuron RNA-seq to study the role of the transcription factor Ikaros in striatal development

Authors: *P. SANDERS[1,2,3,4,5], G. BOMBAU[1,2,3,4,5], M. GALOFRE CENTELLES[1,2,3,4,5], A. GUILLAUMET-ADKINS[6,7], G. RODRIGUEZ-ESTEBAN[6,7], H. HEYN[6,7], J. M. CANALS[1,2,3,4,5]
[1]Univ. of Barcelona - IDIBAPS, Barcelona, Spain; [2]Dept. of Biomed. Sci., [3]Production and Validation Ctr. of Advanced Therapies (Creatio), Univ. of Barcelona, Barcelona, Spain; [4]Neurosci. Institute, Univ. of Barcelona, Barcelona, Spain; [5]Networked Biomed. Res. Ctr. for Neurodegenerative Disorders (CIBERNED), Madrid, Spain; [6]Single Cell Genomics - Sequencing Unit, Ctr. Nacional de Análisis Genómico (CNAG-CRG) - Ctr. for Genomic Regulation (CRG), Barcelona, Spain; [7]Univ. Pompeu Fabra (UPF), Barcelona, Spain

Abstract: Ikaros is a zinc finger transcription factor that is essential for the development of a subset of striatopallidal medium spiny neurons (MSNs), the cell type that is primarily affected in Huntington's Disease (HD). However, both the specific role of Ikaros in MSN development and the identity of Ikaros target genes during neuronal differentiation remain unknown.
To investigate this we combined a human embryonic stem cell *in vitro* differentiation protocol that generates forebrain neurons with a lentiviral inducible Ikaros expression system. Such an approach permits control of both the timing and level of Ikaros expression during neuronal differentiation.
To identify the effects of induced Ikaros expression on gene expression at the single cell level we performed massively parallel RNA single-cell sequencing (MARS-SEQ) on both control neurons and neurons expressing different levels of Ikaros. MARS-SEQ was performed both directly at the end of the induced expression phase (early timepoint) to investigate the direct effects of Ikaros expression, and three weeks post-induction (late timepoint) to explore the long term consequences.

Initial unbiased analysis of expression data from more than 1200 individual neurons at the early timepoint, using principal component analysis and t-distributed stochastic neighbor embedding, reveals that Ikaros expressing neurons have a clearly distinct gene expression profile compared to the control neurons. Both up- and down-regulated putative marker genes for the Ikaros expressing populations have been identified, with the functions of these marker genes suggesting the cellular processes that are regulated by Ikaros. Work is currently underway to verify these observations.
With further analysis of the substantial single neuron transcriptome data sets that we have generated we anticipate that we will establish the specific role of Ikaros during striatal development. Furthermore we expect to identify novel markers for the neuronal sub-types that are present in our cultures, and to improve the efficiency of MSN *in vitro* differentiation for cell therapy treatment of HD.

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Nanosymposium

448. Neuronal Differentiation Mechanisms

Location: 156

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***448.12

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: NS078741
NIH Training Fellowship in Neural Injury and Plasticity, NINDS 5T32NS041218

Title: Pairing your Sox: Cross species function of Sox11 in neural development

Authors: *K. S. SINGLETON[1], J. JIN[2], C. CHEN[2], M. J. DONOGHUE[2,1], E. M. SILVA[2,1]
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Abstract: The development of the central nervous system involves the specification and then the progression of neural stem cells to mature neurons. Each step in this neuronal progression is achieved through changes in cell fate, that are coordinated by precise expression and function of transcriptions factors (TFs). Sox proteins are a large family of highly conserved TFs that, along with partner proteins, regulate the production, differentiation, and maturation of the nervous system. Previous studies have shown that Sox11, a member of the SoxC family, is dynamically expressed in *Xenopus laevis* (frog) and *Mus musculus* (mouse) and plays largely conserved roles in promoting neuronal differentiation in both systems. While deficits in Sox11 function have

been implicated in neurodevelopmental disorder, focal temporal lobe epilepsy and malformations in cortex and spinal cord, regulation of Sox11 expression and mechanisms underlying its function remain poorly understood. Our functional studies in frog and mouse neural development reveal that despite high evolutionary conservation, frog and mouse Sox11 cannot substitute for one another in neuronal development. To address causes for functional differences between frog and mouse Sox11, we compared the mouse and frog Sox11 protein domains specifically hypothesized to be involved in protein-protein, and protein-DNA interactions and analyzed the function of cis- regulatory regions. Our results indicate that a single amino acid difference in the highly conserved HMG domain alters the function of Sox11 in frog and mouse and that post-transcriptional regulation via microRNAs is key to the controlling Sox11's spatial and temporal expression. Assumptions are often made that conserved protein equals conserved function, however, our data demonstrates that even highly evolutionarily conserved TFs may not exhibit the same mechanism or function across species.

Disclosures: K.S. Singleton: None. **J. Jin:** None. **C. Chen:** None. **M.J. Donoghue:** None. **E.M. Silva:** None.

Nanosymposium

448. Neuronal Differentiation Mechanisms

Location: 156

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***448.13

**Topic: ***A.01. Neurogenesis and Gliogenesis

Support: NRF Grant Holder Bursary

Title: Branching patterns of immature neurons in Long-Evans rats exposed to enriched environment

Authors: *C. B. UZOKWE[1,2]
[1]Univ. of Jos, Jos, Nigeria; [2]Anatom. Sci., Univ. of the Witwatersrand, Johannesburg, South Africa

Abstract: This study investigated adult neurogenesis in the dentate gyrus of the hippocampus of the Long-Evans rat exposed to the standard control laboratory environment, running wheel exercise as a single influencing factor and a complex enriched environment for 28 days. Eighteen male Long-Evans rats were trans-cardially perfused with 4% paraformaldehyde in PBS. Brains were carefully removed and frozen sections cut sagittally at 50 µm. These sections were treated with Cresyl violet for cytoarchitecture as well as immunohistochemistry and immunofluorescence techniques employed for the identification of immature neurons. Using the

markers doublecortin (DCX) for neurones and processes, proliferation marker Ki-67. In addition, Giemsa staining was used to identify pyknotic neurons. Cell counts was done for DCX, Ki-67, pyknotic positive cells, and volume density of the dentate gyrus. Results showed a significant increase in brain weight (P=0.5 at 2.0, 2.1 and 2.2 respectively) for the complex enriched group as compared to the running and control groups. Ki-67 immunopositive cells showed variable differences with three-fold increases between the standard control and exercise and the exercise and enriched groups but a six-fold increase between the control and the complex enriched group. The DCX immunopositive results indicated the neuronal numbers, neuron structure, dendritic patterns as well as neuronal arrangements on the dorsal and ventral limbs of the dentate gyrus varied significantly among groups. Apoptotic cell count in the control group had the highest number of cells compared to the exercise and enriched groups, noting a five-fold increase between the control and exercise, a 27-fold increase between the control and enriched and a 21-fold increase between the exercise and complex enriched group. Volumetric density showed a 15-fold decrease between the standard control and exercise group, a five-fold decrease between the exercise and complex enriched and a 19-fold decrease between the control and complex enriched groups but no significant difference was observed between the groups on post hoc analysis. Enrichment has a very potent effect on adult neurogenesis.
Keywords: adult neurogenesis, neurone structure and environmental enrichment.

Disclosures: C.B. Uzokwe: None.

Nanosymposium

449. Dendrite Morphogenesis

Location: 152A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***449.01

**Topic: ***A.05. Axon and Dendrite Development

Support: NIH Grant F32EY025114
ALK is an investigator of the HHMI

Title: Semaphorin 6A elaborates direction-selective retinal circuits in an unexpected way

Authors: *R. E. JAMES, M. P. BROWN, A. L. KOLODKIN
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Abstract: Direction-selective (DS) visual circuitry enables object motion detection, a critical task for survival. Visual information is transmitted from photoreceptors in the outer retina to retinal ganglion cells (RGCs) via excitatory bipolar cell inputs. Various interneurons, including amacrine cells in the inner retina, filter visual information along its route to RGCs. DS RGCs

(DSGCs) are excited in response to motion in preferred directions and fire few action potentials in response to non-preferred motion. This selectivity is conferred by inhibition from starburst amacrine cells (SACs). After integrating both bipolar cell excitatory and SAC inhibitory inputs, DSGCs transmit visual information to retinorecipient targets in the brain through the optic nerve. Semaphorin 6A (Sema6A), a transmembrane guidance cue, facilitates DS circuit elaboration both locally in the retina, where it directs ON (responsive to light onset) and OFF (light offset) SAC lamination and is necessary for ON SAC radial morphology (Sun et al, 2013), and also in the brain, where it targets the axons of certain DSGCs to their postsynaptic nuclei (Sun et al, 2015). The mechanisms used by Sema6A during local SAC circuit refinement are unclear, since Sema6A is expressed by both presynaptic SACs and postsynaptic DSGCs. We tested the hypothesis that SAC-derived Sema6A refines local SAC circuits. We generated mice harboring a *Sema6A* conditional allele that expresses HA-tagged Sema6A in the absence of Cre recombinase. Ubiquitous germline (*Sox2Cre*) and pan-retinal (*Six3Cre*) knockout, but not SAC-specific (*ChatCre*) knockout, of *Sema6A* revealed severe SAC lamination defects. *Sema6A* is also not required in SACs for overall ON SAC radial morphology, but is necessary for ON SAC distal dendrite self-avoidance, similar to previous observations (Sun et al, 2013). We detected broad expression of HA-Sema6A in many RGC subtypes. However, HA-Sema6A was not observed in postnatal day 4 (P4) SACs, when SAC lamination occurs. Conversely, it was detected in all ON SACs at P10, a developmental time when SAC synaptic connections are refined. To probe roles for Sema6A in synaptic refinement, we studied the localization of presynapses labeled by a $Synaptophysin^{TdTomato}$ fusion protein in *Sema6A* mutants. Presynapses were no longer confined to distal ON SAC dendrites in *Sema6A* mutants, showing that Sema6A is required for normal ON SAC presynaptic specialization. Our unexpected results suggest that ON DSGCs interact with SACs during development to elaborate and laminate SAC dendritic arbors, and further suggest that Sema6A functions in ON SAC distal dendrites, where it promotes self-avoidance and synaptic refinement.

Disclosures: **R.E. James:** None. **M.P. Brown:** None. **A.L. Kolodkin:** None.

Nanosymposium

449. Dendrite Morphogenesis

Location: 152A

Time: *Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

Presentation Number: *449.02

Topic: *A.05. Axon and Dendrite Development

Support: NIH Grant NS084111

Title: A scaffold for cGMP-activity is necessary for dendrite formation during neuronal polarization

Authors: *J. SZCZURKOWSKA, S.-I. LEE, M. SHELLY
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Abstract: Studies over the last decade have established axon formation as the initiating event in neuronal polarization. These studies assumed that dendrite formation might be a passive process that follows axon formation by default. We here show that subsequent to axon establishment, dendrite formation is a promotable process, driven by cyclic GMP (cGMP)-activity. We identify a cGMP-scaffold protein that recruits the cGMP-synthesizing enzyme soluble guanylate cyclase (sGC) to upregulate cGMP-levels, and which is necessary for dendrite formation *in vitro* and *in vivo*. Our findings show that the association between the cGMP-synthesis complex members is mediated in the embryonic brain, where their expression was enriched in the dendrites. Importantly, down-regulation of the cGMP-synthesis scaffold protein resulted in cGMP-level decrease in developing neurons. Down-regulation or deletion of the cGMP-scaffold in cultured hippocampal neurons resulted in severe defects in dendrite formation and growth. Furthermore, down-regulation or deletion of the cGMP-scaffold in the embryonic hippocampus *in vivo*, resulted in severe defects in apical dendrite development. Importantly, overexpression of the reconstituted sGC enzyme in the embryonic hippocampus, rescued the effects of the cGMP-scaffold down-regulation on apical dendrite development. Furthermore, we found that the cGMP-scaffold recruits the Plexin co-receptors for Semaphorin3A, a key extracellular regulator of neuronal polarity in the embryonic brain, which mediates a rise in cGMP. We show that the cGMP-scaffold mediated association with Plexin co-receptors is necessary for dendrite development *in vitro* and *in vivo*. Our results support an active, stepwise process for both axon and dendrite formation in neuronal polarization, and show that cGMP-driven signaling is necessary for dendrite establishment during embryonic neuronal development. Selectivity for cGMP-elevation in dendrite formation may be mediated by a gradient of Sema3A generated across the developing neuron, with the highest concentration at the leading process, the nascent apical dendrite. The assembly of cGMP-synthesis enzymes and Sema3A co-receptors on the cGMP-scaffold, would generate a gradient of cGMP-production, in response to Sema3A gradient, with the highest at the nascent apical dendrite, to specifically promote its development and growth.

Disclosures: J. Szczurkowska: None. **S. Lee:** None. **M. Shelly:** None.

Nanosymposium

449. Dendrite Morphogenesis

Location: 152A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***449.03

**Topic: ***A.05. Axon and Dendrite Development

Support: NIH Intramural Program

Title: The effect of Pou4f1/Brn3a on the dendritic morphology of mouse retinal ganglion cells

Authors: *V. V. MUZYKA[1,2], T. C. BADEA[2]
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Abstract: It is well established that transcription factors participate in the regulation of cell type specification. Pou4f1/Brn3a is a member of the Brn3 transcription factor family which regulates the development and specification of retinal ganglion cells (RGCs). In particular, Brn3a is essential for the presence of small midget-like RGCs in the mouse retina. This transcription factor also affects the branching properties of bistratified RGCs. In the current study, we aim to elucidate at what particular time point during mouse development Brn3a is necessary for the establishment of normal dendritic morphologies and survival of the above-mentioned RGC subpopulations. To answer this question, we utilized a genetic intersection strategy combining the 4-hydroxy-tamoxifen(4HT)-inducible Cre allele – $cRet^{CreER}$, and the alkaline phosphatase (AP) reporter Brn3a conditional allele ($Brn3a^{CKOAP}$). Previous experiments (Parmhans, Sajgo et al in preparation) had shown that activation of Cre protein by I.P. 4HT injection in adult $cRet^{CreER}$; $Brn3a^{CKOAP}$ mice, results in the AP labeling of two subpopulatios of RGCs – small "midget-like" and bistratified. $Brn3a^{CKOAP/WT}$ (WT) and $Brn3a^{CKOAP/KO}$ (KO) mice were undistinguishable by the types of AP-marked RGC populations after Cre activation in the adult age. If Cre is activated earlier – at postnatal day 0 (P0) – at least 5 RGC subtypes are AP-marked in the WT animals – 3 mono- and 2 bi-stratified. All "P0-specific" morphological types were present comparatively rarely. In the KO retinas, at least two additional bistratified RGC morphologies with abnormal dendrite branching were observed, in addition to a substantial decrease in monostratified RGCs. All of this leads to the conclusion that cell type-specific Brn3a ablation in early postnatal period reduces the number of small "midget-like" RGCs and results in arbor defects of bistratified RGCs in mouse retina. Based on preliminary data, embryonic Cre activation and Brn3a ablation could lead to even more severe cell number decrease and dendrite branching disturbances.

Disclosures: V.V. Muzyka: None. **T.C. Badea:** None.

Nanosymposium

449. Dendrite Morphogenesis

Location: 152A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***449.04

**Topic: ***A.05. Axon and Dendrite Development

Support: NIH

Title: TP5 regulates the neuronal dendritic spine number, shape and neurotransmitter receptor contents

Authors: *S. P. YADAV[1], M. BHASKAR[2], N. D. AMIN[2], S. SKUNTZ[2], C. A. WINTERS[2], P. GRANT[2], H. C. PANT[2]
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Abstract: Precise regulation of synaptic integrity is essential for neuronal network connectivity and brain functions. The structural and functional changes of excitatory synapses are associated with alterations in dendritic spine number, shape and neurotransmitter receptor contents. These events are exclusively regulated during synapse development and subsequent plasticity in the adult brain. Aberrant dendritic spine morphology or surface abundance of neurotransmitter receptors is frequently associated with nervous system disorders, such as Alzheimer's disease, Parkinson's disease, amyotropic lateral sclerosis, schizophrenia, mental retardation and autism. Cyclin-dependent kinase 5 (Cdk5), plays an essential role in synapse development and functions. It can act as a positive and or negative regulator of synapse development and functions; that is highly dependent on the phosphorylation of specific substrates. Previously, we have identified a peptide TP5 (a truncated fragment of p35, the normal Cdk5 regulator), that specifically inhibits the activity of hyperactive (Cdk5-p25) without affecting normal (Cdk5-p35). The purpose of current study is to elucidate the role of TP5, in regulating the morphology of cultured rat cortical neurons. Embryonic day 18 rat cortices were isolated, minced and dissociated using papain. Neurons were grown on the poly L-lysine coated glass coverslips in Neurobasal media supplemented with B27, penicillin and streptomycin. Neurons were treated with 500 nM TP5 and or a scrambled peptide, fixed in 4%PFA on DIV17 and immunostained for candidate antibodies. We observed increased arborization in a subset of the rat cortical neurons treated with TP5. Number of neurons with higher arborization were significantly less in scrambled peptide treated neurons. In addition, we also noted an increase in dendritic spine number and tested channel density in a subset of the cultured rat cortical neurons, treated with TP5 peptide compared to scrambled peptide. Notable increase in the Rab11 positive recycling endosomal vesicles in the TP5 treated cortical neurons was observed. However, we did not discern these changes in scrambled peptide treated neurons. These results suggest that TP5 has a protective effect on neurons in our culture conditions. Furthermore, enhanced recycling endosome transport

to the axons contributes to higher membrane turnover, a hallmark associated with neuronal arborization. Our results suggest that TP5 can be used as a therapeutic agent to protect the diseased neurons associated with CDK5 hyperactivity.

Disclosures: S.P. Yadav: None. **M. Bhaskar:** None. **N.D. Amin:** None. **S. Skuntz:** None. **C.A. Winters:** None. **P. Grant:** None. **H.C. Pant:** None.

Nanosymposium

449. Dendrite Morphogenesis

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**Topic: ***A.05. Axon and Dendrite Development

Support: NIH R01 NS065856
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The Charles Hood Foundation

Title: Experience-dependent regulation of dendritic arborization in primary visual cortex

Authors: *S. E. RICHARDS[1], A. R. MOORE[3], S. SAXENA[4], S. PARADIS[2], S. D. VAN HOOSER[3]
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Abstract: The visual critical period in the mouse is an epoch of heightened plasticity at the systems, circuit, and cellular level. Spine dynamics change and underlying cellular processes are in constant flux. However, little is known about the morphological changes that occur during this time. The overall arborization of neurons has been studied only sparingly during this period despite the significant influence that even modest changes in morphology could enact. In addition, whether the development of mature dendritic arborization proceeds independently of visual experience, or whether these processes are experience-dependent in the rodent, as in other vertebrate systems, remains largely unknown. Even less is known about the molecules that may mediate this process. The current work has sought to characterize the development of pyramidal neuron dendritic arborization across development in the mouse visual cortex, beginning before eye opening and continuing throughout the critical period. We have found that, while the system shows remarkable stability, lack of visual experience leads to altered dendritic complexity and distribution of dendritic material. We have further characterized the role of one candidate molecule, Rem2, in this process. Similar to results previously observed *in vitro*, loss of Rem2

leads to increased dendritic branching in the rodent visual cortex, characterized by an overall increase in length of the dendritic arbor. Furthermore, our results demonstrate that Rem2 functions to restrict excessive dendritic proliferation that might occur following visual stimulation in the absence of negative regulation. This work provides insight into the developmental progression of dendritic architecture as well as establishes a key molecular regulator of this process.

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Nanosymposium

449. Dendrite Morphogenesis

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**Topic: ***A.05. Axon and Dendrite Development

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Title: miR-125b toggles dynamics and structure of dendritic filopodia in developing hippocampal neurons

Authors: *R. IYER[1,3], T. KIM[2,3], Y. KIM[4,3], M. E. KANDEL[2,3], J. W. MITCHELL[1,3], G. POPESCU[2,3], M. U. GILLETTE[1,3,4]
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Abstract: During wiring of the nervous system, developing dendrites encounter a variety of stimuli that direct their growth and final architecture. Cellular substrates respond to these stimuli, integrating extrinsic information to direct dendritic growth. Of interest in this process are microRNAs, small noncoding RNAs around 22 nucleotides long, which can reversibly repress local translation in dendrites. By responding to local external cues sensed by dendritic filopodia, they participate in the key decision-making processes in developing dendrites: where and how to grow. Here we study the role of miR-125b, a brain abundant microRNA, for its role in the dynamics and structure of filopodia in developing dendrites. We inhibited miR-125b's activity in cultured hippocampal neurons during the early stages of development as filopodia explore their

microenvironment. We show that miR-125b function is critical for maintaining the structural features of filopodia. We also show that: 1) Inhibiting miR-125b increases dendritic expression and localization of the GluN2A subunit of the NMDA receptor, and 2) dendritic GluN2A is correlated with maintaining filopodial morphology. Using whole cell patch-clamp recording, we show that miR-125b inhibition alters neuronal response to spontaneously released glutamate, a dominant mode of glutamate signaling in developing neurons. Using Spatial Light Interference Microscopy (SLIM), we show that miR-125b function contributes to maintaining the dynamicity of filopodia. We propose that miR-125b is critical in maintaining the filopodial phenotype early in dendrite development, thus contributing to dendritogenesis and spinogenesis. Through its regulation of GluN2A, miR-125b shapes neuronal response to the synaptotrophic factor glutamate. These high-resolution analyses reveal fresh insights into the process by which neurons integrate multiple external signals to establish the correct connections. Such insights are critical to understanding the implicated role of miR125b in various neurological disorders like Fragile X Syndrome and Alzheimer's disease.

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Nanosymposium

449. Dendrite Morphogenesis

Location: 152A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***449.07

**Topic: ***A.05. Axon and Dendrite Development

Title: A screen to identify cell surface molecules that coordinate with semaphorin-1a to target olfactory projection neuron dendrites to the destined glomeruli in the *Drosophila* antennal lobe

Authors: *H.-H. YU, H.-C. SHEN
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Abstract: In the *Drosophila* olfactory system, odorant information is detected by olfactory sensory neurons (OSNs) in two peripheral sensory organs, the antennae and maxillary palps, and then sent to the primary olfactory center of the brain, the antennal lobe (AL). The olfactory projection neurons (PNs) populate their cell bodies surrounding to the AL and distribute their dendrites in distinct but overlapping patterns within the AL to receive the olfactory inputs from the OSNs. Most PNs are primarily derived from four neural stem cells (called neuroblasts) and therefore can be assigned as: anterodorsal PNs (adPNs), lateral PNs (lPNs), ventral PNs (vPNs) and lateroventral PNs (lvPNs). In our previous study, we have elucidated a new role of a repulsive transmembrane protein Semaphorin-1a (Sema-1a) in preventing adPNs and vPNs from

aberrant dendritic invasion into a select AL region (the DA3 glomerulus), in which adPNs and vPNs but not lPNs mis-target their dendrites into the DA3 glomerulus in the absence of *Sema-1a*. To explore the underlying mechanism of this Sema-1a-mediated DA3-glomerular dendritic mis-targeting defect, we then conducted an enhancer and suppressor screen by using an RNAi knock-down approach to identify cell surface molecules that can aggravate or ameliorate the Sema-1a-elicited dendritic mis-targeting defect. The results of identified enhancers and suppressors will be presented in the meeting.

Disclosures: H. Yu: None. **H. Shen:** None.

Nanosymposium

449. Dendrite Morphogenesis

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**Topic: ***A.05. Axon and Dendrite Development

Support: Swiss National Foudation Grant 31003A_140940/1

Title: Canonical Wnt signaling regulates dendritic arbor development of layer II pyramidal neurons in the rat retrosplenial cortex

Authors: B. VIALE, L. CONSTANTHIN, V. PETRENKO, R. BOCCHI, A. CONSTESTABILE, P. SALMON, *J. Z. KISS
Univ. of Geneva, Dept. of Neurosciences, Geneva, Switzerland

Abstract: Being densely interconnected with the limbic system and sensory as well as motor cortices, the retrosplenial cortex (RSC) has been implicated in the integration of spatial information and memory, which is essential for spatial navigation. Interestingly, structural and functional abnormalities of RSC have been found in patients suffering from neurodevelopmental disorders such as bipolar disorder, autism spectrum disorder and schizophrenia. While the structure and connectivity of RSC are well documented, the signaling pathways regulating its development are still poorly understood. Wnt signaling has been implicated in several steps of cortical development, including proliferation and specification of neuronal progenitors, and radial migration of late-born pyramidal neurons. The non-canonical Wnt signaling pathways have been implicated in dendritic development and synapse formation of pyramidal neurons in culture. Little is known about the role of canonical Wnt transcription-dependent signaling in dendritic development. Here, we investigated the role of canonical Wnt transcriptional activity in dendritic and synaptic development of layer II pyramidal neurons of RSC. These cells project their apical dendrites to layer I, where they form bundles. Using the TopdGFP transcriptional

reporter, we found that canonical Wnt signaling level increases at the beginning of dendritogenesis. Transient downregulation of Wnt canonical signaling during the early postnatal period leads to a significant, irreversible decrease in dendritic branching, persisting into adulthood. At later time points, canonical Wnt signaling is not necessary for maintaining a correct dendritic arborization. However, its downregulation results in decreased spine density and impaired maturation, as well as reduction in both excitatory and inhibitory synapse densities. We identified neurotrophin-3 (NT3) as a downstream target of canonical Wnt pathway and found its overexpression to rescue both dendritic arbor and spine defects. Together, these results reveal a novel role for canonical Wnt transcriptional activity in dendritic development of layer II pyramidal neurons *in vivo* and suggest a function in postnatal RSC circuit formation.

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Nanosymposium

449. Dendrite Morphogenesis

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**Topic: ***A.05. Axon and Dendrite Development

Support: F30 MH 097427
1RC2NS069488

Title: *In situ* visualization of protein interactions reveals Cdc42's coordination of cytoskeletal pathways during dendrite morphogenesis

Authors: *N. SHARIFAI[1], A. CHIBA[1], D. KAMIYAMA[2]
[1]Biol., Univ. of Miami, Coral Gables, FL; [2]Cell. Biol., Univ. of Georgia, Athens, GA

Abstract: Understanding how simple molecules give rise to neural networks requires a platform that can bridge these worlds of vastly different scale. Using optically transparent Drosophila embryos and Forster Resonance Energy Transfer (FRET) as a proxy for protein-protein interaction, we developed a system to visualize protein signaling directly within its natural context. We investigated the small GTPase Cdc42, mapping when and where it associates with its effectors WASp and Par-6, to better understand how it regulates dendrite morphogenesis in developing pioneer motorneurons. Despite broad co-localization of the three proteins, we found Cdc42's interaction with each partner to be highly restricted to the time and place of dendrite formation. While both interactions precede dendritic sprouting and extend in range as dendrites elaborate, each covers a distinct spatial domain along the dendrite arbor. These patterns help

explain the dendritic branching defects observed when any one of the proteins were knocked down. Conversely, expression of a constitutively active Cdc42 mutant produced ectopic filopodia throughout the neuron, which was mirrored by a spatiotemporal expansion of both interactions. These results demonstrate that Cdc42 interacts with both WASp and Par-6 to establish dendrite morphology, and that their signaling patterns are well-suited to coordinate distinct cytoskeletal elements involved in this process.

Disclosures: **N. Sharifai:** None. **A. Chiba:** None. **D. Kamiyama:** None.

Nanosymposium

450. Advances in Understanding Rett Syndrome Pathophysiology

Location: 140A

Time: *Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

Presentation Number: *450.01

Topic: *A.07. Developmental Disorders

Support: NIH R21NS10085

Title: Dendrimer nanoparticle delivery of antioxidant N-acetyl cysteine improves cognition in female MeCP2-deficient mice

Authors: ***E. S. SMITH**[1], C. L. O'FERRALL[1], M. E. BLUE[2], S. KANNAN[1]
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Abstract: Motor and cognitive deficits are hallmark features of Rett Syndrome (RTT). Similar deficits have been reported in male hemizygous (*Mecp2*-null) mice and to a more limited extent in female *Mecp2*-heterozygous mice, which match the genotype of girls with RTT. Mechanisms involving glial cell activation have been implicated in these motor and cognitive deficits in *Mecp2*-null mice but little is known about the relationship between microglia and these cognitive deficits in *Mecp2*-heterozygous mice. Thus we aimed to (1) study *Mecp2*-heterozygous microglia and (2) attempt to improve function of these microglia and resulting phenotypic features using targeted dendrimer nanoparticle drug delivery of the potent antioxidant/anti-inflammatory N-acetyl cysteine (NAC). Previously, our lab demonstrated that PAMAM dendrimer nanoparticles coupled to NAC (D-NAC) targeted activated microglia and astrocytes, suggesting they may be useful in delivering targeted treatment to glial cells in RTT. Specifically, in the *Mecp2*-null mouse model of RTT, D-NAC administered twice a week lead to marked improvements in the behavioral phenotype, especially pertaining to motor function. However, unlike most girls with RTT *Mecp2*-null mice die prematurely and do not match the genotype of human RTT, which principally affects girls. To assess the therapeutic potential of D-NAC to improve phenotypic

features in a mouse that matches the genotype of RTT, we investigated the impact of D-NAC administration on *Mecp2*-hetereozygous mice. Corroborating other literature, we found that *Mecp2*-heterozygous mice showed hippocampal-dependent learning and memory impairments as defined by deficits in contextual fear conditioning. Preliminary results also indicated increased expression of markers for oxidative stress and phagocytosis in the hippocampus in untreated *Mecp2*-hetereozygous mice. We observed (most prominently) that D-NAC administration improved hippocampal-dependent contextual fear conditioning in *Mecp2*-heterozygous mice. These results demonstrate the potential of D-NAC to improve cognitive impairments in the *Mecp2*-heterozygous mice. Ongoing studies are characterizing the effects on microglial morphology, oxidative stress and phagocytosis.

Disclosures: E.S. Smith: None. **C.L. O'Ferrall:** None. **M.E. Blue:** None. **S. Kannan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder.

Nanosymposium

450. Advances in Understanding Rett Syndrome Pathophysiology

Location: 140A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:15 AM

**Presentation Number: ***450.02

**Topic: ***A.07. Developmental Disorders

Support: Funded by Teva Pharmaceutical Industries Israel

Title: Pridopidine treatment recovers gait abnormalities and rescues impaired BDNF expression in a Rett syndrome mouse model

Authors: *M. GEVA[1], J. DREYMANN[1], S. BARASH[1], T. HANANIA[2], A. ORBACH[1], D. LAIFENFELD[1], I. GROSSMAN[1], R. LAUFER[1], M. R. HAYDEN[1]
[1]Pharmacol., Teva, Netanya, Israel; [2]PsychoGenics Inc., Tarrytown, NY

Abstract: Rett syndrome is an X-linked neurodevelopmental condition, characterized by loss of spoken language, regression of purposeful hand use, distinctive hand stereotypes, and gait abnormalities. The disorder affects ~1 in 10,000 females, with 95% of cases being caused by loss-of-function mutations in the X-chromosome gene encoding methyl-CpG-binding protein 2 (MeCP2), a transcriptional regulatory protein. In the MeCP2 Bird mouse model (Mecp2tm1.1Bird) the males lack *MECP2* ($Mecp2^{-/Y}$) and females express one copy (Mecp2 Het). The behavioral and molecular characteristics of this model recapitulate the pathology and functional deficits of Rett syndrome (Ogier et al., 2007, Stearns et al., 2007, Abdala et al., 2010). Mecp2-deficient males exhibit mobility problems and other Rett Syndrome-like characteristics

starting from 3-8 weeks of age, resulting in shortened life-span. Female mice develop robust deficits despite normal survival, including gait, respiration, motor-coordination and sensory-motor gating abnormalities from as early as 6 weeks of age (Chen et al., 2001). Brain-derived neurotrophic factor (BDNF), a key protein promoting brain plasticity and neuroprotection, is reduced in the cortex of female mice from12 weeks of age. Pridopidine, a drug in clinical development for Huntington Disease (HD) has been shown clinically, and in preclinical HD models, to improve gait and motor behaviors. Pridopidine is a Sigma-1 receptor (S1R) ligand that has been shown to mediate BDNF secretion via S1R. In the present analysis, pridopidine (30 mg/kg bid in male $Mecp2^{-/Y}$ and 3 or 30 mg/kg bid in female Mecp2 Het) was administered orally and its effects on gait, motor and startle response were assessed. BDNF mRNA transcript levels were measured in 12-week-old female brains. Pridopidine (3 mg/kg bid) showed increased startle response compared to vehicle-treated female mice. Pridopidine significantly improved gait features in both males and females, with the higher dose having a more pronounced effect. In addition, pridopidine rescued the downregulated mRNA levels of BDNF IV and BDNF IX transcripts. There is currently no cure or treatment for Rett Syndrome. Pridopidine represents a potential therapeutic approach for this devastating disease.

Disclosures: **M. Geva:** A. Employment/Salary (full or part-time):; Teva. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Teva. **J. Dreymann:** A. Employment/Salary (full or part-time):; Teva. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Teva. **S. Barash:** A. Employment/Salary (full or part-time):; Teva. **T. Hanania:** A. Employment/Salary (full or part-time):; PsychoGenics. 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.; Teva. **A. Orbach:** A. Employment/Salary (full or part-time):; Teva. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Teva. **D. Laifenfeld:** A. Employment/Salary (full or part-time):; Teva. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Teva. **I. Grossman:** A. Employment/Salary (full or part-time):; Teva. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Teva. **R. Laufer:** A. Employment/Salary (full or part-time):; Teva. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Teva. **M.R. Hayden:** A. Employment/Salary (full or part-time):; Teva. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Teva.

Nanosymposium

450. Advances in Understanding Rett Syndrome Pathophysiology

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**Presentation Number: ***450.03

**Topic: ***A.07. Developmental Disorders

Support: R01-NS065027
T32-NS007441

Title: Altered hippocampal inputs to the mPFC result in deficits in social behaviors in Rett syndrome mice

Authors: *M. PHILLIPS[1], L. POZZO-MILLER[2]
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Abstract: Altering the excitatory/inhibitory balance in the medial prefrontal cortex (mPFC) causes autism-like social phenotypes in mice. Using an unbiased machine-learning behavioral classifier, we identified atypical social behaviors and impaired social memory in the *Mecp2* knockout (KO) mouse model of Rett syndrome (RTT), an autism-associated monogenic developmental disorder. Neuronal network activity is lower in the mPFC of *Mecp2* KO mice compared to age-matched WT mice, as estimated by c-Fos immunohistochemistry and high-speed imaging of voltage-sensitive dye (VSD) signals in acute slices. However, stimulation of ventral hippocampal (vHIP) fibers in mPFC slices of *Mecp2* KO mice results in larger amplitude and spatial spread of VSD signals. Normalized to intracortical stimulation in layer 2/3 of the same slices, there is a stronger contribution of vHIP inputs to the *Mecp2* KO mPFC compared to WT mice. In addition, high-frequency stimulation of vHIP afferents in mPFC slices from *Mecp2* KO mice fails to undergo long-term potentiation, as observed in WT slices. To identify active neurons during social memory tasks, we utilized retrobead tracing to label pyramidal neurons in area CA1 and the subiculum (SUB) that project to the mPFC and c-Fos immunohistochemistry. This approach revealed that mPFC-projecting CA1/SUB neurons are selectively activated in WT mice during social tasks. On the other hand, mPFC-projecting CA1/SUB neurons in *Mecp2* KO mice do not show heightened c-Fos levels after social memory tasks. These data suggest that mPFC-projecting vHIP pyramidal cells encode information important for social recognition, and that non-plastic, non-selective inputs from the vHIP in the mPFC of *Mecp2* KO mice may contribute to the observed deficits in social memory and underlie atypical social behaviors. We are currently testing if chemogenetic silencing of the vHIP improves social behaviors in *Mecp2* KO mice, and if vHIP chemogenetic activation in WT mice results in altered network activity and social behaviors and memory phenotypes reminiscent of those observed in *Mecp2* KO mice.

Disclosures: M. Phillips: None. **L. Pozzo-Miller:** None.

Nanosymposium

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Title: Medial ganglionic eminence and cortical organoids model human brain development and interneuron migration

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Abstract: The techniques to generate brain organoids provide unique platforms to model human brain development and neurological disorders. While brain organoids resembling corticogenesis were already established, a system modeling human medial ganglionic eminence (MGE) development, which is a critical ventral brain domain producing cortical interneurons and related lineages, remains to be developed. In our current study, we established a system to generate MGE or cortex-specific organoids (hMGEOs or hCOs) from human pluripotent stem cells. hMGEOs and hCOs recapitulated the developments of human MGE and cortex domains respectively. The transcriptional dynamics and lineage productions during hMGEOs and hCOs development were investigated by performing population and single-cell transcriptomic profiling. Chromatin accessibility landscapes were found to be involved in the transcriptional

regulation during organoids development. Furthermore, both hMGEOs and hCOs efficiently generated physiologically functional neurons and neuronal networks. Finally, we applied fused MGE-cortical organoids (hfMCOs) as a model to investigate human interneuron migration. Together, our study provides a new platform for generating domain- specific brain organoids, for modeling human interneuron migration, and offers deeper insight into molecular dynamics during human brain development.

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Title: Hippocampal circuit dysfunction underlies fear memory deficits in Rett syndrome mice

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Abstract: Intellectual disability is one of the most common and reproducible phenotypes of Rett syndrome (RTT)-a disorder caused by loss-of-function mutations in the gene encoding methyl-CpG-binding protein 2 (*MECP2*). The effects of *MECP2* deficiency on the circuit dysfunction that might underlie this phenotype remain unknown. To evaluate the circuit alterations that might result from *MECP2* deficiency, we used an integrated microscope to study the mouse model of RTT (*Mecp2*$^{+/-}$, RTT mice) and tracked the Ca^{2+} dynamics of hippocampal CA1 excitatory neurons (~200 cells per mouse) during learning and memory retrieval in freely moving mice. Seven RTT mice and ten wild-type (WT) mice were imaged when undergoing contextual fear conditioning and then testing within the same context one hour and one day after the training.

We found that CA1 neurons from freely behaving RTT mice had elevated synchrony in the neuronal firing activity ($p < 0.001$, Kolmogorov-Smirnov test) similar to CA1 neurons from *ex vivo* brain slices of the same model. Further, RTT mice showed reliable deficiencies in long-term contextual fear memory (one day after training, $p < 0.05$, *t*-test) while still retaining their short-term contextual memory (one hour after training, $p = 0.4$, *t*-test). By examining the population Ca^{2+} event vectors of CA1 pyramidal neurons that encode contextual fear memory, we found that the memory representation between learning and long-term retrieval was less correlated ($p < 0.05$, *t*-test) and displayed more variations in firing rates ($p < 0.001$, Levene's test) in RTT mice compared to WT animals, but not between learning and short-term memory retrieval. The inability of CA1 neural ensemble for stable memory representation may be the underlying circuit mechanism for decreased long term memory in RTT mice. These findings reveal the firing and correlations patterns of CA1 neurons during short and long term memory retrieval and highlight the importance of MeCP2 for the proper function of the CA1 circuit, providing insight into how disturbance of the circuit might contribute to the intellectual disability phenotype in RTT.

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Title: Rescue of mTOR/AKT pathway deficits in Rett syndrome mouse model : Translational potential for therapeutic strategy

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Abstract: Rett syndrome (RTT) is an X-linked neurodevelopmental disorder that is caused primarily by mutations in the gene encoding methyl-CpG binding protein 2 (MECP2). Pathological studies of human RTT cases and animal models have all shown a reduction in brain size, increased cell packing density, and aberrant dendrite structure. The major barrier toward

developing an effective therapy for RTT is the lack of understanding of the molecular mechanisms that links MECP2 gene mutation to the specific neuropathology. We have created a "knock-in" *Mecp2* mouse model, which expresses the A140V mutation. Mutant A140V male animals have a very subtle neurological phenotype and a normal life span, but the neuropathological features are similar to other animal models and humans with RTT. Reduced soma and nuclear size in neurons from male *Mecp2 A140V* mutant mice are among the key neuropathological findings. In our studies, we found that mTORC2 pathway is significantly downregulated in *Mecp2 A140V* model, suggesting its influence on neuronal size via the mTORC2 pathway. However, alterations in the activity of the mTOR signaling pathway overlapping both the mTORC1 and mTORC2 were observed through comprehensive protein analysis. We mapped mRNA expression of all mTOR signaling pathway in the adult mouse brain (CNS) using quantitative polymerase chain reaction (qPCR) and found that the rictor expression was significantly downregulated in the *Mecp2 A140V* mice. In contrast, we observed a reduction in the phospho-Akt (s473) levels from the mutant mice brain lysate. We next examined if mTOR activation rescues deficits in Mecp2 mutant animals by crossing female carriers (*Mecp2 A140V*) with the TSC2 ($TSC2^{-/+}$) mutant males, which are characterized by increased mTOR activity. In the genetic rescue experiment, we found that the rictor gene expression level in *A140V-TSC2* mutant mice was rescued to the wild type animal levels. Similarly, we also found the Akt phosphorylation was rescued in A140V-TSC2 mutant mice. We have observed increased phosphorylation of IGFR1 (IGF1 receptor) in *Mecp2 A140V* mice and interestingly, the phosphorylated IGFR1 levels were reduced due to activation of the mTOR pathway in A140V-TSC2 mice. Our findings suggest that the mTOR pathway defect in Rett syndrome model can be rescued. The results of our research defining the role of the mTOR pathway in animal models of RTT leading to the establishment of new mechanistic view - the mTORopathy of RTT, which may also fuel the development of new drug therapies that rescues RTT.

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Title: Perineuronal nets in a mouse model of Rett syndrome: Regulation by activity and disease in hippocampus

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Abstract: Developing neural circuits are shaped by experience in early postnatal life and are particularly sensitive to changes in neuronal activity during critical windows of plasticity. The exact mechanisms underlying such critical periods are not fully understood, however one leading player in limiting synaptic plasticity in adults is a specialized form of extracellular matrix proteins, perineuronal nets (PNNs). PNNs are functionally implicated in inhibiting structural and synaptic plasticity and have been linked to several disorders with severe learning impairments such as the autism spectrum disorder Rett Syndrome. Although PNNs are predominantly localized to inhibitory neurons in the hippocampus and throughout the brain, we have characterized a population of *excitatory* neurons in mouse hippocampal area CA2 with a dense concentration of PNNs surrounding them. Interestingly, CA2 synapses are resistant to some forms of synaptic plasticity, specifically to the induction of long-term potentiation (LTP). We have recently identified PNNs as a key negative regulator of LTP at excitatory synapses in CA2 stratum radiatum; degradation of PNNs in acute hippocampal slices between postnatal day P14-18 was sufficient to enable LTP at normally plasticity-resistant CA2 synapses. We also tested LTP in CA2 at younger ages (P8-11) when PNNs are absent and found that LTP is expressed at CA2 synapses at that age. Next, we investigated how PNNs may be altered during early development in a mouse model of Rett Syndrome (MECP2 KO mice). We found that PNN staining intensity is increased in the MECP2 KO mouse CA2 from P14 to adulthood and that PNNs develop abnormally early in CA2 compared to control littermates. We then tested whether LTP in CA2 of young MECP2 KO mice was prematurely lost coincident with the early PNN expression. We found that indeed, LTP was absent in MECP2 CA2 at P8-11. Given that this effect may be activity-regulated, we then investigated if directly increasing or decreasing neuronal activity of CA2 neurons using chemogenetics *in vivo* 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, disrupts formation and maintenance of PNNs. Overall, the developmental increase of PNNs in CA2 is highly suggestive of an unknown critical period of plasticity in the hippocampus and may ultimately reveal a mechanism behind the severe hippocampal-dependent learning impairments that emerge in infants with Rett Syndrome.

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Title: Altered intracellular chloride level leads to reduced inhibition and cortical network deficits in Rett Syndrome

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Abstract: Rett Syndrome (RTT) is caused by genetic mutations in MEPC2 and leads to autism-like symptoms. Disruption of excitation/inhibition (E/I) balance in the brain has been observed in mouse RTT models, and is considered a potential mechanism for RTT symptoms. Previous *in vitro* studies had showed that Mecp2 mutation in cell culture causes decreased expression of a K^+/Cl^- cotransporter KCC2 that pumps chloride into neurons, and increased intracellular concentration of chloride, which leads to higher $GABA_AR$ reversal potential and reduced inhibition.

We explored this specific mechanism in the brain and the impact of its pharmacological reversal on cortical neuron response properties as well as animal physiology. Bumetanide blocks a $Na^+/K^+/Cl^-$ cotransporter, NKCC1, that pumps chloride out of neurons, and was used in this study to reverse the impact of KCC2 suppression in Mecp2 homozygous male (KO) or heterozygous female (HET) mice.

First we performed perforated patch recordings in brain slices, and found that KO mouse neurons had higher $GABA_AR$ reversal potential than wildtype (WT). Bumetanide treatment restored this heightened reversal potential to WT levels (Banerjee et al., PNAS 2016).

Super-clomeleon is a Cl- sensitive FRET fluorophore that has been used for *in vitro* ratiometric measurement of Cl- concentration. To examine the intracellular Cl^- change *in vivo*, we developed two photon imaging of super-clomeleon in cortical neurons of awake mice. Preliminary data showed increased Cl- in HET mice compared to WT, which was reduced after bumetanide treatment.

To probe the direct effect of altered inhibition in the cortex, we carried out two photon calcium

imaging *in vivo* of primary visual cortex (V1) pyramidal neurons, and tested visual response properties of the same neurons in HET mice before and after bumetanide treatment. Contrast gain control, a property of feedforward inhibition in cortical circuits, was reduced in HET compared to WT mice, and was partially rescued by bumetanide treatment.
Apnea is a prominent symptom of RTT: we performed full body plethysmograph on KO mice to examine the physiological effect of reversing the altered chloride level. While sham injected KO mice showed increased frequency of breath pauses between P28 and P42, bumetanide treated KO mice showed no respiration decline, similar to WT mice.
These results suggest that a specific mechanism of Cl^- imbalance contributes to multiple stages of RTT pathology in a mouse model, and demonstrate that reversing the imbalance can alleviate some symptoms at these stages.

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Title: Total RNA-sequencing of Rett syndrome autopsy samples to facilitate preclinical target identification

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Abstract: Mutations in the *Methyl CpG Binding Protein 2* (*MECP2*) gene are responsible for the neurodevelopmental disorder Rett syndrome (RTT). MeCP2 is a transcription factor and its abundance and ability to complex with HDAC3 is linked to the regulation of chromatin structure. Consequently, loss-of-function mutations in MeCP2 are predicted to affect the expression of a large number of genes. However, to date, studies in mouse models of RTT have identified a

limited number of gene or pathway level disruptions, and even fewer genes have been identified that could be considered amenable to classical drug discovery approaches. This presentation will outline our RNA-sequencing (seq) experiments on 9 motor cortex and 6 cerebellar autopsy tissue samples from age, sex and post-mortem interval matched RTT patients and controls. This approach identified 95 genes that were disrupted over 1.5 fold in the motor cortex and 519 in the cerebellum, with a global trend towards increased expression. Within these results, we observed enrichment in genes and pathways previously associated with autism and autism-associated disorders. A directed profile of existing preclinical RTT targets confirmed that KCC2, $mGlu_5$, and $mGlu_7$ protein expression was decreased in the brains of RTT patients, but failed to quantify any significant changes in BDNF or IGF1 protein levels. A survey of our RNA-seq results also identified a significant decrease in expression of the *muscarinic acetylcholine receptor 4* (*CHRM4*) gene, which encodes a receptor (M_4) that is the subject of multiple large drug discovery efforts for schizophrenia and Alzheimer's disease. *Chrm4* knockout mice exhibit a phenotype analogous to RTT-model mice in cognitive and social domains, and we quantified decreased *Chrm4* expression in the hippocampus and cerebellum of *Mecp2*$^{+/-}$ mice. Excitingly, treatment with an M_4 positive allosteric modulator was sufficient to normalize social and cognitive phenotypes in *Mecp2*$^{+/-}$ mice. Taken together, our data provide novel basic science and translational insights into the clinical etiology of RTT, and advocate for the integration of patient samples early in study design. We will present our most current findings and share our experiences integrating RTT autopsy samples into drug discovery efforts.

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Title: Rett syndrome gene therapy improves survival and ameliorates behavioral phenotypes in MeCP2 null mice

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Abstract: Rett syndrome is a devastating progressive neurodevelopmental autism spectrum disorder affecting approximately 1 in 10,000 girls. Rett patients experience loss of achieved developmental milestones including speech and motor function beginning at 6-18 months of age. Patients typically survive for 40- 50 years, requiring intense supportive measures including 24/7 care. This produces a significant emotional and financial burden on patients and families. Rett syndrome is caused by mutations in the X- linked methyl-CpG binding protein 2 (MeCP2) gene: encoding a ubiquitous transcription factor with activating and repressing functions for thousands of genes in the brain. Recent studies using rodent models have demonstrated that re-expression of MeCP2 ameliorates Rett-syndrome like phenotypes including decreased survival, and abnormalities in motor activity. Thus, we believe that gene therapy is a promising therapeutic strategy for this disease. To this end, we have generated a self-complementary adeno-associated virus serotype 9 vector (scAAV9.MeCP2) expressing the human MeCP2 gene under the control of a truncated MeCP2-promoter. This promoter maintains parts of the endogenous regulatory elements to ensure accurate expression levels of our construct. We determined the efficacy and safety of this vector in male mice (MeCP2 null and wild type) and male non-human primates (NHPs). Mice were injected intracerebroventricularly with multiple doses and behavior (rotarod, open field) and survival were monitored. Weight gain, blood and liver parameters of 5 juvenile NHPs (*M. fascicularis*) were monitored after lumbar intrathecal injection of scAAV9.MeCP2. To date, 3 NHPs were sacrificed for transgene expression and pathology evaluation. We found that all doses of scAAV9.MeCP2 tested in MeCP2 null mice increased survival and rescued behavioral symptoms. The most promising dose increased the median lifespan from 66 to 315 days. No toxicity was observed in wild type mice. In NHPs, weight, blood parameters, and liver enzymes remained normal up to the time of abstract submission (18 months post treatment). No indications of pathology were found in the NHPs that were sacrificed at 5 weeks post injection. Overall, our results show good expression of MeCP2 throughout the whole central nervous system after a single injection. In MeCP2 null mice, treatment more than quadrupled the lifespan indicating high therapeutic potential. We will continue to examine the safety of our vector in treated mice as well as NHPs. Completion of this work will allow IND enabling mouse and NHP safety studies with the goal of initiating a clinical trial in the near future.

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**Topic: ***A.07. Developmental Disorders

Title: The role of the cytoskeleton in mitochondrial trafficking in Rett syndrome

Authors: *W. GOLD[1,2], L. CANTRILL[2,3], N. BAHRAM SANGANI[1], B. LAW[1], V. SHAHEN[1], J. CHRISTODOULOU[1,4,5]
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Abstract: Background: Rett syndrome is a devastating neurodevelopmental disorder, predominantly caused by mutations in the transcriptional regulator Methyl-CpG-binding protein 2 (*MECP2*) gene. A predominance of neuronal and synaptic dysfunction is an overarching feature of Rett syndrome. Defective microtubule dynamics and concomitant aberrant trafficking of brain derived neurotrophic factor (BDNF) has recently been described in Rett syndrome highlighting the importance of the microtubule network. Reduced microtubule stability and defective trafficking of mitochondria has been reported in neurological disorders such as Alzheimer's Disease. As a stable microtubule network is essential for the trafficking of mitochondria to critical regions of the cell such as the synapse, it is possible that mitochondria may be aberrantly trafficked in Rett syndrome.
Aims: To investigate the role of the microtubule network in the trafficking of mitochondria in the *Mecp2*^{T158A} Rett syndrome mouse model.
Methods: Microtubule dynamics was assessed in fibroblast cells from Rett syndrome patients. Cortical neurons were isolated from wild type and *Mecp2*^{T158A} mice and cultured for 6, 10 and 14 days *in vitro*. Live cell imaging was performed at each time point to visualize the trafficking of the mitochondria (stained with MitoTracker). Kymographs were prepared and the velocity of individual mitochondria was measured. Mitochondrial mass was also measured to determine overall mitochondrial number. Finally, other components of the cytoskeleton such as vimentin were assessed too.
Results: Our preliminary results reveal that mitochondria in cortical neurons of the *Mecp2*^{T158A} mice travel on average 5 times slower than that of the wild type mice. We can also show that there is 10 fold more vimentin in patient cells compared to control cells.
Conclusions: Given that mitochondria are essential for energy production, calcium buffering and cell survival, it is not surprising that impaired mitochondrial trafficking is observed in

neurological disorders. Altered mitochondrial trafficking plays a vital role in neuronal dysfunction and pose a potential therapeutic target for Rett syndrome.

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Title: Cell type-specific analysis of gene expression in Rett syndrome by single-cell RNA sequencing

Authors: *W. RENTHAL[1], L. BOXER[2], E. LI[2], S. HRVATIN[1], A. NAGY[2], M. E. GREENBERG[2]
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Abstract: Mutations in the methyl-CpG-binding protein 2 (MECP2) gene cause Rett syndrome, a severe X-linked neurodevelopmental disorder characterized by language impairment, intellectual disability, stereotyped movements, and autism spectrum behavior. In addition to being the leading genetic cause of intellectual disability in girls, the monogenic etiology of Rett syndrome has prompted intense study of how MeCP2 dysfunction leads to dramatic neurological phenotypes. Early studies into MeCP2 function demonstrated that it is highly enriched in neurons, interacts with methylated DNA, and represses gene expression. However, subsequent studies paint a more complex picture because MeCP2 is bound diffusely across the genome, which has made it difficult to identify specific gene targets that mediate the neurodevelopmental disorder. We recently gained some insight into this problem through a meta-analysis of multiple gene expression studies from MeCP2-mutant mice and found that MeCP2 preferentially regulates very long, highly methylated genes. Because DNA methylation patterns are cell type-specific, we hypothesized that MeCP2 regulated genes are also likely to be dependent on cell type. Our study applies recent advances in single-cell RNA sequencing to investigate the MeCP2-dependent gene expression programs across each brain cell type in parallel in both

mouse and human brain. These data suggest that cell type-specific DNA methylation patterns largely determine the extent of gene regulation by MeCP2 within in an individual cell type. Together, these findings provide new insight into the complexity of transcriptional misregulation that occurs in parallel across multiple cell types in Rett syndrome.

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**Presentation Number: ***450.13

**Topic: ***A.07. Developmental Disorders

Support: Brain/MINDS
JSPS
NPO Rett Syndrome Supporting Organization

Title: Generation and analysis of MECP2 mutant marmoset

Authors: *N. KISHI[1,2], K. SATO[3], M. OKUNO[1], T. ITOU[1], H. J. OKANO[4], E. SASAKI[3], H. OKANO[1]
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Abstract: In the human brain, there are two major functional domains. One has been conserved in all mammals through evolution and governs fundamental functions such as reward, emotion and memory; the other is unique to primates, and is acquired through the enlargement of the cerebral cortex governing special functions such as tool use, language, and self-consciousness. Thus, to properly understand these brain functions, we need appropriate animal models for studying each function. Animal models that are used to analyze brain functions are different in each case. In the former, a reductive approach is adopted based on gene manipulation using models such as genetically-modified fish and rodents, while in the latter, the main approach is psychological and involves complex behavior analysis using non-human primates such as macaque monkeys. Many researchers believed that the complementary nature of genetic engineering technologies in rodent and fish models and cognitive neuroscience techniques in primate research would lead to progress in this research field. However, due to lack of appropriate animal models that can be analyzed in both aspects of the brain's functions, contact points between these two approaches have been limited.

The development of genetically engineered non-human primates has attracted attention for its potential to connect the two research fields. Recently, we succeeded in creating the world's first transgenic primate using marmosets. This technological breakthrough provides a potential paradigm shift by enabling researchers to analyze both the brain functional domains using various model marmosets.
Currently, we are developing a technique for creating knockout marmosets using zinc finger nuclease (ZFN) technology. By combining this technique with the development of cognitive information for marmoset brain analysis, innovative MRI imaging technology and marmoset genetic analysis tools, we created and are analyzing MECP2 mutant marmosets suitable for research on Rett syndrome. MRI imaging shows that the brain size of MECP2 +/- marmoset was smaller than wild-type ones by approximately 15% at 24 months of age, and less active than wild-type ones in the daytime.

Disclosures: **N. Kishi:** None. **K. Sato:** None. **M. Okuno:** None. **T. Itou:** None. **H.J. Okano:** None. **E. Sasaki:** None. **H. Okano:** None.

Nanosymposium

451. Astrocytes: Disease Mechanisms

Location: 150B

Time: *Tuesday, November 14, 2017, 8:00 AM - 9:45 AM

Presentation Number: *451.01

Topic: *B.12. Glial Mechanisms

Support: NIH Grant EY019037
Research to Prevent Blindness

Title: Inhibiting EGFR/mTORC1 signaling in optic nerve astrocytes as a novel strategy for the treatment of persistent fetal vasculature (PFV) disease

Authors: ***M. YAZDANKHAH**, T. LUO, I. BHUTTO, R. GREBE, P. SHANG, S. MISHRA, G. LUTTY, S. HOSE, J. S. ZIGLER, Jr, D. SINHA
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Abstract: Purpose: Persistent fetal vasculature (PFV) is a human disease that results from failure of the fetal vasculature to regress normally. Nuc1 is a spontaneous mutation in the *Cryba1* gene (encoding βA3/A1-crystallin). We have previously shown that in Nuc1 rats, normal regression of the hyaloid artery is inhibited and astrocytes abnormally ensheath the retained artery. Moreover, the Nuc1 astrocytes show atypical migration and increased proliferation, compared to controls. In this study we have investigated the molecular mechanisms that control proliferation and migration of astrocytes in Nuc1 rats.

Method: Astrocytes were isolated and expanded in culture from the optic nerve of Nuc1 and wild type (WT) rats. MTS and wound healing assays were performed to investigate proliferation and migration respectively. Western blotting and immunostaining were used to study epidermal growth factor receptor (EGFR)/ mammalian target of rapamycin, complex 1 (mTORC1) signaling in astrocytes. The rate of autophagosome formation and degradation was investigated by transiently transfecting astrocytes with a tandem fluorescently tagged LC3 (RFP-GFP-LC3).
Results: We found that loss of βA3/A1-crystallin leads to aggregation of astrocytes in Nuc1 retina. Cultured Nuc1 astrocytes proliferate and migrate faster than WT. EGFR/mTORC1 signaling pathway and positive regulators of cell cycle are upregulated in Nuc1 astrocytes. Moreover, inhibition of mTORC1 and EGFR by AZD8055 and Gefitinib, respectively, lead to blockage of proliferation and migration of astrocytes *in vitro*. Activation of mTORC1 inhibits autophagy in Nuc1 astrocytes. Furthermore, we found that the lysosomal-mediated clearance of autolysosomes and EGFR in Nuc1 is reduced compared to WT astrocytes.
Conclusion: Our studies provide evidence that loss of βA3/A1-crystallin lead to abnormal proliferation and migration of astrocytes. Furthermore, impaired lysosomal function in Nuc1 astrocytes activates EGFR/mTORC1 signaling, exacerbating abnormal proliferation and migration. Our data suggests that inhibition of the EGFR/mTORC1 pathway may help to develop therapy for PFV, a blinding childhood disease with limited treatment options at present.

Disclosures: M. Yazdankhah: None. **T. Luo:** None. **I. Bhutto:** None. **R. Grebe:** None. **P. Shang:** None. **S. Mishra:** None. **G. Lutty:** None. **S. Hose:** None. **J.S. Zigler:** None. **D. Sinha:** None.

Nanosymposium

451. Astrocytes: Disease Mechanisms

Location: 150B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***451.02

**Topic: ***B.12. Glial Mechanisms

Support: NIH Grant ES021656
NIH Grant ES021656-S1
NIH Grant ES024183
NIH Grant ES 026860

Title: Glial-neuronal signaling mechanisms underlying the neuroinflammatory effects of manganese

Authors: *K. A. POPICHAK, M. F. AFZALI, K. S. KIRKLEY, R. B. TJALKENS
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Abstract: Exposure to increased manganese (Mn) levels causes inflammation and neuronal injury in the cortex and basal ganglia, resulting in the neurodegenerative disease, Manganism. The mechanisms underlying neuronal death from exposure to Mn are not well understood but involve inflammatory activation of microglia and astrocytes. Expression of neurotoxic inflammatory genes in glia is highly regulated through the NF-κB pathway but the key factors modulating glial-glial and glial-neuronal signaling by Mn are not known. We examined the role of NF-κB in Mn induced neurotoxicity by exposing pure microglia, astrocytes (from wild-type and astrocyte-specific IKK knockout mice) and mixed glial cultures to varying Mn concentrations and then treating glia and neurons with the conditioned media (GCM) of each cell type. We hypothesized that mixed glial cultures exposed to Mn (0-100μM) would enhance glial activation and neuronal death compared to microglia, wild type astrocytes or IKK-knockout astrocytes alone or mixed cultures. To determine optimal Mn concentration to induce glial inflammation and neuronal death from GCM, primary cultures of mixed glia, pure astrocytes and microglia were treated with 0-100 μM Mn for up to 24 hr. Under these conditions, we measured inflammatory cytokine release by glia in media via ELISA and NF-κB-mediated inflammatory gene expression by qPCR in glial cells. In mixed glial cultures, Mn exposure enhanced expression of inducible nitric oxide synthase (NOS2) and multiple inflammatory cytokines and chemokines, including TNF, CCL2 and IL-6. Gene deletion of IKK2 in astrocytes dramatically reduced cytokine release in Mn-treated mixed glial cultures. Additionally, measurement of neuronal viability and apoptosis, upon GCM exposure, showed mixed glial cultures induced greater neuronal death than either cell type alone. IKK knockout astrocytes also decreased neuronal death compared to microglia alone, wild type astrocytes or mixed glia. This suggests that NF-κB activation in astrocytes is the primary mediator in Mn neurotoxicity.

Disclosures: K.A. Popichak: None. **M.F. Afzali:** None. **K.S. Kirkley:** None. **R.B. Tjalkens:** None.

Nanosymposium

451. Astrocytes: Disease Mechanisms

Location: 150B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***451.03

**Topic: ***B.12. Glial Mechanisms

Title: Cell polarity in astrocytes - resolving the role of the scaffolding protein Par3 in astrocytes for better or for worse

Authors: *H. M. JAHN[1], J. GÖBEL[1], M. BERGAMI[1,2]
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Abstract: Cell polarity is essential for a vast number of cellular processes, from establishment of apical-basal orientation in epithelial cells to axon specification in neurons. Loss of cell polarity leads to unavoidable disruption of cell physiology with direct implications for tissue development and homeostasis. So-called polarity proteins (and in particular those involved in the assembly of the Par complex) are responsible for establishment and maintenance of polarized functions in cells. In astrocytes, which are cells polarized in nature, this feature becomes even more prominent in response to injury, where they markedly reorganize their morphology and cytoskeleton by extending processes towards the lesion site. Yet, the interplay of known polarity proteins and their activated pathways in astrocytes have been only partially addressed *in vivo*. Here we used a tamoxifen inducible Cre/LoxP approach in mice to specifically investigate the role of the Par complex component Par3 in astrocytes in a setting of injury *in vivo* (GFAP-CreER x Pard3$^{fl/fl}$). We performed a time course analysis of brains derived from adult control and conditional Par3 knockout (cKO) mice following cortical stab wound injury. In absence of Par3, GFAP+ "reactive" astrocytes maintained to large degree their ability to extend processes towards the lesion site, suggesting none or only minor effects on building up a GFAP+ astroglial scar by 7 days after injury. Furthermore, the well-known polarized distribution of the astrocyte-specific protein aquaporin in the astroglial end feet surrounding blood vessels was not particularly disturbed neither ipsi- nor contralateral to the lesion. However, significant differences between the two experimental groups were observed with respect to their inflammation response, with cKO animals showing a larger inflammation area and widespread activation of microglia, speaking in favour of altered microglia/astrocyte inter-cellular communication. These results show that the polarity protein Par3 is likely dispensable for directed reorganization of astroglial protrusions in response to injury, but implicate a crucial role of Par3 in maintaining cell-cell contacts needed to regulate the inflammation response *in vivo*.

Disclosures: H.M. Jahn: None. **J. Göbel:** None. **M. Bergami:** None.

Nanosymposium

451. Astrocytes: Disease Mechanisms

Location: 150B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***451.04

**Topic: ***B.12. Glial Mechanisms

Support: NINDS RO1 083078

Title: Exosomes derived from ischemic astrocytes promote neurovascular protective effects *In vitro*

Authors: *A. ZACHAREK[1,2], M. CHOPP[1], J. CHEN[1]
[2]Neurol. Res., [1]Henry Ford Hosp., Detroit, MI

Abstract: Astrocytes play an important role in maintaining physiological function in the brain, and have a rapid, sensitive response to cerebral injury or ischemic insult. Exosomes derived from astrocytes may regulate neurovascular function after stroke as well as astrocyte-neuron communication. Exosomes contain microRNAs (miRs- small (22-25nt) non-coding regulatory RNAs), proteins, and mRNAs. We tested the hypothesis that astrocyte derived exosomes from various time points after ischemia may differentially regulate microRNA expression and induce neurovascular changes. We focused on miR-29b, miR-126, and miR-223, which have demonstrated neurovascular protective effects.
Methods: Astrocytes were cultured in vitro and subjected to different times of oxygen glucose deprivation (OGD, 0h, 3h, 6h and 12h). Culture supernatant was collected to isolate exosomes. Primary cortical neurons (PCN), oligodendrocytes (OL), and mouse brain endothelial cells (MBEC) were cultured and treated with control, 0h-OGD, 3h-OGD, 6h-OGD and 12h-OGD exosomes extracted from astrocytes (Astro-Exo). LDH, MTS, axonal outgrowth and capillary tube formation was performed..
Results: Astro-Exo treatment significantly decreases MBEC and OL cell death, increases MBEC and OL proliferation and increases MBEC capillary tube formation compared to control. Furthermore, 6h-OGD-Astro-Exo treatment significantly improves beneficial effects, based on MBEC-LDH and MBEC-MTS assays compared to normal-Astro-Exo treatment ($p<0.05$). 6h-OGD-Astro-Exo also significantly increases PCN cell survival and increases axonal outgrowth compared to control or normal-Astro-Exo treatment group ($p<0.05$). 6h-OGD-Astro-Exo treatment significantly increases miR-29b (9.9 fold), miR-126 (11.5 fold) and miR-223 (6.8 fold) expression compared to control or normal-Astor-Exo. Astro-Exo treatment of PCN also decreases TLR2, TLR4, TNFa and IRAK1, and increases BDNF gene expression compared to control ($p<0.05$). 6h-OGD-Astro-Exo treatment even significantly decreases IRAK1 and TLR4, and increases BDNF gene expression compared to normal-Astro-Exo treated group ($p<0.05$).
Conclusion: OGD Astro-Exo enhance MBEC, OL and PCN cell survival, capillary tube formation and axonal outgrowth, as well as increase PCN miR-29b, miR-126 and miR-223, and decrease inflammatory factor expression. Exosomes from ischemic astrocytes may regulate miRNA expression and result in better therapeutic effects than exosomes from non-ischemic astrocytes, and the therapeutic effect of the exosomes derived from ischemic astrocytes may be dependent on the duration of the ischemia.

Disclosures: **A. Zacharek:** None. **M. Chopp:** None. **J. Chen:** None.

Nanosymposium

451. Astrocytes: Disease Mechanisms

Location: 150B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***451.05

**Topic: ***B.12. Glial Mechanisms

Support: East Tennessee State University Research Development Grant 12-018m
The James Martin 21st Century School, Oxford University, UK
AHA Greater Southeast Affiliate Grant-in-Aid 13GRNT16950054

Title: Astrocyte activation and disruption of the neurovascular unit in systemic sepsis and Alzheimer disease

Authors: *C. E. BOND[1], D. B. HOOVER[2]
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Abstract: Astrocytes are essential components of the neurovascular unit, regulating the local cerebral blood flow and maintaining the integrity of the blood-brain barrier through interaction between their end-foot processes and endothelial cells in brain capillaries. Dysfunction of the neurovascular unit has been implicated in a number of degenerative nervous system diseases such as Alzheimer's and Parkinson's, as well as in CNS complications from systemic disorders such as diabetes, chronic heart disease, and sepsis. Interestingly, individuals who survive cardiac arrest & systemic sepsis often demonstrate significant impairments in cognitive abilities, particularly in spatial learning and memory, as well as a predisposition to severe depression, suggesting that certain areas of the brain are highly vulnerable to hypoxia-induced oxidative damage and disruption of the blood-brain barrier. It has been proposed that astroglial inflammatory responses may underlie many of these degenerative processes. Previous studies utilizing an *in vitro* model in primary astrocytes demonstrated their sensitivity to oxidative stress, including striking phenotypic and biochemical, as well as significant mRNA and protein expression changes. In addition, we have shown that oxidative stress inhibits astrocyte mitochondrial respiration, induces upregulation of mitochondrial apoptotic complex initiators, and alters distribution of mitochondrial inner membrane translocase. Here we provide evidence of astrocyte activation and changes in the neurovascular unit in a mouse model of CLP-induced sepsis, in a mouse model of peptide-induced neuronal stress, and in human post-mortem tissue. These results suggest that dysregulation of astrocyte function in disorders that cause oxidative stress in neuronal tissues may be the result of damage to astrocyte mitochondria, and disruption of astrocyte end-foot processes that surround blood vessels, thus compromising blood-brain barrier integrity and contributing to neuronal inflammatory responses.

Disclosures: C.E. Bond: None. **D.B. Hoover:** None.

Nanosymposium

451. Astrocytes: Disease Mechanisms

Location: 150B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***451.06

**Topic: ***B.12. Glial Mechanisms

Title: Role of reactive astrocytes in multiple sclerosis

Authors: *R. R. MASVEKER[1], B. BIELEKOVA[2], P. KOSA[2], J. MILSTEIN[2]
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Abstract: Multiple Sclerosis (MS) is a chronic neuroinflammatory disorder, in which activated immune cells directly or indirectly induce demyelination, leading to axonal degradation. *In vitro* and *in vivo* animal models of MS have identified several astrocyte-related pathogenic processes. However, these pathogenic processes have not been validated in living MS patients, thereby limiting our ability to understand the role astrocyte-specific pathways play in MS progression. Therefore, our goal is to combine *in vitro* models and analysis of patient CSF samples to get better insight into how astrocytes influence MS progression, which may lead to identification of cell-specific biomarkers and potential therapeutic targets. Liddelow et al. (Nature.2017) showed presence of reactive astrocytes in acute demyelinating MS lesions through immunostaining of postmortem brains of MS patients. We have analyzed CSF from patients with neurological disorders and healthy donors (>500) using Somascan, a novel proteomic scan utilizing modified DNA-aptamers to determine the expression of more than 1100 different proteins. Our studies have shown: **1)** Reactive astrocyte-specific markers (SERPING1 and CFB) were significantly elevated only in progressive-MS subgroup. **2)** These reactive astrocyte-specific markers moderately correlate (Spearman $r > 0.25$) with disease-specific measures. Together, Liddelow et al.'s studies and our patients' CSF analyses have suggested a potential involvement of reactive astrocytes in MS progression. Currently, mechanistic studies with primary human astrocytes and *in vitro* blood-brain barrier (BBB) model are being conducted to address three hypotheses in support of our overall goal. Specifically, these hypotheses include: **1)** Comparing Somascan proteomic analysis of supernatants from unstimulated and stimulated astrocytes will be able to identify new reactive astrocyte-specific biomarkers that will then be validated with patient CSF data; **2)** We will be able to elucidate cytotoxic factors released by reactive astrocytes that contribute to axonal degradation; and **3)** Using *in vitro* BBB models, we will be able to indicate potential roles of astrogliosis in BBB disruption occurring in the later stages of MS. Briefly, these mechanistic studies use primary human astrocytes alone or in a BBB model cultured either without treatment or with inflammatory stimuli. The supernatants from these cells are then collected and subjected to proteomic analysis using Somascan.

Disclosures: R.R. Masveker: None. **B. Bielekova:** None. **P. Kosa:** None. **J. Milstein:** None.

Nanosymposium

451. Astrocytes: Disease Mechanisms

Location: 150B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***451.07

**Topic: ***B.12. Glial Mechanisms

Support: NIH Grant MH094268

Title: Astrocytic aldehyde dehydrogenase 7a1 (ALDH7A1) protects the brain from oxidative stress; impairment destabilizes development of prefrontal excitatory/inhibitory balance and adult affective behavior

Authors: *T. E. FAUST[1,2], W. XIN[2], A. AGARWAL[2], T. CASH-PADGETT[1], S. SAHA[1], S. DESHPANDE[1], D. WOOD[1], C. DAVIS[5], A. BONCI[6], D. E. BERGLES[7], H. JAARO-PELED[3], A. SAWA[4]
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Abstract: Neuron-astrocyte interactions may underlie excitatory-inhibitory (E-I) balance and physiological higher brain function; disruption may lead to neuropsychiatric disorders. Through studies of animal models and patient tissues, we have identified aldehyde dehydrogenase 7a1 (ALDH7A1) as an under-characterized, astrocytic enzyme whose loss-of-function might elicit astrocyte-driven neuropsychiatric deficits. Outside the brain, ALDH7A1 is primarily expressed in the liver and has been shown to produce osmolytes, break down reactive aldehydes, and participate the lysine-degradation pathway. Within the brain, ALDH7A1 expression is highly enriched in astrocytes and may serve similar functions as hepatic ALDH7A1. Systemic ALDH7A1 loss of function is known to cause neonatal, vitamin B6-responsive seizures as well as non-responsive cognitive deficits; however, the mechanistic link between enzyme and pathology remains unknown.
To investigate this question, we generated Aldh7a1$^{Flox/Flox}$ mice and Aldh7a1$^{-/-}$ mice. Aldh7a1$^{-/-}$ mice have metabolic blockage of the lysine degradation pathway and increased oxidative stress in prefrontal cortex (PFC). Aldh7a1$^{-/-}$ mice displayed reduced seizure threshold, spatial memory performance, and forced swim test mobility; however, they showed no signs of spontaneous seizure activity by EEG. Intriguingly, when we crossed Aldh7a1$^{Flox/Flox}$ mice with the GLAST-CreER line (Aldh7a1 cKO^{GLAST}) for deletion in postnatal forebrain astrocytes, we observed increased oxidative stress and the same deficit in forced swim mobility, but significantly increased seizure threshold and spatial memory performance compared to littermate controls.

Consistent with the behavioral results, electrophysiological recordings of layer V pyramidal neurons in PFC from adult mice showed an increased E-I ratio in the Aldh7a1$^{-/-}$ mice, but a decreased E-I ratio in the Aldh7a1 cKO^{GLAST} mice.
We hypothesize that Aldh7a1 deletion has a cell-autonomous effect on the ability of astrocytes to respond to stressors; over the course of development, this, in turn, affects levels of oxidative stress in neurons, impairing proper development of E-I balance. To test this hypothesis, we are analyzing co-cultures of WT neurons and Aldh7a1 KO astrocytes as well as the calcium signaling properties of astrocytes in mosaic animals. In addition, we are testing whether antioxidant treatment during postnatal development can rescue the deficits in affective behavior.

Disclosures: **T.E. Faust:** None. **W. Xin:** None. **A. Agarwal:** None. **T. Cash-Padgett:** None. **S. Saha:** None. **S. Deshpande:** None. **D. Wood:** None. **C. Davis:** None. **A. Bonci:** None. **D.E. Bergles:** None. **H. Jaaro-Peled:** None. **A. Sawa:** None.

Nanosymposium

452. Cognitive Aging and Memory

Location: 143A

Time: *Tuesday, November 14, 2017, 8:00 AM - 11:30 AM

Presentation Number: *452.01

Topic: *H.02. Human Cognition and Behavior

Title: Cognitive and white matter microstructure consequences of Alzheimer's disease pathology in an episodic memory system during cognitive aging

Authors: ***H. OH**[1], A. LEVITANUS[2], K. LE[3]
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Abstract: BACKGROUND: Beta-amyloid (Aβ) deposition and tau-protein neurofibrillary tangles, the hallmark features of Alzheimer's disease (AD) pathology, are present in asymptomatic older adults. Early cognitive and structural impacts of these pathologies in the episodic memory system, however, are not fully understood. To better understand how early AD pathologies affect white matter microstructures connecting an episodic memory system and memory, we examined the relationships between Aβ deposition, white matter structural integrity (WMI), tau accumulation, and cognitive correlates among nondemented older adults. METHODS: We assessed white matter integrity and tau pathology that were measured by diffusion tensor imaging (DTI) and AV-1451 tau PET, respectively, in nondemented older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Forty-seven and 22 nondemented older adults were included in DTI and tau PET results, respectively. A level of Aβ deposition was quantified by ^{18}F-Florbetapir positron emission tomography (PET). For amyloid

and tau PET measures, standardized uptake value ratios (SUVRs) were calculated for freesurfer-based anatomical regions and a global amyloid SUVR was computed according to the ADNI processing pipeline. Multiple regressions were conducted to assess the relationships between global amyloid SUVRs, white matter integrity, tau accumulation, and cognitive measures assessing memory. RESULTS: A level of baseline Aβ deposition was associated with lower white matter tract integrity including cingulum and fornix that connect the medial temporal lobe structures with other cortical regions. The baseline Aβ deposition was further associated with tau accumulation in entorhinal cortex, inferiortemporal cortex, fusiform gyrus, parahippocampal gyrus, hippocampus, and right middle frontal gyrus. The level of tau accumulation in anterior cingulate cortex and medial frontal cortex was further associated with lower white matter integrity in uncinate fasciculus and fornix. Lower white matter integrity significantly predicted worse longitudinal memory decline. CONCLUSIONS: The present results suggest that, although subtle, memory impairment and white matter michrostructural changes in the episodic memory system occur due to AD pathologies among nondemented older adults. White matter integrity may play an important role in AD-related changes in the episodic memory system during aging.

Disclosures: H. Oh: None. **A. Levitanus:** None. **K. Le:** None.

Nanosymposium

452. Cognitive Aging and Memory

Location: 143A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***452.02

**Topic: ***H.02. Human Cognition and Behavior

Title: The association of total brain, hippocampal and ventricular volumes with subject and informant clinical dementia rating scale scores

Authors: M. KITNER-TRIOLO[1], S. E. KANDIGIAN[2], Y. AN[1], *S. M. RESNICK[3]
[1]NIA/NIH, Baltimore, MD; [2]Vassar Col., Poughkeepsie, NY; [3]LBN, Natl. Inst. On Aging, Baltimore, MD

Abstract: AD pathology can predate dementia by over a decade, making early detection essential for pre-clinical intervention. The Clinical Dementia Rating Scale (CDR) is the predominant tool used to detect everyday functioning deficits in Mild Cognitive Impairment and dementia. Recent results from the Baltimore Longitudinal Study of Aging (BLSA) demonstrated that CDR informant reports of everyday functioning deficits are an earlier predictor of dementia diagnosis than subject reports. Changes in hippocampal shape and volume predict dementia onset and are highly correlated with subjective memory complaints. The relationships between total brain and ventricular volume changes and CDR subject and informant scores have not been

investigated. Objectives were to investigate the cross-sectional and longitudinal relationships of total brain, hippocampal and ventricular volumes to CDR-S, CDR-I and CDR-C scores. Included were 194 BLSA participants with mean baseline age of 80 years old (range 59 - 98) who have longitudinal total brain, hippocampal and ventricular volume measurements over time and subject (CDR-S), informant (CDR-I) or combined (CDR-C) CDR total scores of 0 or 0.5 at the last visit. Linear mixed effects models with each brain region as outcome variables were used to evaluate the relationships of coincident CDR total and sum of boxes (SOB) scores with brain volumes and brain-volume rates of change prior to the CDR. Cross-sectionally, total brain and hippocampal volume did not relate to CDR total scores (CDR-S, CDR-I, CDR-C). Greater ventricular volume was marginally related to a CDR-C total score of 0.5 and there was no relationship between ventricular volume and CDR-S or CDR-I total scores. Longitudinally, participants with CDR-I or CDR-C=0.5, but not a CDR-S=0.5 had faster rates of hippocampal decline. Participants with CDR-S, CDR-I or CDR-C scores=0.5 had a faster rate of ventricular volume increase. There was a linear relationship between increased ventricular volume and increased CDR-I SOB and between decreased hippocampal and increased ventricular volume and increased CDR-I only. Both decreased hippocampal and increased ventricular volume are significantly related to higher CDR scores. This relationship should be further investigated as potential early markers of cognitive decline, dementia and Alzheimer's disease. It is important to obtain informant information regarding everyday functioning in the early stages of cognitive impairment.

Disclosures: M. Kitner-Triolo: None. **S.E. Kandigian:** None. **Y. An:** None. **S.M. Resnick:** None.

Nanosymposium

452. Cognitive Aging and Memory

Location: 143A

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**Presentation Number: ***452.03

**Topic: ***H.02. Human Cognition and Behavior

Support: Helmholtz Postdoc Grant PD-309
R01AG034570

Title: Effects of age-related tau and amyloid deposition on domain-specific memory function

Authors: *A. MAAß[1,2], D. BERRON[3,1], T. J. MELLINGER[2], R. K. BELL[2], K. SWINNERTON[2], S. L. BAKER[4], E. DUZEL[3,1], W. J. JAGUST[2]
[1]German Ctr. for Neurodegenerative Dis., Magdeburg, Germany; [2]Helen Wills Neurosci. Inst.,

Univ. of California, Berkeley, CA; [3]Inst. of Cognitive Neurol. and Dementia Res. (IKND), Otto-von-Guericke Univ., Magdeburg, Germany; [4]Lawrence Berkeley Natl. Lab., Berkeley, CA

Abstract: The formation of distinct memories for novel events requires the processing of object and spatial information, which is supported by different pathways that converge within the medial temporal lobe. Intriguingly, these pathways might be differentially affected by age-related deposition of neurofibrillary tangles and amyloid plaques (Aß) - the pathologic hallmarks of Alzheimer's disease. The goal of the current study was to test whether object vs. scene memory is differentially affected by aging and how *in vivo* tau and amyloid accumulation contribute to domain-specific memory decline. Forty-five healthy cognitively normal older adults (OA, mean age 78) and ten young adults (mean age 26) performed a continuous recognition memory task that poses high demands on memory precision and dissociates between object vs. scene memory. Subjects had to discriminate between previously seen object or scene images (repeats) and novel but highly similar images (lures). Delayed memory performance for the images was further tested in a recognition test (~1h after start of the previous task), which included the presentation of completely novel foils. In 38 OA, global cortical Aβ burden was measured with [^{11}C] Pittsburgh Compound B (PIB) PET scans and tau accumulation was measured with [^{18}F] AV-1451 PET scans. All PET data were quantified using individual Freesurfer-derived regions of interest in native space. Elderly subjects showed a general decline in accuracy (i.e. corrected hit rates) for the discrimination of lures from repeats in the continuous recognition task (n.s. group x domain interaction). However, OA showed a more pronounced decline in delayed scene than object memory (i.e. corrected hit rates) compared to the YA (group x domain interaction, $p=0.03$). Correlational analyses with PET data in the OA showed a significant association between parahippocampal tau tracer uptake and scene ($r=-0.35$, $p=0.03$) but not object ($r=-0.21$, $p=0.2$) memory. Although parahippocampal tau was related to global amyloid ($r=0.4$, $p<0.01$) there was no association between amyloid burden and memory performance. These preliminary data suggest that tau accumulation in the parahippocampal cortex, which might be exacerbated by the presence of amyloid, drives age-related decline in episodic scene memory.

Disclosures: A. Maaß: None. **D. Berron:** None. **T.J. Mellinger:** None. **R.K. Bell:** None. **K. Swinnerton:** None. **S.L. Baker:** None. **E. Duzel:** None. **W.J. Jagust:** None.

Nanosymposium

452. Cognitive Aging and Memory

Location: 143A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***452.04

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH Grant R01AG044292
NIH Grant F32AG047686

Title: Brain dopamine and tau pathology affect different aspects of memory performance in cognitively normal older adults

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Abstract: The strength and specificity of our memories are profoundly influenced by the value we place on the events and stimuli we experience. Aging is associated with declines in overall memory performance, but also alteration in how stimulus valence affects memory. The influence of motivation, reward, and emotional valence is likely mediated by interactions between medial temporal lobe (MTL) memory structures and striatum, which receives rich dopaminergic innervation and is implicated in reward processing. In older adults (n = 9, mean age 79.6 years-old), we examined the integrity of these systems using PET imaging to assess MTL deposition of aggregated tau ([^{18}F]AV1451) and striatal dopamine synthesis capacity (6[^{18}F]fluoro-L-*m*-tyrosine) in relation to memory performance. Using a novel incidental encoding paradigm, we examined subsequent memory for stimuli (houses) presented simultaneously with monetary reward, loss, or neutral feedback (n = 56 total). One of three valence cues (faces) preceded the onset of house stimuli and predicted monetary outcomes. During a surprise memory test, participants reported memory confidence (1-4 rating) for the previously presented houses and novel foils, and, for endorsed stimuli, selected the associated face cue. Memory confidence in the neutral condition (neutral – foils) was negatively related to MTL AV1451 binding (r = -.68) and to d' for successfully remembered stimuli (r = -.47). We hypothesized that high dopamine synthesis capacity (thought to reflect nonoptimal dopamine function in aging) would predict insensitivity of memory performance to reward. Though dopamine was only modestly related to memory enhancement for rewarded houses (reward – neutral confidence; r = -.37), it was closely linked to the successful associations between remembered houses and cues for the reward condition (r = -.62). These data support an emerging view that accumulation of tau in MTL is associated with decline in memory in aging, and that maintenance of dopaminergic function in aging enhances the specificity of high-value memories.

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Nanosymposium

452. Cognitive Aging and Memory

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**Topic: ***H.02. Human Cognition and Behavior

Support: F32AG050389
R01AG034570

Title: Examining associations between regional tau deposition, white matter microstructure, and cognition in normal aging

Authors: *S. N. LOCKHART[1], A. MAASS[1], S. M. MARKS[1], S. L. BAKER[2], W. J. JAGUST[1,2]
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Abstract: Relations between brain β-amyloid (Aβ), tau, and white matter (WM) microstructure in cognitively normal older adults (OA) are not well understood. We examined how protein deposition seen with PET was associated with WM microstructure, specifically examining progression of tau pathology from medial temporal lobe into advancing Braak stages, as well as associations between WM microstructure and cognition.
56 OA received T1 and diffusion-weighted MRI, and 18F-AV-1451 (tau) PET. 11C-PiB (Aβ) PET was used to calculate a subject-wise global cortical PiB average. Using FreeSurfer v5.3, we segmented T1 MRIs. We coregistered (to T1) and partial volume corrected AV-1451 (80-100 min SUVR, inferior cerebellar grey reference) images, calculated mean AV-1451 in ROIs that reflect Braak stages I/II, III/IV, and V/VI of tau pathology involvement, and used these values to calculate Braak stage diagnoses. We processed diffusion data (FSL) to generate fractional anisotropy (FA) images, which were warped to MNI space (ANTS) and smoothed. Covariates of no interest included age, sex, white matter hyperintensity (WMH) volume (calculated from FLAIR imaging using SPM's Lesion Segmentation Tool, corrected for intracranial volume [ICV]), gray matter volume (corrected for ICV), global PiB, and DTI-AV-1451 delay. We assessed nonparametric statistical relations between voxelwise FA and Braak stage values using FSL randomise; relations were considered significant if passing a $p < .01$ (uncorrected) threshold. Memory was assessed using a composite of VRI and VRII recall, and CVLT short and long-delay free recall. Executive function was assessed with a composite of Trail B minus A, Stroop Correct, and Digit Symbol.
We found negative associations between increasing Braak I/II AV-1451 and FA in right ventral cingulum bundle. Increasing Braak III/IV and V/VI AV-1451 were associated with reduced FA in bilateral corpus callosum and right dorsal cingulum bundle. Mean FA values were extracted from tau-predicted DTI clusters and used to predict cognition. In a model including Braak I/II,

Braak III/IV, and Braak V/VI-predicted FA, as well as age, global PiB, and education, only Braak I/II-predicted FA was positively associated with memory (p = .014); no measures significantly predicted executive function. Braak I/II-predicted FA did not mediate the association between Braak I/II AV-1451 and memory (p = .002).
These results suggest that a progressive pattern of (cross-sectional) tau deposition is reflected in regionally-specific corresponding disruptions to white matter networks and episodic memory performance in OA.

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**Topic: ***H.02. Human Cognition and Behavior

Support: F32AG054116
AG034570

Title: Early accumulation of beta-amyloid drives tau deposition and memory decline in preclinical Alzheimer's disease

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Abstract: Alzheimer's disease (AD) pathology consists of β-amyloid (Aβ) plaques and neurofibrillary tau tangles. Current models of AD pathogenesis postulate that Aβ is an inciting event, leading to tau aggregation and memory loss. Early detection of pathology is crucial to understanding the causes of AD and to prevent progression of the disease. We studied a sample of older adults with preclinical AD (N=71, mean age 75 years) longitudinally and collected tau and Aβ PET scans as well as performed cognitive testing. We measured brain Aβ with [^{11}C] Pittsburgh Compound B (PIB) PET scans, while tau was measured with [^{18}F] AV-1451 PET scans. PIB PET and cognitive testing were conducted longitudinally, with 2-4 time points of PIB (4.48 ± 2.23 years) and 3-10 sessions of cognitive testing (5.7 ± 2.34 years) per subject. AV-1451 PET was obtained at the end of the observation period and evaluated as grouped regions of interest reflecting progression of tau deposition from medial temporal lobes through inferolateral temporal lobes to diffuse cortical regions. These composite regions correspond to anatomical definitions of Braak stages I/II, III/IV, and V/VI respectively. We focused on a composite

episodic memory score, with the goal of determining the strongest predictor of changes in memory over time. Of the Aβ measurements (baseline PIB and change in PIB), baseline PIB was the better predictor of memory decline. However, in individuals with low levels of PIB, change in PIB over time was a superior predictor of memory decline, suggesting that measures of Aβ accumulation may be sensitive biomarkers early in disease progression. Further, we found that change in PIB also best predicted tau deposition in Braak stages III-VI, especially in those with low levels of PIB at baseline. While tau in Braak I/II best predicted memory decline, tau in Braak III-VI mediated the relationship between change in PIB and memory decline, suggesting that Aβ accumulation interacts with tau as the disease progresses leading to memory impairment over time. These findings indicate that increasing Aβ early in the disease is related to tau accumulation, which is in turn associated with memory impairment. Therefore, memory decline and tau deposition can be detected at very early stages of AD pathogenesis, supporting the relevance of early intervention in the pathological process.

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Title: Metabolic inefficiency in early life predicts the spatial pattern of amyloid-β in late life

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Abstract: Amyloid-β plaques are a primary marker of Alzheimer's disease, depositing in a stereotyped spatial pattern across the cerebral cortex. The reason(s) for differences in the

concentration of amyloid-β plaques across the brain remains unknown, although amyloid-β deposition has been linked to both greater energy consumption and connectivity. We used measures of brain function in young adults (ages 21-30), functional connectivity from rs-fMRI (N=62) and cerebral metabolism from FDG-PET (N=13), to predict the spatial pattern of amyloid-β from PIB-PET in cognitively normal older adults (ages 60+, N=140). Voxel-wise measures of connectivity, FDG SUVR, and PIB DVR were characterized for each individual subject and measures averaged across individuals to obtain group estimates. Fully-weighted functional connectivity networks were used to measure correlation strength (i.e. centrality or "hubness") of each voxel with the rest of the brain. Linear regression was then employed to model metabolism from centrality ($R^2 = 0.23$). We used the residual to define a novel metric of metabolic inefficiency, which identified areas of the brain with lower (i.e. efficient) or higher (i.e. inefficient) metabolism than predicted by centrality. We found that metabolically inefficient regions (mean PIB DVR= 1.19 ± 0.12) deposited substantially more amyloid-β than efficient regions (mean PIB DVR = 1.02 ± 0.19). Separate linear regression models of centrality, metabolism, and metabolic inefficiency on amyloid-β deposition revealed that metabolic inefficiency explained substantially more variance in the spatial pattern of amyloid-β ($R^2 = 0.39$) than either metabolism ($R^2 = 0.26$) or centrality ($R^2 = 0.01$). Although centrality and metabolism covary, this work suggests that amyloid-β pathology may begin in metabolically inefficient areas of the brain that are more metabolic than predicted by their network connectivity. While the cause of this vulnerability remains to be determined, reduced efficiency may reflect elevated neural activity that then leads to greater amyloid-β secretion.

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Title: *In vivo* tau pathology predicts impaired NREM sleep oscillations and associated memory function in aging

Authors: *J. R. WINER[1], B. A. MANDER[1], R. F. HELFRICH[2], A. MAAß[3,2], R. T. KNIGHT[2,1], W. J. JAGUST[2], M. P. WALKER[2,1]
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Abstract: Aging disrupts sleep, and these deficits have been proposed to contribute to cognitive decline in later life. Animal models indicate that tau pathology is linked to the disruption of non-rapid eye-movement (NREM) sleep oscillations. However, the impact of tau on sleep oscillations in humans remains unknown, as does any consequence on cognitive function. Here, we test the hypothesis that tau aggregation in the medial temporal lobe (MTL) impairs the coupled relationship between the two key oscillations of NREM sleep—sleep spindles and slow waves, and their known benefits to memory. [^{18}F]AV1451 PET measured *in vivo* tau distribution in cognitively normal older adults (n=20, mean age=76.5). Participants additionally received several nights of sleep EEG recordings and standardized cognitive assessments. Analyses focused on relationships between three measurements: (i) AV1451 tau PET binding in MTL measured as the mean (L+R) standardized uptake value ratio of tracer relative to inferior cerebellar gray matter (SUVR), (ii) EEG phase-amplitude coupling between NREM spindles and slow wave oscillations (Canolty et al., 2006; Dvorak & Fenton, 2014), and (iii) hippocampus-dependent memory performance. Greater tau burden in MTL (AV1451 SUVR) predicted the severity of impaired sleep spindle-slow wave oscillation coupling over the prefrontal cortex ($r>-0.60$; $P<0.005$). Moreover, this tau-related sleep disruption of spindle-slow wave coupling predicted the degree of memory impairment ($r=0.45$, $P=0.04$), despite tau itself not significantly predicting memory function ($r=-0.23$, $P=0.33$). β-amyloid burden, as assessed by a global [^{11}C]PiB PET distribution value ratio, was not associated with degree of coupling impairment ($r=-.33$, $P=0.16$), suggesting specificity to MTL tau pathology and not amyloid. Together, the data support an emerging model in which tau pathology disrupts specific human NREM sleep oscillations, and by way of this disruption, contributes to age-related cognitive decline through impairing sleep-dependent memory. Furthermore, these findings raise the question of whether this relationship also exists in Alzheimer's disease, indicating that sleep disruption may be an under-appreciated contributing factor in aging and dementia, as well as a novel biomarker and possible therapeutic target.

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452. Cognitive Aging and Memory

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**Topic: ***H.02. Human Cognition and Behavior

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Title: Longitudinal cognition in older adults with superior memory performance and preserved brain morphometry

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Abstract: Unusually successful agers (or "SuperAgers") characterized by superior cognitive performance, avoid normal age-related cortical thinning in key regions. It is not known whether differences in performance and brain morphology at baseline are associated with longitudinal cognitive trajectories. We examined 150 participants enrolled in the Berkeley Aging Cohort Study who were aged 70 or older, and had structural MRI and PiB-PET data quantifying β-amyloid in the brain. Of these, 26 met criteria for superior memory performance and were called successful agers (SA): a score of 14 or above on CVLT long delay free recall and normal for age performance on Trails B. 103 participants met criteria for typical older adults (TOA). We examined cortical thickness, hippocampal volume and global PiB distribution volume ratio (DVR). Composite scores were used to measure episodic memory (omitting the CVLT), working memory and processing speed at baseline as well as over longitudinal follow-up (number of follow-ups = 3.7(2.1); follow-up time = 5.2(2.5) years). Multiple linear regression and mixed effects models were used to determine relationships between morphometric measures, PiB and cognition. Cortical thickness analyses revealed several regions of preserved cortical integrity in SA compared to TOA ($p<0.05$, uncorrected), including right anterior cingulate and prefrontal cortex, which have been previously associated with SA. Cortical thickness in these regions was related to baseline memory performance across all participants (controlling for ICV, age, sex, education in each analysis: $R^2=0.12$, $p=0.02$), while mean global cortical thickness was not ($p=0.17$). Similarly, hippocampal volume was greater in SA ($p<0.001$) and associated with baseline memory across participants ($R^2=0.13$, $p=0.01$). Hippocampal volume was also related to memory *decline*, but this effect was driven by TOA ($p=0.02$). There were no differences in PiB DVR between groups, but baseline PiB predicted decline in memory performance only in TOA ($R^2=0.08$, $p=0.016$). A linear mixed effects model with fixed effects for sex, education, age and number of follow-up cognitive visits as well as random effects for participant intercept and slope revealed that memory performance in TOA declines more rapidly than in SA. We show that older adults with superior memory performance decline more slowly than their typically performing peers. TOA memory decline is associated with baseline hippocampal volume and with baseline PiB, but these associations are not present SA. These findings support the idea that SA is an aging trajectory with unique features, including slower age-associated decline in memory performance.

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452. Cognitive Aging and Memory

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**Presentation Number: ***452.10

**Topic: ***H.02. Human Cognition and Behavior

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MRC

Title: Modifiable contributors to cognitive reserve

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Abstract: Cognitive Reserve (CR) is used to explain why some individuals maintain cognitive function despite declining brain health (BH) owing to aging and neurodegenerative disorders. Identification of modifiable contributors to CR would have major implications for public health strategies for preventing dementia. To test the hypothesis that activities in middle age contribute to CR, we analysed data from the Lifetime Experience Questionnaire (LEQ) from retired people aged > 55 in the Cambridge Centre of Ageing and Neuroscience (CamCAN; www.cam-can.org). The LEQ evaluates activities across three phases of adulthood (youth, middle age, old age), divided into activities "specific" to a phase (eg education vs occupation) and "nonspecific" activities (eg reading, sports and social activity). Cognition was assessed by the Cattell test of fluid intelligence. We found: 1) the degree of mental/physical activity in middle age made a unique contribution to Cognition in old age, and 2) this activity moderated the relationship between BH and Cognition.
In multiple regression with all 6 LEQ scores (N=162), plus sex and age, there was a significant, unique contribution to Cognition in old age from middle-age, non-specific activity (MNSA), T(153)=3.26, p=.0014 (R2=7%). The only other LEQ score making a significant contribution was youth specific activity (i.e, education), T(153)=3.27, p=.0013 (R2=7%). While the association of fluid intelligence with education is not surprising, the additional association with MNSA, over and above education, middle-age occupation and, most importantly, current mental and physical activities in old age, is noteworthy.
Further evidence for MNSA contributing to CR would arise if the relationship between Cognition and BH were moderated by MNSA, such that Cognition in individuals with high CR were less dependent on BH. BH was measured by total gray matter (TGM), adjusted for total

intracranial volume (TIV) (N=156). After a median split of MNSA, the correlation between BH and Cognition, after adjusting for age, sex and education, was significant in those with low CR (R=+.22, p=.05), but not in those with high CR (R=+.14, p=.23). This supports the hypothesis that middle-age activity protects cognition against brain atrophy in later years.

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452. Cognitive Aging and Memory

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Topic: *H.02. Human Cognition and Behavior

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Title: Preserved intrinsic functional connectivity in the default mode and salience networks contributes to youthful memory in superaging

Authors: ***J. ZHANG**[1], A. TOUROUTOGLOU[2], J. M. ANDREANO[3], B. C. DICKERSON[4], L. F. BARRETT[1]
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Abstract: Despite advanced age, some older adults, so-called ‘superagers’, maintain youthful memory capacity. While both behavioral and brain structural characteristics have been defined for superagers, no study to date has yet examined the functional profile of their brains. In this study, we took a network approach and examined the intrinsic functional connectivity within the default mode and salience networks among 41 young adults (20 males, 24.5 ± 3.6 years old) and 40 elderly adults (20 males, 66.9 ± 5.5 years old). These two large-scale brain networks were selected due to their respective engagement in memory encoding/retrieval, and attention/executive functions. Participants underwent a resting state scan and two memory tasks. We defined superagers based on their performance compared to young adults on the California Verbal Learning Test Long Delay Free Recall test and replicated their superior memory capacity in a separate recognition memory task. The neuroimaging results demonstrated that superagers had preserved intrinsic functional connectivity within the default mode and salience networks and that stronger intrinsic functional connectivity within each network predicted higher scores on multiple episodic memory tasks. Lastly, a multiple linear regression analysis showed that

intrinsic functional connectivity within each network contributed independently to memory. These results extend our understanding of the superaging brain by establishing intrinsic functional connectivity markers of superaging.

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Nanosymposium

452. Cognitive Aging and Memory

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**Topic: ***H.02. Human Cognition and Behavior

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Title: Associations between simple EEG spectral measures and cognitive function in older adults

Authors: *J. DREO[1,2], M. KURAN[2], L. ZEVNIK[2], J. REJEC[2], Z. PIRTOŠEK[1]
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Abstract: Due to population ageing dementia-related expenses will rise in the coming decades. Even in the absence of disease-modifying therapy developing cost-effective and non-invasive methods of diagnosing Alzheimer's disease is essential to reduce health-care expenses. As part of a Slovenian research initiative aimed at early dementia detection (ADAM project) we performed 64-channel rest EEG recordings on 35 healthy elderly subjects (age: 82+/-9 years, 13 men) in addition to conducting the Montreal Cognitive Assessment (MoCA). EEG data was used to compute three quantitative EEG (qEEG) biomarkers of the widely-described phenomenon of "EEG slowing" which has been associated with dementia and/or poor cognitive performance. These are as follows: A) peak alpha frequency (PAF), B) average alpha band frequency (ABF), and C) theta/alpha spectral power ratio (TAR). All three showed significant ($p<0.05$) correlations (ranges: r = +/- 0.35-0.55) with subjects' MoCA scores during resting with eyes open and closed. Higher PAF and ABF frequencies but lower TAR ratios were associated with better cognitive performance. These results indicate that even simple EEG spectral measures offer valuable insight into the cognitive performance of older adults and might point the way towards development of future EEG-based strategies to predict cognitive decline or dementia development.

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Title: Impaired slow oscillation and sleep spindle coupling predicts memory deficits in older adults

Authors: ***R. F. HELFRICH**, B. A. MANDER, M. P. WALKER, R. T. KNIGHT
Helen Wills Neurosci. Inst., Univ. of California Berkeley, Berkeley, CA

Abstract: A long-standing hypothesis in cognitive neuroscience states that the interaction of the slow oscillation (SO; < 1.25 Hz) and sleep spindles (12-16 Hz) in non-rapid eye movement (NREM) sleep supports memory consolidation. In particular, it has been hypothesized that the exact timing between SOs and sleep spindles is crucial for the timed information transfer supporting long-term memory retention. Despite numerous theoretical accounts, there is no empirical evidence in humans to support this theory. Addressing these fundamental questions, here we recorded a full night of sleep with polysomnography from 20 young (20.4 ± 1.98 years, mean ± SD) and 32 older (73.7 ± 5.26 years) adults, with overnight memory consolidation using a validated sleep-dependent hippocampal memory task. Overnight memory consolidation success was worse in older in comparison to younger adults ($p<0.001$). At the oscillatory level, we found that sleep spindles were nested within slow oscillations during NREM sleep, with the dynamics of this interaction determined using cross-frequency coupling (CFC). Both the overall coupling strength and the timing of coupling between the slow wave and sleep spindles were significantly impaired in older relative to young adults (both $p<0.0005$). However, we found that it was the temporal relationship of coupling, determined by the exact phase of the slow wave at which the sleep spindle occurred, that not only differed between young and older adults ($p<0.0001$), but predicted memory consolidation success in young adults and corresponding failure in older

adults. Specifically, sleep spindles were preferentially coupled to the positive depolarizing up-state of the slow oscillation in younger adults, while in contrast, mean phase was more variable and deviated by approximately 48.8 ± 8.4 deg towards the hyperpolarizing down-state in older adults. Crucially, this temporal measure of phase coupling precision predicted overnight memory retention across individuals ($p = 0.009$), with the greater temporal dispersion in older adults resulting in great overnight forgetting. This effect was robust after controlling for several confounds, such as EEG power or other age-related differences. Our results provide the first evidence demonstrating that the exact timing of SOs and sleep spindles in the human brain supports memory consolidation, and that aging causally impairs this relationship. Age-related deficits in the spatiotemporal coupling of NREM oscillation may therefore be a contributing factor to, and novel theraputic target for, cognitive decline in later life.

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452. Cognitive Aging and Memory

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**Topic: ***H.02. Human Cognition and Behavior

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Title: Hippocampal gray matter integrity declines in healthy aging and relates to mnemonic discrimination

Authors: *A. VENKATESH[1], N. HUFFMAN[1], S. M. STARK[2], C. E. STARK[2], I. J. BENNETT[1]
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Abstract: Using single-tensor diffusion imaging (DTI), our lab previously showed that healthy aging is associated with declines in integrity of white matter tracts connecting the hippocampus to entorhinal cortex (perforant path) and other neocortical structures (fornix, cingulate). Integrity of these white matter connections was also related to the ability to dissociate highly similar memory representations (i.e., mnemonic discrimination) independent of age. In the current study, we examined these relationships for hippocampal gray matter integrity using both single-tensor and multi-compartment diffusion imaging (neurite orientation dispersion and density imaging, NODDI) analyses. Younger (n = 18, 21-38 years) and older adults (n = 22, 59-79 years)

completed a mnemonic discrimination task. In the incidental encoding phase, participants made indoor/outdoor judgments to a series of to-be-remembered objects. In the test phase, they indicated whether a series of probe objects were novel ("new"), repetitions from the memory set ("old"), or similar to memory set objects ("similar"). Mnemonic discrimination was measured as the ability to correctly identify objects similar to memory set items as "similar". A multi-shell diffusion sequence was also acquired on all participants from which both traditional DTI (fractional anisotropy, FA; mean diffusivity, MD; axial diffusivity, AD; radial diffusivity, RD) and novel NODDI (neurite density, ICVF; orientation dispersion index, ODI; CSF volume fraction, FISO) metrics were generated in bilateral hippocampus. Consistent with our earlier work, results revealed significant age-related declines in mnemonic discrimination. Significant age-related declines were also observed in hippocampal gray matter integrity for both DTI (MD, AD, RD) and NODDI (ODI, FISO) metrics. In addition, better mnemonic discrimination was related to better hippocampal gray matter integrity (lower MD, RD) after controlling for age group. These preliminary findings extend our earlier work by (1) demonstrating that diffusion imaging in both white and gray matter is sensitive to the effect of aging on the brain, (2) suggesting that age-related declines in hippocampal gray matter integrity reflect differences in both neuronal and non-neuronal sources of diffusion in younger and older adults, and (3) supporting the notion that mnemonic discrimination is mediated by hippocampal memory systems across the lifespan.

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453. Alzheimer's Disease: Neuroinflammation and Immune Actions

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Alzheimer of Orange County AOC207373

Title: iPS-derived glia for the study of neuroinflammatory mechanisms

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Abstract: iPS-derived glia can be generated using differentiation protocols developed in our lab. This renewable source of primary cells allows for the study of glia biology in the context of inherited AD genetic risk factors. Here, we describe the validation of iPS-derived glia to their primary counterparts and present novel high-throughput functional assays to study the role of genetics in glia function in the context of AD. These assays can also be used to study the role of neuroinflammation and aging on homeostatic glia function, thereby facilitating the identification of altered glia pathways that can serve as potential therapeutic targets to mitigate the effects of the neuroinflammatory cascade that occurs in AD pathogenesis.

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Nanosymposium

453. Alzheimer's Disease: Neuroinflammation and Immune Actions

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**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***453.02

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

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Title: Retinal amyloid-related inflammatory biomarkers for Alzheimer's disease

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Abstract: Increasing evidence indicates that the retina, an ocular CNS tissue, exhibits a wide spectrum of abnormalities in Alzheimer’s disease (AD) patients, including nerve fiber layer thinning, vascular and blood flow changes, and degeneration of retinal ganglion cells (RGCs). Previously, we identified the key pathological hallmarks, Aβ plaques, in the retina of AD patients, including those at early stages. Corroborating these findings, subsequent studies in AD patient retinas showed accumulation of $A\beta_{1-42}$ peptides, Aβ deposits, and pTau. Here, we sought

to investigate the burden and distribution of novel pathological hallmarks of AD along with associated inflammation and cellular degeneration in AD retina at different disease stages, and to correlate with disease in the brain. Our studies indicate a myriad of pathological changes in retinal tissues isolated from mild cognitively impaired (MCI) and AD patients. The pathological hallmarks of AD, Aβ plaques, phosphorylated (p)tau, and neurofibrillary tangles (NFTs), are found to accumulate in distinct cellular layers and peripheral regions of the retina in these patients (n=28) as compared to healthy controls (n=15). Retinal Aβ manifests as extracellular and intracellular deposits that often associate with blood vessels. A 4.7-fold increase in retinal $A\beta_{42}$-containing plaque burden is found in a subset of definite AD patients (n=8) as compared to age- and sex-matched controls (n=7; $p<0.001$, t-test). Along with increased retinal Aβ load, a marked degeneration of retinal neuronal cells is noted in the patients by a quantitative Nissl staining ($p<0.005$). Retinal Aβ deposits are also frequently associated with local inflammation, similar to brain pathology, including reactive astrocytes, activated microglia, and infiltrating immune cells. Iba-1^+ myelomonocytes are involved in uptake of Aβ in the RGC layer. Retinas from age-matched controls showed scarce retinal Aβ deposition with no inflammation. In addition, progressive degeneration of non-neuronal retinal cells was detected in MCI and AD patients. Finally, a noninvasive retinal optical imaging technique developed by our team allowed us to monitor with high spatial resolution the burden as well as appearance and clearance over time of individual amyloid deposits in the retina of living rodent models and AD patients. In conclusion, our data indicate that pathological hallmarks of AD and associated inflammation and degeneration can be found in the retina of MCI and AD patients, mimicking the complex disease manifestation seen in the brain. Thus, these studies precipitate a great need to establish noninvasive retinal imaging as a novel biomarker for AD.

Disclosures: **M. Koronyo-Hamaoui:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroVision Imaging (NVI). **Y. Koronyo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroVision Imaging (NVI). **D. Fuchs:** None. **E. Barron:** None. **S.R. Verdooner:** A. Employment/Salary (full or part-time):; CEO, Neurovision Imaging. **C.A. Miller:** None. **D.R. Hinton:** None. **K.L. Black:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroVision Imaging (NVI).

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Title: Effects of TLR4 inhibition on metabolic and neural consequences of diet-induced obesity

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Abstract: Obesity has increased at an alarming rate across westernized countries, with ~30% of the US adult population classified as obese. Obesity is a major risk factor for a number of diseases and adverse outcomes. Notably, prior research has demonstrated that obesity negatively impacts brain health, leading to impairments in cognition and increased risk for Alzheimer's disease (AD). Though the mechanisms underlying the deleterious neural effects of obesity have yet to be clearly defined, one possible contributor is neuroinflammation. Obesity is associated with increased inflammation both systemically and in the brain. One pathway implicated in mediating the relationship between obesity and inflammation is toll-like receptor 4 (TLR4) signaling. TLR4 is a pattern recognition receptor that upon activation by various ligands, including fatty acids that are abundant in high-fat diets, drives expression of pro-inflammatory cytokines. In the brain, TLR4 is expressed primarily in microglia and less abundantly in astrocytes. Prior rodent studies have shown that genetic knockout and pharmacological inhibition of TLR4 can protect peripheral tissues against the metabolic and inflammatory consequences of diet-induced obesity. However, the potential of TLR4 inhibition to reduce adverse neural outcomes of obesity has not been evaluated. To investigate this issue, we assessed the effects of pharmacological inhibition of TLR4 signaling in a mouse model of diet-induced obesity. Male C57BL6/J mice were maintained for 12 weeks on either a control diet (10% fat) or a nutrient-matched high-fat diet (60% fat) beginning at age 3 months. Simultaneously, animals received regular (6 days/week) administration of either vehicle or the specific TLR4 antagonist TAK-242. Consistent with established findings in this standard obesity paradigm, we found that high-fat diet yielded significant gains in body weight and adiposity as well as a range of metabolic impairments. In general, TLR4 inhibition had very modest effects on systemic metabolic measures. To evaluate the effects of TLR4 inhibition on neural consequences of obesity, we are comparing the effects of TAK-242 versus vehicle treatment on several indices of behavior, glial activation and neuroinflammation, and neural health. Findings from this study will directly inform on the hypothesized contribution of TLR4 signaling as a significant mediator of the myriad of neural consequences of obesity. Understanding the role of specific inflammatory pathways in obesity-induced neural injury holds the promise of identifying novel therapeutic approaches to prevent cognitive impairment and AD risk associated with obesity.

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

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Title: Exposure to traffic-related air pollution particulate matter impacts brain activities

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Abstract: The search for environmental neurotoxic factors in AD and related disorders (ADRD) has recently considered traffic-related air pollution (TRAP) and the fine-size class of air pollution particles, PM2.5. However, in experimental models, the ultrafine-size class of air pollution particles, PM0.25, have higher biological activity than larger particles and can influence processes related to the central nervous system, the function of peripheral phagocytes, and systemic release of circulating cytokines. Using a laboratory-based exposure model, we are examining the role of PM exposure on behavioral, metabolic and inflammatory outcomes. We use TRAP-nPM, collected adjacent to the CA-110 freeway in downtown Los Angeles, which is composed of the water-soluble fraction of ambient PM, composed primarily of organic carbons, nitrate, sulfate and ammonium. In the laboratory, rodents are exposed to 5 hours/day for varying lengths of time, at different stages of life. TRAP-nPM exposure causes select behavioral deficits in hippocampus-mediated contextual memory, measured by the novel object in context test, and increased depressive behavior, measured by the forced swim test. Brain tissue analyses reveal that TRAP-nPM targets select glutamatergic receptors (GluA1). Furthermore, neurite density (sliver staining) is reduced in sub-fields of the hippocampus (CA1>DG). These regional effects correspond with increased microglial activation and reductions of myelin basic protein. Importantly, TRAP-nPM also increases sAPPbeta:sAPPalpha ratios and amyloid-beta peptides in wildtype (C57BL/6) and ADtg (EFAD) mice. In addition to these brain related changes, TRAP-nPM causes metabolic impairments, including effects on body weight, fat mass and adiposity, and glucose regulation. These widespread changes support continued investigations for identifying the underlying molecular mechanisms and possible targets for intervention.

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Title: Voluntary exercise reduces ER stress and neuroinflammatory, behavioral and lysosomal dysfunction in tau transgenic mice

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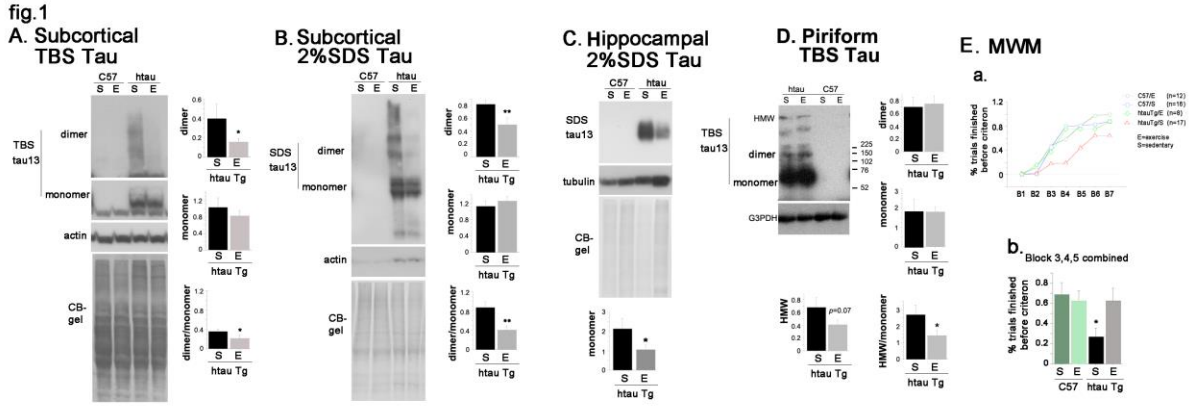
Abstract: Exercise can reduce AD risk and Abeta pathogenesis, but effects on tauopathy, which also contributes to memory deficits, are poorly understood. We therefore investigated the effects of voluntary exercise in the human tau transgenic (Tg) expressing human tau (htauTg). HtauTg mice and wild-type littermates (~ 9 mos) were assigned either to standard housing (sedentary) or housing supplemented with a running wheel (exercise) (n=8-17 per group). After 6 mos, spatial memory was assessed using the MWM, and the brains were examined biochemically or histologically. In the frontal subcortex, hippocampus and piriform cortex, exercise reduced tau tg-associated memory deficits, soluble and insoluble tau aggregates and aggregates of both of myelin basic protein (MBP), a marker of oligodendrocytes and acetylated-tubulin, a marker of microtubule instability, demonstrating a global effect of exercise on protein aggregate clearance. Because exercise can increase autophagy, we examined lysosomal markers LAMP1 and Cathepsin D. Surprisingly, we found tau transgene reduced neuronal LAMP1, which were fully restored by exercise. In the piriform cortex we observed a htau-related increase in phosphorylated Eukaryotic Initiation Factor 2a (pElf2a), a marker for ER stress, which was also reduced by exercise, paralleling tau-dependent lysosomal dysfunction. Further tg-dependent deficits in the neurotransmitter choline acetyl transferase, synaptic proteins and neuroinflammatory markers (measured by Iba1-positive microglia) were also corrected by exercise. Exercise ameliorated tg-dependent increases of carbonyls only in the SDS soluble

fraction. Our data demonstrate that long-term voluntary physical exercise is effective in reducing, not only tau, but also MBP and tubulin aggregation, protecting ChAT neurons, restoring synaptic function and improving memory, suggesting the involvement of multiple mechanisms in intracellular and extracellular removal of tau aggregates and supporting a causal role of these aggregates in memory deficits.



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

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Title: Ibuprofen suppresses aberrant tau kinases and ptau

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Abstract: Frequent non-steroidal anti-inflammatory drugs (NSAIDs) use including ibuprofen (Ibu) is associated with reduced AD risk, neuritic dystrophy, Aβ, inflammation, gliosis and

inflammatory cytokines in many AD models. Kotlinek et al found that ibu successfully ameliorated cognitive deficits in Tg2576 mice while Aβ was unchanged suggesting the possibility of Ibu being able to prevent cognitive deficits (and possibly neuroprotection) independent of gross effects on Aβ. In AD and animal models there is aberrant activation of mitogen-activated protein (MAP) kinases, also known as tau kinases because of their role in phosphorylating the microtubule protein tau and promoting Tau aggregates. Because the literature supports a causal role for aberrant activation of these tau kinases in amyloid-dependent neurodegeneration, we explored the impact of Ibu in in vitro and in vivo models. Specifically we evaluated whether Ibu can impact Aβ-induced activation of tau kinases (extracellular signal regulated kinase (ERK), c-Jun N-terminal kinases (JNK) and p38 MAP kinases), using both *in vivo* and *in vitro* models. we also explored the Ibu effect on glutamate induced tau kinases to explore the relationship between tau kinases activation and excitotoxicity, which is also thought to play an crucial role in AD. First, in an *in vivo* A*ß* infusion model, rats were placed on Ibu from 19-22 months of age, and Aβ oligomers (with HDL carrier) were infused icv during the last 4 weeks of Ibu treatment. Second, Tg2576 mice were fed Ibuprofen from 14-17 months of age or third, ApoE3 or E4 cross 5xFAD (EFAD) mice were fed ibuprofen from 4-5 to 8-9 months and finally, primary hippocampal neurons were exposed to Aβ or glutamate/NMDA to examine the influence of Ibu on tau kinases. Results: In the rat infusion model, Aβ oligomer increased pERK 175% ($p<0.05$), while Ibu reduced Aβ-dependent pERK 44% ($p<0.01$), pJNK 19% ($p<0.05$), p-p38 44% ($p<0.05$) and ERK related-epitope on p422S tau 36% ($p<0.05$). In the Tg2576 mouse, Ibu reduced pERK in hippocampal pyramidal neurons ($p<.0001$). In the EFAD mice, ibuprofen reduced PHF-1 ptau without limiting cytokines. In cultured neurons, 1 μM Aβ oligomer induced pERK started from 10 min, persisted till 15 hr, Ibu limited Aβ/excitotoxic glutamate dependent phosphorylation of tau kinases. Conclusion: Ibu is effective in suppressing sustained Aβ dependent ptau, by limiting aberrant ERK, JNK and pP38 induction. The protective effects of Ibu likely involve suppression of chronic Aβ -induced tau kinase activation and intiation of tauopathy. This may explain why NSAIDs appear protective only at early stages of AD pathogenesis but fail to protect once tauopathy is fully seeded

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453. Alzheimer's Disease: Neuroinflammation and Immune Actions

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Title: Elevation of inflammation mediators in synaptosomes from AD and Down's syndrome cortex

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Abstract: *APOE* is well known to induce a number of pro-inflammatory cytokines that include IL1β and IL6, and it's clear that these *APOE* -mediated changes can be dependent or independent from Aβ deposition. Highlighting the importance of inflammation pathways in the synaptic compartment, recent work shows that *APOE* mediates synapse pruning by astrocytes. Our previous work has shown that ~65% of AD cortical synaptosomes accumulate oligomeric Aβ42, and recent results showed reduced synaptic function, indexed by LTP, in AD synaptosomes. Hypothesizing that inflammatory signaling is altered in the synaptic compartment in AD, we have examined candidate cytokines previously linked to both *APOE* and AD. Experiments compared cortical synaptosomes from aged normal controls, AD cases, and Down's syndrome (DS), and tested the hypothesis that synaptic cytokine alterations are associated with Aβ accumulation in terminals. Using flow cytometry, we measured immunolabeling for five cytokines: IL-6, TLR-4, TGFβ1, IL1β, and IL10, in synaptosomes (P2 fraction; 10,000 events/sample) prepared from cryopreserved cortical samples. To determine whether changes were associated with Aβ, in some experiments synaptosomes were dual labeled for a cytokine together with anti-Aβ antibody. In a separate experiment, ELISA was used to measure synapse-associated IL1β in *APOE4* carriers. Synaptic labeling in aged control samples (n=8) was highest for TGFβ1 (22.6%), which regulates a number of other inflammatory mediators. The positive fraction for TGFβ increased to 34.3% in AD (n=8), and to 34.8% in DS (n=8; $p<0.003$). TLR4 labeled 6.1% of synaptosomes in aged controls; this increased to 19.0% in AD ($p<0.04$), and to 15.4% in DS ($p<0.006$). Compared to TGFβ1 and TLR4, the levels of IL6, IL1β and IL10 were much lower, labeling only 2.1-6.1% of total synaptosomes. However, small but significant increases in all three cytokines were observed in AD and/or DS samples compared to controls. Dual labeling experiments demonstrated that TGFβ labeling was markedly higher in Aβ-positive synaptosomes for all three comparison groups. In AD but not control cases, synapse-associated IL1β was increased by *APOE4* ($p<0.03$). These results show activation of inflammatory pathways in synaptosomes from AD and DS cortex, and indicate that cytokine alterations can be modulated by accumulation of Aβ within synaptic boutons and by *APOE4*. Understanding the contribution of neuroinflammation pathways will be important for optimization of therapeutics that protect synapses.

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Title: ABCA-1 agonist treatment as a potential therapeutic for ApoE4 hypolipidation and impaired ABCA-1 activity in Alzheimer's disease

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Abstract: Background: Carrying the ApoE4 genotype is the strongest genetic risk factor for developing Alzheimer's disease (AD). We hypothesize that lower ABCA1 activity in ApoE4 genotype is associated with hypolipidation of ApoE4 and that this impairment can be rescued by the ABCA-1 agonist CS-6253.
Methods and Results: Complementary rodent and human studies were employed to assess ApoE lipidation and ABCA-1 activity. First, a cohort of 4-months old female mice (n=6-8 per group, ApoE4 vs ApoE3 TR mice) was treated with either PBS or CS-6253 (20mg/kg/48h) for 6 weeks. Treatment was associated with an increase in large brain ApoE4 particles, decreased intraneuronal Abeta and tau, enhanced synaptic functions (VGLUT1), and improved cognition. Second, cerebrospinal fluid (CSF) samples from 59 older individuals with and without cognitive impairment were analyzed for ApoE particle size as a proxy for lipidation using native PAGE. ABCA-1 function of CSF was assessed using ABCA-1 mediated cholesterol efflux capacity assay in cells that selectively express ABCA-1. Lipidation profile of ApoE and ABCA-1 cholesterol efflux capacity were assessed before and after treatment with the ABCA-1 agonist CS-6253 ex vivo. CSF ApoE was resolved in four distinct bands by electrophoresis α_0 (>669 KDa), α_1 (600 KDa), α_2 (440 KDa) and α_3 (232-140 KDa). CSF from ApoE4/4 individuals (n=3) had reduced capacity to induce cholesterol efflux compared to CSF from ApoE3/3 individuals (n=31). To study the effect of CS-6253 on efflux, cells were incubated with CSF and CS-6253. Dose-response experiment with CS-6253 showed an increase in efflux at 0.25 µM with

saturation at 1.0 µM. CS-6253 was able to increase ABCA-1 mediated cholesterol efflux capacity of CSF from both ApoE3/3 and ApoE4/4 individuals ($p<0.01$). However, the increase in ABCA-1 activity was less in ApoE4/4 compared with ApoE3/3 containing CSF (31.45% vs 68.03%, n=3, $p<0.005$). The relative ratio of α_0 and α_1 (larger) ApoE bands in CSF were significantly lower in ApoE3/4 (n=25, $p<0.05$), and ApoE4/4 (n=3, $P<0.001$) compared to ApoE3/3 (n=29).
Conclusions: Compared with ApoE3, brain ApoE4 in mice and CSF ApoE4 in humans demonstrate lower ABCA-1 activity and smaller ApoE particles suggesting hypolipidation of ApoE4. The lower ABCA-1 activity was ameliorated by CS-6253. Inducing brain ABCA-1 activity is a potential therapeutic strategy in AD.

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Invest NI

Title: Sub-chronic to chronic high-fat diet feeding affects cognitive function, inflammation and insulin signalling in the brain

Authors: *P. A. DENVER[1,2], V. A. GAULT[3], P. L. MCCLEAN[4]
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Abstract: Type 2 diabetes mellitus (T2DM) and obesity increase risk of developing AD. Insulin resistance and inflammation are common features of T2DM and obesity and defective neuronal insulin signalling and neuroinflammation also occur early in AD and have been correlated with cognitive deficits. This suggests that insulin resistance and neuroinflammation may influence the

pathophysiology of AD.
This study investigated the effects of 7-18 days (G1), 19-34 days (G2), 8-10 weeks (G3) and 19-21 weeks (G4) HFD-feeding on learning and memory in mice, using novel object recognition (ORT) and Morris water maze (MWM) paradigms. Protein and genetic markers of insulin signalling and inflammation were also measured in the brain, by qPCR and immunohistochemistry.
Seven days exposure to HFD impaired working memory in ORT, deficits which remained apparent at later time points. Minimal differences were observed in MWM performance, in all but G4, in which HFD-fed mice displayed impaired memory retention. Eighteen days HFD increased microglia, astrocytes and oxidative stress in cortex and hippocampus, while phosphorylated insulin receptor substrate-1 (IRS-1 $pSer^{616}$) increased in cortex. Immunoreactivity of these markers in HFD mice fluctuated from 18 days to 21 weeks. Synaptophysin levels were increased in the cortex and hippocampus of HFD-fed mice from day 18 to week 10. Expression of ERK2, mTOR, NF-κB1, PKCθ and TLR4 mRNA was decreased in the brains of 10-week HFD-fed mice, but increased in the brain at week 21 in HFD-fed mice, along with augmented expression of GLP-1 receptor and IKKβ.
This study illustrates that HFD feeding detrimentally affects recognition memory from as early as 7 days and shows that while 18 days HFD feeding increases markers of inflammation, oxidative stress and insulin resistance in the brain, there is a fluctuating pattern, in response to sustained exposure to HFD. Synapse density is increased by sub-chronic HFD feeding, while transcription of inflammatory and insulin signalling genes in the brain is differentially affected by varied exposure to HFD. This highlights the influence of metabolic insults on inflammation and insulin signalling in the brain and suggests that obesity and/or HFD feeding *per se* detrimentally affects cognition.

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BX 0002476 (GMC)

Title: Dietary n-6 linoleic acid (high LA diet) and its n-6 metabolite DPAn-6 attenuate neuroinflammation and promote amyloid-β clearance

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Abstract: Polyunsaturated fatty acids (PUFAs) and their oxygenated metabolites modulate neuroinflammation, which is genetically implicated in Alzheimer's disease (AD). Many dietary n-3 PUFA metabolites are anti-inflammatory and appear to lower AD risk. Despite dietary n-6 PUFAs including linoleic acid (LA) providing cyclooxygenase (COX) substrates for pro-inflammatory prostaglandins, higher dietary PUFA intake, mainly LA, appears to reduce AD risk and cognitive decline. We hypothesized that LA metabolites {like docosapentaenoic acid (DPAn-6)} protect against AD, since they exert peripheral anti-inflammatory activity. Using two preclinical animal models of AD {EFAD (with accelerated pathology) and Tg2576 mice} and in vitro Aβ oligomer- or LPS-stimulated microglial BV2 cells, we investigated possible mechanisms for dietary LA influence on neuroinflammation and amyloid accumulation. We found that in the brains of both models, high dietary LA robustly reduced amyloid burden, COX2 expression and pro-inflammatory cytokines (IL1β, IL-6 and TNFα) but elevated anti-inflammatory IL-10 compared to standard diet. Both high dietary LA and ApoE isotype influenced brain fatty acid desaturase FADS1(delta5)) and FADS2(delta4/6/8) activities, altering brain fatty acid composition, reducing the arachidonic acid precursor DGLA (20:3n-6) and elevating DPA (22:5n-6), and this effect was most robust in E4FAD mice. Even with the late intervention, high LA diet reduced amyloid, suggesting increased clearance. In cultured microglial BV2 cells, DPAn-6 similarly stimulated Aβ oligomer clearance and inhibited LPS-induced COX2 expression. This is the first report showing that high LA, an essential dietary factor with positive protective epidemiology, can effectively inhibit COX2 expression and neuroinflammation, and is associated with increased levels of its metabolite, DPAn-6, which directly promotes microglial Abβ aggregate phagocytosis and COX-2 reduction. While low dose chronic COX2 inhibition with NSAIDs may lower AD risk, our study suggests that the high LA diet or DPA (n-6) supplements may exert similar protective action through immunomodulatory mechanisms but with fewer side effects and therefore suitable for AD prevention.

Disclosures: Q. Ma: None. **B. Teter:** None. **M.R. Jones:** None. **T. Morihara:** None. **S.A. Frautschy:** None. **G.M. Cole:** None.

Nanosymposium

453. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: 146C

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***453.11

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

Support: Irish Research Council

Title: Long-term exercise delays onset of cognitive decline in a mouse model of Alzheimer's Disease: Analysis of changes in hippocampal neurogenesis and neuroinflammation

Authors: *A. M. KELLY, ***A. M. KELLY**, S. M. RYAN, R. HENNESSY, M. A. LYNCH
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Abstract: Introduction: Alzheimer's disease (AD) is a progressive, neurodegenerative condition and is one of the leading causes of dementia. Altered adult hippocampal neurogenesis has been observed in several models of AD concomitant with declining cognitive function. There is also significant evidence from post-mortem analysis of human AD brains, and animal models of AD, that neuroinflammation contributes to the etiology of AD. Exercise is a well-established promoter of hippocampal neurogenesis and cognitive performance and has anti-inflammatory properties. It has also been shown to alleviate AD-related pathologies in several models of AD. **Aim:** The aim of this study is to determine whether regular treadmill exercise can delay the onset of cognitive decline in the APP_{SWE}/PS-1ΔE9 AD model and to examine underlying changes in hippocampal neurogenesis and markers of neuronal plasticity and neuroinflammation. **Materials and Methods:** Three-month-old WT and APP_{SWE}/PS-1ΔE9 mice were allocated to sedentary or exercise groups. Exercise mice ran on a treadmill five times per week for six months. Recognition and spatial memory was assessed by the novel object recognition and object location tasks at three, five, seven and nine months old. At eight months, half the mice in each group received daily injections of BrdU (50 mg/kg; i.p.) for seven days. Following the last session of cognitive testing at nine months old, mice were sacrificed and tissue was stored for later analysis. **Results:** At three and five months old, WT and APP_{SWE}/PS-1ΔE9 mice displayed identical cognitive performance. At seven and nine months old, sedentary APP_{SWE}/PS-1ΔE9 mice displayed significant cognitive deficits while their exercising counterparts displayed normal recognition and spatial memory. mRNA analysis revealed no changes in gene expression of *bdnf, trkB, p75, igf-1* or *vegf* but expression of *il-1β* and *cd11b* was increased in APP_{SWE}/PS-1ΔE9 mice. Western blotting analysis revealed no changes in activation of TrkB, CREB, Akt and synapsin. Immunohistochemical analysis indicates modest changes in neurogenesis associated with exercise or genotype. **Conclusion:** Behavioural data suggest that regular exercise begun before the development of pathology in the APP_{SWE}/PS-1ΔE9 mouse can confer cognitive

protection. The underlying mechanisms may depend on exercise-related modulation of inflammation rather than neurogenesis.

Disclosures: **A.M. Kelly:** None. **S.M. Ryan:** None. **R. Hennessy:** None. **M.A. Lynch:** None.

Nanosymposium

454. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: 144A

Time: *Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

Presentation Number: *454.01

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

Support: NIH U01AG046139
R01AG018454
P50AG047266
AWD01223

Title: Immunotherapeutic targeting of corticotropin-releasing hormone in alzheimer's disease

Authors: ***H. S. FUTCH**[1], B. D. MOORE[1], P. E. CRUZ[1], T. B. LADD[1], V. Q. TRUONG[1], P. CHAKRABARTY[2], Y. LEVITES[2], T. E. GOLDE[3]
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Abstract: Studies of monozygotic twins have suggested that non-genetic risk factors are involved in the development of Alzheimer's Disease. One non-genetic risk factor that has been associated with increased risk for AD is increased chronic psychological stress. A substantial amount of research has been done investigating a key stress-response mediator, corticotropin-releasing hormone (CRH), and its interactions with AD relevant processes. CRH signaling can induce increases in amyloid beta (Aβ) peptide levels and tau phosphorylation in mouse models of Aβ pathology. Thus far, efforts to target the CRH signaling pathway have focused on CRH receptor antagonists. Unfortunately, clinical trials implementing CRH receptor antagonists have been unable to show therapeutic effects. Therefore, while dysregulation of CRH signaling is implicated in a plethora of highly prevalent stress related disorders in addition to AD, receptor-based interventions have not shown efficacy in humans. To this end, we aimed to create and test novel immunotherapeutic approaches to decrease CRH signaling in the brain. Utilizing active vaccination, hybridoma technology, and molecular cloning we have developed a panel of anti-CRH monoclonal antibodies for use as novel anti-CRH therapeutics. In addition, we have obtained DNA sequences from our antibodies and have created an anti-CRH single-chain variable fragment (scFv) construct which retains affinity for CRH and is able to be packaged into

recombinant Adeno-associated Virus (rAAV) vectors, which can be injected directly into the brains of AD relevant mouse models. These immunotherapies have shown to be able to block the effects of CRH on Aβ production in an *in vitro* model. Progress on the implementation of these immunotherapies *in vivo*, and their effects on stress-induced increases in Aβ and tau phosphorylation, will also be presented. To our knowledge, these are the first studies attempting to use an immunotherapy to target the activity of a neuropeptide within the CNS. Collectively, these studies aim to provide a novel therapeutic strategy to targeting CRH signaling and to evaluate the efficacy of this strategy in transgenic mouse models of AD-relevant proteinopathies.

Disclosures: H.S. Futch: None. **B.D. Moore:** None. **P.E. Cruz:** None. **T.B. Ladd:** None. **V.Q. Truong:** None. **P. Chakrabarty:** None. **Y. Levites:** None. **T.E. Golde:** None.

Nanosymposium

454. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: 144A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***454.02

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

Support: Illinois Department of Public Health 63282003D
Illinois Health Improvement Association
SIU School of Medicine Foundation
Center for Alzheimer's Disease and Related Disorders
Kenneth Stark Endowment

Title: Neurotransmission spanning the Alzheimer's disease continuum: Glutamatergic tone, cognition, and early intervention

Authors: *E. R. HASCUP[1,2], S. O. BRODERICK[1], K. N. HASCUP[1]
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Abstract: Gradual increases in neuronal soluble amyloid-β $(Aβ)_{42}$ is among the earliest changes associated with Alzheimer's disease (AD) and our laboratory recently showed that $Aβ_{42}$ evokes glutamate (Glu) release via a presynaptic α7nAChR mechanism *in vivo*. Furthermore, we reported that KCl-evoked hippocampal Glu release was elevated prior to cognitive decline in a transgenic mouse model of AD, AβPP/PS1 mice. The current studies build upon this knowledge by investigating 1) how hippocampal Glu neurotransmission changes throughout the continuum of AD progression, 2) if early intervention alters disease outcome, 3) potential mechanisms for early changes in Glu neurotransmission, and 4) the specific role of $Aβ_{42}$ in AD progression and

Glu neurotransmission using a novel knock-in mouse model of AD, $APP^{NL-F/NL-F}$ mice, which are on the same C57BL/6J background as AβPP/PS1 mice. To address these questions, mice underwent cognitive evaluation using the Morris water maze (MWM) followed by *in vivo* hippocampal Glu neurotransmission at 2-4, 6-8, 12-15, and 18-20 months of age. At 2-4 mos, we observed a significant increase in KCl-evoked Glu release in the CA1 of AβPP/PS1 vs C57BL/6J mice (2.9 ± 0.3 vs. 9.0 ± 1.1 µM, n = 10-13; $p<0.001$) that became less severe with disease progression and loss of significance by 18-20 mos (4.2 ± 0.7 vs. 5.9 ± 1.0 µM, n = 10-13). We also observed elevated hippocampal VGLUT1 protein in 6-8 month old AβPP/PS1 mice compared to age-matched controls. Conversely, basal Glu levels at 2-4 mos were similar (0.9 ± 0.3 vs. 0.9 ± 0.5 µM; n = 9-11), but gradually increased with disease progression, becoming significant at 18-20 mos (0.5 ± 0.1 vs. 1.8 ± 0.3 µM; n = 7-13; $p<0.01$). Interestingly, early treatment with a mGluR group II agonist, LY379268, had no effect on cognition or glutamatergic tone in 12-15 mos mice. However, preliminary data support that early treatment with neuroprotective Riluzole, was able to restore CA1 basal (C57BL/6J vehicle, AβPP/PS1 vehicle, AβPP/PS1 Riluzole: 0.7 ± 0.1, 1.7 ± 0.5, and 0.6 ± 0.1 µM, respectively; n = 6-7; $p<0.01$) and evoked (4.5 ± 0.9, 7.9 ± 2.2, and 4.0 ± 0.7 µM, respectively; n = 6-7) Glu levels. Additionally, Riluzole prevented long-term memory decline (annulus 40 entries: 6.7 ± 0.8, 4.2 ± 0.8, 6.7 ± 0.8, respectively; n = 9-10; $p< 0.05$) in AβPP/PS1 mice by 12-15 months of age, indicating that early intervention focused on Glu neurotransmission may be able to slow or stop AD progression. Histological studies to help elucidate the underlying mechanisms responsible for these observations are ongoing, as are experiments in $APP^{NL-F/NL-F}$ mice; both will be presented.

Disclosures: E.R. Hascup: None. **S.O. Broderick:** None. **K.N. Hascup:** None.

Nanosymposium

454. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: 144A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***454.03

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

Support: VA merit 1I01BX002572-01A2

Title: The pivotal role of spleen tyrosine kinase in the pathobiology of alzheimer's disease

Authors: *J. E. SCHWEIG, H. YAO, D. BEAULIEU-ABDELAHAD, G. AIT-GHEZALA, M. MULLAN, F. CRAWFORD, D. PARIS
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Abstract: Pathological hallmarks of Alzheimer's disease (AD) include tau hyperphosphorylation and aggregation, as well as increased neuritic dystrophy associated with Aβ-plaques. Previously, we have shown that Aβ production and tau hyperphosphorylation are reduced *in vitro* and *in vivo* following inhibition of the spleen tyrosine kinase (Syk). In this subsequent study, we provide evidence for a pathological activation of Syk in cortical neurons of AD patients compared to healthy subjects. We also show that three different mouse models of AD exhibit a similar increased Syk activation compared to wild type littermates. Tg PS1/APPsw and Tg APPsw mice show an age-dependent increase of Syk activity in microglia and dystrophic neurites (DNs) associated with Aβ-plaques. In tau overexpressing Tg Tau P301S mice, Syk activation is increased in hippocampal and cortical neurons displaying hyperphosphorylated, conformationally altered and aggregated tau species. Furthermore, neurons displaying pathologically high Syk activation also exhibit more tau pathology than neurons that have a low amount of Syk activation, implying a role of Syk in the formation of pathological tau species *in vivo*. This notion is further supported by the fact that Syk overexpression in human neuron-like SH-SY5Y cells leads to an increased tau hyperphosphorylation and accumulation *in vitro*. In conclusion, Syk appears to be part of a self-propagating mechanism initiated by Aβ and tau pathologies. Therefore, a pharmacological interruption of this positive feedback loop by inhibiting Syk could represent a promising treatment for AD.

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Nanosymposium

454. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: 144A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***454.04

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

Support: Illinois Department of Public Health 63282003D
Illinois Health Improvement Association
Southern Illinois University School of Medicine Foundation
Center for Alzheimer's Disease and Related Disorders
Kenneth Stark Endowment

Title: Riluzole, but not LY379268, is an effective prodromal treatment in the AβPP/PS1 model of Alzheimer's disease

Authors: *K. N. HASCUP[1], S. O. BRODERICK[2], E. R. HASCUP[3]
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for Alzheimer's Dis. and Related Di, [3]Neurology, Neurosci. Institute, Ctr. for Alzheimer's Disease, Pharmacol., Southern Illinois Univ. Sch. of Med., Springfield, IL

Abstract: Evidence supports soluble amyloid-β $(A\beta)_{42}$ as the neurotoxic species associated with Alzheimer's disease (AD) and elicits glutamate release through presynaptic α7 nicotinic acetylcholine receptors. Furthermore, 2-4 month old AβPP/PS1, a model of progressive $A\beta_{42}$ accumulation, has elevated hippocampal glutamate compared to age-matched C57BL/6J mice. Despite glutamate's role in learning and memory, chronically elevated glutamate levels may lead to excitoxicity and cognitive decline associated with AD. We hypothesized that prodromal treatment with either LY379268 (a metabotropic glutamate group II agonist) or Riluzole (neuroprotective against excitoxicity) in AβPP/PS1 mice would decrease hippocampal glutamatergic tone and improve cognition. From 2-6 months of age, male AβPP/PS1 mice were given either LY379268 (3.0 mg/kg; i.p., twice weekly) or Riluzole (12.5 mg/kg b.w. / day; voluntary oral administration), or vehicle controls (saline and 1% sucrose, respectively). Age-matched C57BL/6J mice receiving vehicle served as additional genetic background controls. At 12 months, mice underwent cognitive testing using the Morris water maze (MWM) spatial learning and memory paradigm followed by *in vivo* hippocampal glutamate analysis using an enzyme-based microelectrode array for discrete measurements in the dentate (DG), CA3 and CA1. LY379268 did not improve cognition nor significantly decrease glutamatergic signaling in AβPP/PS1 mice compared to controls. We observed Riluzole treated AβPP/PS1 mice enter the annulus 40 during the MWM probe challenge more times than AβPP/PS1 control mice, and similar to C57BL/6J control mice (6.6 ± 1.1, 4.2 ± 1.1, 6.7 ± 1.1 entries; n=9-10; $p<0.05$). Riluzole treated AβPP/PS1 had reduced basal glutamate compared to AβPP/PS1 and C57BL/6J control mice (n=6-7) in the DG (0.5 ± 0.1, 1.2 ± 0.2, 0.7 ± 0.1 μM) CA3 (0.5 ± 0.1, 1.1 ± 0.2, 0.8 ± 0.1 μM) and CA1 (0.6 ± 0.1, 1.7 ± 0.5, 0.7 ± 0.1 μM; $p<0.01$). Stimulus-evoked (70 mM KCl, pH 7.4, isotonic, 150 nl) glutamate release in Riluzole treated AβPP/PS1 was reduced in AβPP/PS1 control mice, similar to C57BL/6J control mice, in the CA3 (4.8 ± 0.7, 8.8 ± 2.3, 4.6 ± 1.4 μM) and the CA1 (4.0 ± 0.7, 7.9 ± 2.2, 4.5 ± 0.9 μM), but not the DG (9.8 ± 3.3, 10.7 ± 2.3, 4.6 ± 0.7 μM). Clearance of locally applied 100 μM glutamate (isotonic, pH 7.4, 4-10 μM) in the hippocampus was similar across Riluzole treated and control mice. These data support that prodromal treatment with Riluzole in AβPP/PS1 improves cognition and reduces hippocampal glutamate neurotransmission through a presynaptic rather than uptake mechanism, and may be a viable treatment option in early AD.

Disclosures: K.N. Hascup: None. **S.O. Broderick:** None. **E.R. Hascup:** None.

Nanosymposium

454. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: 144A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***454.05

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

Title: Theraputic effect of PD-1/PD-l1 axis checkpoint blockade in tau and amyloid-beta mouse models of Alzheimer’s disease

Authors: *N. ROSENZWEIG, K. BARUCH, M. SCHWARTZ
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder, which is associated with unresolved chronic neuroinflammation. Nevertheless, while immunosuppressive drugs have failed in the clinic in treating this disease, recruitment of monocytes-derived macrophages to the central nervous system (CNS) was shown to play a beneficial role in limiting disease pathology. Here, we hypothesized that systemic immune suppression might curtail the ability to mount the protective, cell-mediated immune responses that are needed for brain repair. We used the 5XFAD and human-tau (htau) double-mutant (K257T/P301S) mouse models, and tested the effect on pathology of immune checkpoint blockade directed against the programmed death-1 (PD-1) pathway.
We show in 5XFAD mice that immune checkpoint blockade directed against the programmed death-1 (PD-1) pathway results in an IFN-gamma-dependant systemic immune response, which is followed by the recruitment of myeloid cells to the brain. When induced in mice with established pathology, PD-1 blockade leads to clearance of cerebral amyloid-beta plaques, improved cognitive performance and neuronal rescue. We further examined the effect of PD-1/PD-L1 axis blockade in the human-tau (htau) double-mutant (K257T/P301S) mouse model, demonstrating that both PD-1 and PD-L1 blockade results in improved cognitive performance in this non-amyloid AD mouse model.
Our findings suggest that much like the situation in cancer immunotherapy, in order to mobilize immune cells to fight pathology, peripheral immunity should be boosted, rather than suppressed. Taken together, these findings identify immune checkpoint blockade as a novel therapeutic strategy for AD and, potentially, for other neurodegenerative diseases.

Disclosures: N. Rosenzweig: None. **K. Baruch:** None. **M. Schwartz:** None.

Nanosymposium

454. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: 144A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***454.06

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

Title: Engineered zinc finger protein transcription factors as a next-generation platform for single gene regulation throughout the central nervous system

Authors: *B. ZEITLER[1], K. MARLEN[1], Q. YU[1], H.-O. NGUYEN[1], I. ANKOUDINOVA[1], S. DEVOS[2], S. WEGMANN[2], L. ZHANG[1], J. C. MILLER[1], E. J. REBAR[1], B. T. HYMAN[2], H. S. ZHANG[1], M. C. HOLMES[1], B. E. RILEY[1]
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Abstract: The advent of next-generation gene editing and gene regulation technologies based on Zinc Finger Protein (ZFP), TALE, and CRISPR/Cas9 DNA binding domains affords new opportunities for the potential treatment of neurodegenerative disorders. Here we present an in-depth characterization of the development path for ZFP-Transcription Factors (ZFP-TFs) in the central nervous system (CNS), including the activity, specificity, and delivery parameters that enable potent and durable *in vivo* target engagement following a single administration. For this work, we focused on targeting the Microtubule Associate Protein Tau (MAPT) gene, which is strongly linked to the pathogenesis of Alzheimer's disease and numerous other tauopathies. ZFPs were designed to bind within a 1.5 kb region surrounding the MAPT Transcription Start Site (TSS) and fused to the human KRAB transcription factor repression domain (ZFP-TF). In Neuro2A cells, approximately one-third of ZFP-TFs were capable of reducing tau mRNA levels by 50% to >95% with saturating dose-response profiles. A subset of ZFPs was also evaluated in primary mouse neurons using AAV9 delivery in the context of either a ubiquitous promoter (CMV) or three neuronal promoters (Synapsin1, CAMKIIα, and MeCP2). Each promoter achieved 90 - 99% tau reduction in neurons with varying EC50s. Using an extensive transcriptome-wide analysis in multiple cell types including primary neurons, we identified candidates with a range of specificities, including ZFP-TFs with single-gene specificity for MAPT. We then tested a set of ZFP-TFs in wild-type mice by direct stereotactic injection to the hippocampus. We found that the ZFPs that yielded the greatest degree of tau reduction *in vivo* correlated best with *in vitro* measures of global specificity - rather than activity - suggesting that high levels of specificity are critical for maximum efficacy in the brain. Three routes of AAV-ZFP-TF administration were tested in wild-type mice: direct intraparenchymal (IP) delivery to the hippocampus, intracerebroventricular (ICV) delivery to the CSF, and intravenous (IV) delivery. We demonstrate neuronal-restricted expression of the ZFP within the CNS, including conditions that result in sustained tau reduction following a single dose. Thus, a development pipeline focused on both potency of target engagement and global specificity can readily identify

ZFP-TFs that are capable of driving stable disease target reduction via multiple routes of AAV administration.

Disclosures: **B. Zeitler:** A. Employment/Salary (full or part-time):; Sangamo Therapeutics, Inc.. **K. Marlen:** None. **Q. Yu:** None. **H. Nguyen:** None. **I. Ankoudinova:** None. **S. DeVos:** None. **S. Wegmann:** None. **L. Zhang:** None. **J.C. Miller:** None. **E.J. Rebar:** None. **B.T. Hyman:** None. **H.S. Zhang:** None. **M.C. Holmes:** None. **B.E. Riley:** None.

Nanosymposium

454. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: 144A

Time: *Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

Presentation Number: *454.07

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

Support: NIH grants R01 AG032611
NIH grants R01 NS077239

Title: Dynamic characterization of brain uptake of tau antibodies, their entry into neurons and efficacy in clearing tau aggregates in live animals by two-photon imaging

Authors: ***Q. WU**[1], Y. LIN[1], J. GU[1], E. M. SIGURDSSON[2]
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Abstract: Tau immunotherapies are a promising approach for Alzheimer’s disease and related tauopathies. Our group published the first reports showing the effectiveness of active and passive tau immunizations in mouse models (Asuni et al, J Neurosci 2007; Boutajangout et al, J Neurochem 2011). These findings have now been confirmed and extended by many groups and several Phase 1-2 clinical trials are underway. Interestingly, the mechanisms of antibody-mediated clearance of tau aggregates are relatively unclear, and a better understanding of the pathways involved is likely to improve the efficacy of future trials. Two monoclonal antibodies (mAbs) that we have generated against the P-Ser396, 404 tau region, 4E6 and 6B2, have markedly different properties. 4E6 is more effective in various culture, *ex vivo* and *in vivo* models in preventing/reducing tau pathology and associated cognitive impairments, whereas 6B2 or rather its smaller derivatives may be better suited as diagnostic imaging markers. For an insight into their efficacy differences, we investigated by *in vivo* two-photon imaging the dynamics of brain and neuronal uptake of 4E6 and 6B2 and their ability to clear tau aggregates in live transgenic htau/PS1 tauopathy mice (18-22 months old). Our two-photon findings show that both mAbs readily cross the blood brain barrier and are primarily found within neurons (about

80%). mAbs co-localized with pathological tau marker, 1-fluoro-2,5-bis (3-carboxy-4-hydroxystyryl) benzene (FSB), as assessed 4 days after femoral injection, with R=0.55 and R=0.64, respectively, compared to IgG control with R=0.25. Moreover, only 4E6 cleared tau pathology, compared to 6B2 or control IgG, based on clearance of the FSB signal over 14 days, assessed *in vivo* at day 1, 4, 7 and 14 ($p=0.001$). The most pronounced effect of 4E6 on reducing FSB signal, compared to day 1 (100%), was seen at day 7 (29%) and 14 (25%), compared to IgG or 6B2 (day 7: 71% and 73%; day 14: 56% and 66%, respectively, $p<0.05$). This outcome is in agreement with our published findings on 4E6's efficacy in other models (Congdon et al., Mol Neurodegener, 2016). This type of a two-photon imaging approach provides valuable insight into the dynamics of uptake of mAbs and the clearance of their pathological targets in live animals, and may clarify their mechanism of action.

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Nanosymposium

454. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: 144A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***454.08

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

Support: Alzheimer's Association
Cure Foundation
Georgetown University
NCATS TL1-TR001431
Georgetown-MedStar CERSI Scholars

Title: Tau and astrocyte pathology are reduced in a mouse model of tauopathy following pazopanib treatment

Authors: *M. JAVIDNIA[1,2], M. L. HEBRON[1], C. E.-H. MOUSSA[1]
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Abstract: Tauopathies are neurodegenerative disorders associated with pathological changes in the microtubule-associated protein 'tau', including Alzheimer's disease (AD) and frontotemporal

dementia with Parkinsonism linked to chromosome 17 (FTDP-17). Tau is a basally phosphorylated protein which becomes hyperphosphorylated (p-tau), dissociates from microtubules, and leads to aggregates such as tau 'tangles'. There are currently no treatments available for these diseases. Our laboratory has shown tyrosine kinase inhibition to be a novel therapeutic approach for the treatment of neurodegenerative disorders. Using a new mouse model of tauopathy which expresses human mutant (P301L) tau under a mouse prion protein promoter (TauP301L), we show extensive tau pathology throughout the brain. Further, we found significantly higher levels of glial fibrillary acidic protein (GFAP) staining with no change in ionized calcium-binding adapter molecule 1 (IBA1). In TauP301L mice, we found astrocytes containing p-tau (AT180), reminiscent of human tauopathies. Daily intraperitoneal treatment with 5mg/kg of the tyrosine kinase inhibitor pazopanib for 3-4 weeks significantly reduced tau and astrocyte pathology in TauP301L mice. Treatment did not alter measured chemokines or cytokines within the blood or the brain. These data suggest a unique interplay between P301L tau and astrocytes but not microglia. Additionally, treatment with pazopanib is able to reduce both GFAP levels and p-tau. Future studies aim to determine the role of astrocytes in the clearance or propagation of p-tau.

Disclosures: M. Javidnia: None. **M.L. Hebron:** None. **C.E. Moussa:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intellectual property.

Nanosymposium

454. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: 144A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***454.09

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

Support: NIH Grant AG039668
New Jersey Health Foundation Grants
NSF Grant IOS-1347090

Title: Inhibition of β-secretase activity prevents accumulation of amyloid-β (Aβ), but does not block Tau phosphorylation and aggregation in a neuronal cell culture model of sporadic Alzheimer's disease

Authors: *V. MURESAN, Z. LADESCU MURESAN
Pharmacology, Physiol. and Neurosci., Rutgers The State Univ. of New Jersey, Newark, NJ

Abstract: Our goal is to understand the modifications in the physiology of the neuron that facilitate the development of sporadic Alzheimer's disease (AD), and to identify the mechanisms that lead to the generation and oligomerization of Aβ, and aggregation of hyperphosphorylated Tau (pTau), in the absence of disease-causing genetic mutations. Ultimately, we aim to develop strategies that interfere with these mechanisms, and block both the Aβ and the pTau pathology. Towards this end, we developed an "Alzheimer's-in-a-dish" model that reproduces the AD-specific intraneuronal accumulation of oligomeric Aβ and aggregated pTau under conditions of cellular stress typical of old age: genotoxic (UV irradiation), metabolic (anisomycin), oxidative (hydrogen peroxide), osmotic (sorbitol), or inflammatory (IL-1β). With CAD neurons, we show that all these conditions block axonal transport, and initially cause the phosphorylation of the Aβ precursor protein (APP) at Thr668 by JNK. We find that this phosphorylation is enabled by the APP binding protein, Fe65, which recruits a JIP-3/JNK complex to the APP accumulated in the soma. Phosphorylation increases APP's susceptibility to amyloidogenic cleavage, leading to the accumulation of Aβ in the soma. In addition, via a mechanism independent of APP cleavage, phosphorylation of APP causes the release of Fe65 (due to diminished affinity for pAPP), which then translocates into the nucleus and upregulates the expression of GSK3β, the kinase that phosphorylates Tau. Preventing the recruitment of the phosphorylation complex by knocking down Fe65 blocks APP phosphorylation, and eliminates both Aβ and pTau accumulation, as do specific inhibitors of JNK. These data show that the Fe65-dependent phosphorylation of APP by JNK is required for the stress-induced intraneuronal accumulation of Aβ and pTau. According to the pathogenic model proposed here, drugs blocking the activity of secretases, while diminishing Aβ pathology, would not prevent the Tau pathology, which relies on Fe65 translocation into the nucleus - an event primed by the phosphorylation of APP, but independent of APP cleavage. Indeed, knocking down BACE1 expression prevents accumulation of Aβ, but does not block Tau phosphorylation and aggregation. This could explain why therapeutic approaches targeting β- and γ-secretase, avidly pursued by the pharmaceutical industry, have not been so far successful in AD clinical trials. Our study suggests that blocking the phosphorylation of APP, caused by multiple forms of environmental stress or trauma, could be effective in preventing both the intraneuronal accumulation of Aβ, and the phosphorylation and aggregation of Tau.

Disclosures: V. Muresan: None. **Z. Ladescu Muresan:** None.

Nanosymposium

454. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: 144A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***454.10

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

Support: W. Garfield Weston Foundation
NIH Grant R01 EB003268
CIHR Grant MOP 119312
Canada Research Chairs Program

Title: Large animal evaluation of clinical scale methods for focused ultrasound treatments of Alzheimer's disease

Authors: R. M. JONES[1], M. A. O'REILLY[1], L. DENG[2], K. LEUNG[2], D. MCMAHON[1], *K. HYNYNEN[1]
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Abstract: Transient Blood-Brain Barrier (BBB) opening via focused ultrasound (FUS) and circulating microbubbles (MBs) has been shown to reduce Aβ plaque pathology and improve spatial memory in transgenic mouse models of Alzheimer's disease (AD). This approach is under clinical testing for enhanced chemotherapy delivery to brain tumors with a commercial device [Huang *et al ISMRM* 2016]. However, more robust methods are needed to carry out the controlled large volume treatments required for AD in a clinically acceptable timeframe. We have shown that 3D mapping of subharmonic MB activity can be used to calibrate exposure levels for BBB opening [Jones *et al IEEE IUS* 2016]. Here we evaluate the safety and efficacy of this approach during volumetric sonications in large animals.
FUS and Definity^{TM} MBs were used to open the BBB unilaterally in rabbits and pigs under MRI-guidance at 3T. The treatments were performed using a clinical scale transmit/receive prototype (30 cm diam., 256 elements x 3 frequencies: 306/612/1224 kHz). The array was focused transcranially without aberration correction and pulsed FUS (612 kHz, 10 ms bursts, 0.5-1 Hz PRF) was applied during MB infusion (20 μL/kg, 1 min). Receiver signals captured at the subharmonic (306 kHz) were beamformed in 3D near the target. Pressure was increased each burst (10-20 kPa steps *in situ*) until spatially coherent MB activity was detected; proximal tissue volumes were exposed at 50-100% of the value required to induce this MB behavior via rapid electronic steering (6 x 6 grid, 1 mm spacing, 10 ms bursts & 1 Hz PRF per point, 2 min). Initial testing was carried out in the thalamus of rabbits (107 grids, n = 13, 2-4 kg). Following this pilot study, chronic testing (1-4 weekly sessions) of hippocampal BBB opening was performed in pigs (28 grids, n = 6, 10-20 kg). These animals received daily neurological testing starting 24 h before the first session. Animals were sacrificed 1 h - 7 days after their final session.
Following subharmonic detection, multipoint sonications induced volumetric BBB openings (100 ± 25 mm^3 on T_1w MRI) in all animals (1-6 targeted volumes per animal). Hypointense regions on T_2*w MRI were occasionally seen at target levels of 75% and above but not at 50%. Neurological testing did not show any effects from the chronic group. Follow-up MRI 1 week following each session confirmed BBB restoration. H&E staining revealed a few extravasated erythrocytes in the perivascular space within the treated volumes (10 ± 3 clusters) 7 days post-FUS. Our results suggest subharmonic MB imaging can calibrate FUS exposure levels for safe BBB opening over large volumes, and that repeated exposures in a structure relevant to AD is tolerated in healthy swine.

Disclosures: **R.M. Jones:** None. **M.A. O'Reilly:** None. **L. Deng:** None. **K. Leung:** None. **D. McMahon:** None. **K. Hynynen:** None.

Nanosymposium

454. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: 144A

Time: *Tuesday, November 14, 2017, 8:00 AM - 10:45 AM

Presentation Number: *454.11

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

Title: Fasudil, a Rho kinase inhibitor, as a preventative therapeutic for Alzheimer's disease

Authors: ***M. WILLEMAN**[1,2,3,4], P. SHUKLA[1], A. L. SINIARD[2], M. DE BOTH[2], T. WANG[2], T. DUNCKLEY[1], P. PIRROTTE[2], S. ODDO[1], M. HUENTELMAN[2]
[1]Arizona State Univ., Phoenix, AZ; [2]Neurogenomics, Translational Genomics Res. Inst., Phoenix, AZ; [3]Arizona Alzheimer's Consortium, Phoenix, AZ; [4]Evelyn F. McKnight Brain Inst. at the Univ. of Arizona, Tucson, AZ

Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disease that affects 5.4 million Americans. AD leads to memory loss, changes in behavior, and death. The key hallmarks of the disease are amyloid plaques and tau tangles, consisting of amyloid-β oligomers and hyperphosphorylated tau, respectively. Current treatment options for AD are only used for mild to moderate dementia or moderate to severe dementia, and do not affect the pathology that leads to dementia symptoms. Further, the first neuritic plaque is observed 1-2 decades prior to the onset of dementia. Current research into new treatment options aims to treat AD prior to pathology, and to decrease amyloid pathology or tau pathology, or to improve cognition, or some combination of the three. Variation in KIBRA have been shown to be correlated with differences in cognition in healthy adults, and proteins upstream of KIBRA have been studied in association with learning and memory to determine if drugs for those proteins can be used to affect cognition. One of these drugs is Fasudil, a Rho-associated, coiled-coil-containing protein kinase (ROCK) inhibitor. ROCK is an enzyme that plays important roles in neuronal cells including mediating actin organization and dendritic spine morphogenesis. Fasudil has been shown to increase learning and working memory in aged rats, but another ROCK inhibitor, Y27632, was shown to impair learning and memory. We are interested in exploring how these, and other ROCK inhibitors, may be acting mechanistically to result in very different outcomes in treated animals. Preliminary research on thirteen different ROCK inhibitors provides evidence that while Fasudil and a novel ROCK inhibitor, T343, decrease the ratio of phosphorylated tau (p-tau) to total tau in vitro, Y27632 increased the ratio at a low dosage (LD-10) and decreased it at a high dosage (LD-50) Meanwhile, another novel ROCK inhibitor, T299, increased the p-tau to total tau

ratio at a high dosage. Further, and in vivo study using triple transgenic AD mice provides evidence that Fasudil treatment improves spatial reference memory in wild-type mice, and improves fear memory in both AD and wild-type mice. Meanwhile, Y27632 treatment further impairs spatial reference memory in AD mice. Fasudil also decreases tau phosphorylation and Aβ in vivo, while Y27632 causes a significant increase in the p-tau to total tau ratio and increases soluble Aβ42 in vivo.

Disclosures: M. Willeman: None. **P. Shukla:** None. **A.L. Siniard:** None. **M. De Both:** None. **T. Wang:** None. **T. Dunckley:** None. **P. Pirrotte:** None. **S. Oddo:** None. **M. Huentelman:** None.

Nanosymposium

455. Alpha-Synuclein: Models and Mechanisms

Location: 147A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***455.01

**Topic: ***C.03. Parkinson's Disease

Support: DFG Center for Nanoscale Microscopy and Molecular Physiology of the Brain

Title: PrP^C mediates alpha-Synuclein synaptic dysfunction in the hippocampus

Authors: *T. F. OUTEIRO[1], D. G. FERREIRA[1], H. V. MIRANDA[2], M. SCHMITZ[1], I. ZERR[1], L. V. LOPES[3]
[1]Univ. Med. Ctr. Goettingen, Goettingen, Germany; [2]Chronic Dis. Res. Center, NOVA Med. Sch., Lisbon, Portugal; [3]Inst. de Medicina Molecular, Fac Med. Lisbon, Lisbon, Portugal

Abstract: Synucleinopathies, such as Parkinson's disease and dementia with Lewy bodies, are neurodegenerative disorders characterized by the accumulation of α-synuclein (aSyn) in intracellular inclusions known as Lewy bodies (LBs). LBs accumulate throughout the brain as disease progresses, but the precise significance of these inclusions in disease pathogenesis is still unclear. Currently, prefibrillar, soluble aSyn oligomers are considered early and key intermediates in the disease-related synaptic dysfunction that is common to various synucleinopathies. Recently, we identified the cellular prion protein (PrP^C) as a key mediator of aSyn-associated synaptic dysfunction. Impairment of long term potentiation (LTP) induced by exposure to aSyn was blocked in PrP null mice and was rescued upon PrP^C blockade. We found that extracellular aSyn oligomers form a complex with PrP^C at the post-synaptic density, inducing the phosphorylation of intracellular Fyn kinase via the metabotropic glutamate receptor 5 (mGluR5). aSyn engagement of PrP^C/Fyn signaling causes NMDA receptor (NMDAR) activation and, consequently, dysregulation of calcium homeostasis. We are now investigating

these processes in vivo, which should inform about novel possibilities for therapeutic intervention in PD and other synucleinopathies.

Disclosures: T.F. Outeiro: None. **D.G. Ferreira:** None. **H.V. Miranda:** None. **M. Schmitz:** None. **I. Zerr:** None. **L.V. Lopes:** None.

Nanosymposium

455. Alpha-Synuclein: Models and Mechanisms

Location: 147A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***455.02

**Topic: ***C.03. Parkinson's Disease

Support: NIH 1R01 NS064963
Hirschfield Foundation

Title: Molecular investigations into the presynaptic functions of synucleins

Authors: *S. S. CHANDRA, K. J. VARGAS
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Abstract: α-Synuclein, a presynaptic protein, plays a central role in the pathophysiology of Parkinson's disease (PD). α-Synuclein is the lead therapeutic target for PD, with several strategies to lower α-synuclein levels being tested in clinical trials. Hence, there is great interest in elucidating the physiological function(s) of α-synuclein and how they impact presynaptic functions. We and others have previously shown that synucleins can sense and generate membrane curvature, properties consistent with roles in synaptic vesicle exo- and endocytosis. Recently, with αβγ-synuclein triple knock out mice, we showed that a conserved function of synucleins is to regulate the kinetics of synaptic vesicle endocytosis (SVE). Here, we pinpoint the molecular functions of α-synuclein in SVE using several independent approaches. Using membrane recruitment assays, we discovered that synucleins act at early steps of SVE to regulate the normal recruitment of a subset of endocytic proteins to synaptic membranes. These proteins include those that function in exo-endocytosis coupling as well as early coat assembly proteins. Thus, we conclude that α-synuclein is an early endocytic protein. We also describe the effects of PD α-synuclein mutants on endocytic protein recruitment, and SVE. Our data point to changes in SVE and synaptic vesicle organization, leading to progressive synaptic deficits and concomitant neurodegeneration in PD.

Disclosures: S.S. Chandra: None. **K.J. Vargas:** None.

Nanosymposium

455. Alpha-Synuclein: Models and Mechanisms

Location: 147A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***455.03

**Topic: ***C.03. Parkinson's Disease

Support: Department of Medicine, BUSM

Title: Pathogenic synergy between PARK14/Ca^{2+}signaling and α-synuclein aggregation in a new bigenic mouse model of age-dependent Parkinson's disease

Authors: *V. M. BOLOTINA[1], A. YEN[1], F. NIPA[1], J. W. SHIM[1], M.-F. CHESSELET[2], E. MASLIAH[3]
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Abstract: Recently we discovered a new sequence of pathological events that can be triggered by idiopathic, or genetic defects in PARK14/PLA2g6-dependent store-operated Ca^{2+} (PLA2g6/Ca^{2+}) signaling leading to autophagic dysfunction, progressive loss of dopaminergic (DA) neurons in substantia nigra pars compacta (SNc), and Parkinson's disease (PD)-like motor dysfunction in PLA2g6ex2^{KO} mouse model.
Here we present first evidence for pathogenic synergy between PLA2g6/Ca^{2+} dysfunction and α-synuclein (α-syn) aggregation, and introduce a novel bigenic mouse model that expresses human WT α-syn and carries inducible Cre/PLA2g6ex2^{KO} (Thy1/αSyn^{hWT} x Cre/PLA2g6ex2^{KO}). Progression of PD-like motor dysfunction, age-dependent α-syn spreading and PD-related neuropathological changes in the brain was compared in bigenic mice and age-matched animals from the parent Thy1/αSyn^{hWT} and Cre/PLA2g6ex2^{KO} lines. We found that induction of PLA2g6/Ca^{2+} deficiency in 3 month old bigenic mice expressing human α-Syn enhanced its aggregation in DA neurons, and triggered rapid loss of DA neurons in SNc and accelerated PD-like motor dysfunction. At 6 months of age (3 months after tamoxifen treatment) these mice showed about 50% loss of DA neurons in SNc and dramatic increase in the number of missteps in the balance beam test. None of these defects could be found in 6 months old WT, PLA2g6ex2KO or Thy1/αSyn animals treated with tamoxifen. Importantly, induction of PLA2g6ex2^{KO} deficiency also accelerated aggregation of phosphorylated α-Syn in locus coeruleus, dorsal motor nucleus and DA neurons in SNc. Thus, our novel Thy1/αSyn^{hWT} x Cre/PLA2g6ex2^{KO} mouse model can closely follow Braak's stages of PD in humans, and can present one of the most complete PD-like phenotypes, including progressive synucleinopathy, significant loss of DA neurons in SNc and age-dependent motor dysfunction. The results of these studies strongly suggest that idPD-associated defects in PARK14/PLA2g6-dependent Ca^{2+}

signaling can be a previously unknown trigger or accelerator of α-Syn aggregation and their pathogenic synergy may be a critical determinant of idPD.

Disclosures: V.M. Bolotina: None. **A. Yen:** None. **F. Nipa:** None. **J.W. Shim:** None. **M. Chesselet:** None. **E. Masliah:** None.

Nanosymposium

455. Alpha-Synuclein: Models and Mechanisms

Location: 147A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***455.04

**Topic: ***C.03. Parkinson's Disease

Support: Michael J Fox Foundation Access Data-Biospecimens Program
R21 NS093435-01
NIGMS MERIT Postdoctoral Fellowship 5 K12 GM088010-05
NIHR01-NS064090

Title: Alpha-Galactosidase deficiency in Parkinson's disease brain is associated with the pathologic accumulation of alpha-synuclein

Authors: *J. J. SHACKA[1], M. NELSON[2], M. BOUTIN[3], T. TSE[1], X. OUYANG[2], J. ZHANG[2], C. AURAY-BLAIS[3]
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Abstract: The aberrant accumulation of alpha-synuclein is believed to contribute to the onset and pathogenesis of Parkinson's disease (PD). The autophagy-lysosome pathway (ALP) is responsible for high capacity clearance of alpha-synuclein. ALP dysfunction is documented in PD and pre-clinical evidence suggests inhibiting the ALP promotes the pathological accumulation of alpha-synuclein. We previously identified the pathological accumulation of alpha-synuclein in brains of mice deficient for the soluble lysosomal enzyme alpha-Galactosidase A, which hydrolyzes glycosphingolipids. In the present study we quantified alpha-Galactosidase A levels & activity and levels of its glycosphingolipid metabolites in postmortem temporal cortex specimens from control patients and PD patients staged with respect to alpha-synuclein containing Lewy body pathology. We observed in late-stage PD temporal cortex a significant decrease in the 46 kDa active species of alpha-Galactosidase A by western blot as well as a significant decrease in alpha-Galactosidase A activity. Decreased alpha-Galactosidase A activity/levels correlated significantly with significant increases in alpha-synuclein

phosphorylated at serine 129 (p129S) that were also observed specific to late-stage PD temporal cortex. Mass spectrometric analysis of 29 different isoforms of globotriaosylceramide (Gb3), suspected hydrolysis products of alpha-Galactosidase A revealed no significant differences with respect to different stages of PD temporal cortex. However, significant correlations were observed with increased levels of several Gb3 isoforms and with a decrease in alpha-Galactosidase A activity and/or an increase in p129S-alpha-synuclein. Analysis of other lysosomal enzymes in late-stage PD temporal cortex revealed a significant decrease in activity for cathepsin D but not of glucocerebrosidase, although a significant correlation was observed between decreasing glucocerebrosidase activity and increasing p129S-alpha-synuclein. Together our findings indicate alpha-Galactosidase A deficiency in late-stage PD brain that correlates significantly with the pathological accumulation of alpha-synuclein, and suggests the potential for alpha-Galactosidase A and its glycosphingolipid metabolites as putative biomarkers for PD.

Disclosures: J.J. Shacka: None. **M. Nelson:** None. **M. Boutin:** None. **T. Tse:** None. **X. Ouyang:** None. **J. Zhang:** None. **C. Auray-Blais:** None.

Nanosymposium

455. Alpha-Synuclein: Models and Mechanisms

Location: 147A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***455.05

**Topic: ***C.03. Parkinson's Disease

Support: Identification of Robust and Relevant Pre-Clinical Phenotypes for LRRK2 Therapeutics

Title: Comparative analysis of the sensitivity and specificity of ser(P)-129 α-synuclein monoclonal antibodies

Authors: *S. CHANDRA, V. DELIC, X. HU, V. KRENDELCHTCHIKOVA, A. B. WEST
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Abstract: α-Synuclein (α-syn) is an abundant presynaptic protein that is the primary constituent of Lewy bodies and neurites that are major pathological hallmarks of Lewy body diseases (LBDs). The majority of α-syn in these inclusions is phosphorylated on the serine-129 amino acid (Ser(P)-129), while Ser(P)-129 levels are very low or undetectable in the cytosol of healthy neurons. There are mixed reports regarding the specificity of different monoclonal antibodies used in rodent tissues to assess α-syn related pathologies. As such, a benchmark antibody that allows cross-study analysis does not yet exist. The goal of this study is to evaluate the commercially available Ser(P)-129 α-syn monoclonal antibodies that include clones 81a,

EP1236Y, MJF-R13, and pSyn64 for their application in paraformaldehyde-fixed primary neurons and rodent tissue immunohistochemistry and immunofluorescence. In either primary neurons or *in vivo,* Lewy body disease-reminiscent pathology was induced through the exposures of α-syn preformed fibrils (PFFs). PFFs, generated from recombinant α-syn, can corrupt and seed the recruitment of endogenous α-syn into fibrillar aggregates weeks after the initial exposures. Brain tissue or neurons from Sprague-Dawley rats and C57Bl/6J mice exposed to PFFs or control monomeric protein were compared to neurons from α-syn knockout rodents to assess antibody specificity and sensitivity. Substantial differential off-target labeling was observed between the different antibodies, and recommendations for applications towards specific protocols are given.

Disclosures: S. Chandra: None. **V. Delic:** None. **X. Hu:** None. **V. Krendelchtchikova:** None. **A.B. West:** None.

Nanosymposium

455. Alpha-Synuclein: Models and Mechanisms

Location: 147A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***455.06

**Topic: ***C.03. Parkinson's Disease

Support: EU grant agreement 602646

Title: Identifying PET imaging biomarkers of alpha-synuclein pathology

Authors: *K. HERFERT[1], N. LANDECK[3], L. KUEBLER[2], A. MAURER[2], F. SCHMIDT[4], A. LEONOV[5], S. RYAZANOV[5], C. GRIESSINGER[5], A. GIESE[6], D. KIRIK[3], B. J. PICHLER[2]
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Abstract: Alpha-synuclein (αSYN) is the main component of Lewy Bodies and accumulating evidence suggest that αSYN is a possible mediator of synaptic dysfunction and DAergic degeneration in Parkinson´s disease (PD). However, pathogenically relevant biomarkers of αSYN aggregation are still lacking. We investigated the relationship between αSYN aggregation and disease progression in an αSYN-overexpression rat model of PD using *in vivo* PET imaging. In addition, we tested tritiated derivatives of anle138b, which were previously shown to interfere with the pathological aggregation of αSYN [1] towards their binding affinities to human αSYN

fibrils.
Rats were injected with either AAV-αSYN (n=49) or AAV-GFP (n=46) into the right substantia nigra (SN). The left striatum served as control. Dynamic PET scans were performed with ^{11}CPIB, ^{11}C-methylphenidate, ^{11}C-DTBZ and ^{11}C-raclopride 1, 3, 5 and 9 month (m) after injection and the animals were sacrificed after each time point. Histological and biochemical methods were used to identify αSYN levels in CSF and brain tissue. DAergic cell loss was determined by stereological quantification of VMAT2 positive neurons in the SN.
In vitro saturation binding assays were performed using recombinant human αSYN fibrils. Total binding was obtained after incubation with the radioactive solutions (0.02–48nM) and nonspecific binding was determined in the presence of a 1μM excess of the corresponding nonradioactive compound.
Our data show that D2 receptor occupancy changes provided the most reliable imaging readout for αSYN pathology. While AAV-αSYN injections reduced VMAT2 and DAT expressions at the 3-9 month time points, but also to a smaller extend in AAV-GFP injected rats, ^{11}Craclopride binding was consistently increased by 20-26% in AAV-αSYN rats from early to late time points, but unaffected in AAV-GFP rats. In addition, our data show specific binding of ^{11}CPIB to αSYN fibrils *in vitro* and a progressive binding in AAV-αSYN rats from 1m (BP_{ND}=0.03) to 3m (BP_{ND}=0.07), 5m (BP_{ND}=0.12) and 9m (BP_{ND}=0.10). DA levels in the striatum and insoluble αSYN aggregates correlated to ^{11}CPIB binding. Using saturation binding experiments, we observed a clear specific binding of the selected compounds with K_d-values ranging from 2.4±3.5nM to 126.5±27.1nM.
We could show that D2 receptor occupancy changes as well as ^{11}C-PIB binding changes provided the best readout for αSYN pathology. Our next steps include the comparison of K_d values from the tritiated compounds to Aβ and τ fibrils to confirm αSYN selectivity. In addition, PET tracers from the two best compounds will be developed and tested *in vivo*.
[1] Wagner J, et al. Acta Neuropathol. 2013;125:795–813

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Nanosymposium

455. Alpha-Synuclein: Models and Mechanisms

Location: 147A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***455.07

**Topic: ***C.03. Parkinson's Disease

Support: European Union's Seventh Framework Programme under REA grant agreement n°602646

Title: Quantification of molecular and functional changes in a rat model of Parkinson's disease using a simultaneaous PET/fMRI protocol

Authors: *L. KUEBLER[1], K. HERFERT[1], N. LANDECK[2], A. MAURER[1], M. AMEND[1], A. THIELCKE[1], S. BUSS[1], S. MARCIANO[1], R. STUMM[1], H. F. WEHRL[1], D. KIRIK[2], B. J. PICHLER[1]
[1]Werner Siemens Imaging Center, Dept. of Preclinical Imaging & Radiopharmacy, Univ. of Tübingen, Tübingen, Germany; [2]Brain Repair and Imaging in Neural Systems (BRAINS) Unit, Dept. of Exptl. Med. Sci., Lund Univ., Lund, Sweden

Abstract: The accurate diagnosis of Parkinson's disease (PD) remains challenging as no current imaging tracer exhibiting sufficient specificity and sensitivity to detect alpha-synuclein (αSYN) aggregates *in vivo* is on the horizon. The aim of the current study was to establish a [^{11}C]Raclopride (RAC) positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) protocol to simultaneously quantify molecular changes of dopamine (DA) receptor occupancy and functional neuronal changes as a marker for presynaptic dysfunction in an αSYN overexpression rat model of PD. This protocol aims to investigate treatment effects on αSYN aggregation. To measure functional changes in four rats, a 20-slice blood-oxygen-level dependent (BOLD) imaging sequence covering the whole brain (Echo-planar imaging, repetition time: 2500 ms, echo time: 18 ms, voxel size: 0.27 x 0.27 x 0.80mm^3) was used. It was applied over 80 minutes using a 7T animal MR. Simultaneous RAC-PET was obtained using a small animal PET insert. RAC was injected as a fast i.v. bolus (30 s) injection followed by a constant infusion of 488 ± 173MBq, with a bolus to infusion rate ratio of 34 min. Animals were kept under 1.3 % isoflurane. Time activity curves from the striata (STR) and cerebellum (CER) were generated and the STR/CER (DVR)-1 was calculated. BOLD-fMRI data were preprocessed using SPM and time signal curves of the STR were extracted. Next, rats were injected with an adeno-associated virus expressing human αSYN into the right substantia nigra. A second PET/fMRI scan was acquired 5 months after surgery using an amphetamine (AMPH) challenge (1 mg/kg) 40 minutes after start of PET/MR acquisition to stimulate DA release from presynaptic DAergic terminals. The relative BOLD signal was constant over the whole scan time while RAC DVR-1 values reached steady state 25 minutes after injection for a period of 55 minutes. In both,

PET and fMRI no difference between the right and left STR was observed. After viral injection, the DVR-1 in the right STR was increased by 22 % compared to the left STR, whereas the BOLD signal showed no difference. AMPH challenge reduced RAC binding over time in the right and left STR and increased the BOLD signal with a more pronounced increase in the left striatum. However, in some animals motion artifacts in the BOLD signal were observed. We present a novel simultaneous RAC-PET/fMRI protocol for future applications in animal models of PD. Data indicate that RAC-PET could reliably detect αSYN pathology, while the BOLD signal change was observed after AMPH challenge. To avoid motion artifacts in future experiments a muscle relaxant will be used.

Disclosures: **L. Kuebler:** None. **K. Herfert:** None. **N. Landeck:** None. **A. Maurer:** None. **M. Amend:** None. **A. Thielcke:** None. **S. Buss:** None. **S. Marciano:** None. **R. Stumm:** None. **H.F. Wehrl:** None. **D. Kirik:** None. **B.J. Pichler:** None.

Nanosymposium

455. Alpha-Synuclein: Models and Mechanisms

Location: 147A

Time: *Tuesday, November 14, 2017, 8:00 AM - 10:30 AM

Presentation Number: *455.08

Topic: *C.03. Parkinson's Disease

Support: JSPS KAKENHI 23591265
JSPS KAKENHI 26461287

Title: Direct association of alpha-synuclein oligomers and calcium binding protein 1 mediate the aberrant form of calcium-induced calciuim release from IP_3 receptor

Authors: ***K. YAMAMOTO**[1], Y. IZUMI[2], H. SAWADA[1]
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Abstract: There is a growing body of evidence showing α-synuclein oligomers as potential culprits in the pathogenesis of Parkinson's disease (PD). In general, PD vulnerable neurons have a common physiological phenotype; autonomous pacemaker, broad and slow spiking, and lower expression of Ca^{2+} binding protein, which increase cytosolic Ca^{2+} and augment metabolic burden in these neurons. By contrast, neocortical pyramidal neurons, in which α-synuclein aggregation causes PD dementia (PDD) or dementia with Lewy body (DLB), do not have such features, raising a question how oligomeric α-synuclein accumulated in the cytoplasm can pathologically modify neuronal activities and intracellular Ca^{2+} dynamics in neocortical neurons. We examined how intraneural α-synuclein oligomers act on neuronal excitabilities and Ca^{2+} dynamics of

pyramidal neurons in mice neocortical slices. For whole cell recording, we infused the pipette solution including higher order α-synuclein oligomer (αSNo) in comparison with α-synuclein-containing solution without higher order oligomer. Spike firing frequency and afterhyperpolarization (AHP) current charge (I_{AHP}) were measured under applying the blockers of channels and receptors, Ca^{2+} binding proteins or their antibodies associated with cytosolic Ca^{2+} dynamics. Intracellular application of αSNo reduced the spike frequency during multiple spikes, elongated the duration of AHP, and enlarged I_{AHP}. Pharmacological experiments indicated that the functional coupling of L-type Ca^{2+} channel, SK-type potassium channel, and IP_3 receptor (IP_3R) was responsible for this αSNo-mediated alteration of spike firing and I_{AHP}. Further electrophysiological observations and immunoprecipitation experiment revealed that higher order α-synuclein oligomers directly bind Ca^{2+} binding protein 1 (CaBP1), which is distributed in rodent and human central neurons including neocortex pyramidal neurons and is a negative regulator of IP_3R gating, pull it away from IP_3R, and mediated an aberrant form of Ca^{2+}-induced Ca^{2+} release from IP_3R during multiple spikes. These results suggest that α-synuclein oligomers are directly associated with CABP1, hamper CaBP1-mediated inactivation of IP_3R and lead to spike-induced Ca^{2+} release from IP_3R without increasing Ca^{2+} influx or IP_3, which would not physiologically occur in neocortical pyramidal neurons. This aberrant mechanism may cause mitochondrial Ca^{2+} burden and be the underlying molecular machinery for neuronal vulnerability of the neocortex in PDD/DLB patients.

Disclosures: K. Yamamoto: None. **Y. Izumi:** None. **H. Sawada:** None.

Nanosymposium

455. Alpha-Synuclein: Models and Mechanisms

Location: 147A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***455.09

**Topic: ***C.03. Parkinson's Disease

Title: Potent small molecule Parkin activators for treating Parkinson's disease

Authors: P. ARSENAULT[1], M. KUMAR[2], I. SOKIRNIY[1], F. WANG[1], B. CUNNION[1], J. WU[1], D. STERNER[1], J. WEINSTOCK[3], M. MATTERN[3], V. L. DAWSON[4], T. M. DAWSON[2], *S. KUMAR[3]
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Abstract: Parkin, an ubiquitin E3 ligase, has emerged as a critical regulator of mitochondrial dynamics as well as a protector of neuronal health. Parkin exists in an auto-inhibited state and is

subjected to phosphorylation and activation by kinases in a spatio-temporal fashion. Upon mitochondrial damage, Parkin is phosphorylated by PINK1, and activated Parkin ubiquitylates several mitochondrial substrates leading to changes in mitochondrial dynamics. Importantly, inactivating mutations in both Parkin and PINK1 are seen in Parkinson's disease (PD) patients, underscoring their involvement in the pathological process. Moreover, accumulation of damaged mitochondria and proteotoxic stress resulting from alterations in the UPS have been implicated in PD. More recently, Parkin was shown to promote mitochondrial biogenesis through ubiquitylation and degradation of PARIS, a co-repressor of PGC1α, the master regulator of mitochondrial biogenesis. In addition, Parkin protects neuronal health by promoting degradation of AIMP2. The restoration of Parkin functions in dopaminergic neurons could improve neuronal health and have a profound impact on Parkinson's disease progression. Using Progenra's proprietary UbiPro^{TM} HTS platform we have successfully identified small molecule activators of Parkin. Here we present the biochemical and cellular characterization of potent and selective Parkin activators that restore Parkin function in a PINK1 independent manner. Specifically, we show that these molecules are able to modulate mitochondrial dynamics in a variety of Parkin expressing cell lines including neuronal cell lines. Most importantly, small molecule Parkin activators promote the degradation of mitochondrial and cytosolic Parkin substrates in both cultured neuronal cell lines and hES cell derived neuronal cultures. Development of these novel Parkin activators offers potentially viable therapeutic options to slow the progression of Parkinson's disease by promoting mitochondrial and neuronal health.

Disclosures: **P. Arsenault:** A. Employment/Salary (full or part-time):; Progenra Inc. **M. Kumar:** None. **I. Sokirniy:** A. Employment/Salary (full or part-time):; Progenra Inc. **F. Wang:** A. Employment/Salary (full or part-time):; Progenra Inc. **B. Cunnion:** A. Employment/Salary (full or part-time):; Progenra Inc. **J. Wu:** A. Employment/Salary (full or part-time):; Progenra Inc. **D. Sterner:** A. Employment/Salary (full or part-time):; Progenra Inc. **J. Weinstock:** A. Employment/Salary (full or part-time):; Progenra Inc. **M. Mattern:** A. Employment/Salary (full or part-time):; Progenra Inc. **V.L. Dawson:** None. **T.M. Dawson:** None. **S. Kumar:** A. Employment/Salary (full or part-time):; Progenra Inc.

Nanosymposium

455. Alpha-Synuclein: Models and Mechanisms

Location: 147A

Time: *Tuesday, November 14, 2017, 8:00 AM - 10:30 AM

Presentation Number: *455.10

Topic: *C.03. Parkinson's Disease

Support: APDA
NINDs

Michael J. Fox Foundation
Falconwood Foundation

Title: Stimulation of Sonic Hedgehog (Shh) signaling reduces formation and display of L-Dopa induced dyskinesia (LID) in models of Parkinson's Disease (PD)

Authors: *L. B. MALAVE[1,2,3], A. H. KOTTMANN[1,2,3]
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Abstract: In Parkinson's Disease (PD), dopamine (DA) levels fall due to progressive DA neuron degeneration causing a DA hypersensitive striatum. DA substitution therapy ameliorates many but not all symptoms and, worse, induces debilitating L-Dopa induced dyskinesia (LID). Since DA neurons communicate with their targets by several different cell signaling molecules, not just dopamine, these observations suggest that reduced levels of other DA neuron secreted factors besides dopamine might play critical roles in the pathophysiology of PD. We previously found that all DA neurons produce Shh, a cell trophic factor, throughout life and release it in the striatum. There Shh activates the G-protein coupled receptor (GPCR) smoothened (Smo) on cholinergic (ACh) interneurons and inhibits the transcription of the dopaminotrophic factor GDNF and the muscarinic autoreceptor M2. Recently aberrant neuronal activity of ACh neurons correlated with increased MAP kinase activation selectively in the dorso-lateral striatum became implicated in LIDs. For example LIDs are suppressed by chronic nicotine, the ablation or long duration optogenetic stimulation of ACh neurons and boosting M4 receptor signaling. We hypothesize that L-Dopa therapy results in an imbalance of Shh and DA signaling in the striatum which causes drug- induced pathologies in PD through reduced ACh activity.
We investigated the effect of the pharmacological activation or inhibition of Smo as an adjuvant treatment to L-DOPA therapy using the unilateral 6-OHDA - and the genetic aphakia - model of LID. We find that the pharmacological stimulation of Smo by the Smo specific agonists SAG or PUR inhibits MAP kinase activation selectively in ACh neurons of the dorso-lateral striatum and reduces expression of LID in response to L-Dopa dosing in both models. Conversely, we find that the genetic ablation of Shh from DA neurons or the pharmacological inhibition of Smo increase MAP-kinase pathway activation in ACh neurons, and formation and expression of LID. In addition we find that Shh signaling from DA neurons regulates glutamatergic synapse morphology on cholinergic neurons. Our results implicate reduced Shh signaling in LID and support the use of Shh agonists as an adjuvant during L-Dopa treatment as a therapeutic strategy.

Disclosures: L.B. Malave: None. **A.H. Kottmann:** None.

Nanosymposium

456. Application of Imaging Techniques in Neurodegenerative Diseases

Location: 152B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***456.01

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

Support: NIRG- 14-320049

Title: Mapping the subcortical to cortical spread of degeneration in preclinical Alzheimer's disease

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Abstract: The basal forebrain (BF) is among the first brain structures to degenerate in Alzheimer's disease (AD). In cognitively normal older adults expressing abnormal cerebrospinal levels of beta amyloid, we previously demonstrated with in vivo structural magnetic resonance imaging (MRI) that BF degeneration precedes and predicts the cortical spread of AD pathology. In line with post-mortem histology, these MRI findings point to the destruction of cholinergic neurons—a primary component of the BF—as driving this pattern.
In vivo imaging of the cholinergic system thus holds incredible promise for novel biomarkers and therapeutic strategies aimed at identifying the earliest signs of AD pathology and preventing its spread. However, current human in vivo imaging methods cannot distinguish cell-type specific markers of BF degeneration. While the BF contains all of the brain's intrinsic cholinergic neurons, it is also populated by other cell types, making it difficult to infer from structural MRI whether the observed pattern of preclinical BF degeneration is specifically cholinergic.
In the present study, we developed novel analytical methods to triangulate—from in vivo MRI data—structural degeneration of the cholinergic BF system at preclinical stages of AD. Data were provided by the Alzheimer's Disease Neuroimaging Initiative. To do so, we isolated subregions of the BF (nucleus basalis, septal nucleus/diagonal band) known to differ in two key structural properties specific to their cholinergic cell populations: (1) cholinergic cortical projection targets and (2) cholinergic cell concentration. We then compared subregional BF degeneration over a two year period among three groups: Cognitively normal adults with normal cerebrospinal beta amyloid (CN NAβ), and cognitively normal or mildly impaired adults with abnormal Aβ (CN AAβ/ MCI AAβ).
In the MCI AAβ group, we confirmed with multivariate searchlight analysis that each BF subregion predicted degeneration in distinct cortical areas that closely match their known cholinergic cortical projections. We then demonstrated with a 'reverse' searchlight analysis (cortical to BF) that these distinct cortical areas could predict subregional BF degeneration in an

independent sample of CN adults. Next we confirmed that the rate of degeneration in each BF subregion differed according to its cholinergic cell concentration. In both CN AAβ and MCI AAβ groups, higher subregional concentration of cholinergic cells yielded higher rates of degeneration. We provide unprecedented evidence that cell-type specific degeneration of the cholinergic system can be leveraged from subregional volumetric analysis of in vivo MRI data.

Disclosures: T.W. Schmitz: None. **R.N. Spreng:** None.

Nanosymposium

456. Application of Imaging Techniques in Neurodegenerative Diseases

Location: 152B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***456.02

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

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Title: A novel phasing analysis for amnestic and non-amnestic phenotypes of Alzheimer's disease

Authors: *F. DA RE[1,4], J. S. PHILLIPS[1], S. X. XIE[2], L. DRATCH[1], C. FERRARESE[5], D. J. IRWIN[1], C. T. MCMILLAN[1], E. LEE[3], L. M. SHAW[3], J. Q. TROJANOWSKI[3], D. A. WOLK[1], M. GROSSMAN[1]
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Abstract: Amnestic Alzheimer's disease (aAD) is defined by early atrophy of the medial temporal lobes (MTL) before spreading to neocortex. Following early memory difficulty, patients show impairments in other cognitive domains. In contrast, atypical Alzheimer's disease (AD) variants are characterized by early impairment in non-memory domains. The anatomical progression of pathology over time in these variants is unclear. The prevailing hypothesis states that these patients have relative sparing of MTL; instead, pathology originates in focal areas of neocortex. We tested this assumption using a novel cross-sectional magnetic resonance imaging

(MRI)-based phasing algorithm. We selected 279 T1-weighted anatomical MRI scans from 149 AD patients with pathology confirmed by autopsy or CSF data. Using 238 scans from 115 elderly controls, we generated an atrophy map for each scan based on a grey matter volume threshold of $Z < -1.0$. Then, we computed disease progression models for each phenotype: amnestic AD (68 scans), logopenic variant primary progressive aphasia (lvPPA, 90 scans), posterior cortical atrophy (PCA, 51 scans), corticobasal syndrome (CBS, 31 scans), and behavioural/dysexecutive-variant AD (bvAD, 39 scans). Finally, we inferred the anatomical onset and progression of disease based on frequency of regional atrophy, defining 4 phases in 120 anatomical regions-of-interest (ROIs) for each variant. Phase 1 was inferred from the most frequently atrophied 10% of ROIs; Phase 2 comprised ROIs atrophic in 80-90% of scans, and Phase 3 and 4 within the ranges 70-80% and 60-70% respectively. Finally, we assigned a phase to each MRI: Phase 1 if at least 75% of Phase 1 ROIs were atrophic, Phase 2 if a Phase 1 MRI showed atrophy in 75% of the Phase 2 ROIs, and so on up to Phase 4. This system exhibited a high correlation with: a) Braak stages in the aAD cohort, and b) the regional burden of tau and neuronal loss in patients with autopsy data. The distribution of atrophy uniquely identified each variant. Phase 1 ROIs, which represent the origin of disease, included MTL for the aAD group (spared in other phenotypes), left lateral temporal lobe for lvPPA, occipito-parietal cortex for PCA, temporo-parietal cortex for CBS, and fronto-temporal cortex for bvAD. MRI phases were correlated with disease duration independently of age and with several neuropsychological assessments, including the MMSE. The anatomical origin of atrophy was consistent with the dominant phenotype in each group. MRI-based phasing thus represents an innovative approach to study the neocortical origin and spread of disease in non-amnestic AD variants.

Disclosures: **F. Da Re:** None. **J.S. Phillips:** None. **S.X. Xie:** None. **L. Dratch:** None. **C. Ferrarese:** None. **D.J. Irwin:** None. **C.T. McMillan:** None. **E. Lee:** None. **L.M. Shaw:** None. **J.Q. Trojanowski:** None. **D.A. Wolk:** None. **M. Grossman:** None.

Nanosymposium

456. Application of Imaging Techniques in Neurodegenerative Diseases

Location: 152B

Time: *Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

Presentation Number: *456.03

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

Support: R01-EB00454
R01-AG027771-01A2
R03AG047461

Title: HFE mutations alter white matter diffusion and relaxation parametrics in alzheimer's disease

Authors: C. J. PURNELL[1], J. WANG[2], P. J. ESLINGER[3], Q. X. YANG[2], J. R. CONNOR[1], *M. D. MEADOWCROFT[1,2]
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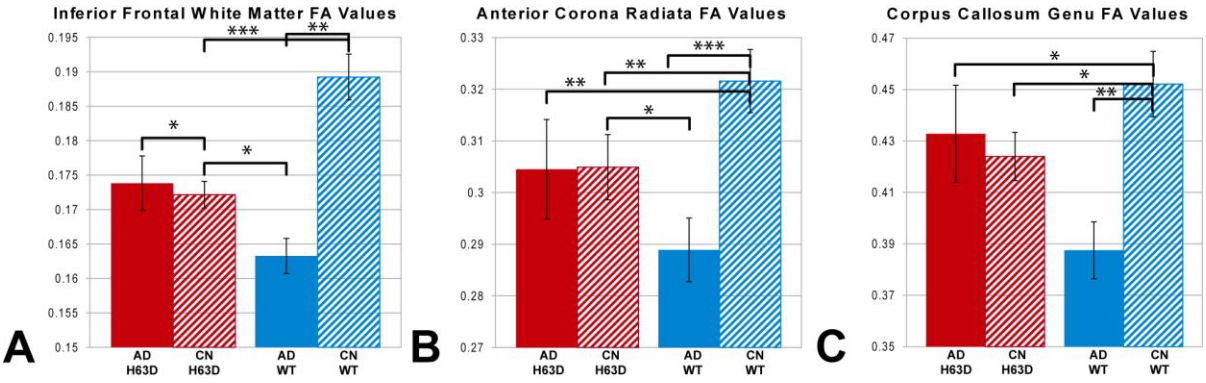
Abstract: Introduction
HFE polymorphisms have been implicated as a contributory factor in the development of neurodegenerative disorders, including Alzheimer's disease (AD). Mutations in this iron homeostatic gene may contribute to amyloidosis or the resulting inflammatory cycle, leading to neurodegeneration. Our previous work has shown reduced white matter relaxation and diffusion parametrics in cognitively normal HFE mutation carriers. This work aimed to test the hypothesis that AD subjects with HFE mutations have reduced white matter integrity compared to HFE-wild type (WT) AD carriers.
Methods
Cognitively normal (N=45, 27 HFE-H63D/+) and mild AD (N=26, 8 HFE-H63D/+) subjects were recruited for this study. FA, MD, and MO diffusion tensor and relaxation parametric maps obtained on a 3T MRI system were calculated and statistical analysis conducted.
Results
Cognitively normal subjects with HFE-H63D mutations exhibit MRI parametrics that converge towards AD HFE-WT metrics in prefrontal white matter. The data demonstrate that AD HFE-H63D mutation carriers are not demonstrating a decrease in apparent white matter integrity compared to AD HFE-WT carriers. The preservative effect was most significant in the same regions as observed in cognitively normal subjects, primarily the prefrontal WM and genu of the corpus callosum in both relaxation and DTI metrics. Statistical analysis of the interaction between AD status and genetics replicates these findings.
Discussion
Although no difference was detected between the H63D-HFE and wild type AD patients in clinical cognitive scores, H63D-HFE mutations in AD patients appears to be preservative for white matter parametric diffusion and relaxation biomarkers of AD. The H63D-HFE AD group trends towards similarity with the cognitively normal subjects. It is paradoxical that the H63D-HFE mutation may be altering AD pathology towards preservation of white matter. Further study will look into the hypothesized cause of the WM observations as a result of oligodendrocyte myelination vulnerability to altered iron homeostasis.



Disclosures: **C.J. Purnell:** None. **J. Wang:** None. **P.J. Eslinger:** None. **Q.X. Yang:** None. **J.R. Connor:** None. **M.D. Meadowcroft:** None.

Nanosymposium

456. Application of Imaging Techniques in Neurodegenerative Diseases

Location: 152B

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

Support: NIH Grant F32AG050434-01A1
NIH Grant AG038357
Larry L. Hillblom Foundation Grant 2015-A-034-FEL
Alzheimer's Association Grant PCTRB-13-288476
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NIH Grant R21 NS76171

Title: Distinct spatiotemporal patterns of resting state neuronal synchronizations in Alzheimer's disease

Authors: ***K. RANASINGHE**[1], J. CHA[2], L. B. HINKLEY[4], A. J. BEAGLE[2], A. LA[2], D. MIZUIRI[5], S. HONMA[3], V. BOURAKOVA[2], W. J. JAGUST[6], J. F. HOUDE[7], B. MILLER[2], G. D. RABINOVICI[2], K. A. VOSSEL[9], S. S. NAGARAJAN[8]
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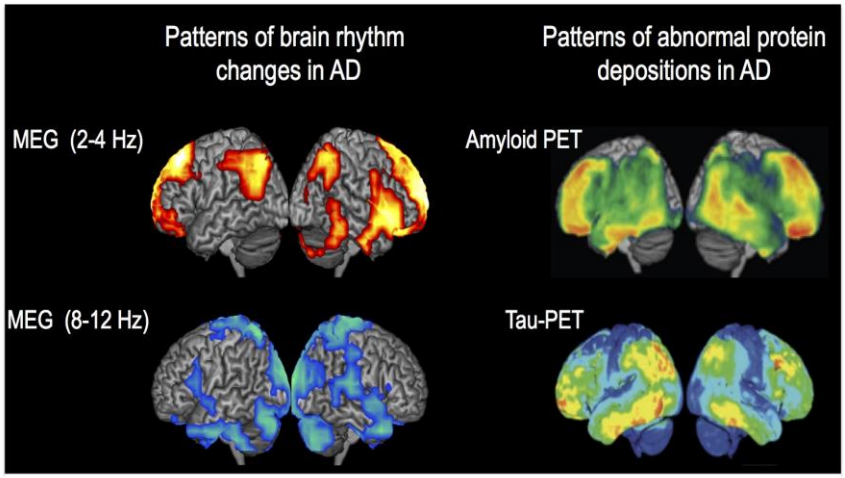
Abstract: Alzheimer's disease (AD) is characterized by progressive loss of memory and other cognitive functions. There are three main phenotypic clinical presentations of AD including amnestic/dysexecutive (Amn/dys), logopenic variant primary progressive aphasia (lvPPA), and posterior cortical atrophy (PCA). Neuroimaging studies have implicated unique anatomic involvements in each variant. Resting-state brain oscillations represent coordinated activity in large groups of neurons and is a useful tool to quantify functional network integrity of neural circuits.We hypothesized that resting state brain oscillations will show unique deficits in each variant of AD. We examined Amn/dys (n=30), lvPPA (n=15) and PCA (n=13) patients using magnetoencephalogrpahy, compared to a control group (n=20). A subset of patients was further evaluated with Positron Emission Tomography (PET) with amyloid tracers (amyloid-PET) and tau tracers (Tau-PET). We examined the global resting-state functional connectivity within delta-theta (2-8Hz), alpha (8-12Hz), and beta (12-30Hz) frequency oscillations, in each patient group, compared to age-matched controls. We found that each AD variant shows distinct anatomic patterns of hyposynchrony within alpha and beta band oscillations. In contrast, within delta-theta band, all three variants showed spatially nonspecific patterns of hypersynchorny Moreover, the anatomic pattern of delta-theta hypersynchrony closely resembled the amyloid deposition in the brain while the alpha band hyposynchrony closely resembled the tau deposition in the brain, as revealed by PET imaging. The current results demonstrate the first evidence of direct neuronal activity patterns recorded in a comprehensive evaluation of the three AD variants. Unique spatial distributions of hyposynchony within alpha and beta bands, and distinctive temporal patterns of increased and decreased synchronizations indicate that network failure in each syndrome is driven by diverse cellular and molecular mechanisms



The brain images on the left column show abnormalities of brain rhythms detected by magnetoencephalography (MEG) in patients with Alzheimer's disease (AD) compared to healthy elderly. The hot color scheme indicates increased patterns and cool color scheme indicates decreased patterns. As illustrated, AD patients showed increased patterns in lower frequency rhythms (2-4 Hz). In contrast, the higher frequency rhythms (8-12 Hz) show decreased patterns in AD patients. The brain images on the right column show the patterns of abnormal protein depositions in the brain in AD patients, as detected by positron emission tomography (PET). The color scheme from cool colors to hot colors indicates the degree of protein deposition ranging from low to high. The pattern of amyloid-protein deposition closely mirrored the increased 2-4Hz frequency pattern (depicted on the left column), whereas the pattern of tau-protein deposition mirrored the reduced 8-12 Hz pattern (depicted on the left column).

Disclosures: **K. Ranasinghe:** None. **J. Cha:** None. **L.B. Hinkley:** None. **A.J. Beagle:** None. **A. La:** None. **D. Mizuiri:** None. **S. Honma:** None. **V. Bourakova:** None. **W.J. Jagust:** None. **J.F. Houde:** None. **B. Miller:** None. **G.D. Rabinovici:** None. **K.A. Vossel:** None. **S.S. Nagarajan:** None.

Nanosymposium

456. Application of Imaging Techniques in Neurodegenerative Diseases

Location: 152B

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Presentation Number: *456.05

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

Support: U01AG032438

Title: Cerebral microbleed characterization in autosomal dominant Alzheimer disease

Authors: ***N. JOSEPH-MATHURIN**[1], E. MCDADE[1], T. BLAZEY[1], K. KANTARCI[2], C. JACK[2], K. FRIEDRICHSEN[1], Y. SU[1], B. GORDON[1], R. HORNBECK[1], B. ANCES[1], M. RAICHLE[1], V. BUCKLES[1], K. PAUMIER[1], J. MORRIS[1], R. BATEMAN[1], T. BENZINGER[1]
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Abstract: Many anti-amyloid treatments have shown increased risks of cerebral microhemorrhages (MCHs) in Alzheimer's disease (AD) patients during clinical trials. MCHs are detectable with gradient-echo (GRE) MR imaging sequences and are part of the constellation of amyloid-related imaging abnormalities (ARIA). The FDA has recommended monitoring for ARIA including MCHs during trials. The presence of 5 or more MCHs has been suggested as a criteria of exclusion for trials. The aim of this study was to define the prevalence of MCHs and their evolution with the disease process in a population affected by autosomal dominant Alzheimer's disease (ADAD).
Non-carriers (NC, n=58, age=40.6±9.7years) and mutation-carriers (MC, n=108, age=41.6±9.5years) underwent GRE MR sequences to detect MCH. All subjects had at least 2 imaging visits spaced by 1.9±1.1years. MCH number, and other ARIA including siderosis, and macroscopic hemorrhages were visually quantified on each scan. Longitudinal analysis were performed to characterize the pattern of progression of MCHs with the mutation type, estimated year to symptom onset (EYO) for preclinical participants, and dementia using clinical dementia rating (CDR).
MCH were observed in 12% of mutation carriers (n=18). They were found in 13 *PSEN1*, 1 *PSEN2* and 4 *APP* carriers but the mutation type did not significantly affect the increase rate per year. For participants presenting MCH at baseline, the rate of increase per year was 0 for the NC participants and 0.88±3.66 for the MC participants overall. It is noteworthy that participants with

2 MCHs or more at baseline presented an increased rate of 7.05±3.04 MCHs per year. In the MC participants, the increased rate per year was higher once past the estimated symptom onset (EYO>0, p<0.0005) and when they were cognitively impaired (CDR>0, p<0.005). Siderosis were detected in participants with (n=3) or without (n=2) MCH. Macrohemorrhages were present only in 2 participants with MCHs within the *APP* mutation type and could not be directly correlated with MCH.
This study highlights the natural history of MCH in an ADAD population. In clinical trials of ADAD participants, increases in MCH over time may relate to the underlying ADAD mutation rather than medication side effect.

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Nanosymposium

456. Application of Imaging Techniques in Neurodegenerative Diseases

Location: 152B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***456.06

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

Support: NIH Grant DC014296

Title: FTP tau PET imaging in semantic variant primary progressive aphasia

Authors: *B. C. DICKERSON[1], S. MAKARETZ[1], M. QUIMBY[1], J. COLLINS[1], N. MAKRIS[2], S. MCGINNIS[1], A. SCHULTZ[1], N. VASDEV[3], K. JOHNSON[1], *B. C. DICKERSON[1]
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Abstract: Objective: The semantic variant of Primary Progressive Aphasia (svPPA) is a form of PPA that is typically associated with Frontotemporal Lobar Degeneration (FTLD) with long TDP-43-positive neuropil threads and dystrophic neurites (FTLD TDP-43 Type C pathology), and is only rarely due to a primary tauopathy or Alzheimer's Disease (AD). We undertook the present study to investigate the uptake, localization, and magnitude of the presumed tau PET tracer [^{18}F]Flortaucipir (FTP; formerly known as T807 or AV1451) in a series of patients with semantic variant PPA, with the hypothesis that most patients would not show tracer uptake appreciably different from controls.

Methods: FTP and [^{11}C]PiB PET imaging as well as MRI imaging was performed in a series of 7 patients with svPPA and in 20 controls. FTP signal was analyzed by visual inspection and by quantitative comparison to controls, with and without partial volume correction.
Results: All 7 patients showed elevated FTP uptake in the anterior temporal lobe with a leftward asymmetry that was not observed in healthy controls. This elevated FTP signal was largely co-localized with regions of neurodegeneration. This was evident on both visual inspection and quantitative cortical surface-based analysis. Of the 7 patients included in this series, 5 were amyloid negative, 1 was amyloid positive, and 1 has an unknown amyloid status.
Conclusions: A series of patients with clinical profiles, structural MR, and amyloid PET imaging typical for svPPA FTP signal was unexpectedly elevated with a spatial pattern localized to areas of atrophy and presumed neurodegeneration. This raises questions about the possible off-target binding of this tracer to non-tau molecules associated with neurodegeneration. Further investigation with autopsy analysis will help illuminate the binding target(s) of FTP in cases of suspected FTLD-TDP neuropathology.

Disclosures: **S. Makaretz:** None. **M. Quimby:** None. **J. Collins:** None. **N. Makris:** None. **S. McGinnis:** None. **A. Schultz:** None. **N. Vasdev:** None. **K. Johnson:** None. **B.C. Dickerson:** None.

Nanosymposium

456. Application of Imaging Techniques in Neurodegenerative Diseases

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Wellcome Trust (RG73750)
Biotechnology and Biological Sciences Research Council (BB/H008217/1)

Title: Resting state brain dynamics identify behavioural variant frontotemporal dementia

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Abstract: Normal human behaviour is determined by interactions both within and between large-scale functional brain networks. Neurodegenerative processes target such networks, often early in the course of disease. It has been proposed that network connectivity can be a useful non-invasive marker, but different types of connectivity may vary in identification of different

syndromes, and have different future roles in monitoring disease progression, subtypes and treatment. Connectivity can be estimated from task-free functional magnetic resonance imaging (fMRI), also known as resting-state fMRI (rs-fMRI). However, common correlational methods are confounded by patient-group differences in the neurovascular signalling.
To estimate network interactions at the neuronal rather than vascular level, we used generative models (i.e. Dynamic Causal Modelling, DCM) that specified both the neural interactions and a flexible neurovascular forward model. We assessed directed connectivity within and between three key large-scale networks (salience network, fronto-parietal network, and default mode network), which were defined in an independent age-matched population-based sample (www.cam-can.com, N = 298). The networks' parameters were optimized to spectral dynamics of rs-fMRI data in 19 behavioural variant frontotemporal dementia (bvFTD) patients and 19 group-matched healthy controls. Alternative measures of brain structure and brain function within the networks (grey matter volume and functional connectivity) were also tested for classification.
Using 10-fold cross validation, we found 91% classification accuracy using DCM-based effective connectivity measures, which was significantly higher compared to other structural and functional measures (77% and 68%, respectively). We found that connectivity parameters important for discrimination were connections both within and between these networks. In particular, we found consistently a reduced stability of neural activity within the nodes of the salience network and the fronto-parietal network (but not the default mode network), as expressed by accelerated decay of neural information. Furthermore, the modulatory connectivity of two major nodes, dorsal anterior cingulate (part of salience network) and right prefrontal cortex (part of fronto-parietal network), decreased for the patient group.
Our findings suggest that the balance of excitatory connectivity between networks and the stability of intrinsic neural representations in core regions of these networks are altered in neurodegenerative disease.

Disclosures: **K.A. Tsvetanov:** None. **J.B. Rowe:** None.

Nanosymposium

456. Application of Imaging Techniques in Neurodegenerative Diseases

Location: 152B

Time: *****Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

Presentation Number: *****456.08

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

Support: Mason Foundation CT23152

Title: PiB-PET and pathological assessment of beta-amyloid in frontotemporal dementia syndromes

Authors: *R. H. TAN[1], J. KRIL[3], Y. YANG[1], J. HODGES[1], V. VILLEMAGNE[4], J. KWOK[1], L. M. ITTNER[5], G. M. HALLIDAY[2]
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Abstract: The clinical distinction between frontotemporal dementia (FTD) and Alzheimer's disease (AD) remains challenging, with ~25% of patients with an FTD syndrome found to have AD at autopsy, a difficulty likely to be overcome with the use of *in vivo* β-amyloid imaging. Importantly however, prior to the publication of the updated pathological criteria for AD in 2012, only neuritic plaques were used for diagnostic confirmation of AD. As such, knowledge on the prevalence of β-amyloid deposition in the ~75% of patients with an FTD syndrome that do not fulfil pathological criteria for AD is lacking. To address this, the present study assessed β-amyloid deposition in a large series of 94 autopsy-confirmed FTD cases without pathological AD. We report β-amyloid deposition in 38% of patients with behavioral variant FTD and in 37% of patients with a primary progressive aphasia (comprised of 29% of patients with semantic-variant PPA and 50% patients with non-fluent progressive PPA). The presence and topographical progression of β-amyloid was found to increase with age in FTD, as observed in controls. β-amyloid deposition was identified in a similar proportion of FTD cases with and without a genetic mutation or co-existing motor impairment. In addition to this, the present study assessed the pathological accuracy of PiB-PET imaging in a cohort of patients with clinical FTD followed to autopsy (n=15). AD pathology was identified in all cases with a high PiB retention (n=4) and in one case with a low PiB retention. A strong regional correlation was identified between the volume fraction of histological β-amyloid with PiB standard uptake value ratio scaled to the white matter. Together, by assessing a large pathologically-confirmed series of FTD cases, the present study provides a pathological reference for the proportion of patients with β-amyloid, as well as the burden of β-amyloid in these patients, that may aid the interpretation of future *in vivo* assessments of β-amyloid in FTD syndromes.

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Nanosymposium

456. Application of Imaging Techniques in Neurodegenerative Diseases

Location: 152B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

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**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: DoD grant W81XWH-16-1-0744

Title: Brain functional network impairments and abnormal processing at rest in Gulf War Illness: A resting state fMRI study

Authors: *K. GOPINATH[1], *K. GOPINATH[1], U. SAKOGLU[2], B. A. CROSSON[3], R. HALEY[4]
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Abstract: Up to 250,000 veterans of the 1991 Gulf War suffer from illness (GWI) characterized by multiple deficits in cognitive, emotion, vision, somatosensory and pain domains as assessed by analysis of self-reported symptoms. In this study we employed resting state fMRI (rsfMRI) to map impairments in brain function in GWI with advanced network analysis. 22 veterans with GWI (mean age 49.4 yrs.) and 30 normal controls (NC) (mean age 49.8 yrs.), were scanned in a Siemens 3T MRI scanner using a 12-channel Rx head coil. Written informed consent was obtained from all participants in the protocol approved by the local Institutional Review Board. rsfMRI data were acquired with a 10-min whole-brain gradient echo EPI (TR/TE/FA = 2000/24ms/90°, resolution = 3mm x 3mm x 3.5mm). The preprocessed rsfMRI data for all subjects were temporally concatenated and a group spatial independent component analysis (ICA) was performed which yielded 27 group ICs. Voxel-wise GWI vs NC t-tests were conducted on the back-reconstructed and scaled subject-level components for each IC in order to examine between-group differences in functional connectivity (FC) within the resting state brain function networks represented by that IC. The GWI group exhibited significantly (multiple-comparison corrected $p < 0.05$) increased resting state functional connectivity (rsFC) in the visual attention network compared to NC but decreased FC in visual processing networks like the ventral visual stream and visual memory. This is consistent with symptoms of deficits in visual processing reported by GWI patients. GWI group also exhibited higher rsFC in perceptuomotor network compared to NC as well as increased rsFC between perceptuomotor and default mode networks (DMN) consistent with symptoms of heightened state of vigilance during rest reported by GWI patients. Further GWI group exhibited increased rsFC in somatosensory pain perception areas including the recruitment of dorsolateral prefrontal cortex into the pain neuromatrix. This is consistent with symptoms of chronic pain observed in GWI patients. GWI

group also exhibited increased rsFC within affective processing networks and increased FC of limbic areas to DMN during rest consistent with symptoms of persistent mood disturbances reported by GWI veterans. Apart from this GWI group also exhibited decreased rsFC in executive function and language processing networks consistent with symptoms of deficits observed in these domains. Thus ICA of rsfMRI data is able to reveal impairments and abnormal processing in brain function networks consistent with symptoms of GWI, thereby providing a key to understanding the mechanisms underlying this illness.

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Nanosymposium

457. Therapeutics for Affective Disorders: Development, Delivery, and Animal Models

Location: 147B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***457.01

**Topic: ***I.05. Biomarker and Drug Discovery

Support: Chinese FRFCU 2016QN81017
Chinese NSF 61673346
Chinese NSF 81600982

Title: Superadditive neuromodulation induced by focused ultrasound-induced blood-brain barrier opening combined with intravenous GABA antagonists

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Abstract: Focused ultrasound (FUS) can safely and temporarily disrupt the blood-brain barrier (BBB) with the presence of circulating microbubbles. As we all know, many medical agents cannot get into the brain parenchyma easily because of protective function of the BBB and molecular size and properties, thus this technology has been used to deliver therapeutic drugs to enhance the treatment of diseases such as brain tumors in animal model. Our previous studies reveled that FUS-induced BBB opening alone can induced neuromodulation as evidenced by the changes in somatosensory evoked potentials (SSEPs) and blood-oxygen-level dependent (BOLD) signals, and that FUS-induced BBB opening is accompanied by targeted reversible changes in neuron responses. In the present study, we proposed that FUS-induced BBB opening combined with intravenous administration of picrotoxin, a GABA antagonist, could induce superadditive effect of local neuronal activities. We presented FUS with 0.55-mechanical index

(MI) at the left primary somatosensory cortex forelimb region (S1FL, 1 mm posterior and 4 mm lateral to the bregma) for 90 s with the concurrent injection of intravenous microbubbles (SonoVue® SF6-coated, 10 μl/kg). We then injected intravenously picrotoxin (0.4 or 1 mg/kg) following FUS-induced BBB disruption. Behavioral tests and neuronal activities were evaluated by mechanical nociceptive threshold (MNT) testing and SSEPs recording, respectively, before and after FUS exposure. SSEPs showed that the amplitudes of SSEPs were significant increase in left S1FL (FUS exposure site), as compared with right S1FL within 1-h post-FUS ($p<0.05$). MNT values showed that the paw withdrawal threshold decreased in the rat's right forelimb as compared with the rat's left forelimb within 3-h post-FUS ($p<0.05$). These results indicated FUS combined with picrotoxin, GABA antagonist, could induce superadditive effect on the tactile sensitivity and neuronal activity and its effect increase with dosages. This present study proposed a novel non-invasive, reversible and local neuromodulation method that is suitable for neurophysiological experiments and clinical applications.

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Nanosymposium

457. Therapeutics for Affective Disorders: Development, Delivery, and Animal Models

Location: 147B

Time: *Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

Presentation Number: *457.02

Topic: *I.05. Biomarker and Drug Discovery

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Lonza Houston
Giving/Grousbeck

Title: Anc80L65 as a new gene transfer tool for the central nervous system

Authors: ***E. HUDRY**[1,2], E. ANDRES-MATEOS[3], E. P. LERNER[4], A. VOLAK[5], O. COHEN[1], B. T. HYMAN, MD,PhD[6], L. H. VANDENBERGHE[7]
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Abstract: Considering their excellent safety profile and ability to transduce non-dividing cells, adeno-associated vectors (AAV) have shown great promise in the treatment of neurologic

disorders. Interestingly, the characterization of novel serotypes able to cross the blood brain barrier (BBB) after intravenous delivery has opened new opportunities for non-invasive brain delivery. However, the efficacy of those vectors is often conditional to the use of a self-complementary genome, which greatly limits their cloning capacity. Anc80L65, a novel vector designed from *in silico* reconstruction of the viral evolutionary lineage, has previously demonstrated excellent transduction capabilities in muscles, liver and retina, outperforming other conventional AAV. Here, we hypothesize that Anc80L65 may also emerge as an alternative tool to for gene delivery to the central nervous system. To test this hypothesis, we initially compared the capacity of single stranded (ss) Anc80L65 or ssAAV9 encoding a Firefly luciferase reporter gene to target the brain ($2.5x10^{12}$vg/kg) after intravenous injection into adult mice. Using whole body bioluminescence imaging, we observed that Anc80L65 consistently led to higher luciferase signal in the head region than AAV9, a sustained effect over 40 days. To further assess the transduction capacity of Anc80L65 in the CNS at a cellular level, tail vein injections of $4x10^{13}$vg/kg of ssAnc80, ssAAV9 and scAAV9 encoding for green fluorescent protein (GFP) were performed. The overall GFP signal intensity could be detected across the entire neural tissue one month after Anc80L65 injection, and was dramatically increased when compared with ssAAV9. Co-staining for GFP and markers of different neural cell types revealed that Anc80L65 mostly transduced neurons and astrocytes. Using an unbiased stereological approach, we reported that a single injection of ssAnc80 led to the transduction of 6.8±1.3% of neurons and 26.7±5.3% of astrocytes, which was significantly higher that ssAAV9 (2.3±0.7% and 6.2±2.3% respectively), but did not reach the levels of scAAV9 (11.9±4.7% and 45.9±6.2%, respectively). While the difference in efficacy between Anc80L65 and ssAAV9 is subtler after direct intraparenchymal injection in the striatum, Anc80L65 was able to diffuse much further than ssAAV9 after ICV infusion, eventually leading to widespread GFP expression in the cerebellum. These data suggest that Anc80L65 may be a highly efficient gene transfer vector for the central nervous system, thus opening novel potential therapeutic avenues using this ancestral AAV variant.

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Nanosymposium

457. Therapeutics for Affective Disorders: Development, Delivery, and Animal Models

Location: 147B

Time: *Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

Presentation Number: *457.03

Topic: *I.05. Biomarker and Drug Discovery

Support: Neuroscience program, Central Michigan University
College of Medicine, Central Michigan University
Chemistry and Biochemistry, Central Michigan University
Field Neurosciences Institute
John G. Kulhavi Professorship

Title: Novel Mixed surface PAMAM dendrimers cross the blood-brain barrier when systemically administered to C57BL/6J mice

Authors: *B. SRINAGESHWAR[1], S. T. PERUZZARO[2], M. M.-M. ANDREWS[2], K. JOHNSON[3], A. HIETPAS[3], B. CLARK[3], C. MCGUIRE[3], E. D. PETERSEN[2], J. KIPPE[4], A. N. STEWART[2], O. V. LOSSIA[2], A. AL-GHARAIBEH[5], A. ANTCLIFF[2], R. CULVER[2], D. SWANSON[3], G. L. DUNBAR[6], A. SHARMA[3], J. ROSSIGNOL[7]
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Abstract: Dendrimers are 3-dimensional branched polymeric nanoparticles that are widely used in biomedical application. The polyamidoamine (PAMAM) dendrimers have the potential to carry drugs in their cavity and/or DNA and plasmids complexed to them that can be targeted to cells both *in vitro* and *in vivo*. A major hurdle for drug delivery into the central nervous system (CNS) is the presence of blood brain barrier (BBB), which is selectively permeable to the molecules including some of the potential drugs to treat neurodegenerative diseases. Lipid-based nanoparticles of less than 1nm diameter are capable of passing through the BBB by diffusing through the tight junctions. However, the rate of drug delivery is highly reduced. One of the widely used methods for drug administration into the CNS is by intracranial (IC) injections. This method has disadvantages due to its invasive nature and increased risk, as well as the limited range of dispersion in neural tissue that is usually needed to treat some of the neurodegenerative diseases. Since route of administration and surface chemistry of the drug/biomolecule play vital roles in the efficacy of the treatment as well as the clinical utility, we developed a PAMAM dendrimer nanoparticle having mixed anionic-cationic surface to deliver drug systemically through blood vessels that can reach the CNS. Our results show that *in vivo* administration of a generation-4 mixed-surface PAMAM dendrimer can cross the BBB when injected through the carotid artery or into the parenchyma of the region of interest (such as the striatum) in C57BL/6J mouse model. We found that the neurons and glial cells were able to uptake the PAMAM dendrimers *in vitro* and *in vivo*. This proof of principle suggests that drugs/biomolecules may provide an effective means of delivering therapeutics to patients suffering from Huntington's disease.

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Nanosymposium

457. Therapeutics for Affective Disorders: Development, Delivery, and Animal Models

Location: 147B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***457.04

**Topic: ***I.05. Biomarker and Drug Discovery

Support: NIH grant R01 NS092838
NIH grant R21 NS090049

Title: The dynamics of intrathecal bolus and solute entrance into perivascular spaces

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Abstract: The goal of our studies was to investigate the dynamics of in vivo transport of solutes administered to the cerebrospinal fluid (CSF) and evaluate the potential routes of non-diffusional solute entrance from the CSF to the CNS. To observe solute transport by PET, experimental macromolecules were labeled with ^{124}I or ^{89}Zr and administered intrathecally (IT) to rats and cynomolgus monkeys. Dynamic imaging data and multiple whole-body images were acquired using Siemens MicroPET focus 220 imager. To evaluate the routes of macromolecule entrance from the CSF to the CNS, a model fluorescent macromolecule capable of labeling multiple cell types was administered intrathecally in rats; the microdistribution of the label was studied by fluorescence photoimaging in unstained cryosections. The initial solute distribution in the CSF greatly depended on the injected volume. Solutes injected at a high volume immediately translocated to the cervical/basal cerebral area (up to >90% of the injected dose). The subsequent solute spread was slow in the spinal CSF (millimeters per hour) but fast in the cerebral CSF (complete equilibration within 30 min). No evidence of directional solute flows anywhere in the CSF was found. In rats lymphatic drainage from the CSF was detected in the deep anterior cervical area (ca. 3% of the ID). In monkeys, no evidence of significant lymphatic drainage from the CSF was found in any region (<0.3% ID in total). The routes of translocation were further investigated by tracing the administered fluorophores. Massive labeling of the perivascular channels entering the CNS from the outer as well as the inner boundaries was observed throughout the CNS, with highest perivascular entrance densities at the internal boundaries. The overall mechanistic landscape of the cerebrospinal solute transport significantly differs from the

paradigm suggesting that CSF bulk flows prevail outside the CNS, whereas interstitial flows prevail within. The major factor of the initial distribution of the administered drug is the hydrostatic compliance of the compartment. The secondary drug distribution in the CSF is an interplay of hydrostatic and hydrodynamic factors and molecular recognition. The subsequent phase of drug entrance into the CSF depends on active perivascular transport, molecular recognition and diffusion. The observed transport phenomena can explain most, if not all, known but insufficiently understood effects of IT administered drugs. The observed transport timeframes suggest a possibility for optimizing IT schedules of existing drugs, as well as a strong potential for developing highly effective, targeted novel intrathecal therapies in the near future.

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Nanosymposium

457. Therapeutics for Affective Disorders: Development, Delivery, and Animal Models

Location: 147B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***457.05

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NCCIH/ODS P50 AT008661-01
VA career scientist award
Altschul foundation

Title: Epigenetic modulation of synaptic plasticity promotes resilience against stress disorder and depression

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Abstract: Depression is associated with a multitude of pathological processes. Growing evidence suggests chronic stress induces epigenetic changes, mainly histone acetylation or methylation and DNA methylation, in specific limbic brain regions that leads to permissive or restrictive transcription of select genes in affected neurons, which ultimately influences stress responses. Previous evidence demonstrated that repeated social defeat stress (RSDS) induces a transient decrease of histone H3 acetylation in the nucleus accumbens (NAc) in a mouse model of depression. Moreover, pharmacological inhibition of histone deacetylates (HDACs) or genetic manipulation of histone deacetylase 2 (HDAC2) by overexpression of dominant negative HDAC2 in the NAc leads to global normalization of stress-induced aberrant gene expression and

exerts potent anti-depressant-like effects in behavioral testing. These observations support histone acetylation as a promising target for novel treatment of depression, however, the development of currently available HDAC inhibitors for treating psychiatric disorders is largely hindered by their lack of specificity and limited blood brain barrier (BBB) penetration. We have identified a phytochemical GMJW-12 through high-throughput screening of bioactive compounds from a polyphenol-rich preparation that can modulate synaptic plasticity using primary medium spiny neurons (MSNs). Preliminary studies using the RSDS mouse model demonstrated that oral administration of GMJW-12 can improve stress-induced depression-like phenotypes. Further mechanistic studies revealed that GMJW-12 modulates synaptic plasticity by increasing histone acetylation along the promoter and upstream regions of select synaptic genes e.g. the RAS-related C3 botulinum toxin substrate 1 (Rac1) gene, through reduced expression of histone deacetylase 2 (HDAC2). The bioactivity of GMJW-12 is specific and only selectively inhibits HDAC2 while sparing other classes of HDACs. Moreover, GMJW-12 does not effectively interact with monoaminergic systems that are targeted by classical antidepressants. Our studies provide novel experimental evidence that GMJW-12 can modulate stress-induced depression-like phenotypes through epigenetic modulation of synaptic plasticity in the NAc. Given the excellent safety and drug-like profile, the lack of direct interaction with key molecular components of the monoaminergic system and ability to efficiently cross the BBB, GMJW-12 can immediately translate into human clinical studies for the treatment of stress disorders and depression either alone or in combination with currently available antidepressants.

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Nanosymposium

457. Therapeutics for Affective Disorders: Development, Delivery, and Animal Models

Location: 147B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***457.06

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Large retrospective study of electroconvulsive therapy investigates therapeutic effects associated with postictal suppression and anesthesia type

Authors: *W. M. INGRAM[1], S. POLER[2], F. T. NAHI[3], S. L. LARSON[4]
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Abstract: Electroconvulsive therapy (ECT) is an effective and rapid treatment for severe depression, however predictors of therapeutic outcome remain insufficiently understood. Seizure duration is commonly used as a predictor of therapeutic response but may not be optimal [1,2].

Three small prospective studies have provided evidence that other measurable ictal electroencephalogram (EEG) parameters, specifically postictal suppression, may be correlated with patient response to ECT treatment [2-4]. In addition, limited studies suggest that postictal suppression response may depend on the type of anesthesia used during the procedure [5]. We have conducted a retrospective study on 200 patients that received ECT treatment at a large integrated health care system. Outpatients were administered measures of depression (Beck's Depression Inventory) and mental status (Mini-Mental State Examination) prior to ECT treatment and again two weeks following completion of the course of ECT. EEG parameters and anesthesia type and dosage were collected for each ECT treatment and analyzed for correlation with acute therapeutic response to treatment. To our knowledge, this is the largest study reported to date investigating predictors of ECT response to treatment.

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Nanosymposium

457. Therapeutics for Affective Disorders: Development, Delivery, and Animal Models

Location: 147B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***457.07

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NICCH grant P50 AT008661-01
VA career scientist award

Title: Characterization of DHCA as a novel microbiome-derived epigenetic modifier in attenuation of inflammatory response in human PBMCs

Authors: *J. WANG[1,2], G. PASINETTI[1,2]
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Abstract: Currently available treatments for Major Depressive Disorder (MDD) mainly target neurochemical or neurobiological mechanisms. It is estimated that conventional pharmacological treatments produce temporary remission in less than 50% of patients. Thus, there is an urgent need for a wider spectrum of novel therapeutics to target newly discovered underlying disease mechanisms. The contribution of systemic inflammation to depression has received increasing attention in the past two decades and the consistently elevated expression of peripheral interleukin 6 (IL-6) in depression makes it a plausible therapeutic target. We recently identified a select phytochemical, DHCA, derived from gastrointestinal absorption and/or post-absorptive intestinal microbiome metabolism of a polyphenol-rich preparation is effective at reducing stress-mediated IL-6 production in a well-established repeated social defeat stress experimental mouse model of depression. We found that DHCA reduces IL-6 production through inhibition of DNA methylation at the CpG-rich IL-6 sequence introns 1 and 3. The current studies are designed to explore whether DHCA can similarly modulate IL-6 production in humans using peripheral blood mononuclear cells (PBMCs) and to investigate the underlying mechanisms. PBMCs from six healthy donors were treated with DHCA and challenged with the toll-like receptor 4 agonist, lipopolysaccharide (LPS). We found that treatment of PBMCs with DHCA significantly reduced the LPS-induced production of IL-6 protein as well as the expression of messenger RNA. We also found that the reduction of IL-6 is associated with significantly reduced expression of DNA-methyltransferase 1 (DNMT1), an enzyme that not only plays a key role in methylation maintenance but also plays an active role in *de novo* methylation processes. To investigate the potential methylation mechanisms, we cloned the ~280 bp CpG-rich DNA sequences from the human IL-6 promoter or introns into basic (with no promoter or enhancer) or promoter (with minimal EF1 promoter with no enhancer) pCpG-free Lucia plasmid and identified the CpG-rich DNA sequences in which modification of methylation can influence the expression of the reporter gene. We are currently confirming the role of specific CpG methylation in the DNA isolated from human PMBCs using methylation-specific PCR in order to evaluate the effect of DHCA in modulating these sites. Our study provides experimental and mechanistic evidence to further develop DHCA as a therapeutic agent for depression and other inflammation-mediated disorders such as rheumatoid arthritis.

Disclosures: J. Wang: None. **G. Pasinetti:** None.

Nanosymposium

457. Therapeutics for Affective Disorders: Development, Delivery, and Animal Models

Location: 147B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***457.08

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Lundbeck A/S
Innovation Fund Denmark
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Instituto de Salud Carlos III PI16/00287 co-financed by the European Regional Development Fund "A way to build Europe"·

Title: Modulation of thalamo-cortical activity by ketamine in rats

Authors: *M. AMAT FORASTER[1], P. CELADA[2,3,4], A. A. JENSEN[5], N. PLATH[1], F. ARTIGAS[2,3,4], K. F. HERRIK[1]
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Abstract: Background: Faster and more effective antidepressant treatments are needed to overcome the limitations of current monoamine-based drugs. Interestingly, sub-anesthetic doses of ketamine have been shown to produce immediate and persistent antidepressant effects. However, ketamine use is limited by its psychotomimetic properties and abuse potential. Therefore, we investigated the actions of ketamine on thalamo-cortical networks to increase our knowledge of the brain circuitry affected by ketamine and thus elucidate the mechanism underlying its antidepressant effects, ultimately leading to the development of novel antidepressants without ketamine's side effects. Methods: We conducted single unit and local field potentials recordings in the mediodorsal (MD), centromedial (CM) and reticular (RtN) nucleus of the thalamus, as well as in the medial prefrontal cortex (mPFC) of freely-moving (except RtN) and chloral hydrate anesthetized male Wistar rats, using microelectrode arrays and glass electrodes. The acute effects of ketamine (3 and 10 mg/kg s.c. in freely-moving rats; 1, 2 and 5 mg/kg i.v. in anesthetized rats) on the firing properties and oscillations of these neuronal populations were assessed. The effects of ketamine at 24 hours post administration were also examined in the freely-moving recordings. Results: In anesthetized rats, ketamine acutely decreased the discharge rate of RtN, MD/CM and layer VI mPFC neurons projecting to the thalamus. In addition, ketamine modulated oscillatory rhythms, reducing the power of low frequency oscillations in anesthetized rats and increasing gamma oscillations in both freely-moving and anesthetized rats. Moreover, increases in high frequency oscillations were observed in freely-moving rats. These effects were short-lasting since they were not present at 24h post administration. Further analysis is needed to characterize the changes observed on the firing characteristics in freely-moving rats. Conclusion: This study provides insights on the neurobiological changes that occur in the thalamo-cortical networks by ketamine both acutely and at 24 hours post administration. Ongoing efforts to characterize the firing rates of these neuronal populations in freely-moving rats will be crucial to understand the implications of the observed effects by ketamine in the thalamo-cortical networks of anesthetized rats.

Disclosures: **M. Amat Foraster:** A. Employment/Salary (full or part-time):; Lundbeck A/S. **P. Celada:** A. Employment/Salary (full or part-time):; Institut d'Investigaciosn Biomèdiques de

Barcelona, CSIC-IDIBAPS CIBERSAM. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Co-IP of a grant agreement IDIBAPS-Lundbeck. **A.A. Jensen:** A. Employment/Salary (full or part-time):; University of Copenhagen. **N. Plath:** A. Employment/Salary (full or part-time):; Lundbeck A/S. **F. Artigas:** A. Employment/Salary (full or part-time):; Institut d'Investigaciosn Biomèdiques de Barcelona, CSIC-IDIBAPS CIBERSAM. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; PI of a grant agreement IDIBAPS-Lundbeck. F. Consulting Fees (e.g., advisory boards); Member of Advisory Boards for Lundbeck. **K.F. Herrik:** A. Employment/Salary (full or part-time):; Lundbeck A/S.

Nanosymposium

457. Therapeutics for Affective Disorders: Development, Delivery, and Animal Models

Location: 147B

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***457.09

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: IMHRO

Title: The GTPase RhoA mediates negative outcomes to stress in the nucleus accumbens

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Abstract: Stress exposure causes lasting adaptations in brain motivational circuits which can precipitate the development of psychiatric illnesses such as depression. Previous work indicates stress alters synaptic plasticity and induces dendritic atrophy in the nucleus accumbens (NAc), a key structure for motivated behavior. Dendritic atrophy of NAc medium spiny neurons (MSNs) is associated with negative outcomes to stress, and can arise from cytoskeleton destabilization. Here we investigated the role of the GTPase RhoA and its downstream effector ROCK, in mediating cytoskeleton destabilization and stress-susceptibility. We used social defeat stress to induce depression-like behavior and dendritic atrophy, and found increased RhoA expression and ROCK activity in the NAc of stress-susceptible mice. To determine if increased RhoA expression was restricted to D1 or D2 receptor expressing MSNs, we used transgenic D1- or D2-Cre mice crossed with RiboTag mice to isolate ribosome-associated mRNA in specific cell-types. Cell-type specific qRTPCR revealed RhoA expression is increased exclusively in D1-MSNs, but ROCK expression is increased in both D1-and D2-MSNs of stress-susceptible mice.

We found stress-susceptibility could be prevented with intra- NAc RhoA inhibition prior to social defeat. Conversely, constitutively active RhoA in the NAc promoted susceptibility to subthreshold stress. We also treated mice systemically with a ROCK inhibitor for 7 days after social defeat, and found ROCK inhibition could reverse the susceptible phenotype without affecting stress-naïve or resilient animals. Our data demonstrate a role for RhoA in mediating susceptibility to social defeat stress, and indicate compounds targeting this pathway may be useful as anti-depressants. Our future experiments will address the contributions of RhoA to stress-susceptibility in a cell-subtype specific manner.

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Nanosymposium

458. Social Decision-Making

Location: 150A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***458.01

**Topic: ***H.02. Human Cognition and Behavior

Title: Neural prediction of community support providers

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Abstract: The receipt of high-quality social support bolsters individuals' mental and physical health. It is often beneficial for members of a community to keep in mind the people likely to provide social support, such that one knows whom to turn to in times of distress. Here, we test the hypothesis that people passively keep track of the individuals who are likely to provide social support within their community. We recruited 97 students from two freshman dormitories and had them nominate individuals in their dorm who provide them with eight different types of social support (e.g., companionship, social advice, emotional support). We computed a sociometric index of social support by taking a weighted sum of the number of nominations received by a given individual. Individuals who scored in the top, middle and bottom tercile on this metric were designated as high, medium and low support providers respectively. In a separate session, we scanned a subset of the participants (N=50) as they passively viewed photos of their dormmates. Participants were told to attend to the photos, but were not otherwise instructed on what to think about. We trained a Lasso-PCR algorithm on the BOLD data of participants from one of the dorms (N = 26) to identify a pattern of BOLD activity that monotonically increased when participants viewed dormmates with increasing levels of

sociometric social supportiveness. We then tested the algorithm on the BOLD data of participants from the other dorm (N = 24). Neural activity in the mentalizing network reliably predicted when participants were viewing dorm members who were low, medium and high support providers. On average, the predicted and actual levels of social supportiveness were moderately correlated ($r = 0.35$, $p < 0.001$). As a second measure of prediction accuracy, we computed the forced-choice classification accuracy when the algorithm was used to classify which of two patterns was associated with viewing faces of individuals who score higher on social supportiveness. Classification accuracy was significantly above chance when distinguishing between viewing high support providers and viewing medium or low support providers, but not significantly different from chance when distinguishing between viewing medium and low support providers. These results suggest that participants' brains automatically detect high social support providers, even when not explicitly instructed to do so. Our method also demonstrates the possibility of out-of-sample prediction of high support providers from the brain activity of a subset of individuals in a community.

Disclosures: Y. Leong: None. **S. Morelli:** None. **R. Carlson:** None. **M. Kullar:** None. **J. Zaki:** None.

Nanosymposium

458. Social Decision-Making

Location: 150A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***458.02

**Topic: ***G.03. Emotion

Support: ERC 295673

Title: First person experience in virtual reality modulates cortical synchronization and connectivity during perception of approaching social threat

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Abstract: In most human-to-human threat incidents the aggressor physically intrudes the personal space of the victim. So far it has not been feasible to investigate the brain basis of these dynamics experimentally. In this fMRI study, we utilized virtual reality training from first person perspective of a female character and a 3D video to simulate approaching social threat. We

compared brain activity during the perception of the 3D video after first person perspective training (Fig 1A) to third person perspective training (Fig 1B).
Threat perception after first person perspective training increased intersubject correlation (ISC; N = 20) in the supramarginal, early visual and posterior parietal cortex. Moreover, we found increased cortical connectivity using Granger Causality (Fig. 1, top) from visual and premotor cortex to parietal cortex, which may indicate the encoding of space near the body and the initiation of a response to threat, and a central role of the supramarginal gyrus, relating body-threatening information to the self. We also revealed communication between the cortex and the basolateral complex of the amygdala (BLA) in the first person perspective session (Fig 1A). When looking in more detail, we found that in female participants, identification with the victim following training increased ISC in the BLA when the aggressor entered the intimate space. Lastly, we investigated the brain dynamics as a function of the approach of the aggressor. The ISC and connectivity changes in supramarginal gyrus and premotor cortex after first person perspective training could be linked to the time in which the aggressor entered the personal space, while visual and posterior parietal cortex changes were linked to intimate space intrusion. Our results show that VR training from the first person perspective of a female character modifies subsequent perception of approaching threat and demonstrate the necessity for future fear and aggression studies of taking the critical properties of naturalistic situations into account.

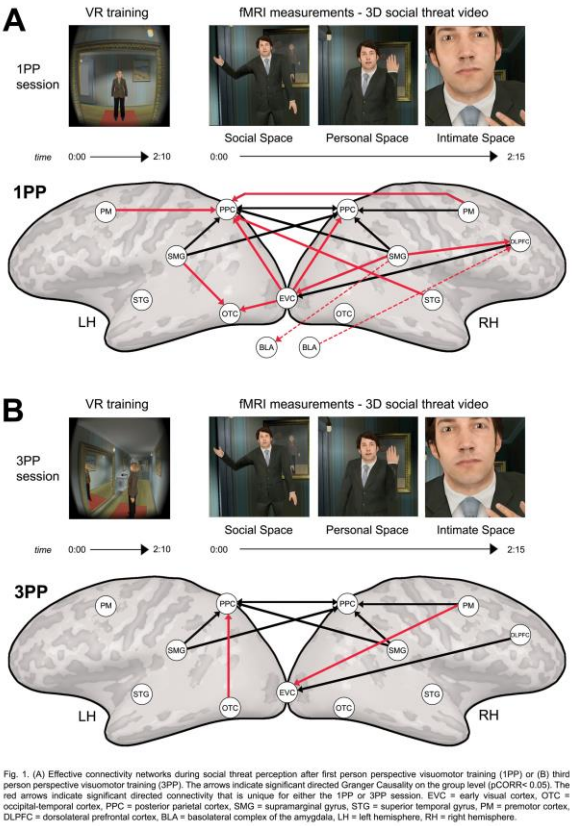

Fig. 1. (A) Effective connectivity networks during social threat perception after first person perspective visuomotor training (1PP) or (B) third person perspective visuomotor training (3PP). The arrows indicate significant directed Granger Causality on the group level (pCORR< 0.05). The red arrows indicate significant directed connectivity that is unique for either the 1PP or 3PP session. EVC = early visual cortex, OTC = occipital-temporal cortex, PPC = posterior parietal cortex, SMG = supramarginal gyrus, STG = superior temporal gyrus, PM = premotor cortex, DLPFC = dorsolateral prefrontal cortex, BLA = basolateral complex of the amygdala, LH = left hemisphere, RH = right hemisphere.

Disclosures: A.W. de Borst: None. **M.V. Sanchez-Vives:** None. **M. Slater:** None. **B. de Gelder:** None.

Nanosymposium

458. Social Decision-Making

Location: 150A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***458.03

**Topic: ***H.02. Human Cognition and Behavior

Support: Economic and Social Research Council (ES/L003139/1)

Title: Cooperation and trust between identity groups: An fMRI study

Authors: *S. HONG[1], *S. HONG[1], A. MOORE[2], N. ROBERTS[3], K. NICOL[4], L. CRAM[1]
[1]Sch. of Social and Political Sci., [2]Psychology, [3]Clin. Res. Imaging Ctr. (CRIC), Queen's Med. Res. Inst., [4]Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: Perceived trustworthiness of other race groups has been found to influence social decisions (Stanley et al 2012), but there are no equivalent studies that investigate trust decision-making with regard to national bias. We investigate the neural correlates of cooperation and defection when participants engage in a cooperative game with opponents of different perceived nationalities using a Stag Hunt (SH) task. We predicted that cooperation with opponents of different perceived nationalities would modulate brain regions involved in Theory of Mind and reward processing: medial prefrontal cortex, orbitofrontal cortex and ventral striatum. We also predicted that emotional brain regions would be modulated depending on perceived opponent nationality in the task. Right-handed, healthy Scottish participants underwent blood oxygenation level-dependent(BOLD) contrast fMRI scanning(N28, mean age 27.81, fifteen females). We modified the stimuli of SH task(Yoshida et al, 2010) by adding different identity groups as opponents using UK and EU national flags(the Saltire, St George's Cross, Union Jack, or EU). Participants could choose whether to cooperate with opponents for greater mutual reward(20 points) or to defect and gain a lower reward individually(10 points). fMRI results showed activation in superior occipital lobe, calcarine, and cuneus to be significantly greater when participants cooperated with English and EU opponents(out-groups) compared to when they cooperated with Scottish opponents(in-group). Defecting on Scottish opponents compared to defecting on English opponents significantly activated putamen, caudate, insula, orbital superior frontal cortex, superior temporal pole, inferior orbital frontal cortex, and pallidum. The results suggest that cooperation with different identity groups may increase visual attention and can be related to reward expectation(Thomas et al, 2013). Ventral striatum and anterior insula involvement in defection suggests that defecting on the in-group rather than the out-group may require increased emotional processing.

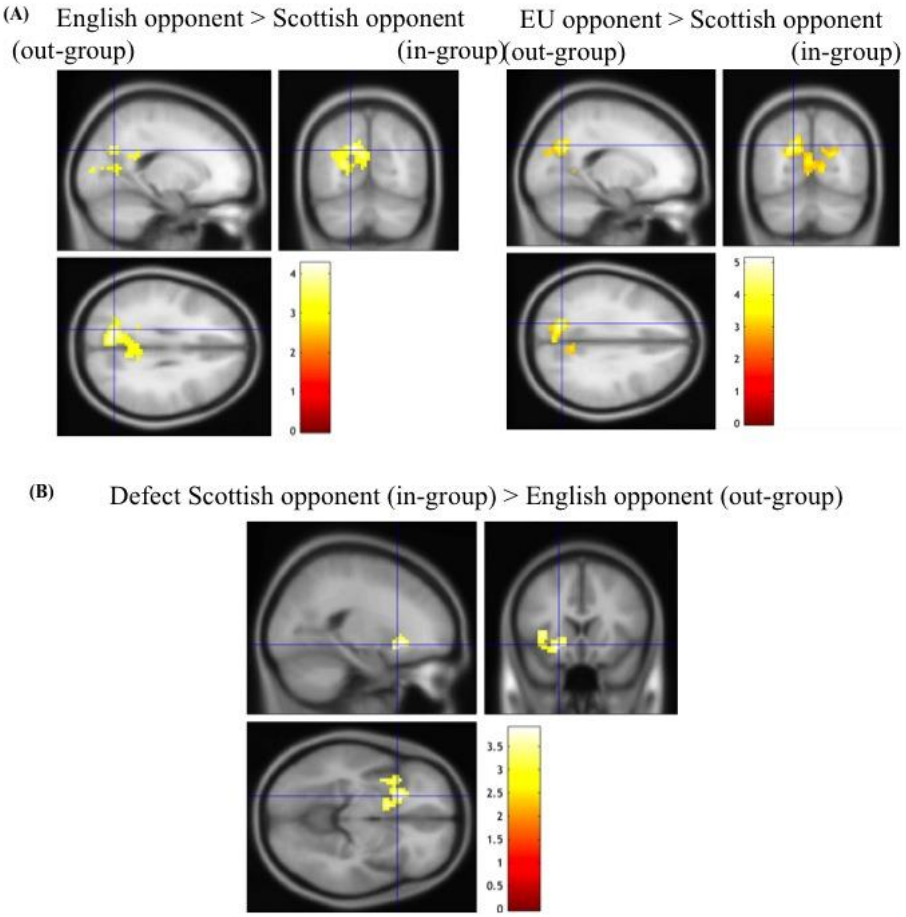

Figure 1. (A) Cooperation with different identity opponents compared to in-group significantly activated superior occipital lobe, calcarine, precuneus, and cuneus **(B)** Defecting in-group compared to defecting English opponent significantly activated putamen, caudate, insula, orbital superior frontal cortex, superior temporal pole, inferior orbital frontal cortex, and pallidum (p (uncorrected) <.005 at a voxel level, and then p (FWE) <.05 at a cluster level for correcting multiple comparisons)

Disclosures: S. Hong: None. **A. Moore:** None. **N. Roberts:** None. **K. Nicol:** None. **L. Cram:** None.

Nanosymposium

458. Social Decision-Making

Location: 150A

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Presentation Number: *458.04

Topic: *H.02. Human Cognition and Behavior

Support: JSPS Grant 17K13177

Title: Neural correlates of being imitated and imitating: A hyperscanning fMRI study

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Abstract: Imitation is a primitive social interaction whereby face and behavior of an individual (initiator) are observed and replicated by another (responder). Neural substrates of imitation have been shown to include the mirror neuron system, whereas those of being imitated is less known. We hypothesized that the sense of being imitated is related to the contingency detection. To dissect the neural underpinning of being imitated in comparison with those of imitating, we conducted hyper-scanning fMRI with 16 pairs of healthy normal volunteers. They underwent facial imitation task through a double-video system that enables participants to engage online interaction. Paired participants were assigned to either an initiator or a responder before each trial. The initiator was prompted to express happy, sad, or non-emotional (opening mouth) faces, and the responder imitated the initiator's facial expression. During a control condition, both participants were prompted to make the same facial expressions simultaneously, controlling for contingency. Imitating condition compared with control condition activated bilateral putamen, fusiform gyrus, and precuneus, and the left pre-supplementary motor area (pre-SMA) extending to the anterior cingulate cortex (ACC), and the inferior frontal gyrus (IFG). Being imitated condition compared with control condition activated the bilateral cerebellum, the temporoparietal junction (TPJ), ACC extending to the anterior rostral medial prefrontal cortex, and right IFG extending to the anterior insula, and right pre-SMA. The present study showed the neural substrates of being imitated was distinct from imitating. First, the left IFG was involved in the imitating process, whereas the right IFG in the being-imitated. The left IFG may involve more in the motor control, whereas the right counterpart in the emotional process of the observed emotion, interfacing with the limbic system via the insula. Second, TPJ was specifically involved in the being-imitated. TPJ is related to the self-other distinction critical for contingency detection. Finally, the cerebellum is involved in being-imitated. The cerebellum may be related to the temporal processing between the self-action and the following action of others, again essential for contingency detection.

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Nanosymposium

458. Social Decision-Making

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**Presentation Number: ***458.05

**Topic: ***H.02. Human Cognition and Behavior

Support: KAKENHI #15H01846
KAKENHI #26350987
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KAKENHI #15K12775
KAKENHI #16H01486
KAKENHI #15H05875

Title: Why and how inter-individual neural synchronization occur by joint attention? Inter-individual network-level Hebbian learning account

Authors: *T. KOIKE[1], H. C. TANABE[2], S. ADACHI-ABE[3], E. NAKAGAWA[1], S. OKAZAKI[4], A. T. SASAKI[5], K. SHIMADA[6], S. K. SUGAWARA[1], H. K. TAKAHASHI[7], K. YOSHIHARA[8], N. SADATO[1]
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Abstract: Attention can be shared between individuals through eye contact and joint attention (JA). In JA, initiator volitionally selects a shared object through gaze (IJA) which direction is followed by the responder (RJA). By our two-day hyperscanning fMRI in which JA task was conducted between the two eye contact tasks, JA was shown to induce shared attention represented and retained by pair-specific neural sync in the right inferior frontal gyrus (IFG) during eye contact, while middle temporal gyrus (MTG) showed consistent inter-brain sync (Koike et al. 2016). In our previous study, we assumed that the forward model for social interaction, represented by connectivity from the IFG to MTG, causes a MTG sync even before JA tasks. However, mechanisms for emergence of inter-brain sync on the IFG was unclear. In this study, we hypothesized that inter-brain sync on the IFG was induced by inter-individual Hebbian learning during JA, that is mediated by volitional processes. To test the hypothesis, we reanalyzed the data (Koike et al., 2016). In terms of inter- and intra-individual neural sync, JA-induced pair-specific neural sync of the right IFG during eye contact was positively correlated with the enhanced intra-brain functional connectivity between the right IFG and MTG. In terms of brain activation, JA tasks commonly recruited the fronto-occipito-parietal regions. In addition,

the anterior cingulate cortex (ACC) and the right anterior insular cortex (AIC) were activated by volitional selection during IJA. Hypothesizing that the control of one's gaze adjusted with that of partner (inverse model) was generated and shared between initiator and responder during JA task, we applied the dynamic causal model analysis with four ROIs: the right IFG, MTG, AIC, and ACC. Both IJA and RJA commonly enhanced the effective connectivity from the MTG to IFG, representing the inverse model. IJA increased the net effective connectivity from the ACC through the AIC towards the IFG, reflecting the enhanced volitional process of the direction of one's visual attention. RJA enhanced the effective connectivity from the AIC towards the MTG, indicating the site effect of attention. We revealed that the neural representation of the shared attention was the MTG-IFG network which connectivity was modulated by the saliency network, i.e. AIC, such that the activation of the IFG of the initiator contingently activate the IFG of the responder through the induced effective connectivity of MTG towards IFG connectivity, thence inter-individual Hebbian association to occur. JA induced shared action representation of MTG-IFG connectivity that comprises the intra- and inter-individually synchronized network.

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Nanosymposium

458. Social Decision-Making

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Presentation Number: *458.06

Topic: *H.02. Human Cognition and Behavior

Support: Hilibrand Foundation for Autism Research
NIMH (R01 MH100028)

Title: Computational models differentiate between the social learning strategies of typically developing adolescents and adolescents with autism

Authors: ***G. ROSENBLAU**[1,2], C. W. KORN[3], A. DUTTON[2], D. LEE[4], K. PELPHREY[1,2]
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Abstract: Treatments for adolescents with autism spectrum disorder (ASD) seek to optimize social skills, in particular learning to take another person's perspective. A mechanistic

understanding of how social learning strategies of adolescents with ASD differ from those of typically developing (TD) adolescents is currently lacking. Here, we devised a novel preference task, in which TD adults (N=21), TD adolescents (N=21), and adolescents with ASD (N=20) rated the preferences of other people for a number of items (such as activities) and received trial-by-trial feedback about the others' actual preference ratings. After completing the task, participants rated their own preferences for these items. Inferences about others relied on a combination of reinforcement learning and participants' own preferences (i.e., combination model) in TD adolescents and adults. ASD adolescents, however, relied only on their own preference to rate that of the other (i.e., self-preference model). The distinction between learning strategies of TD and ASD groups was corroborated by our neuroimaging results. Model variables were reflected in brain activity of all three groups. In adolescents with ASD, inferences predicted by self-preferences correlated with activity in a broad network of regions including posterior midline regions, amygdala and cerebellum. In the TD groups, inferences and prediction errors estimated by the combination model scaled with medial prefrontal cortex (MPFC) activity. In adolescents with ASD, the MPFC was less attuned to social inferences and prediction errors. To summarize, we demonstrated that computational models adopted from reinforcement learning theory can be used to differentiate social learning strategies between TD and ASD populations.

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Nanosymposium

458. Social Decision-Making

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**Presentation Number: ***458.07

**Topic: ***H.02. Human Cognition and Behavior

Title: Learning to approach or avoid in anticipation of rewards and losses: Insights across the human lifespan

Authors: *M. BETTS[1], M. GUITART MASIP[2], I. APOSTALOVA[3], R. BUCHERT[3], V. PEROSA[4], K. KRAUEL[5], J. TEGELBECKERS[5], A. RICHTER[6], H. AMTHAUER[7], E. DUZEL[4]
[1]German Ctr. For Neurodegenerative Dis. (DZNE), Magdeburg, Germany; [2]Aging Res. Center/Karolinska Inst., Stockholm, Sweden; [3]Univ. Med. Ctr. Hamburg - Eppendorf, Hamburg, Germany; [4]Inst. Cognitive Neurol. and Dementia Res., Magdeburg, Germany; [5]Child and Adolescent Psychiatry, Otto von Guericke Univ., Magdeburg, Germany; [6]Leibniz Inst. For Neurobio., Magdeburg, Germany; [7]Charité – Universitätsmedizin Berlin, Berlin, Germany

Abstract: The interaction between action and valence significantly influences appropriate and inappropriate choices whereby reward facilitates learning of active choices and punishment facilitates learning of passive choices. These behavioural tendencies can be described as Pavlovian biases which serve to accelerate learning in those circumstances most commonly encountered during decision making yet may also corrupt the flexibility of instrumental learning. Here, we used an orthogonalised go no-go task (Guitart-Masip et al., 2012) to characterize Pavlovian biases across the lifespan (participants aged between 7 and 78 years) and aimed to relate Pavlovian biases to grey matter density (using 7 Tesla high resolution MRI) and dopamine synthesis capacity (using F-DOPA PET).
Across the lifespan, all participants demonstrated greater accuracy for go choices when the outcome was a reward and for no-go choices when the outcome was avoidance of losses, confirming human decision making across the lifespan is influenced by Pavlovian control. However an increase in the Pavlovian bias was observed in middle and older ages compared to children and younger adults. Children demonstrated a Pavlovian bias equivalent to that observed in younger adults yet had difficulties in learning to inhibit their responses regardless of the affective valence of predicted outcomes. Computational modelling indicated that behavioural inflexibility in children was largely attributed to a greater bias towards action responses. In contrast, overall learning in midlife and older adults was associated with an increased Pavlovian bias coupled with reduced reward and punishment sensitivity.
A voxel based morphometry (VBM) analysis using 7 Tesla MRI images from young and older adults revealed that the structural integrity of the dorsal striatum correlated with a modelling parameter pertaining to learning rate in older adults. In a PET study, assessment of dopamine synthesis capacity in the striatum of older individuals from the same sample, revealed a significant positive correlation with action responses coupled to reward and dopamine synthesis capacity in the ventral striatum. However no relationship between learning rate and dopamine synthesis capacity in the dorsal or ventral striatum was observed.
Collectively these results demonstrate marked asymmetry in learning across the lifespan is attributed to a heuristic Pavlovian bias that increases in midlife and old age. Furthermore the striatum may be a key structure to predict flexible instrumental learning in old age. However additional approaches are warranted to probe age-related changes in Pavlovian control.

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Nanosymposium

458. Social Decision-Making

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**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***458.08

**Topic: ***H.02. Human Cognition and Behavior

Support: Penn State Social, Life, & Engineering Sciences Imaging Center 3T MRI Facility NIH Grant UL1TR000127
USDA 2011-67001-30117

Title: Children's brains respond more to winning money than food, regardless of weight status

Authors: *S. ADISE[1], C. F. GEIER[2], N. J. ROBERTS[2], A. M. CAPRIO[1], C. BELKO[3], N. A. REIGH[1], C. N. WHITE[4], K. L. KELLER[1]
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Abstract: How the brain responds to anticipating and receiving rewards has been linked to weight gain and obesity in adults. Previously, we found that children's brains respond more to anticipating food compared to money and neutral rewards, and these effects were independent of child weight status. However, the effect of *reward receipt* on brain responses in children of varying body weights is not known. We measured BOLD response with fMRI to assess brain activation in *a priori* defined reward and inhibitory control regions. Sixty-one, 7-11 year-olds (31 healthy weight; 30 overweight/obese) performed a card-guessing task with 3 reward anticipation conditions (food, money, neutral) and 6 possible outcomes (win or no win). Mixed models revealed main effects of reward receipt in several reward processing regions, including left striatum and right ventral striatum (VS), medial prefrontal cortex (mPFC), and orbitofrontal cortex (OFC) (p's < 0.001). In addition, we also observed main effects of reward receipt in inhibitory control regions such as the right dorsolateral prefrontal cortex (dlPFC) and left inferior frontal cortex (p's < 0.001). Post-hoc analyses indicated that activation in the striatum, VS, and dlPFC was higher for winning money vs. food and neutral. Additionally, BOLD responses in the VS, mPFC, OFC, and dlPFC were greater for winning money over neutral (p's < 0.005). Only activation in the OFC was higher for winning food vs. neutral (p < 0.05). There were no main effects or interactions between weight status and reward condition in any of the regions tested. Findings suggest that regardless of weight status, the brain responds more to winning money vs. food rewards in regions implicated in reward processing and inhibitory control. Although we previously found that children's brains responded more to anticipating food regardless of weight status, the current results in the same cohort suggest that *winning money over food* is actually associated with greater brain response. Similarly, these effects were independent of weight

status, which contradicts previous studies. Future studies are needed to relate brain responses to receipt of rewards to objective measures of eating behavior, as these studies may shed light on neurobiological risk factors for obesity.

Disclosures: S. Adise: None. **C.F. Geier:** None. **N.J. Roberts:** None. **A.M. Caprio:** None. **C. Belko:** None. **N.A. Reigh:** None. **C.N. White:** None. **K.L. Keller:** None.

Nanosymposium

458. Social Decision-Making

Location: 150A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***458.09

**Topic: ***H.02. Human Cognition and Behavior

Support: NIDA Grant DA027764

Title: The social value of positive autobiographical memory retrieval

Authors: *M. E. SPEER, V. MAI, M. R. DELGADO
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Abstract: Positive memory retrieval elicits pleasant feelings that can combat negative affective states and enhance well-being. However, not all positive memories are created equal. When thinking about our most treasured memories, they are likely experiences shared with other people (e.g., birthday party) rather than by oneself (e.g., receiving good grades). We explored whether the social context within a positive memory enhanced its subjective value and contributed to an individual's well-being. Participants (Study 1; N = 47) were asked how much they would be willing to pay to re-experience positive memories that occurred with socially close others (high-social), with acquaintances (low-social) or alone (nonsocial). When controlling for how positive each memory made them feel, participants were still willing to pay 1.5 times more for high-social than for low-social or nonsocial memories. Likewise, participants chose to reminisce about high-social memories more frequently (56% of the time) than less social ones of equal positive feeling ($p = .025$). In a re-analysis of fMRI data where positive memories were classified by social context (Study 2; N = 19), recalling social relative to nonsocial memories engaged the ventromedial PFC and posterior cingulate cortex, potentially related to increased social processing, even when controlling for positive feeling. Finally, we examined the benefit of social context by asking participants (Study 3; N = 20) to recall social and nonsocial memories after acute stress exposure. Participants whose positive memory recall included higher social context (i.e., experienced with close others) showed a greater dampening of the physiological stress response (i.e., cortisol). Taken together, these findings suggest that social context inherent in a

positive memory enhances its value, providing a possible mechanism by which positive reminiscence aids well-being and coping with stress.

Disclosures: M.E. Speer: None. **V. Mai:** None. **M.R. Delgado:** None.

Nanosymposium

458. Social Decision-Making

Location: 150A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***458.10

**Topic: ***H.02. Human Cognition and Behavior

Title: Paying to seek or avoid social interactions

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Abstract: Interacting with other people is a major source of happiness for most human beings. However, social interactions do not always evolve according to expectations and may result in the reception of negative social feedback. While many people spend money to seek social interactions with other people, anxiety about possible negative social feedback may lead some people to withdraw from social interactions, causing in some cases considerable loss of private and professional opportunities. To quantify the costs of pro-sociality and social anxiety, we devised a psychophysic task allowing to determine how much money participants would spend to avoid or seek a simple social interaction with uncertain outcome. In a sample of healthy participants, the more anxious participants paid to avoid the interaction, while the less anxious paid to seek the interaction. These differences were not found in a control condition in which the interaction partner was a computer instead of a human, demonstrating that risk aversion differences cannot explain our findings. Separate valence ratings of the interaction outcomes did not significantly vary between participant groups, suggesting that the observed effects were not due to differences in the valuation of the outcomes themselves. Our results demonstrate that tendencies towards pro-sociality and social anxiety among healthy participants are both costly. Our experiment allows to directly compare the costs of these personality traits and may prove useful for investigating treatment effects of social anxiety and probing the neural correlates of social decision-making.

Disclosures: J.W. Schultz: None. **G. Chakkour:** None. **A. Franke:** None. **R. Hurlemann:** None.

Nanosymposium

458. Social Decision-Making

Location: 150A

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**Presentation Number: ***458.11

**Topic: ***H.02. Human Cognition and Behavior

Support: Wellcome Trust Career Development Fellowship Grant R01AG040640

Title: How the brain uses reward distributions to compute inequality and value

Authors: *F. GESIARZ[1], J. E. DE NEVE[2], T. SHAROT[1]
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Abstract: Rewards are almost never obtained in isolation. Rather, humans attain rewards in a social context, where comparisons can be made with many others. Here we ask how the brain uses such rich information to determine subjective value. In particular, which properties of the reward distributions are used and how are they combined to reach a measure of value? In a controlled laboratory experiment we vary the statistical properties of the income distribution of a group of individuals, loosely mimicking that of different countries on each trial. We then examine how the brain uses the statistical information embedded in such contexts to compute the subjective value of rewards and a measure of (in)equality. Using behavioural ratings and BOLD response in reward processing regions, we show that subjective value is best accounted for by a model that expresses value as a weighted sum of a person's rank and relative position in the income range. This model, which is based on Parducci's range-frequency theory, outperformed models based on inequality aversion, value-normalization and prospect theory. Further, we found that judgements of inequality were highly biased by the position of the individual in the distribution. In particular, the higher the position of the individual the more likely they were to perceive an unequal distribution as equal. Our findings provide a model of how people judge their (miss)fortune and that of others in a social context.

Disclosures: F. Gesiarz: None. **J.E. De Neve:** None. **T. Sharot:** None.

Nanosymposium

458. Social Decision-Making

Location: 150A

**Time: ***Tuesday, November 14, 2017, 8:00 AM - 11:00 AM

**Presentation Number: ***458.12

**Topic: ***H.02. Human Cognition and Behavior

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University Grant for Research Facility and Project, Kochi University of Technology

Title: Neuro-representational accounts for process-dependent fairness decisions

Authors: *R. AOKI[1], T. IMAI[2], S. SUZUKI[3], K. IZUMA[4], Y. YOMOGIDA[5], K. IIJIMA[5], R. ADOLPHS[2], C. F. CAMERER[2], K. NAKAHARA[1], K. MATSUMOTO[5]
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Abstract: Decisions about social justice require consideration of *processes* in addition to *consequences*. For instance, a given level of distributive inequality would be perceived as just if it resulted from fair processes but unjust if resulted from unfair processes. Economic theories relying only on outcomes (i.e., consequentialist models) do not explain such process dependence in fairness preferences. We used behavioral modeling together with multivoxel pattern analysis of functional magnetic resonance imaging (fMRI) data, and found that process-dependent fairness preferences arise from context-dependent changes in neural representations of decision-related variables (e.g., efficiency and equality). Participants (n = 35) were scanned while they made third-party fairness decisions about how to allocate money to pairs of anonymous recipients. Efficiency (the sum of payoffs allocated to a recipient pair) and equality (the absolute difference in payoffs within a pair, multiplied by -1) varied from trial to trial. Critically, there were two contexts by which we operationalized unfair and fair processes: In the "FIX" context, it was predetermined which recipient in a pair would get a larger/smaller stake, whereas in the "LOT" context, a random lottery gave the same chance to both recipients. We used representational similarity analysis to examine how decision variables were encoded as distinct multivoxel patterns. Behavioral results showed that participants had higher preferences for efficiency over equality in LOT compared with FIX context ($z = 3.71$, $P < 0.001$, Wilcoxon signed-rank test). This clearly indicates that people do care about processes in making fairness decisions. Neurally, the anterior insula (AI) and ventromedial prefrontal cortex encoded key decision variables: efficiency, equality, and decision value derived from a utility model. Moreover, the encoding strength of efficiency (but not equality) in the AI increased in LOT relative to FIX context ($z = 3.44$, $P < 0.001$), which mirrored the behavioral shift in the

preference for efficiency. Furthermore, the encoding strength of efficiency in the AI accounted for individual differences in preferences for efficiency in a context-independent manner (FIX: $r = 0.62$, $P < 0.001$; LOT: $r = 0.44$, $P = 0.009$, Spearman correlation). Encoding strength of the context per se was correlated across participants with the context-dependent change in preference ($r = 0.58$, $P < 0.001$) in the anterior temporal lobe. These findings provide a neural mechanism explaining why people's fairness decisions change depending on processes, and inform economic theories and policies that take procedural fairness into account.

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Nanosymposium

542. Control of Neuronal Firing

Location: 150A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***542.01

**Topic: ***B.09. Physiological Properties of Neurons

Support: Ministry of Science and Technology of China 2015CB559200
National Natural Science Foundation of China 81371432

Title: The epigenetic factor CDYL inhibits intrinsic neuronal excitability and suppresses epileptogenesis through repression of axonal nav1.6 sodium channel expression

Authors: *Z. HUANG, S. LAI, Y. LIU, M. FAN, M. LI
Mol. and Cell. Pharmacol., Peking Univ., Beijing, China

Abstract: Activity-dependent neural plasticity is fundamental for animal behaviors such as learning and memory. It is becoming increasingly clear that, additional to "Hebbian" synaptic plasticity, alteration in intrinsic excitability plays a critical role in shaping the overall neural plasticity. However, how neuronal intrinsic excitability is regulated is still not fully understood. Here we report that the epigenetic factor Chromodomain Y-like (CDYL) protein is a critical regulator for the initiation and maintenance of activity-dependent intrinsic neuroplasticity. Genome-wide ChIP-sequencing analysis revealed that CDYL regulates multiple neuronal functional pathways including voltage-gated ion channels in mouse brains. We showed that CDYL binds to a regulatory element in the intron region of SCN8A and mainly recruits H3K27me3 activity for transcriptional repression of the gene. Injection of lentivirally-delivered CDYL shRNA to rat hippocampal neurons resulted in augmented Nav1.6-mediated sodium currents, lower neuronal threshold and increased seizure susceptibility, whereas transgenic mice

over-expressing CDYL had higher neuronal threshold and were less prone to epileptogenesis. Finally, examination of human brain tissues revealed decreased expression of CDYL and increased expression of SCN8A in the temporal lobe epilepsy group. Together, our findings indicate CDYL is a critical player for experience-dependent gene regulation in controlling intrinsic excitability, which potentially contributes to learning and memory and CNS disorders involving change in neuronal activities such as epilepsy.

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Nanosymposium

542. Control of Neuronal Firing

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Presentation Number: *542.02

Topic: *B.09. Physiological Properties of Neurons

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National Natural Science Foundation of China 81371432

Title: Axonal D2 receptors induce functional plasticity by modulation of cav3.2 calcium channels in stellate cells of entorhinal cortex

Authors: ***X. JIN**, Q. CHEN, Z. HUANG
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Abstract: Medial entorhinal cortex (MEC) plays a key role in the processing of spatial information. Dopaminergic fibers from Ventral Tegmental Area innervate majority of cortex including mEC. It is unknown about the function of mEC dopamine D2 receptors (D2Rs) in spatial cognition. By optogenetics, stimulating dopaminergic fibers and making electrophysiological recordings from mEC layer II stellate cells, we show that activation of axonal D2Rs by endogenous dopamine release or selective D2R agonist results in an elevated action potential (AP) threshold and decreased intrinsic excitability of layer II stellate cells. The alteration in the neuronal intrinsic function is modulated by inactivation of axon initial segments (AIS) T-type Ca^{2+} channels in D2R-PKA dependent manner. Striking, pharmacological inhibition or knocking down D2Rs in the superficial layer of mEC disrupted spatial cognition. This represents a unique cellular mechanism by which D2Rs modulate the function of mEC stellate cells, which is possibly involved in the regulation of EC function.

Disclosures: **X. Jin:** 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.; 973 Program: 2015CB559200 to Z.H., 81371432 to Z.H.. **Q. Chen:** None. **Z. Huang:** None.

Nanosymposium

542. Control of Neuronal Firing

Location: 150A

Time: *Tuesday, November 14, 2017, 1:00 PM - 3:30 PM

Presentation Number: *542.03

Topic: *B.09. Physiological Properties of Neurons

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Bob and Mary Jane Engman
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Paul G Allen Family Foundation

Title: Hyper-excitability of Dentate gyrus (DG) granule neurons and CA3 hippocampal neurons derived from patients with Bipolar Disorder

Authors: *S. STERN[1], R. SANTOS[2], C. MARCHETTO[3], A. SARKAR[4], A. G. BANG[6], M. ALDA[7], F. H. GAGE[5]
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Abstract: Bipolar disorder (BD) affects 2-3% of the world population. People with BD experience disabling episodes of mania and depression, often associated with cognitive changes, physical morbidity and some of the highest risk of suicide. The introduction of induced pluripotent stem cells technology allowed for a large advance in the study of human brain disorders. Using iPSCs derived from Epstein-Barr virus (EBV)-immortalized B-lymphocytes, we derived dentate gyrus (DG) granule neurons of BD patients vs. controls. Using whole cell patch clamp, we found that DG neurons derived from BD patients are hyperexcitable. Moreover, neurons that were derived from BD patients who respond to lithium treatment, have very different intrinsic properties than neurons derived from patients non-responsive to lithium, suggesting two two distinct subtypes of BD. Training a Naïve Bayes classifier with the electrophysiological features of these neurons, predicts with more than 92% accuracy which of

the patients will respond to lithium. Despite their very different functional profiles, both populations of neurons from lithium responsive BD patients and lithium non-responsive BD patients share a large, fast after-hyperpolarization (AHP). We therefore suggest that the large, fast AHP is a key feature of BD and a main contributor to the fast, sustained spiking abilities of BD neurons. We continued with the derivation of CA3 hippocampal neurons for the same patients and measured the differences between DG and CA3 neurons in the control and BD patients. Generally we observed that CA3 neurons mature slower, but after maturation can produce more spiking activity than DG granule neurons. Validating what appears as general hippocampal hyperexcitability, we found that CA3 BD neurons were also hyperexcitable compared to CA3 control neurons, and their intrinsic properties also depend on the patient's response to lithium. We conclude with a NEURON computational model of a BD vs. a control DG and CA3 neurons, which reproduces experimental results.

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Nanosymposium

542. Control of Neuronal Firing

Location: 150A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***542.04

**Topic: ***B.09. Physiological Properties of Neurons

Support: NSF Grant IOS-1353724
NJCBIR Fellowship CBIRFEL002
NIH/NIGMS Training Fellowship T32 GM8339
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Title: Brain-Derived Neurotrophic Factor regulates the development of electrical activity in hippocampal neuron networks cultured on microelectrode arrays

Authors: *K. M. O'NEILL[1,2], B. L. FIRESTEIN[1]
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Abstract: Brain-derived neurotrophic factor (BDNF) plays important roles in the maturation of neurons by regulating dendritic arborization and synaptogenesis. Changes to the morphology of dendrites or structure of synapses can affect the activity of a neuron and, thus, its contribution to the larger network into which it is integrated. The effects of BDNF on the activity of single neurons *in vitro* have been widely investigated, but it is not yet understood how BDNF affects

the development and activity of *in vitro* neuronal networks. The advent of microelectrode array (MEA) technology in recent decades has allowed for the monitoring of the development of *in vitro* neuronal network activity. MEA recordings are noninvasive, thus allowing for multiple recordings of the same neuronal culture, and have been used extensively to characterize the development of neuronal network activity in dissociated cultures. Our previous results examining the role of BDNF in modulating the dendritic arbor during the active branching period suggest an additional role for BDNF in regulating the development of neuronal networks. In this work, we use 64-electrode MEAs to record network activity from dissociated hippocampal neurons. We ask how BDNF regulates neuronal network development by applying BDNF for 72 hr at concentrations of 25 and 50 ng/ml to these networks. We performed recordings of spontaneous activity and quantified the short- and long-term effects of BDNF application on neuronal network dynamics. We examined parameters describing the overall activity (spiking, bursting, etc) and the synchronization of these networks and found that the two treatments exerted distinct effects on network dynamics. In general, treatment with 50 ng/ml BDNF promotes changes to a greater number of parameters in the long-term compared with treatment with 25 ng/ml BDNF. Several parameters - such as the spike rate variability, composition of individual bursts (burstlets), interburstlet interval, and average synchronization - significantly increase at one week after treatment with 50 ng/ml BDNF. The effects on the networks caused by treatment with the lower concentration, 25 ng/ml BDNF, differ substantially: spike rate and number of global bursts significantly decrease at one week after treatment. Finally, the most surprising finding was that changes to the network only occur one week after treatment end. No changes in network dynamics are observed compared to the control immediately after treatment ends, suggesting that homeostatic mechanisms exist to prevent abrupt changes in network activity. These results suggest that BDNF may mediate distinct effects on neural networks depending on concentration.

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Nanosymposium

542. Control of Neuronal Firing

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**Presentation Number: ***542.05

**Topic: ***B.09. Physiological Properties of Neurons

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Title: Role of the axon initial segment of midbrain dopaminergic neurons in the control of spontaneous frequency *In vivo*

Authors: C. C. CANAVIER[1], R. MEZA[2], L. LOPEZ-JURY[2], *P. HENNY[2]
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Abstract: The spontaneous tonic discharge activity of nigral dopamine neurons plays a fundamental role in dopaminergic signaling. To investigate the role of neuronal morphology and architecture with respect to spontaneous activity in this population, we visualized the 3D structure of the axon initial segment (AIS) along with the entire somatodendritic domain of mouse dopaminergic neurons, previously recorded in vivo. We observed a positive correlation of the firing rate with both proximity and size of the AIS. Computational modeling showed that the size of the AIS is the major causal determinant of the tonic firing rate in the intact model, by virtue of the higher intrinsic frequency of the isolated AIS, whereas position correlates with firing rate only due to a correlation between size and position. Thus morphology plays a critical role in setting the basal tonic firing rate, and in turn controlling striatal dopaminergic signaling that mediates motivation and movement.

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Nanosymposium

542. Control of Neuronal Firing

Location: 150A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***542.06

**Topic: ***B.09. Physiological Properties of Neurons

Title: Axon initial segment plasticity and its influence on neural function

Authors: *Y. LIU[1,2], Y. ZHANG[1,2]
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Abstract: Axon initial segment (AIS) is a specialized structure near the start of the axon where action potentials are initiated. Emerging evidence demonstrates that AIS plays essential roles in neuronal polarity, action potential initiation, neurodegenerative diseases and brain damage. It is now well accepted that the AIS is not just a rigid structure that generates action potentials each time the membrane potential reaches a threshold value. Indeed, the AIS continuously adapts to its surrounding environment and undergo changes in its length or location over a period of days,

as a homeostatic response to perturbation in input.
Here, we aimed to investigate the AIS structure plasticity, including AIS spatial distribution, mechanic characteristics and the influence of synaptic transmission under different concentration of glucose. Our data showed that when neurons are under the condition of low concentration of glucose, the AIS is longer and locates more distally along the axon; when the concentration of glucose is high about 50 mM, the AIS is shorter and shows no significant difference in location. Meanwhile, when AIS is far from soma, its modulus reduces and hardness decreases. Additionally, *In vivo* studies showed that when mice hippocampus slices are under the condition of low concentration of glucose, LTP inducing rate increased significantly and AIS is away from the soma while the concentration is higher, LTP is significantly suppressed. LTP is blocked when mice are anesthetized with isoflurane and the location of AIS shows no difference with wild type mice.
The very specific molecular architecture of AIS is crucial for neuronal function. However, the precise dynamics and functions of the plasticity remain to be established. We still need more evidence which may contribute to the study of learning and memory.
Keywords: AIS plasticity glucose LTP

Disclosures: Y. Liu: None. **Y. Zhang:** None.

Nanosymposium

542. Control of Neuronal Firing

Location: 150A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***542.07

**Topic: ***B.09. Physiological Properties of Neurons

Support: FAPESP
CAPES
CNPq

Title: Electrophysiological characterization of expiratory motoneurons of rats submitted to sustained hypoxia

Authors: *M. P. SILVA, D. J. A. MORAES, L. H. BONAGAMBA, W. A. VARANDA, B. H. MACHADO
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Abstract: Expiration is considered in eupnea a passive process compared with the active inspiration. Hypoxia may modify this process and make the expiration active. However, there is a lack of information about the electrophysiological properties of expiratory motoneurons and

their possible changes in conditions in which the expiration becomes active. Here we characterized the electrophysiological properties of abdominal-projecting expiratory motoneurons combining retrograde tracer, immunofluorescence and whole cell patch clamp, in thoraco-lumbar spinal cord slices from juvenile Wistar rats. The results show that expiratory motoneurons excitability is mainly dependent on synaptic inputs since its blockage hyperpolarized their resting membrane potential (-69.3 ± 0.9 mV *vs* -71.8 ± 0.9 mV) and decreased their firing frequency (7.6 ± 1 Hz *vs* 1.2 ± 0.7 Hz, n=18). Regarding passive properties, no significant changes were observed in the input resistance and excitability of these cells after synaptic blockage. We also observed that voltage-dependent sodium channels, Tetraethylammonium chloride and 4-aminopyridine sensitive potassium channels are involved in the genesis of action potentials in these cells, but not in the large conductance calcium-activated potassium channels. Furthermore, motoneurons of rats previously submitted to short-term sustained hypoxia (FiO_2 10%, 24 hours) presented: a) depolarization of the resting membrane potential (-69.3 ± 0.9 mV *vs* -66.5 ± 0.7 mV), b) enhancement of the firing frequency (7.6 ± 1 Hz *vs* 16.8 ± 3 Hz, n=18), and c) a drop in the input resistance (0.35 ± 0.05 GΩ *vs* 0.18 ± 0.03 GΩ) of expiratory motoneurons. However, these changes were abolished by synaptic blockers and are due to increases in the frequency (6 ± 1 Hz *vs* 2.2 ± 0.6 Hz, n= 11), as well in the amplitude (97 ± 10 pA *vs* 31 ± 5 pA) of excitatory post-synaptic currents. We conclude that synaptic input determines the excitability of expiratory motoneurons and hypoxia does not change the intrinsic properties of these cells.
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Nanosymposium

542. Control of Neuronal Firing

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**Presentation Number: ***542.08

**Topic: ***B.09. Physiological Properties of Neurons

Title: Regulation of neuronal firing set point by mitochondrial enzyme DHODH

Authors: *B. STYR[1], N. GONEN[1], I. VERTKIN[1], I. SHAPIRA[1], E. RUPPIN[2,3], I. SLUTSKY[1,4]
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Abstract: Homeostatic compensations act to ensure stability of neuronal activity over a wide range of spatial and temporal scales. Like other homeostatic processes in biology, neuronal homeostasis is theorized to be guided by self-monitoring feedback loops that help to maintain a stable set-point value for desired functional properties, such as mean firing rate. The set-point value around which the system is stabilized is predicted to have major consequences to neuronal tissue function and health. This is because all compensatory and regulatory mechanisms, act in reference to this set-point value. However, in spite of its enormous importance, the mechanisms that regulate neuronal firing set point are currently unknown. Several lines of evidence point to an important role for energy metabolism in maintaining the steady-state functions of neuronal networks, yet very little is known about the role of metabolism in firing homeostasis. To address this question, we combined long-term recordings of spikes using micro-electrode arrays (MEA), together with patch-clamp measurements and imaging of synaptic activity and synaptic ATP levels under the highly-controlled environment of cultured hippocampal networks. Using this system, we explored the relationships between mitochondrial functions, firing rates at the level of individual neurons and neuronal populations, intrinsic neuronal excitability and excitation-inhibition (E/I) balance in cultured hippocampal networks. Our results suggest that inhibition of dihydroorotate dehydrogenase (DHODH), a mitochondrial enzyme that participates in pyrimidine *de novo* synthesis and regulates mitochondrial electron transport chain reaction, reduces mean firing rate, intrinsic neuronal excitability, spontaneous and miniature excitatory postsynaptic currents (sEPSC and mEPSC) with no significant change in inhibitory postsynaptic currents, inducing a reduction in the E/I balance in the network. Notably, the reduction in intrinsic excitability, E/I balance and firing rate was stable and long-lasting at a timescale of up to 4 days. Furthermore, DHODH inhibition does not block homeostatic adaption mechanisms, but constrains them to a lower set-point value of firing. These results place DHODH activity as a critical regulator of spontaneous firing, and implicate mitochondrial function as a key and novel regulator of spiking set-point value. These findings help shed new light on the causes that lead on dysregulation of neuronal network activity and may allow for new types of intervention that use the network's own regulatory programs to ameliorate pathological network states.

Disclosures: B. Styr: None. **N. Gonen:** None. **I. Vertkin:** None. **I. Shapira:** None. **E. Ruppin:** None. **I. Slutsky:** None.

Nanosymposium

542. Control of Neuronal Firing

Location: 150A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***542.09

**Topic: ***B.09. Physiological Properties of Neurons

Support: unrestricted educational grant from Lundbeck

Title: Serotonergic modulation of layer II/III prefrontal interneurons: An electrophysiological and neuroanatomical study

Authors: *J. V. SCHWEIMER, T. SHARP
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Abstract: Cortical neuronal activity underlies a complex network of excitatory and inhibitory neurons, which is heavily influenced by neuromodulatory input. This complex system of excitation and inhibition is crucial to proper cortical executive function, but so far only poorly understood. Cortical interneurons can be separated into 3 groups, a) parvalbumin-expressing (PV), b) somatostatin-expressing, and c) interneurons that express the ionotropic $5HT_3$ receptor (Rudy et al. 2010). Interestingly, in the prefrontal cortex (PFC) $5HT_3R$ interneurons are predominantly located in the superficial layers (I-III), where they make up the majority of interneurons (Lee et al. 2010, Morales and Bloom, 1997). However, to date very little is known about superficial layer interneurons, in particular $5HT_3R$ interneurons.
To better understand the influence of neuromodulatory serotonergic input onto superficial layer interneurons in the medial PFC, we used a combination of electrophysiology and neuroanatomy. For this, we recorded single-units during dorsal raphe stimulation, local field potentials and electrocorticograms in urethane-anaesthetised rats, followed by juxtacellular labelling and neurochemical identification using antibodies (e.g. PV, CCK, and calretinin).
The majority of recorded, and juxtacellular-labelled interneurons in this study had low firing rates (<2Hz), and wide action potential widths (~1ms) similar to excitatory pyramidal neurons. Only a few PV interneurons were encountered in the supercial layers, these had higher firing rates (>7Hz) and narrow action potential widths (<0.6ms). Some slow-firing interneurons exhibited a fast-excitatory response to raphe stimulation, which is due to $5HT_3$ receptor activation (Puig et al, 2004), this effect could be blocked with a $5HT_3R$ antagonist like ondansetron, and histological results showed that these interneurons belong to a heterogenous group which can express CCK or calretinin among other neuronal markers . Other labelled interneurons, typically either exhibited a slow and broad excitation (>100ms) or an inhibition during raphe stimulation, which corresponds to effects of other metabotropic 5HT receptors and/or other synaptic effects.
Our results reveal histological and physiogical evidence of distinct GABAergic interneuron subtypes in the cortex. It provides important in vivo data of identified superficial-layer interneurons in the mPFC, which hopefully in the future will lead to a better understanding of this network.

Disclosures: J.V. Schweimer: None. **T. Sharp:** None.

Nanosymposium

542. Control of Neuronal Firing

Location: 150A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***542.10

**Topic: ***H.01. Animal Cognition and Behavior

Support: NIH R21NS101482

Title: The transcription factor, Shox2, regulates ion channel expression and neuronal function in the thalamus

Authors: *D. YU[1], S. ROWE[1], L. SCHRADER[1,2]
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Abstract: SHOX is a homeobox gene known to be involved in limb and heart development. Dysfunction of the SHOX gene is the main cause of several disorders in humans, including Turner Syndrome, which is characterized by shortened limbs, heart defects, and in some cases cognitive disorders. Recent studies have shown that the SHOX homolog in mice, *Shox2*, is important for proper development of various organs and pacemaker function in the heart, but the role of *Shox2* in the brain is still unknown. Our X-gal staining and immunohistochemistry results showed that *Shox2* is expressed in most nuclei of the dorsal thalamus in adult mice. This suggests a role for *Shox2* in function of the dorsal thalamus in adult mice. In order to study the role of *Shox2* in thalamic functions, we utilized tamoxifen-inducible cre-loxP recombination method to induce *Shox2* knock out (KO) in $Rosa^{CreERt/+,}$ $Shox2^{-/f}$ mice. Our behavior results showed that *Shox2* KO caused somatosensory function deficits in the paw sensation test and impaired memory in the object recognition test. RT-qPCR on thalamus tissue from *Shox2* KO mice and control littermates showed that expression of Cacna1g, HCN2 and HCN4 mRNA was significantly decreased in *Shox2* KO mice compared to littermate controls. Further, electrophysiological studies using whole-cell patch clamp recordings found that the isolated T-type Ca^{2+} and I_H current in neurons in the anterior paraventricular thalamus (PVT) of *Shox2* KO mice were significantly decreased compared to that in littermate controls. Finally, attached-cell recordings revealed that cell excitability and spike patterns of PVT neurons significantly changed in KO mice compared to littermate controls. These results show that *Shox2* is important in maintenance of thalamus cell excitability and functions partially through transcriptional regulation of T-type Ca^{2+} and HCN channel subtypes. We are currently performing unbiased mRNA-sequencing and chromatin immunoprecipitation sequencing experiments to determine other binding targets of *Shox2* in adult mouse thalamus. Future studies will address the role of *Shox2* in thalamocortical oscillations.

Disclosures: D. Yu: None. **S. Rowe:** None. **L. Schrader:** None.

Nanosymposium

543. Brain Wellness and Aging

Location: 143A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***543.01

**Topic: ***C.01. Brain Wellness and Aging

Support: Fonds de recherche du Québec – Santé
Hôpital du Sacré-Coeur de Montréal
NIH Grant MH091037
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AG024190
AG027297
AG028383

Title: The tyrosine phosphatase STEP is involved in age-related memory decline

Authors: *J. BROUILLETTE[1], D. CASTONGUAY[3], J. DUFORT-GERVAIS[3], C. MENARD[4], M. CHATTERJEE[5], R. QUIRION[7], B. BONTEMPI[8], J. S. SCHNEIDER[9], A. F. ARNSTEN[10], A. C. NAIRN[6], C. M. NORRIS[11], G. FERLAND[2], E. BEZARD[12], P. GAUDREAU[13], P. J. LOMBROSO[10]
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Abstract: Cognitive disabilities that occur with age are a common and expensive health problem. Age-associated memory deficits are observed across many species, but the underlying molecular mechanisms remain to be fully determined. Here we report elevations in the levels and activity of striatal-enriched protein tyrosine phosphatase (STEP) in aged memory-impaired mice and rats, in aged rhesus monkeys, and in human patients diagnosed with amnestic mild cognitive impairment (aMCI). The accumulation of STEP with aging is related to dysfunction of the ubiquitin-proteasome system (UPS) that normally leads to the degradation of STEP. Higher level of active STEP is linked to enhanced dephosphorylation of its substrates GluN2B and ERK1/2, CREB inactivation, and decrease in total levels of GluN2B and BDNF. These molecular events are reversed in aged STEP knock-out (KO) and heterozygous (Het) mice, which perform

similarly to young control mice in the Morris water maze (MWM) and Y-maze tasks. In contrast, viral mediated STEP overexpression in the hippocampus is sufficient to induce memory impairment in the MWM and Y-maze tests, and these cognitive deficits are reversed by the STEP inhibitor TC-2153. In aged LOU/C/Jall rats, a model of healthy aging with preserved memory capacities, there are stable levels of STEP and GluN2B, and unaltered phosphorylation of GluN2B and ERK1/2. In aMCI patients, higher STEP levels correlate with poorer cognitive scores in the mini-mental state examination (MMSE) and with increased levels of amyloid-beta (Aβ) and neurofibrillary tangles (NFTs) in the hippocampus. Altogether, these data suggest that elevated STEP levels that occur with advancing age in several species contributes to the cognitive declines associated with aging.

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Nanosymposium

543. Brain Wellness and Aging

Location: 143A

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Presentation Number: *543.02

Topic: *C.01. Brain Wellness and Aging

Support: NIH Grant NS054162-01
Joseph Drown Foundation grant

Title: Brain infiltration by age-related CD8 T cells promotes progressive neurodegeneration and proteinopathy

Authors: *C. J. WHEELER
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Abstract: Sporadic Alzheimer's disease (AD) is characterized by progressive neurodegeneration with amyloid (Abeta) plaque and neurofibrillary deposits in brain. Aging is the only known cause of sporadic AD. Immune processes such as neuroinflammation contribute to AD pathophysiology, and infiltration into mouse brain by adaptive immune (CD8 T) cells mediates cognitive decline in tau-transgenic mice. Although CD8 T cell infiltration into brain also increases with age, it's not known if this is solely due to changes in aging CD8 T cells. Similarly, whether such infiltration independently influences cognition or neuropathology is unknown. We induced age-related changes in CD8 T cells by homeostatic expansion in young nude mice. The

resulting homeostatically-induced CD8 T cells (“hiT cells”) infiltrated brain, and ultimately led to profound cognitive decline progressing from hippocampus-dependent to amygdala-dependent learning. Neuropathology reminiscent of sporadic AD also developed with age in hiT-bearing nude mice, most prominently including progressive neurodegeneration with brain atrophy, and fibrillar tau deposition. Modest amyloidopathy, involving Abeta40 and diffuse plaque accumulation exclusively, also occurred in these mice. Brain infiltration and neurodegeneration in hiT-bearing nude mice was dependent on lytic (Perforin1) and proinflammatory (IFNgamma) T effector functions, respectively. Transfer of hiT cells into wild-type mice was sufficient to induce rapid neuronal marker loss, and synergized with brain injury to reveal amyloidosis and greatly increase fibrillar tau accumulation. The effects of hiT cells on molecular neuropathology in wild-type but not nude mice, were prevented by anti-CTLA4 antibody, suggesting modulation by distinct immune cells. Finally, effector protein and immune receptor specificity associated with hiT cells in mice were significantly elevated in AD brain, but were decreased in blood of cognitively impaired patients. These findings indicate that age-related changes in CD8 T cells increase their infiltration into young mouse brain, which requires Perforin1. Once inside brain, these cells promote progressive neurodegeneration with modest amyloidopathy, and more prominent tauopathy, due in part to IFNgamma-mediated neuroinflammatory activity. These findings point to CD8 T cell aging as a novel factor upstream of prominent neuropathologic features of sporadic AD. Further dissection of this model should increase our understanding of sporadic AD pathophysiology, identify potential targets for disease intervention, and elucidate physiological mechanisms of age-related tissue destruction.

Disclosures: **C.J. Wheeler:** Other; inventor on U.S. Patent WO/2017/040594.

Nanosymposium

543. Brain Wellness and Aging

Location: 143A

Time: *****Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

Presentation Number: *****543.03

Topic: *****C.01. Brain Wellness and Aging

Support: NIH NIA R01AG048232
NIH NIA RF1AG053001

Title: Examining the effects of de novo NAD+ in Alzheimer's disease: Modulating immunometabolism and mitochondrial bioenergetics

Authors: ***P. S. MINHAS**[1], *P. S. MINHAS[1], S. MHATRE[2], Q. A. WANG[2], P. K. MOON[3], M. CORONADO[4], C. DOVE[5], A. RUBIN[2], C. TSAI[2], A. JOSHI[6], D. MOCHLY-ROSEN[7], D. BERNSTEIN[4], K. ANDREASSON[2]

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Abstract: Metabolism of the essential amino acid tryptophan (TRP) by the kynurenine pathway (KP) gives rise to neuroactive compounds including quinolinic acid and kynurenic acid. While the KP is thought to lead to neurodegeneration by excitatory transmission, the KP also serves as the sole source for biosynthetic de novo NAD+. In macrophages and microglia, the rate-limiting enzyme of the KP is indoleamine-2,3-dioxygenase 1 (IDO1). Recent studies implicate maladaptive microglial immune responses in AD, so we investigated the function of immune IDO1 in human and mouse models of AD. To our surprise, we found that IDO1-/- macrophages and microglia that lack de novo NAD+ synthesis exhibited decreased basal respiration, oxygen consumption, NAD+ levels, and ATP production. In addition, IDO1-/- microglia and macrophages exhibit a Warburg (aerobic glycolysis) phenotype with generation of higher levels of reaction oxygen species (ROS) and pro-inflammatory cytokines. Electron microscopy revealed mitochondria from IDO1-/- macrophage and microglia exhibited gross morphological abnormalities including reduction in cristae and aberrant cristae morphology. Blue Native Gel Electrophoresis revealed a decrease in complex I activity in the electron transport chain within mitochondria, and enzymatic assays revealed suppression of sirtuin activity, consistent with a decline in NAD+/NADH levels. Untargeted metabolomics on macrophages treated with IDO1 inhibitor 1-MT and those from IDOKO mice both revealed an increase in glycolytic metabolism and accumulation of pro-inflammatory fatty acids as well as a decreased in TCA cycle intermediates, amino acid metabolism, and subsequent anaplerosis. Kynurenine (KYN) administration to these cells rescued metabolic and inflammatory deficits. Interestingly, LC-MS analysis from AD patients indicated decreased levels of KYN, KYN/TRP ratio, and downstream KP metabolites. Finally, IDO1 deletion in APPSwe-PS1ΔE9 mice aggravated inflammation and increased amyloid deposition. To our knowledge, this is the first study to implicate active de novo NAD+ synthesis within tissue and its role in AD pathology. Taken together, our findings suggest that IDO1-driven immune KP activity is beneficial in models of AD through metabolic and anti-inflammatory effects.

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Nanosymposium

543. Brain Wellness and Aging

Location: 143A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***543.04

**Topic: ***C.01. Brain Wellness and Aging

Support: Georgia Institute of Technology Petit Institute Seed Grant
Woodruff School Startup Funds at Georgia Institute of Technology

Title: Heme and hemoglobin modulate amyloid beta-mediated astrocyte activation

Authors: *S. B. SANKAR[1], R. DONEGAN[2], A. REDDI[2], L. WOOD[3]
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Abstract: Recent findings of vascular permeability in Alzheimer's disease (AD) patients with mild cognitive impairment together with reports of blood leakage into postmortem late-stage brains suggest that vascular leakage may play a prominent role in promoting AD pathogenesis. Additionally, the appearance of cerebral amyloid angiopathy, with significant amyloid beta (Aβ) deposition on the vascular walls of up to 80% of AD patients, suggests a relationship between vascular dysfunction, blood-leakage into the parenchyma, and Aβ pathology. Little is known about how RBC extravasation resulting from vascular dysfunction may contribute to AD pathogenesis. RBCs are primarily comprised of the oxygen-binding protein, hemoglobin (Hb), which upon catabolism, releases four iron-binding heme groups. While both heme and hemoglobin have been reported to interact with Aβ and are elevated in AD brain tissues, their effects remain unclear. In this work, we hypothesized that Hb and heme would modulate astrocyte response in the AD microenvironment. To test this, we conditioned primary astrocyte cultures with combinations of Hb, heme, and Aβ. As expected, astrocytes became reactive and expressed a broad collection of pro-inflammatory cytokines involved in immune cell activation and chemotaxis (e.g., IL-6, MCP-1, MIP-1α) when treated with a physiologically relevant concentration of Aβ1-42 (50nM). However, when co-treated with Aβ1-42 and heme or Hb (50nM), cytokine expression was broadly suppressed. Further, Aβ1-42 internalization was strongly reduced and Akt/mTor signaling was modulated in heme-treated astrocytes, suggesting that heme may modulate astrocyte phagocytic capacity. Together, our data indicate that Hb and heme suppress astrocyte capacity to clear Aβ and further implicate vascular permeability as a contributor to AD pathogenesis.

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Nanosymposium

543. Brain Wellness and Aging

Location: 143A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***543.05

**Topic: ***C.01. Brain Wellness and Aging

Support: AG051496

Title: Aberrant myelin phagocytosis by complement-expressing microglia causes obesity-induced white matter damage

Authors: *G. R. HOWELL[1], L. C. GRAHAM[2], W. A. GRABOWSKA[2], Y. CHUN[2], S. RISACHER[3], V. PHILIP[2], A. J. SAYKIN[4]
[1]Jackson Lab., Bar Harbor, ME; [2]The Jackson Lab., Bar Harbor, ME; [3]Indiana Univ., Indianapolis, IN; [4]Radiology and Imaging Sci., Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Multiple studies show diet-induced obesity increases risk for vascular decline and white matter damage that have been observed in multiple dementias such as vascular dementia and Alzheimer's disease. Here, we confirmed a strong correlation between obesity (BMI >30) and white matter damage using diffusion tension imaging data generated through the Alzheimer's disease Neuroimaging Initiative (ADNI). However, the precise mechanisms by which diet-induced obesity causes white matter damage are not known. To address this, we used chronic consumption of a westernized diet for mice to model key aspects of obesity in humans. Mice fed the western diet from 2 to 12 months of age became obese with increased levels of blood glucose, showed reduced locomotor activity, increase anxiety and performed poorly in cognitive tasks such as spontaneous alternation and spatial novelty. Vascular dysfunction and white matter damage, in the form of diffuse demyelination, were confirmed using biochemical and histological approaches. Acute diet consumption showed that glial activation (astrocytosis and microglia activation) and vascular dysfunction preceded white matter damage. Transcriptional profiling of specific brain regions was employed to identify potential mechanisms by which obesity-induced glial activation and vascular dysfunction caused white matter damage. Genes involved in phagocytosis and myelin production were differentially expressed in western diet-fed mice compared to mice fed a control chow. These results predicted that the western diet caused an imbalance to myelin turnover leading to excessive removal of myelin by phagocytic microglia. Aberrant myelin turnover was confirmed using high-resolution 3D imaging. Despite an increase in the number of oligodendrocytes and oligodendrocyte precursors, increased numbers of complement-expressing microglial cells were observed phagocytosing myelin resulting in an overall reduction in myelin. Electron microscopy showed loosely packed, ballooned myelin surrounding axons. Exercise prevented this imbalance in myelin phagocytosis and white matter damage despite a significant increase in weight. Western diet fed mice that had access to a running wheel also showed no signs of vascular dysfunction and cognitive decline. These data support adaptations in diet and levels of physical activity to preserve vascular health, reducing risk for age-dependent cognitive decline and dementias such as vascular dementia and Alzheimer's disease. Our data also suggest targeting specific aspects of myelin turnover, particularly mononuclear phagocytes, may prevent or reduce risk for white matter damage.

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Nanosymposium

543. Brain Wellness and Aging

Location: 143A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***543.06

**Topic: ***C.01. Brain Wellness and Aging

Support: CHDI Foundation

Title: The intersection of Golgi stress and redox homeostasis in Huntington's disease

Authors: *J. I. SBODIO, B. D. PAUL, S. SNYDER
Johns Hopkins Univ., Baltimore, MD

Abstract: The Golgi apparatus is a dynamic organelle that plays a vital role in protein trafficking. Perturbations of the Golgi structure has frequently been linked to neurodegenerative processes. The Golgi apparatus is fragmented in Amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD). We had shown previously, that elevated Golgi stress is also associated with Huntington's disease. One of the Golgi proteins, Acyl CoA binding domain containing 3 (ACBD3) is upregulated in HD, eliciting Golgi stress. Similar to ER stress, Golgi stress is emerging as a distinct signaling process. We show that low grade Golgi stress can actually prove beneficial and counteract cytotoxicity occurring during neurodegeneration. Here, we the mechanism of action these agents that can afford neuroprotection. Our findings reveal that pathways involved in antioxidant defense are upregulated in response to Golgi stress. Stimulation of these pathways result in decreased levels of reactive oxygen species and improved redox balance which is responsible for cytoprotective response to stress stimuli. We identify a molecular link between redox imbalance and Golgi stress during neurodegeneration in HD. This may be beneficial in other diseases involving redox imbalance and is applicable for therapeutic intervention.
* Equal contribution

References

1. Sbodio JI[#], Snyder SH[*] and **Paul BD**[#,*]Transcriptional control of amino acid homeostasis is disrupted in Huntington's disease. ***Proc Natl Acad Sci USA***. 2016, 113:8843-8848.
2. Sbodio JI, **Paul BD**, Machamer C and Snyder SH. Golgi protein ACBD3 mediates neurotoxicity associated with Huntington's disease. ***Cell Reports*** 2013, 4:890-897.

Disclosures: J.I. Sbodio: None. **B.D. Paul:** None. **S. Snyder:** None.

Nanosymposium

543. Brain Wellness and Aging

Location: 143A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***543.07

**Topic: ***C.01. Brain Wellness and Aging

Support: CHDI

Title: Metabolic control of redox balance in Huntington's disease

Authors: *B. D. PAUL[1], J. I. SBODIO[2], S. SNYDER[2]
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Abstract: Perturbations in redox imbalance has frequently been reported in Huntington's disease, but their origins have remained unclear. We show that oxidative stress is linked to perturbations in amino acid metabolism, specifically those linked to deficits in sulfur metabolism. Mutant huntingtin suppresses corrective and cytoprotective responses to elevated oxidative stress. Here, we report that the transsulfuration pathway responsible for not only synthesis of the amino acid cysteine and its metabolites, but also glutathione, the major antioxidant in cells is dysregulated at the level of activating transcription factor 4 (ATF4), the master regulator of amino acid biosynthetic enzymes. This abnormality results in chronic oxidative stress as well as aberrant and inadequate response to stress stimuli including amino acid deprivation. Ameliorating oxidative imbalance by upregulating the transsulfuration pathway via multiple pathways rescues the protective response mechanisms to stress. We hve identified compounds that activate the transsulfuration pathway and promote neuronal health in HD. In particular, we show that compounds that elicit subtoxic low grade stress can afford cytoprotection by upregulating adaptive response pathways. Our findings reveal the molecular basis for the decline in protective pathways and identify a molecular link between redox imbalance and metabolic dysfunction during neurodegeneration in HD. This signaling cascade may be relevant to other diseases involving redox imbalance and deficits in amino acid metabolism and identifies metabolic hubs for therapeutic intervention.

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3. Paul BD* and Snyder SH*. H_2S: a novel gasotransmitter that signals by sulfhydration. ***Trends Biochem Sci*** 2015, 40:687-700.
[#] Equal contribution, [*] corresponding authors

Disclosures: **B.D. Paul:** None. **J.I. Sbodio:** None. **S. Snyder:** None.

Nanosymposium

543. Brain Wellness and Aging

Location: 143A

Time: *Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

Presentation Number: *543.08

Topic: *C.01. Brain Wellness and Aging

Title: Direct interaction of molecular chaperone

Authors: ***Y. ATOMI**[1], Y. FUJITA[2], E. KATAYAMA[3], E. FUJITA[1], M. SHIMIZU[1], S. HAYASAKI[1], A. ATOMI[1]
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Abstract: αB-crystallin (αB) is known to be associated with several neurodegenerative diseases such as Alzheimer's, Parkinson's and polyglutamine diseases, all of which include the formation of protein aggregates/deposition as a part of a disease mechanism. Although the exact reason why αB is induced and associates with these protein aggregates has not been known, we hypothesize its protecting role for brain homeostasis, because αB is an immediate-responding chaperon also for tubulin/microtubule (MT). αB is reported to co-localize with tau-immunoreactive inclusions. Tau protein was initially isolated as the heat stable MAPs (MT-associated proteins) essential for MT assembly. As part of our continuous efforts to clarify the role of αB as chaperon for tubulin/MT, here we identified MAP2 as a direct binding partner for αB from a heat stable tau containing fraction of brain tubulin. We have previously reported that αB works as molecular chaperone for tubulin (Ohto et al., 2007) and microtubule (MT) (Fujita et al., 2004), resulting in playing a role increased resistance of MT against nocodazole treatment and calcium in both myoblast C2C12 cells and C6 glioma cells. In the present study using purified αB, the deletion-constracts of αB and tubulin and heat-stable MAPs, both from porcine brain. αB -MT interactions were examined in vitro. αB did't interact with MT reconstituted by PC-tubulin but directly associated with the MAPs, by biochemical, micrographic and electro-micrographic analyses. Nocodazole treated to MT are resistant to disassembly in the existence of αB compared with in the non-existence (high frequency of longer MT by histogram analysis). No difference of disassembly was seen against cold buffer condition despite of the existence of αB. The interaction of αB with MAP-MT was analyzed using deletion mutants of αB and realized through the N-terminal region, which is specific for αB having three phosphorylation serines, while the C-terminal αB domain interacts with the free forms of tubulin dimers. αB is essential for mainteing structural homeostasis having dynamic instability intrinsic to MT system. From

these results for tubulin/MT system described above, αB basically works as a molecular chaperone for in neurological system against various stresses prior to apoptosis and/or simultaneously to protect apoptosis of stressed cells. Since αB may be related to protein degradation system via ubiquitin-proteasome, αB may also work a role as a E3 ligase for tubulin/MAPs like tau to recognize special client proteins.

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Nanosymposium

543. Brain Wellness and Aging

Location: 143A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***543.09

**Topic: ***C.01. Brain Wellness and Aging

Support: Z01 ES100221

Title: Transcriptome profiling of hippocampal subregions reveals a role for mitochondria in CA2 physiology and function

Authors: *S. FARRIS, J. M. WARD, Y. WANG, K. CARSTENS, S. M. DUDEK
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Abstract: Many neuronal functions, including memory storage, are thought to require *de novo* transcription and translation. In neurons, local regulation of RNA affords tight spatial and temporal control over gene expression so that in response to neuronal activity or injury, proteins can be rapidly synthesized to modify neuronal connections that are often hundreds of microns away from the cell body. However, the molecular mechanisms regulating RNA in specific cell-types in vivo are lacking. Furthermore, how RNA regulation may be contributing to cell-type specific functions is completely unknown.
In general, hippocampal neurons are extremely vulnerable to seizure, ischemic insult and trauma; however, nearly 40 years ago it was observed in both humans and animal models that neurons in area CA2 are impervious to these insults. Gene ontology analyses of RNA-Seq studies comparing CA2 neurons to neighboring CA1, CA3 and DG neurons revealed that genes involved in mitochondrial function are enriched in CA2. Given the well-established link between mitochondria, intracellular calcium regulation, and programmed cell death, we hypothesized that CA2 neurons may have increased mitochondrial function that renders CA2 neurons resistant to cell death.
Specifically, we discovered that CA2 neurons have the highest amount of mitochondrial RNA

compared to neighboring subregions, indicating that CA2 neurons have either more mitochondria or more mitochondrial transcription. Indeed, we found that CA2 neurons have a greater mitochondrial DNA (mtDNA) copy number per cell compared to CA1 neurons without differences in mitochondrial number or size, suggesting that CA2 neurons have more mtDNA template per mitochondria. Moreover, nuclear-encoded mitochondrial genes including the mitochondrial calcium uniporter, *Mcu*, and its regulatory proteins, *Mcur1* and *Micu1*, were also enriched in CA2, supporting the case that mitochondrial function is enhanced in CA2 relative to neighboring subregions. Enrichment of these genes in CA2 neurons was validated using single molecule fluorescent in situ hybridization. Future studies assessing the role of mitochondrial calcium signaling in CA2 after injury may identify novel strategies to promote central nervous system (CNS) repair. These studies have far-reaching implications given that CNS cells notoriously have minimal capacity to regenerate after injury.

Disclosures: S. Farris: None. **J.M. Ward:** None. **Y. Wang:** None. **K. Carstens:** None. **S.M. Dudek:** None.

Nanosymposium

543. Brain Wellness and Aging

Location: 143A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***543.10

**Topic: ***C.01. Brain Wellness and Aging

Support: NIH Grant AG045571
NIH Grant AG043270
Davee Foundation

Title: Cognitive superagers are protected from cholinergic axonal abnormalities found in cognitively normal elderly

Authors: A. REZVANIAN, T. GEFEN, *S. WEINTRAUB, E. BIGIO, E. ROGALSKI, M.-M. MESULAM, C. GEULA
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Abstract: The majority of individuals who live to old age demonstrate a decline in cognitive abilities. However, there appear to be some elderly individuals who withstand age-related cognitive decline compared to their cognitively normal peers. We have coined the term ‘SuperAger’ to refer to individuals over age 80, whose performance on tests of memory is at least equivalent to healthy 50-65 year-olds, with performance on non-memory tests at least

equivalent to their cognitively normal aged peers. In prior studies, we have demonstrated age-related abnormalities in cortical cholinergic axons in cognitively normal individuals. These abnormalities take the form of individual ballooned terminals, terminal swellings in a chandelier arrangement, and thickened axons with no branches. Such axonal abnormalities were sparse in normal young individuals, emerged in middle-aged participants, and increased in density in the normal elderly. The purpose of this study was to investigate the presence and density of cortical cholinergic axonal abnormalities in SuperAgers. Acetylcholinesterase histochemistry was used to visualize cholinergic axons. The density of axonal abnormalities in the entorhinal cortex was estimated using stereological methods. The density of cholinergic axonal abnormalities was significantly less in SuperAgers when compared with cognitively normal elderly ($p<0.05$). This difference was primarily due to less chandelier terminal swellings ($p<0.005$) and ballooned terminals ($p<0.05$). No differences were observed in thickened axons between the two groups. These results suggest that SuperAgers are relatively protected from age-related abnormalities in cortical cholinergic axons. Given the role of cortical cholinergic innervation in cognitive processing, it is likely that the integrity of this innervation in SuperAgers contributes to their exceptional cognitive status.

Disclosures: **A. Rezvanian:** None. **T. Gefen:** None. **S. Weintraub:** None. **E. Bigio:** None. **E. Rogalski:** None. **M. Mesulam:** None. **C. Geula:** None.

Nanosymposium

543. Brain Wellness and Aging

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Topic: *C.01. Brain Wellness and Aging

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The Davee Foundation

Title: Neurofibrillary tangle and amyloid plaque burden in the oldest-old with superior memory and the full range of alzheimer pathology

Authors: ***C. GEULA**[1], A. REZVANIAN[2], G. KIM[3], T. GEFEN[4], S. WEINTRAUB[5], E. J. ROGALSKI[6], M.-M. MESULAM[7], M. CORRADA[8], C. KAWAS[8]
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Chicago, IL; [6]1.?Cognitive Neurol. and Alzheimer's Dis. Center, CNADC, Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [7]Norrthwestern Univ., Cognitive Neurol. and Alzheimer's Dis. Ctr., Chicago, IL; [8]Univ. of California at Irvine, Irvine, CA

Abstract: Recent reports indicate that a subpopulation of cognitively normal elderly meet pathologic criteria for diagnosis of Alzheimer's disease (AD) at post-mortem examination, characterized by high densities of neurofibrillary tangles (NFTs) and amyloid plaques (APs). In a previous semi-quantitative investigation of a cohort of eight 90+ participants (95-100 years) with relatively superior memory performance, we reported the full range of Alzheimer pathology; despite similarly superior memory performance, some brains displayed very sparse NFT/pre-NFTs and diffuse APs, while others showed extensive distributions of NFTs and cored/neuritic plaques. The purpose of the current study was to quantitatively investigate NFT/pre-NFT and AP burden in the hippocampus and prefrontal cortex (Brodmann area 9) of these brains. Antibodies to paired helical filaments (PHF-1) and amyloid-β peptide (6E10) were used to visualize pre-NFT/NFT and AP, respectively. Pre-NFTs/NFTs were quantified numerically and AP burden was assessed using ImageJ software to calculate the percent area occupied by plaques. In the hippocampus, the density of NFTs was lowest in the brain designated as Braak stage I (BS I) of tangle deposition, and highest in a case with BS VI, showing a very consistent correlation between Braak staging and NFT density ($p<0.005$; $r=0.9674$). NFT burden in BA9 showed the same trend, such that a higher NFT density in the hippocampus accurately predicted a greater density of NFTs in BA9 ($p=0.0049$; $r=0.9248$). There was no correlation between AP densities in the hippocampus and BA9 ($p>0.05$; $r=0.3159$). The relationship between pre-NFTs/NFTs and APs remained relatively close in both the hippocampus ($p=0.0043$; $r=0.7762$) and BA9 ($p=0.0013$; $r=0.2439$). Qualitative examination of HLA-DR-positive microglial activation, a marker of inflammation, showed a general increase with progressive Braak staging, suggesting that microglia activation closely correlates with pathologic burden. These results indicate that a range of AD pathology, including densities and distributions consistent with a pathologic diagnosis of AD, can be present in the oldest old with similar above-average memory capacity. It appears that brains of some elderly are protected from processes that lead to NFT/AP formation, while others are resistant to the deleterious effects of NFTs/APs.

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Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

Location: 152A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***544.01

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

Support: NIH R01 AG022560

Title: Lack of adverse phenotypes related to BACE1 inhibition in adult conditional knockout of BACE1 in mice

Authors: *M.-H. OU-YANG[1], J. KURZ[2], T. NOMURA[4], J. POPOVIC[1], T. RAJAPAKSHA[1], H. DONG[3], A. CONTRACTOR[4], D. M. CHETKOVICH[2], W. G. TOURTELLOTTE[5], R. J. VASSAR[1]
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Abstract: β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) is the β-secretase protease that cleaves APP to initiate the production of neurotoxic amyloid-β (Aβ) peptide. Cerebral accumulation of Aβ is a defining pathological hallmark of Alzheimer's disease (AD) and a large body of evidence indicates that Aβ is involved in the pathogenesis of this devastating neurodegenerative disorder. Inhibiting BACE1 and thus Aβ production has therefore emerged as an attractive therapeutic intervention for AD. However, the safety of BACE1 inhibition has been questioned, because BACE1 has a wide array of substrates, and proper cleavage of these substrates may be necessary for normal physiology. Constitutive BACE1 knockout ($BACE1^{-/-}$) mice that are devoid of normal BACE1 substrate processing from the moment of conception have been reported to exhibit runting and compromised survival, hypomyelination, spontaneous seizures and abnormal EEGs, and memory deficits. The extent to which these phenotypes are related to BACE1 deficiency during development versus an ongoing requirement for BACE1 activity in adults is unknown. This question has critical implications for the treatment of elderly AD patients with BACE1 inhibitor drugs, several of which are being tested in clinical trials. To investigate the consequences of BACE1 inactivation in adults, here we have generated mice in which exon 2 of the BACE1 gene is flanked with loxP sites ($BACE1^{fl/fl}$) and crossed them to either CamKIIα-iCre mice that express Cre recombinase in early postnatal forebrain excitatory neurons ($BACE1^{fl/fl}$; CamKIIα-iCre) or $R26CreER^{T2}$ mice that express from the ROSA26 locus a Cre-estrogen receptor fusion enabling ubiquitous temporally controlled BACE1 gene deletion upon activation by tamoxifen ($BACE1^{fl/fl}$; $R26CreER^{T2}$-TAM). We found that postnatal forebrain neuron and ubiquitous adult conditional BACE1 knockouts fully rescue the above constitutive BACE1 knockout phenotypes, with the exception of partial rescue of runting and seizure in postnatal forebrain neuron knockouts. We conclude that once development is completed, BACE1 inhibition in the adult should be well tolerated.

Disclosures: M. Ou-Yang: None. **J. Kurz:** None. **T. Nomura:** None. **J. Popovic:** None. **T. Rajapaksha:** None. **H. Dong:** None. **A. Contractor:** None. **D.M. Chetkovich:** None. **W.G. Tourtellotte:** None. **R.J. Vassar:** None.

Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

Location: 152A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***544.02

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

Title: Computational analysis used for structure and function of PSEN1 involved in neurodegeneration for Alzheimer's disease

Authors: *M. CORREDOR[1], A. SOTO[2], P. ARAQUE[4], A. VILLEGAS[3]
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Abstract: The people diagnosed with familial Alzheimer's disease, carry strong risk factor, because they inherited mutated genes such as presenilin (PSEN1, PSEN2) and amyloid peptide precursor (APP). This class of Alzheimer's disease has not clearly defined all molecular pathogenic mechanisms and the current investigation in this topic has associated the mechanism to amyloid cascade. PSEN1 analysis provided evidence of a nine transmembrane structure with cleavage and assembly into the γ-secretase complex prior to insertion into the plasma membrane. However, because this is a protein with large numbers of hydrophobic regions, it is unlikely that x-ray crystallography will provide definitive proof of the structure (1). PEN1 constitutes the catalytic subunit of the γ-secrease protein complex (2). This was one the first proteins identified in extensive mutations of the early stages of Alzheimer's disease. In recent years there has been accepted a model without completely convincing. Mutations in PSEN1 are the most frequent cause in Alzheimer's disease in Mendelian families (3). The main objective of this work is to elucidate the most significant mutations regarding the three-dimensional structure of PSEN1 and to relate them to Alzheimer's disease. The non-synonymous mutations of the trans-membrane regions: T245P, A246E, A246P, L248R, L248R, L250S, L250V, Y256S, A260V, V261F, V261L, E280A, L381F, L381V, G384A, F386S, S390I, S390N, V391F , L392P, L392V, G394V, A396T, N405S, A409T. The aligned three-dimensional structures were analyzed and the electrostatic potentials were determined . The results indicate that several of the mutations identified have a close relationship with the disease since structural changes are transcendental. Observing the aligned three-dimensional structures, there are important differences in some alpha helices, not only affect by the conformation but also the charge. The charge analysis, hydrophobicity, van der Waals, acidity and basicity in some regions, changes due to the composition of amino acids, especially when variations occur between non polar and polar residues. The hybrid QM/MM (quantum mechanics-molecular mechanics) strengthen the molecular model supporting computational analysis. Variations of the structural conformations have been greatly affected. When we analyze the relationship between the putative structure of PSEN-1 with several non-synonymous mutations, it is clear that some of them affect the protein

function of PSEN-1 and γ-secretase.
1- Spasic D, et al. 2006. J. Biol. Chem. 281 (36): 26569-77.
2- Bai, X. C., et al 2015. Nature, Aug 17
3- Tol, J., et al 1998. Revue neurologique, 155, S10-6.

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Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

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Presentation Number: *544.03

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

Support: T32 AG20506

Title: Changes in kinetics and newly generated soluble APP-β in the human central nervous system in Alzheimer's disease

Authors: ***J. A. DOBROWOLSKA ZAKARIA**[1], B. W. PATTERSON[3], R. J. BATEMAN[4], R. J. VASSAR[2]
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Abstract: The amyloid hypothesis proposes that increased production and/or decreased clearance of amyloid-beta (Aβ) leads to higher order amyloid structures that initiate a cascade of events, culminating in neuronal death manifesting as Alzheimer's disease (AD). Sequential cleavage of Amyloid Precursor Protein (APP) generates Aβ. APP may be processed in one of at least two pathways, initially being cleaved by either α- or β-secretase (BACE1). BACE1 cleavage of APP releases soluble APP-β (sAPPβ) and subsequent cleavage by γ-secretase produces Aβ. Alternatively, α-secretase cleavage of APP precludes Aβ formation and produces soluble APP-α (sAPPα). In some studies BACE1 and sAPPβ are increased in cerebrospinal fluid (CSF) and post-mortem AD brain. Our previous data demonstrate an increase in CSF sAPPβ: sAPPα ratio in AD subjects versus age-matched controls, indicating a shift toward BACE1 processing of APP under pathophysiological conditions. Further, sAPPβ and Aβ concentrations are highly positively correlated in human CSF, and a stable isotope labeling kinetics (SILK) study suggests about 50% of AD patients may overproduce Aβ. Together these findings suggest increased BACE1 activity may cause increased Aβ in an AD subpopulation. However, this has not been directly assessed.

Using highly sensitive SILK/immunoprecipitation/liquid chromatography-mass spectrometry methods, we quantified sAPPβ and sAPPα kinetics in CSF from human AD subjects and controls to determine β- and α-secretase activity in human CNS. Results suggest sAPPα has a marginally faster turnover compared to sAPPβ; this difference is accentuated in the presence of brain amyloidosis. Further, newly generated sAPPβ:sAPPα ratio is higher with amyloid deposition, and sAPPβ, when normalized to sAPPα, positively correlates with brain amyloid load. We will next expand this proof-of-concept study to include a larger sample size. We hypothesize that approximately half of AD patients overproduce Aβ due to increased BACE1 activity as measured by increased absolute production of sAPPβ. By directly measuring the kinetics and newly generated sAPPβ *in vivo*, we are determining if, and by how much, BACE1 activity is increased in AD subjects. These results would allow for characterization of AD subpopulations most likely to benefit from BACE1 inhibitors. Outcomes will elucidate human CNS APP physiology and AD pathophysiology and also prove useful for measuring pharmacodynamic effects of candidate therapeutics. BACE1 is currently a high priority target for AD, thus results of altered BACE1 activity in AD are critical for understanding AD pathophysiology and development of disease modifying therapeutics.

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Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

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Center for Chronic Disorders of Aging at PCOM
Division of Research at PCOM

Title: Chlamydia pneumoniae-infection upregulates astrocyte BACE1 and PSEN1 protease expression and activity to promote Alzheimer Disease pathology

Authors: Z. AL-ATRACHE[1], A. CADER[2], D. LOPEZ[1], S. HINGLEY[1], *D. M. APPELT[3]
[1]Bio-Medical Sci., [2]Neurosci., Philadelphia Col. of Osteo. Med., Philadelphia, PA; [3]Ctr. for Chronic Disorders of Aging, Philadelphia Col. Osteo. Med., Philadelphia, PA

Abstract: Despite the prevalence of dementia reaching almost 50 million people worldwide, the Alzheimer Disease (AD) community is far from realizing an efficacious treatment or cure. Epidemiologic studies strongly suggest that the pathophysiology of late-onset AD versus early-onset AD has environmental rather than genetic etiologies, thus revealing numerous potential therapeutic targets to limit disease progression. Utilizing molecular and biochemical approaches, this research explores the role of an infectious pathogen, *Chlamydia pneumoniae* (*Cpn*), as an environmental trigger for AD pathology. We hypothesized that *Cpn* infection of human astrocytes alters the expression of the β-amyloid precursor protein (βAPP)-processing proteases, ADAM10, BACE1, and PSEN1, to promote the formation of β-amyloid (Aβ), the pathologic hallmark of AD. To test this hypothesis, human astrocytoma cells were infected with *Cpn in vitro* over the course of 6-72 hrs and the gene and protein expression, as well as the enzymatic activity, of ADAM10, BACE1 and PSEN1 were qualitatively and quantitatively assessed. Relative to that of uninfected astrocytes, BACE1 and PSEN1 protein levels were enhanced 48-72 hrs post-*Cpn* infection. To confirm the augmented enzymatic activity of BACE1 and PSEN1, fluorescence intensity of Aβ, ELISA-quantified levels of soluble-βAPP, and FRET-quantified levels of fluorescent BACE1 cleavage products were analyzed; all revealed temporally similar increases. These findings are the first to suggest that *Cpn* infection of human astrocytes promotes the formation of Aβ through the upregulation of glial β-, and γ-secretases (BACE1 and PSEN1, respectively), but not α-secretase (ADAM10) at the protein and genetic level, thereby providing further evidence for a direct link between this respiratory pathogen and the pathologic neurodegeneration of AD.

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Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

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

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IIRG-11-205149

Title: PS1/γ-secretase promote angiogenesis and angiogenic complexes via ephrinB2 processing a function inhibited by PS1 FAD mutants

Authors: *A. GEORGAKOPOULOS, Y. YOON, G. VOLOUDAKIS, N. WARREN, N. ROBAKIS
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Abstract: Cerebral microvasculature abnormalities are implicated in the genesis of Alzheimer's disease (AD). EphB4/ephrinB2 system is an important regulator of the vascular system in both development and adulthood. Binding of EphB4 receptor to its transmembrane ligand ephrinB2 on the surface of endothelial cells of blood vessels stimulates angiogenesis and the cytoplasmic domain of ephrinB2 is necessary for this function. We found that Presenilin1 (PS1), of the γ-secretase proteolytic complex, which plays a central role in familial AD (FAD) regulates the EphB4-Fc-induced processing of ephrinB2 in primary endothelial cells in a γ-secretase-dependent manner producing cytosolic peptide ephrinB2/CTF2, which corresponds to ephrinB2 cytoplasmic domain, and that EphB4-Fc-induced sprouting and tube formation depend on γ-secretase activity. Overexpression of ephrinB2/CTF2 significantly increases endothelial cell sprouting and tube formation and mutations that inhibit its phosphorylation at conserved tyrosine residues or removal of its PDZ-binding domain hinder its angiogenic activity. We also found that EphB4-Fc increases the VE-cadherin/Rok-α and VE-cadherin/Raf1 angiogenic complexes in a PS1/γ-secretase-dependent manner in primary endothelial cells and that overexpression of ephrinB2/CTF2 also promotes the formation of these complexes. Furthermore we found that EphB4-Fc induces phosphorylation of Myosing Light Chain 2 (MLC2) at VE-cadherin cell-cell contact sites in a PS1/γ-secretase-dependent manner and that peptide ephrinB2/CTF2 has similar function. Together the above raise the possibility that PS1/γ-secretase affect the EphB4/ephrinB2-induced angiogenesis by regulating proteolytic processing of ephrinB2, increasing angiogenic complex formation and stabilizing the endothelial junctions. Primary cortical endothelial cells expressing PS1 FAD mutants M146V and I213T fail to respond to EphB4-Fc by forming sprouts and tubes *in vitro* suggesting that these mutants impair angiogenic activity of brain endothelial cells *in vivo*. The above provide a potential pathogenic mechanism for the impaired vascular integrity observed in AD brains.

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Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

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**Presentation Number: ***544.06

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

Support: UCLA Easton Center for AD Research

Title: Differential inhibition of the alpha-secretase ADAM10 by amyloid-beta variants containing FAD mutations

Authors: *A. HATAMI[1], S. DUTTA[2], P. SPILMAN[1], A. RODRIGUEZ[2], J. RASKATOV[2], V. JOHN[1]
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Abstract: Background. The amyloid-beta (Aβ) peptide is produced following the sequential cleavage of the amyloid precursor protein (APP) by β- and γ-secretase, and is implicated in Alzheimer's disease (AD). APP is also cleaved by the α-secretase ADAM10 to generate soluble APPα (sAPPα), which is a neuroprotective and neurotrophic molecule. We have previously shown that oligomers of Aβ can inhibit ADAM10 activity (Spilman et al., *J Alzheimers Dis*, 2016). This may be a novel toxic mechanism of Aβ in AD pathogenesis, as ADAM10 inhibition results in decreased sAPPα levels while increasing the pool of membrane-associated APP susceptible to β-cleavage by BACE1. The specific conformations of Aβ oligomers capable of inhibiting ADAM10 and the extent to which they inhibit this enzyme are as yet unknown. We have recently shown that Aβ peptides containing mutations associated with familial AD (FAD) (Hatami et al., *J Biol Chem*, 2017) and those containing chiral substitutions adopt distinct conformations and have a wide range of aggregation kinetics.
Methods. We tested the abilities of 11 Aβ40 variants containing FAD mutations, as well as Aβ peptides containing chiral substitutions, to inhibit ADAM10 activity using a fluorogenic assay utilizing a short peptide cleaved by ADAM10, and by assessing the cleavage of a substrate comprising the C-terminal 125 amino acids of APP conjugated to maltose-binding protein. We aggregated the Aβ peptides under 2 different conditions over a 7-day time course and assessed ADAM10 inhibition in the presence of the peptides at time 0, and 3 and 7 days after the initiation of aggregation. The conformational profiles and aggregation kinetics of the peptides were characterized using a panel of amyloid conformation-specific monoclonal antibodies by immunoblot.
Results. Aβ peptides containing mutations associated with FAD and those with chiral mutations adopt different sets of amyloid conformations and have different aggregation kinetics. The distinct ensembles of amyloid conformations adopted by the Aβ variants during the aggregation time course differentially inhibited ADAM10 activity.

Conclusions. Our findings for the first time highlight a potential novel toxic mechanism associated with specific conformations of Aβ that warrant further investigation and could lead to identification of specific conformations that may be cleared by immunotherapy to produce therapeutic benefit in AD.

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Nanosymposium

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Title: ER-associated degradation regulates gamma-secretase activity, memory function and Alzheimer's amyloid pathology

Authors: ***L.-L. JIANG**, B. ZHU, T. HUANG, Y. ZHAO, D. ZHANG, H. XU
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Abstract: Endoplasmic-reticulum-associated degradation (ERAD) is an important protein quality control system maintaining protein homeostasis. The constituents of the ERAD complex and its role in neurodegeneration are not yet fully understood. Here, we characterize and demonstrate that the ER protein membralin is a component of ERAD. Nicastrin, a key component of the γ-secretase complex, is a membralin binding component and membralin-associated ERAD substrate. Membralin deficiency affects γ-secretase activity. Modulating membralin results in neuronal death, and exacerbates synaptic/memory deficits and β-amyloid pathology in a mouse model of AD. Our results identify membralin as a novel ERAD component and demonstrate a critical role for ERAD in the pathogenesis of AD.

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Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

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Title: Presenilin 1, a double agent, decreases abeta levels through activation of autophagy

Authors: *V. BUSTOS[1], M. PULINA[1], F. GORELICK[3], M. FLAJOLET[2], P. GREENGARD[4]
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Abstract: Presenilin 1 (PS1) is the catalytic subunit of the γ-secretase complex, which cleaves βCTF to produce Aβ. Although PS1 plays a central role in the pathogenesis of Alzheimer's disease, little is known about the mechanisms that regulate its function. Here we show that phosphorylation of PS1 at Ser367 reduces levels of Ab in vivo, but does not affect γ-secretase activity. We identified CK1γ2 as the endogenous kinase responsible for the phosphorylation of PS1 at Ser367. Overexpression of CK1γ leads to an increase in PS1 Ser367 phosphorylation and to a decrease in Aβ levels in cultured cells. Transgenic mice in which Ser367 of PS1 was mutated to Ala, show dramatic increases in Aβ peptide and in βCTF levels *in vivo*. PS1 phosphorylated at Ser367, but not non-phosphorylated PS1, interacts with Annexin A2, which in turn interacts with the lysosomal SNARE Vamp8. Annexin A2 facilitates the binding of Vamp8 to the autophagosomal SNARE Syntaxin 17 to modulate the fusion of autophagosomes with lysosomes. Thus, PS1 phosphorylated at Ser367 has an anti-amyloidogenic function, promoting autophagosome-lysosome fusion and increasing βCTF degradation. Our results demonstrate that PS1 is a double agent, regulating Aβ levels in a bidirectional manner. Thus, in addition to its known role as the catalytic subunit of the γ-secretase complex that processes βCTF to increase Aβ, selective phosphorylation of PS1 on Ser367 decreases Aβ levels by increasing βCTF degradation through autophagy. Drugs designed to increase the level of PS1 phosphorylated at Ser367 should be useful in the treatment of Alzheimer's disease.

Disclosures: V. Bustos: None. **M. Pulina:** None. **F. gorelick:** None. **M. flajolet:** None. **P. Greengard:** None.

Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

Location: 152A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***544.09

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

Support: CIHR MOP-97825

Title: BACE1 cleavage site selection critical for amyloidogenesis

Authors: Z. WANG, S. ZHANG, F. CAI, M. ZHANG, Y. WU, *W. SONG
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Abstract: Mutations in amyloid β precursor protein (APP) gene alter APP processing, either causing familial Alzheimer's Disease (AD) or protecting against dementia. Under normal conditions beta-site APP cleaving enzyme 1 (BACE1) cleaves APP at minor Asp^{1} site to generate C99 for amyloid β protein (Aβ) production, and predominantly at major Glu^{11} site to generate C89, resulting in truncated Aβ production. We discovered that A673V mutation, the only recessive AD-associated APP mutation, shifted the preferential β-cleavage site of BACE1 in APP from the Glu^{11} site to the Asp^{1} site both *in vivo* and *in vitro*, resulting in a much higher C99 level and C99/C89 ratio. All other mutations at this site, including the protective Icelandic A673T mutation, reduced C99 generation and decreased the C99/C89 ratio. Furthermore, A673V mutation caused stronger dimerization between mutant and wildtype APP, enhanced the lysosomal degradation of the mutant APP and inhibited γ-secretase cleavage of the mutant C99 to generate Aβ, leading to recessively-inherited AD. The results demonstrate that APP673 regulates APP processing and the BACE1 cleavage site selection is critical for amyloidogenesis in AD pathogenesis, and implicate a pharmaceutical potential for targeting the APP673 site for AD drug development.

Disclosures: Z. Wang: None. **S. Zhang:** None. **F. Cai:** None. **M. Zhang:** None. **Y. Wu:** None. **W. Song:** None.

Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

Location: 152A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***544.10

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

Support: NIH 1DP3DK094292
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Program for Neurology Research and Discovery

Title: Metformin decreases APP protein level and phosphorylation through AMPK-mediated inhibition of the JNK signaling pathway

Authors: *B. KIM, C. BACKUS, E. L. FELDMAN
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Abstract: Alzheimer’s disease (AD) is the most common form of dementia and is expected to affect over 13.8 million people by 2050. In parallel, the prevalence of metabolic syndrome (MetS), including obesity and diabetes, among US adults aged 18 years or older has also risen by more than 35% in last 20 years. 29.1 million Americans had diabetes in 2012, and more than 2 in 3 adults were considered overweight or obese. Multiple studies report a strong connection between MetS AD. Therefore, anti-diabetic drugs have been proposed as a potential therapeutic treatment for AD. Metformin is the most widely prescribed anti-diabetic drug due to its safety and low cost. Because of its positive effect on glucose and fatty acid metabolism, metformin is expected to have a beneficial role in AD. However, reports are conflicting about the effect of metformin on AD. Depending on the cell type and treatment condition, metformin can increase or decrease amyloid beta (Aβ) production and tau phosphorylation, and also exacerbate or alleviate cognitive dysfunction in AD or diabetes/obesity animal models. Metformin exerts its anti-diabetic effect by activating AMP-activated protein kinase (AMPK), a key player in the regulation of the energy metabolism. In AD, the role of AMPK is also controversial, with reports suggesting both beneficial and detrimental effects on the progression of AD.
In this study, we examined the effect of AMPK activation on amyloid precursor protein (APP) in cortical neurons in order to address the efficacy and mechanisms of metformin in an AD model. Treatment of the HK-532 human cortical stem cell line or rat primary embryonic cortical neurons with metformin or the AMPK activator, AICAR, decreased APP protein levels and induced dephosphorylation of APP at threonine 668 (T668). When phosphorylated at T668, APP undergoes conformational changes that affect proteolytic cleavage and increase Aβ production. Along with decreasing Aβ in the culture supernatant, activation of AMPK decreased BACE, nicastrin, and secretase, and increased ADAM10. Furthermore, metformin or AICAR treatment resulted in the dephosphorylation of JNK. When the cells were treated with metformin or

AICAR along with the JNK inhibitor SP600125, there was almost a complete decrease of APP protein levels and phosphorylation. These results suggest that metformin alleviates AD pathology through AMPK activation-mediated inhibition of the JNK pathway.
This work was supported by the National Institutes of Health (1DP3DK094292, 1R24082841 to E.L.F.), and the Program for Neurology Research and Discovery (www.pnrd.umich.edu).

Disclosures: B. Kim: None. **C. Backus:** None. **E.L. Feldman:** None.

Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

Location: 152A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***544.11

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

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Title: Functional pruning of mitochondria by amyloid-beta: A hypothesized ameliorating action of amyloid-beta in hypoxia-associated neurodegenerative disease

Authors: *D. R. PEPPERBERG
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Abstract: The function of mitochondria, which are oxygen-requiring generators of metabolic energy (e.g., ATP) in brain tissues, is impeded by cerebral hypoperfusion and resulting oxygen insufficiency (hypoxia), a process thought to contribute to the development of sporadic Alzheimer's disease. Numerous studies have described impairing/inhibitory actions of amyloid-beta (Aβ) on mitochondria. However, there is also evidence that hypoxia, by upregulating HIF-1 and β-secretase (BACE), stimulates Aβ generation. Here I propose a hypothesis that seeks to resolve this apparent paradox. The central concept is that, in early-stage or otherwise mild hypoxia, Aβ ameliorates hypoxic burden by functionally impairing, i.e., "pruning", a portion of the mitochondrial population, thereby reducing the number of metabolic energy-generating mitochondria in the cell. The hypothesis derives from two key assumptions: (1) metabolic energy consumption by processes that support maintenance/function of a given mitochondrion is

essentially fixed and highly resistant to hypoxia-induced decreases in the mitochondrion's overall production of metabolic energy; and (2) Aβ-mediated impairment/pruning is a stochastic, all-or-none event that (reversibly or irreversibly) eliminates all energy production by the mitochondrion, including that which serves the intrinsic processes. These assumptions lead to a simple model in which both Aβ40 and Aβ42 (two principal Aβ forms), via the pruning action, ameliorate hypoxic burden by increasing metabolic energy that is exportable by remaining functional mitochondria for non-mitochondrial energy-dependent processes. This amelioration is hypothesized to operate in the context of other Aβ actions that are directly/indirectly toxic to cell components, and which establish a toxic positive feedback cycle (hypoxia ---> HIF-1↑ ---> BACE↑ ---> Aβ↑---> hypoxia↑). With prolonged hypoxia, these toxic actions ultimately overwhelm Aβ's ameliorating effect and lead to Aβ accumulation and cell deterioration/death. The present hypothesis accounts for multiple features of Aβ's association with sporadic Alzheimer's disease. It proposes a protective role for Aβ in the early-stage development of sporadic Alzheimer's, and perhaps also of other hypoxia-associated neurodegenerative diseases/disorders.

Disclosures: D.R. Pepperberg: None.

Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

Location: 152A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:30 PM

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

Support: PD/BD/105915/2014
NIH R01 NS056049

Title: Endolysosomal dysfunction in neurons produces exosomes enriched for APP C-terminal fragments and bioactive lipids

Authors: *A. M. MIRANDA[1], Z. M. LASIECKA[2], Y. XU[2], S. SHAHRIAR[2], R. B. CHAN[2], T. G. OLIVEIRA[3], G. DI PAOLO[2]
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Abstract: Growing evidence suggests that endolysosomal and autophagic defects are key pathological features of neurodegenerative disorders, including Alzheimer's disease (AD). Our recent lipidomic study showed a selective reduction in phosphatidylinositol-3-phosphate (PI3P) in the brain of patients with AD as well as in mouse models thereof. PI3P is synthesized

primarily by the lipid kinase Vps34 (also known as class III PI 3-kinase) and is a master regulator of endosomal and autophagy pathways. Our previous work has shown that mimicking the PI3P deficiency by silencing Vps34 in neurons caused endosomal enlargement in addition to aberrant trafficking and processing of amyloid precursor protein (APP), all of which are important pathological features of AD. However, it is still unclear how disrupting PI3P signaling impairs neuronal endosomal and lysosomal function and its relationship with altered APP metabolism. Here we show that pharmacological inhibition of Vps34 in primary neurons induces endosomal enlargement and accumulation of Rab5-positive APPL1 compartments. Vps34 inhibition also enhanced the levels of a variety of lipids known to accumulate as a result of endolysosomal dysfunction, namely dihydrosphingolipids. Additionally, PI3P depletion led to a blockade of autophagosome formation and a prominent accumulation of ubiquitin-positive structures which co-localize with markers of endolysosomal membrane damage. PI3P depletion also caused a profound alteration in APP metabolism. First, the rate of degradation of APP COOH-terminal fragments (CTFs) was dramatically diminished. Additionally, large amounts of APP-CTFs were released in lysobisphosphatidic acid- and sphingolipid-enriched exosomes in a neutral sphingomyelinase 2-dependent (but ESCRT-independent) fashion, suggesting that elimination of CTFs via the exosome pathway alleviates the cellular burden. We also found that genetic ablation of Vps34 in pyramidal neurons from postnatal forebrain phenocopies the observed endolysosomal dysfunction with protein and lipid accumulation, including APP-CTF misprocessing and exosomal release, prior to massive neurodegeneration. Our results therefore establish Vps34 as a critical regulator of the endolysosomal and autophagy pathways in neurons, controlling the metabolism of APP and late-endosomal/lysosomal lipids, and highlight the importance of exosomal release as a coping mechanism against endolysosomal stress.

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Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

Location: 152A

Time: * Tuesday, November 14, 2017, 1:00 PM - 4:30 PM

Presentation Number: * 544.13

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

Support: University of Manchester

Title: The effects of soluble amyloid precursor protein α (sAPPα), a non-amyloidogenic cleavage product of APP, at the synapse of human induced pluripotent stem cell-derived neurons

Authors: *N. J. CORBETT, A. C. JONES, H. A. ROWLAND, K. FISHER, N. M. HOOPER
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Abstract: The “amyloidogenic” processing of the amyloid precursor protein (APP) produces amyloid-β, which causes a range of detrimental effects in the neuron, such as synaptic loss, and plays a key role in Alzheimer’s disease. In contrast, “non-amyloidogenic” processing, which involves the cleavage of APP by α-secretase, produces soluble amyloid precursor protein α (sAPPα) that has neuroprotective effects. However, the exact mechanisms of action of sAPPα, and the identity of its cell-surface receptor(s), are yet to be fully elucidated. To study the effects of sAPPα on the structure, function and composition of synapses, cortical neurons derived from human induced-pluripotent stem cells (iPSCs) were treated with, or without, recombinant sAPPα. At 60 and 90 days after neural induction, neurons were analysed using immunohistochemistry, flow cytometry, immunoblotting and membrane potential assays. By day 60, deep layer cortical neurons were derived from healthy patient iPSCs and functional synapses were present along the neurites 90 days after neural induction. When sAPPα was administered, synaptogenesis occurred along the neurites of these cortical neurons. A range of molecular and histological techniques were used to understand how sAPPα is able to cause synaptogenesis. sAPPα was internalised within 10-30 minutes. To identify the receptors of sAPPα, isolation and pulldown experiments were performed followed by mass spectrometry and immunoblotting analysis. Particular attention was paid to APP itself, the neurotrophin receptor p75(NTR) and the sortilin-related receptor SORLA, as they have been previously suggested as receptors of sAPPα. All three receptors are known to be in the synapse; however, at day 60 p75(NTR) showed perisomatic localisation only, similar to that of synaptophysin, whilst both APP and SORLA showed staining throughout the neuron. These results suggest a role of sAPPα in synaptogenesis, potentially via the three identified receptors, and that this role is dependent on the age of the neuron. Synaptic pathology is an initial event in Alzheimer’s disease, and therefore, understanding the mechanisms of action of sAPPα at the synapse may highlight potential therapeutic strategies.

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Nanosymposium

544. Alzheimer's Disease: APP and Its Processing

Location: 152A

Time: * Tuesday, November 14, 2017, 1:00 PM - 4:30 PM

Presentation Number: * 544.14

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

Support: NIH/NINDS R01NS45860 to D.M.K/R.E.T.

Title: Palmitoylated app forms dimers, cleaved by bace

Authors: *R. BHATTACHARYYA[1], R. H. FENN[2], R. E. TANZI[3], D. M. KOVACS[4]
[1]Neurobio. of Dis. Laboratory, Genet. and Aging Unit, Massachusetts Gen. Hosp., Charlestown, MA; [2]Genet. and Aging Res. Unit, Massachusetts Gen. Hosp., Boston, MA; [3]Massachusetts Gen Hosp, Harvard Med. Sch., Charlestown, MA; [4]Neurobio. of Dis. Lab. / Genet. and Aging Res. Unit / MIND / Neurol., Massachusetts Gen. Hosp. / Harvard Med. Sch., Charlestown, MA

Abstract: A major rate-limiting step for Aβ generation and deposition in Alzheimer's disease brains is BACE1-mediated cleavage (β-cleavage) of the amyloid precursor protein (APP). We previously reported that APP undergoes palmitoylation at two cysteine residues (Cys^{186} and Cys^{187}) in the E1-ectodomain. 8-10% of total APP is palmitoylated *in vitro* and *in vivo*. Palmitoylated APP (*pal*APP) shows greater preference for β-cleavage than total APP in detergent resistant lipid rafts. Protein palmitoylation is known to promote protein dimerization. Since dimerization of APP at its E1-ectodomain results in elevated BACE1-mediated cleavage of APP, we have now investigated whether palmitoylation of APP affects its dimerization and whether this leads to elevated β-cleavage of the protein. Here we report that over 90% of *pal*APP is dimerized while only ~20% of total APP forms dimers. *Pal*APP-dimers are predominantly *cis*-oriented while total APP dimerizes in both *cis*- and *trans*-orientation. *Pal*APP forms dimers 4.5-times more efficiently than total APP. Increasing *pal*APP levels increased APP dimerization in cells. Conversely, inhibition of APP palmitoylation by pharmacological inhibitors reduced APP-dimerization in coimmunoprecipitation and FLIM/FRET assays. Finally, *in vitro* BACE1-activity assays demonstrate that palmitoylation-dependent dimerization of APP promotes β-cleavage of APP in lipid-rich detergent resistant cell membranes (DRMs), when compared to total APP. Most importantly, generation of $sAPP_{\beta}$-$sAPP_{\beta}$ dimers is dependent on APP-palmitoylation while total $sAPP_{\beta}$ generation is not. Since BACE1 shows preference for *pal*APP dimers over total APP, *pal*APP dimers may serve as novel targets for effective β-cleavage inhibitors of APP as opposed to BACE1 inhibitors.

Disclosures: R. Bhattacharyya: None. **R.H. Fenn:** None. **R.E. Tanzi:** None. **D.M. Kovacs:** None.

Nanosymposium

545. Synaptic Signaling Deficits in Alzheimer's Disease II

Location: 144A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***545.01

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

Title: Computational approaches to untangling networks of dementia

Authors: *E. L. OHAYON[1], A. LAM[3,2]
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[3]Physicians Committee For Responsible Med., Washington, DC

Abstract: Using large-scale spatial computational network models of aging we illustrated over a decade ago how changes to network geometry through cell loss could fundamentally change the activity dynamics of a network even if the properties of the surviving cells remained constant. Although there has been a substantial increase in interest in network mechanisms of aging as well as extensive work showing the role networks can play in dementia, the full importance of network geometry as a potential proximate cause -- not just a symptom of cellular degeneration -- has not been fully appreciated. In this presentation we revisit the original work and extend it to encompass embodied computational models. Large-scale neural network simulations (100,000 cells) with variable spatial features (e.g., density, heterogeneity, excitatory-inhibitory balance) were connected to an external chassis (robot) resulting in spontaneous activity ranging from seizure-like oscillations (reminiscent of the increases in epilepsy incidents reported in aging) to functional behavioral movement. We demonstrate how such computational findings may be extended to help guide other forms of human-based research ranging from iPSC cultures to human clinical studies, while also raising ethical concerns and the need for boundaries. Moreover, we demonstrate how such research can help highlight: [1] the importance of searching beyond the molecular mechanisms of Alzheimer's disease and related dementias (ADRD) [2] how the embodied aspects of network activity connect to the widely recognized cognitive and social dimensions of ADRD [3] how such research may go beyond aging and neurodegeneration to fold back into insights regarding the role spatial network structure may play in dynamical tuning during healthy brain development.

Disclosures: E.L. Ohayon: None. **A. Lam:** None.

Nanosymposium

545. Synaptic Signaling Deficits in Alzheimer's Disease II

Location: 144A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***545.02

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

Support: NIH NINDS R21NS084328
NIH NIA K01AG0479
Alzheimer's Association 2016-NIRG-397279
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Title: Identifying regulators of lipid dyshomeostasis for mitigation of A-β triggered synapse loss

Authors: *L. B. MCINTIRE[1], S. PAMPOU[2], C. KARAN[2], T.-W. KIM[1]
[1]Pathology and Cell Biology, Taub Inst. for Res. on Alzheimer's Dis., [2]Columbia Univ., New York, NY

Abstract: Synapse loss is better correlated to cognitive impairment than amyloid plaque load or tangle pathology. In animal models, behavioral deficits precede plaque accumulation suggesting the importance of soluble amyloid β-peptide (Aβ) species. Aβ oligomers have been shown to lead to synaptic loss and synaptic impairment including electrophysiological responses, receptor trafficking, spine morphology, and behavior. The loss of post-synaptic proteins, including Post-Synaptic Protein-95 (PSD-95), AMPAR and NMDAR has been shown in neurons treated with Aβ oligomer and animal models of AD. Phosphoinositides (PI) have immerged as a critical class of phospholipids which play a role in AD, mediating neuronal function, receptor trafficking and synaptic loss. Work from our lab and others confirms the depletion of PI levels in human AD brain and plasma suggesting a role in pathogenesis of the disease. Phosphatidylinositol 4,5-bisphosphate [PI(4,5)P_2] is a critical PI, key for neuronal function and cell signaling. We found that PI(4,5)P_2 is reduced in response to Aβ42 oligomer treatment and in a synapse enriched fraction from brains of a mouse model of AD. The genetic disruption of a PI(4,5)P_2 phosphatase, Synaptojanin 1 (Synj1) resulting in maintenance of PI(4,5)P_2 levels ameliorated Aβ-triggered synaptic defects and AD associated behavioral phenotypes in a mouse model of the disease. Synj1 has been shown to play an important role in endocytosis, actin destabilization and membrane fission. Critically, Synj1 could be acting downstream of Aβ and upsteam of receptor trafficking since AMPAR and NMDAR trafficking have been shown to depend on PI(4,5)P_2 metabolism. As a strategy to probe cellular mechanisms underlying PI mediated synapse loss triggered by Aβ oligomers, we screened for PI modifying enzymes, regulatory factors and functional binding partners which can prevent Aβ oligomer induced synapse loss. We developed an assay to detect synapse loss in mouse embryonic stem cell derived neurons (ESN) a scalable and physiological neuronal model amenable to mid to high throughput platforms. These neurons display prominent loss of post-synaptic protein 95 (PDS-95) after treatment with Aβ. We established and miniaturized an assay to detect synapse loss triggered by Aβ. Using RNA interference to screen, candidate components of the PI metabolic pathway were probed for their contribution to synapse maintenance in spite of Aβ. We expect that this approach will be able to identify novel targets for amelioration of Aβ-triggered synaptic loss. These studies will identify PI dependent cellular pathways underlying Aβ-triggered deficits and may identify novel therapeutic targets.

Disclosures: L.B. McIntire: None. **S. Pampou:** None. **C. Karan:** None. **T. Kim:** None.

Nanosymposium

545. Synaptic Signaling Deficits in Alzheimer's Disease II

Location: 144A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***545.03

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

Support: BrightFocus Foundation Award A2012624

Title: Increasing the frequency of slow cortical oscillations exacerbates the neuropathophysiology of Alzheimer’s disease

Authors: *K. KASTANENKA, M. CALVO RODRIGUEZ, S. TAKEDA, M. ARBEL, A. KIM, J. M. HAWKES, R. LOGAN, D. FENG, X. CHEN, B. J. BACSKAI
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Abstract: Neuronal activity patterns are disrupted in neurodegenerative disorders, including Alzheimer’s disease (AD). One example is disruption of corticothalamic slow oscillations important for consolidation of memories during sleep. Slow waves are periodic oscillations in neuronal activity occurring at a frequency of <1Hz. We have recently reported that the power, but not the frequency of slow waves is downregulated in APP mice. Optogenetic rescue of slow oscillations by increasing activity in cortical pyramidal neurons at the frequency of slow waves resulted in restoration of slow wave power, halted amyloid plaque deposition and prevented neuronal calcium dysregulation associated with this pathology. Based on these results, we hypothesized that driving this circuit at an increased rate would exacerbate the activity dependent progression of amyloid deposition and calcium overload. We used light activation of Channelrhodopsin-2 (ChR2) at twice the normal frequency of slow oscillations in the cortex of an animal model of AD (APPswe:PS1dE9 mice). We used in vivo microdialysis to measure levels of soluble amyloid beta acutely in interstitial fluid of these mice in real time both prior to as well as during the treatment and detected activity dependent increases in soluble Abeta. Additionally, we performed in vivo multiphoton imaging of amyloid plaques and calcium levels using neuronally expressed YC3.6 in a chronic treatment paradigm. Increasing the frequency of slow waves by a factor of two for 1 month resulted in increased amyloid production, increased amyloid plaque deposition, disruptions in neuronal calcium homeostasis, and loss of synaptic spines. Therefore, while restoration of physiological circuit dynamics is sufficient to abrogate the progression of Alzheimer's disease pathology and should be considered an avenue for clinical treatment of patients with sleep disorders, pathophysiological stimulation of neuronal circuits leads to activity dependent acceleration of amyloid production, aggregation and downstream neuronal dysfunction.

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Nanosymposium

545. Synaptic Signaling Deficits in Alzheimer's Disease II

Location: 144A

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Title: Suppression of eukaryotic elongation factor 2 phosphorylation alleviates memory and synaptic plasticity defects in a mouse model of Alzheimer's disease

Authors: ***B. C. BECKELMAN**[1], W. YANG[3], X. ZHOU[4], T. MA[2]
[1]Neurosci. Grad. Program, [2]Intrnl. Medicine-Geriatrics, Wake Forest Sch. of Med., Winston Salem, NC; [3]Intrnl. Medicine-Geriatrics, Wake Forest Baptist Med. Ctr., Winston Salem, NC; [4]Intrnl. Medicine-Geriatrics, Wake Forest Baptist Med. Ctr., Winston-Salem, NC

Abstract: Alzheimer’s disease (AD) is characterized by memory loss and synaptic plasticity deficits. Both long-term forms of memory and synaptic plasticity require *de novo* protein synthesis, and accumulating evidence suggests a link between mRNA translation defects and cognitive impairments in neurodegenerative diseases such as AD. We and others have recently demonstrated that phosphorylation of eukaryotic elongation factor 2 (eEF2) is upregulated in the brains of AD model mice and *post mortem* human AD patients. Phosphorylation of eEF2 by its only known kinase, eEF2 kinase (eEF2K), blocks eEF2 activity and suppresses general protein synthesis. Previously, we showed that beta-amyloid (Aβ)-induced hippocampal long-term potentiation (LTP) failure is improved by NH125, a small molecule inhibitor of eEF2K. In the current study, we use a genetic approach to knockdown eEF2K in Tg19959 AD model mice and investigate whether AD-associated impairments of memory and synaptic plasticity can be mitigated by eEF2K suppression. Heterozygous eEF2K knockdown mice (eEF2K+/-) were crossed with the Tg19959 AD mouse model to generate wildtype, Tg19959, eEF2K+/-, and Tg19959/eEF2K+/- littermates. Genetic reduction of eEF2K rescued impairments of hippocampal-dependent memory in Tg19959 mice. Correspondingly, eEF2K knockdown alleviated AD-associated hippocampal LTP failure. Further, dysregulations of synaptic proteins

in AD, including decreased CAMKII phosphorylation and reduced levels of GluA1 AMPARs were restored in Tg19959/eEF2K+/- mice. Finally, Golgi-Cox analysis revealed increased spine density in Tg19959/eEF2K+/- CA1 neurons. Our findings indicate that suppression of eEF2K/eEF2 phosphorylation may be an effective therapeutic intervention for AD pathophysiology.

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Nanosymposium

545. Synaptic Signaling Deficits in Alzheimer's Disease II

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Time: *Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

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

Support: NIH Grant NS37853 (C.I.)
AG051179 (M.I.)
BrightFocus Foundation (M.I.)

Title: Distinct biophysical and pharmacological properties of voltage-gated L-type Ca^{2+} currents in the hypothalamic neurons of wild-type and amyloid precursor protein overexpressing mice

Authors: ***G. WANG**, M. ISHII, L. PHAM, C. IADECOLA
Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: Disruption of calcium (Ca^{2+}) homeostasis is one of the major mechanisms by which amyloid-beta (Aβ) alters neuronal function (*Cell* 2012, 148: 1204). We previously reported that L-type Ca^{2+} currents (I_{Ca}) in hypothalamic arcuate (ARC) neuropeptide Y (NPY) neurons in slices from Tg2576 mice overexpressing amyloid precursor protein (APP) displayed left-shifted current-voltage (I/V) relationship curves compared to WT ARC NPY neurons, suggesting that L-type I_{Ca} in ARC NPY neurons from APP slices had a propensity to be activated at more hyperpolarized membrane potentials than those from wild-type (WT) slices (*SfN* 2016). However, whether L-type I_{Ca} in other hypothalamic neuronal populations also have such a propensity and how Ca^{2+} dyshomeostasis affects L-type I_{Ca} in APP ARC NPY neurons remain elusive. In this study, using whole-cell voltage-clamp and 5mM Ba^{2+} as the charge carrier, we first examined the I/V curves of L-type I_{Ca} in unlabeled neurons from the paraventricular nucleus (PVN) of the hypothalamus in WT and APP slices. Although the I/V curves of L-type I_{Ca} in APP ARC GFP-NPY neurons were left-shifted (the potential reaching peak currents: WT at 0 mV, APP at -20 mV, $P<0.05$, n=20-27), there was no shift in the I/V curves of L-type I_{Ca} in APP PVN neurons (the potential reaching peak currents: WT at 0 mV, APP at 0 mV, $P>0.05$, n=6).

Pharmacologically, the left-shifted I/V curves of L-type I_{Ca} in APP ARC NPY neurons were partially reversed by the CaMKII inhibitor KN93 (10 µM) [vehicle (Veh): -31.1±5.2pA /pF, KN93: -48.6.6±7.6pA/pF at -10mV; P<0.05, N=7] and the IP_3 inhibitor 2APB (50 µM) (Veh: -99.8±18.4pA/pF, 2APB: -59.6±7.7pA/pF at -20 mV; P<0.05, N=4). However, both KN93 and 2APB had no effects on I/V curves of I_{Ca} in WT ARC NPY neurons or in PVN neurons from WT or APP slices (P>0.05, N=4-5). The selective L-type Ca^{2+} channel blocker nimodipine (NMD, 2µM) fully inhibited L-type I_{Ca} in WT ARC NPY neurons (Veh: -98.4±10.3pA/pF, NMD: 0.22±4.5pA/pF; P<0.01, N=8) but only partially inhibited I_{Ca} in APP ARC NPY neurons (Veh: -72.5±16.5pA/pF, NMD: -16.7±6.3pA/pF; P<0.05, n=6). NMD (2µM) also partially inhibited L-type I_{Ca} in WT and APP PVN neurons (P<0.05, n=6). We conclude that APP overexpression can specifically disrupt the intracellular Ca^{2+} homeostasis in ARC NPY neurons by activating voltage-gated L-type Ca^{2+} influx at hyperpolarized membrane potentials via CaMKII and IP_3-dependent mechanisms, an effect that was not seen in PVN neurons. The data are consistent with the hypothesis that Ca^{2+} dyshomeostasis underlies the mechanisms leading to early weight loss and hypothalamic dysfunction seen in Alzheimer's disease (*Cell Metabolism* 2015, 22, 761).

Disclosures: G. Wang: None. **M. Ishii:** None. **L. Pham:** None. **C. Iadecola:** None.

Nanosymposium

545. Synaptic Signaling Deficits in Alzheimer's Disease II

Location: 144A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***545.06

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

Support: NIH-CA111891
CA165202
The Harriet and John Wooten Foundation for Alzheimer's and Neurodegenerative Diseases Research

Title: Re-evaluating Rho GTPase signaling as a potential therapeutic target for Alzheimer's disease

Authors: *Y. ZHU[1], B. AGUILAR[1], C. BOYKIN[1], T. TRAN[2], Q. LU[1]
[1]Anat. and Cell Biol., Brody Sch. Of Med., Greenville, NC; [2]Psychology, East Carolina Univ., Greenville, NC

Abstract: Deterioration of synaptic plasticity and neural connections play a crucial role in the development of Alzheimer's disease (AD). Therefore, interventions that help balance architectural changes of dendritic spines may be key to impeding AD progression. It is known

that small GTPases of the Rho family (RhoA, Rac1 and Cdc42) control the dynamic cytoskeletal reorganization of dendritic spines. The aberrant activity of Rho GTPases has been implicated in a variety of neural disorders and neurotraumas but their contribution to AD pathogenesis is of debate. Due to the complexity of Rho GTPase signaling, it is important to investigate the interaction and activity between each member of this family at different stages of AD progression. Based on the immunohistochemical analysis, we showed that Rho GTPase activity was altered in the brain of AD patients as well as in the triple-transgenic (3xTg-AD) AD mouse model. We then examined the effects of ZCL compounds known to modulate Rho GTPases, in altering behavioral and cognitive outcomes using 3xTg-AD mice. Our data indicate that species-typical behaviors, such as burrowing and nesting, are severely impaired in the 3xTg-AD mice. However, ZCL compounds were shown to significantly improve the performance of species-typical behaviors, which are parallels to human activities of daily living (ADL). Additionally, agitated or aggressive responses to the handlers, which were often observed in the 3xTg-AD mice, were also attenuated by the ZCL compounds treatment. Cognitive performance, as assessed by spatial learning in the Morris water maze and associative learning in trace eyeblink classical conditioning, further confirmed the beneficial effects of ZCL compounds in facilitating learning and memory in 3xTg-AD mice, thus emphasizing the critical role of Rho GTPases in enhancing cognitive function. Modulating Rho GTPase signaling can improve the performance of species-typical behaviors and preserve learning and memory function in the 3xTg-AD mice. These studies highlight the potential of selective Rho GTPase activity as therapeutic targets in future drug development endeavors.

Disclosures: Y. Zhu: None. **B. Aguilar:** None. **C. Boykin:** None. **T. Tran:** None. **Q. Lu:** None.

Nanosymposium

545. Synaptic Signaling Deficits in Alzheimer's Disease II

Location: 144A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***545.07

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

Support: BrightFocus Foundation Postdoctoral Fellowship A2016360F

Title: Deficient postsynaptic KIBRA signaling underlies tau-mediated synaptic dysfunction and memory loss

Authors: *T. E. TRACY[1,2], Y. LI[1], D. LE[1], Y. ZHOU[1], L. GAN[1,2]
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Abstract: Tau accumulation in the brain coincides with synapse loss and cognitive decline in tauopathies such as Alzheimer's disease (AD). Pathogenic tau triggers synaptic dysfunction underlying memory deficits in mouse models of tauopathy. How tau disrupts the postsynaptic signaling mechanisms that regulate synaptic strength is unclear. Pathogenic acetylated tau obstructs long-term potentiation (LTP) at hippocampal synapses by reducing postsynaptic levels of KIBRA (KIdney/BRAin protein). However, the molecular mechanisms that link KIBRA downregulation with synaptic dysfunction and memory loss in AD is unknown. To examine the impact of KIBRA deficiency on cognition in mice with increased tau levels, we crossed transgenic mice expressing wild-type human tau (tauWT) with heterozygous KIBRA mice. We found that tauWT mice with reduced KIBRA levels had impaired spatial memory, suggesting that KIBRA deficiency exacerbates tau-mediated cognitive decline. Overexpression of KIBRA in neurons with pathogenic tau rescued LTP by restoring postsynaptic actin polymerization and AMPA-type glutamate receptor (AMPAR) trafficking. KIBRA has several functionally distinct protein interaction domains that modulate specific protein complexes important for neuronal function. KIBRA could modulate LTP through its interactions with AMPAR-regulating complexes, actin cytoskeletal networks, or kinase signaling pathways. Interestingly, expression of the C-terminal domain of KIBRA was sufficient to rescue the tau-induced LTP deficit. These findings suggest that tau promotes memory loss by inhibiting postsynaptic signaling in synaptic plasticity that requires the C-terminal domain of KIBRA.

Disclosures: **T.E. Tracy:** None. **Y. Li:** None. **D. Le:** None. **Y. Zhou:** None. **L. Gan:** None.

Nanosymposium

545. Synaptic Signaling Deficits in Alzheimer's Disease II

Location: 144A

Time: *Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

Presentation Number: *545.08

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

Support: Munich Cluster for Systems Neurology (SyNergy)
Alzheimer Forschung Initiative
ERC
EU FP7 program
Deutsche Forschungsgemeinschaft IRTG 1373
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Title: BACE inhibition rescues neural circuit impairments in a mouse model of Alzheimer´s disease

Authors: *M. A. BUSCHE[1,2], A. KESKIN[2], M. KEKUS[2], H. ADELSBERGER[2], U. NEUMANN[4], D. SHIMSHEK[4], B. SONG[2], B. ZOTT[2], T. PENG[5], H. FÖRSTL[3], M. STAUFENBIEL[6], I. NELKEN[7], B. SAKMANN[2], A. KONNERTH[2]
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Abstract: Abnormal accumulation of amyloid-β (Aβ) proteins in the brain contributes to the development of Alzheimer´s disease (AD). A key enzyme involved in the generation of Aβ is the β-secretase BACE for which powerful inhibitors, already used in human clinical trials, have recently been developed. While it has been shown that BACE inhibition can reduce cerebral Aβ levels, it is unknown whether it can also block neural circuit and memory impairments. Here we employed in vivo calcium fluorescence imaging for an in depth analysis of an AD mouse model. We demonstrate that in addition to reducing Aß-burden, the BACE inhibition rescues neuronal hyperactivity (fraction of hyperactive neurons = 50.60 ± 9.53 % in control group vs. 11.15 ± 4.62 % in treatment group, $P = 0.0002$), impaired long-range circuit function (fronto-occipital correlation coefficient = 0.29 ± 0.05 in control group vs. 0.53 ± 0.06 in treatment group, $P = 0.0005$) and spatial memory deficits (discriminatory water maze; treatment group vs. control group: $t(358)=2.35$, $P = 0.0193$, permutation test $P = 0.004$). We found that the functional neuronal impairments re-appeared after infusion of soluble Aβ. Our findings provide experimental evidence that these AD-related neuronal alterations depend on Aβ and highlight the benefits of BACE inhibition for the effective treatment of AD-related pathophysiological and cognitive impairments.

Disclosures: **M.A. Busche:** None. **A. Keskin:** None. **M. Kekus:** None. **H. Adelsberger:** None. **U. Neumann:** A. Employment/Salary (full or part-time):; Novartis. **D. Shimshek:** A. Employment/Salary (full or part-time):; Novartis. **B. Song:** None. **B. Zott:** None. **T. Peng:** None. **H. Förstl:** None. **M. Staufenbiel:** A. Employment/Salary (full or part-time):; Novartis. **I. Nelken:** None. **B. Sakmann:** None. **A. Konnerth:** None.

Nanosymposium

545. Synaptic Signaling Deficits in Alzheimer's Disease II

Location: 144A

Time: *Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

Presentation Number: *545.09

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

Support: Academy of Finland
Sigrid Jusélius Foundation

Title: Elucidating the role of Methyl-CpG-binding protein 2 in Alzheimer's disease-related synaptic dysfunction

Authors: *M. A. TAKALO[1], M. MARTTINEN[1], T. NATUNEN[1], K. PALDANIUS[1], A. HAAPASALO[2], M. HILTUNEN[3]
[1]Inst. of Biomedicine, [2]A.I. Virtanen Inst. for Mol. Sci., [3]Univ. of Eastern Finland, Kuopio, Finland

Abstract: Cognitive impairment and synaptic dysfunction in Alzheimer's disease (AD) are strongly correlated with structural changes in post-synaptic dendritic spines. Dysfunction of Methyl CpG-binding protein 2 (MeCP2) leads to synaptic defects in various neurodevelopmental disorders. Expression of several genes involved in structural and functional synaptic plasticity is under regulation of MeCP2. Recently, it has been shown to contribute in tau-related changes as well as synaptic dysfunction upon amyloid-B peptide (AB) -induced neuroinflammation, suggesting that MeCP2 plays a role in AD pathogenesis.Here, we used global transcriptomic, proteomic, and phosphoproteomic data obtained from post-mortem human temporal cortical samples to assess AD-related changes in MeCP2 with respect to advancing neurofibrillary pathology (Braak stages 0-VI). While multiple comparison of Braak stages 0-VI did not reveal changes in MeCP2 mRNA or protein levels, we found significant alterations in activity-dependent phosphorylation of MeCP2 in early stages of AD. These changes correlated with the mRNA expression of BDNF, a gene known to be regulated by MeCP2, highlighting the significance of MeCP2 in synaptic regulation. In preliminary mechanistic examinations, the overexpression of wild-type MeCP2 in mature mouse primary hippocampal neurons was found to cause morphological changes in the dendritic spines. We have established a novel in vitro co-culture model of hippocampal neurons and microglial cells, in which lipopolysaccharide (LPS) and interferon- Γ (IFN- Γ) -induced neuroinflammation leads to a robust increase in the production of tumor necrosis factor A (TNF A) and nitric oxide (NO) and a significant reduction in the density and spine head size of the functionally strong mushroom spines. These effects were rescued by pre-treating the cultures with inducible NO-synthase inhibitor. Further mechanistic studies using this model are undergoing to address the role of MeCP2 phosphorylation changes in synaptic structural plasticity, neuronal viability, neuroinflammation, and MeCP2 downstream signaling.In line with previous reports, our preliminary findings highlight the importance of MeCP2 in the synaptic regulation and further suggest a potential role for MeCP2 in early-stage synaptic dysfunction of AD. Therefore, a comprehensive characterization of MeCP2-related synaptic mechanisms may provide insights into the early stages of AD pathophysiology.

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Nanosymposium

545. Synaptic Signaling Deficits in Alzheimer's Disease II

Location: 144A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***545.10

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

Support: BBSRC
ARUK
Alzheimer's Society
MRC
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MNDA

Title: Axonal transport of Cdk5/p35 is mediated by a lemur tyrosine kinase2-Kinesin1 complex

Authors: *G. M. MOROTZ, E. SEDLAK, A. VAGNONI, W. NOBLE, C. C. J. MILLER
Dept. of Basic and Clin. Neurosci., King's Col. London, IoPPN, London, United Kingdom

Abstract: Cyclin dependent kinase 5 (Cdk5) and its activator subunit p35 are strongly linked to Alzheimer’s disease and related dementias. Cdk5/p35 regulate a variety of physiological processes within the synapse and defects in this regulation may contribute to the neurodegenerative process. Within neuronal cell bodies Cdk5/p35 localises to Golgi but despite the fundamental importance of Cdk5/p35 to synaptic function, the mechanisms by which it is transported through axons and delivered to synapses are not known. Lemur tyrosine kinase-2 (LMTK2) is a member of the membrane anchored lemur kinase family and has been shown to be a direct binding partner for Cdk5/p35. LMTK2 specifically interacts with p35. Here, we show that LMTK2 mediates axonal transport of Cdk5/p35 on Kinesin-1 molecular motors. Kinesin-1 is a major microtubule-associated molecular motor protein that mediates axonal transport of a large number of cargoes in neurons. Most functional Kinesin-1 is a hetero-tetramer consisting of two Kinesin-1 heavy chains motors and two Kinesin-1 light chains (KLCs); KLCs are involved in cargo binding.
We demonstrate that in neurons, Cdk5/p35 is complexed with Kinesin-1/KLCs via LMTK2. Moreover, we demonstrate that LMTK2 is transported through axons on Kinesin-1 motors and that siRNA loss of LMTK2 or KLCs disrupts axonal transport of Cdk5/p35. Finally, we show that siRNA knockdown of LMTK2 disrupts Cdk5/p35 mediated synaptic vesicle endo/exocytosis. Thus, LMTK2 is required for delivery of Cdk5/p35 to synapses via anterograde axonal transport. Interestingly, recent genome-wide gene expression analyses have identified reduced levels of LMTK2 as one of the major changes in transgenic mouse models of Alzheimer’s disease. Loss of LMTK2 may therefore contribute to synaptic dysfunction in dementia via disruption to axonal transport of Cdk5/p35.

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Nanosymposium

545. Synaptic Signaling Deficits in Alzheimer's Disease II

Location: 144A

Time: *Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

Presentation Number: *545.11

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

Title: TMS, a useful biomarker for detecting functional decline in the early staged dementia

Authors: ***T. MURAKAMI**[1], Y. UGAWA[2,3]
[2]Neurol., [3]Advanced Clin. Res. Center, Fukushima Global Med. Sci. Ctr., [1]Fukushima Med. Univ., Fukushima, Japan

Abstract: Introduction: Long-term potentiation (LTP) synaptic plasticity plays a key role in memory formation and learning new skills. Accumulation of amyloid-beta protein (Aβ) in the brain causes the impairment of LTP, triggering dementia in Alzheimer's disease (AD). Aβ deposition begins in the preclinical stage; about 10-15 years prior to the onset of cognitive decline. Currently, amyloid imaging using positron emission tomography and measurements of Aβ in cerebrospinal fluids (CSF) are known as the most reliable biomarker for diagnosing early and preclinical staged dementia. However, such tests simply reflect amyloid pathology but not neural function. The aim of this study is to investigate the utility of cortical synaptic plasticity examination using non-invasive transcranial magnetic quadripulse stimulation (QPS) for the diagnosis of early staged dementia. Methods: Eight patients with dementia; 3 early AD and 5 amnesic mild cognitive impairment (aMCI), and 6 age-matched subjects with normal cognition (NC) participated in this study. We sampled CSF and measured Aβ40, Aβ42 and total Tau proteins. Facilitatory QPS was performed over the left primary motor cortex (M1) hand area. Single-pulse transcranial magnetic stimulation (TMS) was applied over the left M1 hand area and motor evoked potentials (MEPs) were recorded from the right first dorsal interosseous muscle before and after QPS every 10 min for 1 hour. Short-latency afferent inhibition (SAI) was also measured in each group. Results: Aβ-ratio (Aβ40/Aβ42) in CSF were significantly higher in patients with early AD than in subjects with NC. Patients with aMCI had moderate increases of Aβ-ratio. QPS failed to induce LTP-like synaptic plasticity in early AD and aMCI patients, while it induced normal LTP in subjects with NC. The magnitude of QPS-induced LTP-like plasticity correlated negatively with Aβ-ratio. SAI revealed no significant difference among three groups. Discussion: QPS can detect abnormal synaptic plasticity even in patients with mild cognitive decline or preclinical staged dementia. Impairment of LTP-like plasticity can be explained by

accumulation of Aβ. The synaptic plasticity evaluation using TMS may be a useful biomarker for detection of functional decline in early staged dementia.

Disclosures: **T. Murakami:** None. **Y. Ugawa:** None.

Nanosymposium

546. Models, Mechanisms, and Modifiers of Amyotrophic Lateral Sclerosis (ALS)

Location: 146C

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 2:30 PM

**Presentation Number: ***546.01

**Topic: ***C.05. Neuromuscular Diseases

Support: Target ALS

Title: Insights into MEA recordings of iPS cells in ALS patients

Authors: *J. KOH, D. MOAKLEY, E. BEREZOVSKI, A. DEVLIN, J. PEREIRA, B. WAINGER
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Abstract: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and fatal motor neuron degenerative disease. ALS is characterized by clinical symptoms of lower motor neuron dysfunction including muscle wasting, weakness and fasciculations as well as upper motor neuron dysfunction including spasticity and hyperreflexia. 10% of ALS is due to familial and due to single-gene mutations, whereas the vast majority of ALS is apparently sporadic. Induced pluripotent stem cell (iPSC) -derived motor neurons from ALS patients have been used for disease modeling.
Abnormal intrinsic hyperexcitability has been shown in ALS iPS cells, and mirrors clinical hyperexcitability shown in ALS patients using transcranial magnetic stimulation and threshold tracking nerve conduction studies. However, after many weeks in culture, ALS iPSC neuronal hyperexcitability was followed by hypoexcitability. In order to address this change in more depth, we used multielectrode array (MEA), in which neurons are cultured and recorded on grids of extracellular electrodes, thus enabling long-term longitudinal recording. We record diverse features including firing rate and network properties. While MEA is useful for capturing large scale recordings of neurons, confounding factors of the MEA, such as electrodes that show no activity or variability in the number of neurons recorded by each electrode, exist and may distort measurements of the recordings using simple metrics. Here, we cluster spike morphology to estimate the firing properties of individual motor neuron units and apply this tool in order to examine the longitudinal firing pattern of ALS iPSC-derived neurons.

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Nanosymposium

546. Models, Mechanisms, and Modifiers of Amyotrophic Lateral Sclerosis (ALS)

Location: 146C

Time: *Tuesday, November 14, 2017, 1:00 PM - 2:30 PM

Presentation Number: *546.02

Topic: *C.05. Neuromuscular Diseases

Support: ALS Finding a Cure Grant 5290189

Title: Properties of motor neurons in spinal cord from TDP-43 Q331K knock-in mouse model of ALS

Authors: ***J. P. WHITT**[1], A. M. DUFFY[1], J. SREEDHARAN[4], J. R. FALLON[2], R. H. BROWN[5], D. LIPSCOMBE[3]
[1]Neurosci., [2]Dept Neurosci, [3]Brown Univ., Providence, RI; [4]Babraham Inst., Cambridge, United Kingdom; [5]Neurol., Univ. of Massachusetts Sch. of Med., Worcester, MA

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive and usually fatal neurodegenerative disease that, in late stages, is characterized by degeneration and ultimately death of motor neurons. It is critical to understand the mechanistic basis of ALS to inform new treatment strategies, and to identify the origin of disease initiation to prevent it progression. There is evidence that altered electrophysiolgical properties of motor neurons precede the behavioral phenotypes of neurodegeneration in both vertebrate and invertebrate ALS models, and a subset of fast-firing motor neurons, that may innervate fast twitch type IIb muscle fibers, are lost in mouse models of ALS. We used the TDP-43 Q331K homozygote knock-in mouse model to compare the properties of identified motor neurons in acute spinal cord slices using whole cell patch clamp recording methods. The mice exhibit locomotor defects at 3 months of age. Therefore, we optimized our protocols to successfully record from spinal cord slices from 2- and 6-month-old mice that were pre- and post-symptomatic. To visualize neurons innervating either fast or slow twitch muscles, we inject a 2% (w/v) solution of Evans Blue Dye (EVB) into either the tibialis anterior (TA), ~90% fast twitch (type II) muscle fibers, or soleus muscle, ~50% slow twitch (type I) muscle fibers similar to the approach used by Hadzipasic et al., 2014. By this method, within 24 hours post injection, we labeled ~ 25% of motor neurons in each lumbar section of the spinal cord. We successfully recorded from identified motor neurons in spinal cord slices (300 um) from 2 and 6 month animals. We analyzed a total of 11 passive and active electrophysiological properties and spontaneous synaptic events in motor neurons. Using these data, we will perform cluster analysis to determine if there are changes in excitability of motor

neurons, if these changes are specific to neurons that innervate particular muscle type, and if they are due to intrinsic or extrinsic mechanisms. By combining behavioral and electrophysiological analyses, we will form a comprehensive definition regarding the time course and pathophysiology of motor neuron dysfunction in this ALS mouse model.

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Nanosymposium

546. Models, Mechanisms, and Modifiers of Amyotrophic Lateral Sclerosis (ALS)

Location: 146C

Time: *Tuesday, November 14, 2017, 1:00 PM - 2:30 PM

Presentation Number: *546.03

Topic: *C.05. Neuromuscular Diseases

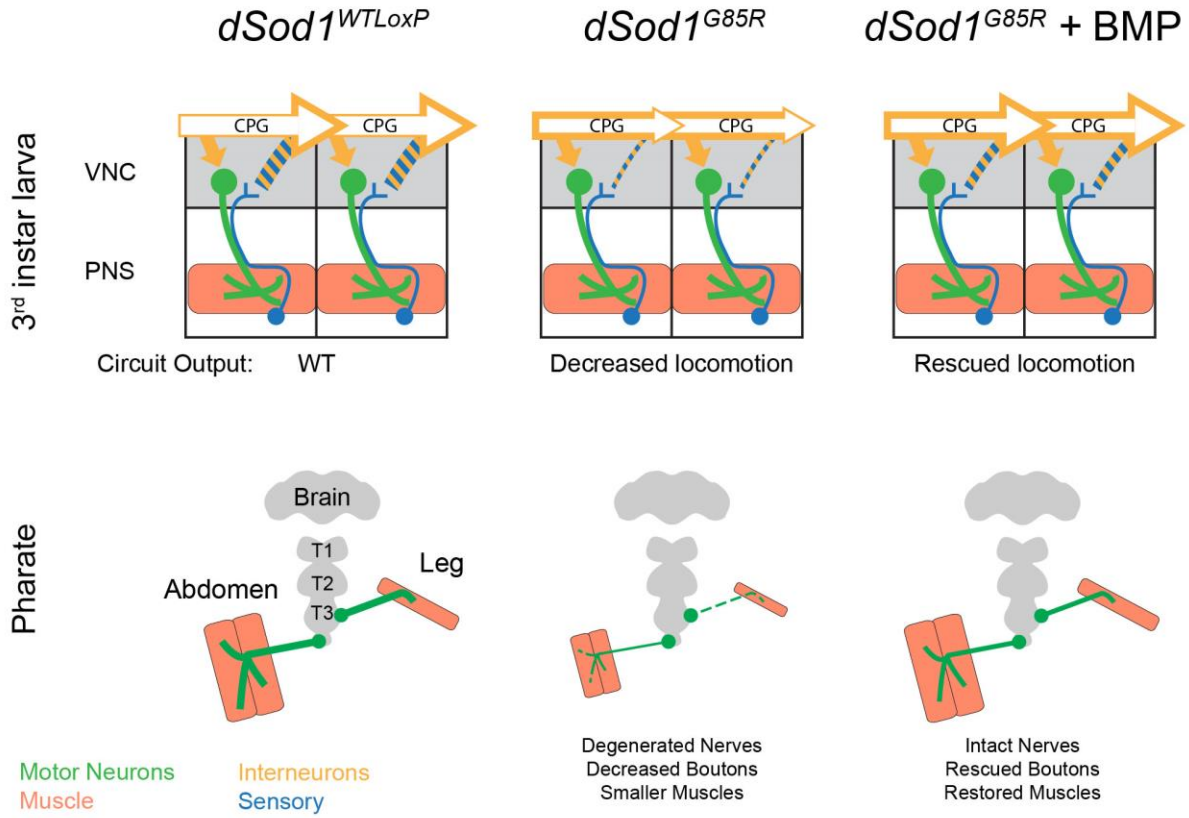
Support: NIH GM068118
NIH T32DK060415
ALS Finding a Cure Foundation
The Judith and Jean Pape Adams Foundation
Brown Institute for Brain Science Robin Chemers Neustein Graduate Award

Title: Activation of BMP signaling in non-motor neurons rescues motor dysfunction in a *Drosophila* model of amyotrophic lateral sclerosis

Authors: ***A. H. HELD**, P. MAJOR, D. LIPSCOMBE, K. WHARTON
Brown Univ., Providence, RI

Abstract: Several cellular mechanisms likely contribute to Amyotrophic Lateral Sclerosis progression, but determining which changes occur first, and which are secondary consequences has been difficult. At the point of diagnosis in humans, there is typically substantial motor neuron degeneration, limiting studies that might provide insight into the point of disease origin. Animal models of ALS are therefore invaluable for exploring disease progression. We took advantage of a *Drosophila Superoxide Dismutase 1* (*dSod1*) knock-in model that contains a mutation synonymous to the human $SOD1^{G85R}$ mutation, and exhibits end-stage symptoms that parallel human ALS. End stage $dSod1^{G85R}$ animals display motor dysfunction, substantial neuromuscular junction degeneration, and die shortly after failing to emerge from the pupal case. Interestingly, earlier stage animals have motor dysfunction without defects in neuromuscular junction morphology or a decrease in neurotransmission to muscle. We've found that defects in feedback from the peripheral nervous system to the central locomotor pattern generator account for this early locomotor change. This feedback defect could be caused by changes in

proprioceptors and/or the integration of their output by interneurons. We were then able to alleviate locomotor phenotypes by activating the BMP signaling pathway in both proprioceptors and excitatory interneurons. This non-motor neuron activation of BMP signaling allows 20% of *dSod1*^{G85R} animals to emerge from the pupal case and improves end stage motor neuron morphology. Our results suggest that non-motor neurons contribute to motor dysfunction, and that activating cellular processes under the control of BMP signaling in non-motor neurons can alleviate motor phenotypes. Future studies will 1) determine how circuitry changes influence the onset and progression of ALS-like phenotypes and 2) identify which cellular processes regulated by BMP signaling alleviate motor dysfunction.



Disclosures: **A.H. Held:** None. **P. Major:** None. **D. Lipscombe:** None. **K. Wharton:** None.

Nanosymposium

546. Models, Mechanisms, and Modifiers of Amyotrophic Lateral Sclerosis (ALS)

Location: 146C

Time: *Tuesday, November 14, 2017, 1:00 PM - 2:30 PM

Presentation Number: *546.04

**Topic: ***C.05. Neuromuscular Diseases

Support: ALS Association Grant ID 15-IIP-203
ALS Finding a Cure
Judith & Jean Pape Adams Charitable Foundation

Title: Multiple genetic models and modifiers of Amyotrophic Lateral Sclerosis in *C. elegans*

Authors: *S. N. BASKOYLU[1], K. S. YANAGI[1], M. B. WALSH[1], J. YERSAK[2], P. J. O'HERN[1], J. LINS[1], J. SIMON[1], L. STINSON[1], S. GROSSER[1], A. MAHAPATRA[1], A. C. HART[1]
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Abstract: Amyotrophic lateral sclerosis (ALS) is an adult-onset, fatal neurodegenerative disorder marked by the progressive loss of glutamatergic and cholinergic motor neurons. Approximately 10% of ALS patients have a familial history of motor neuron disease. Mutations in more than 16 genes have been linked to familial ALS (fALS), including *SOD1*, *TDP-43*, *FUS* and *C9ORF72*. We hypothesize that mutations in these genes may lead to motor neuron death via one, or a few, pathways. To examine the impact of ALS-associated mutations in different genes, we generated single copy fALS knock-in models in *Caenorhabditis elegans (C. elegans)*. We characterized the models using well-defined genetic, behavioral and pharmacological assays. Many of the models lead to disrupted synaptic signaling at the neuromuscular junction. Furthermore, exogenous stressors revealed or aggravated defects associated with fALS mutations. A subset of fALS mutations lead to stress-induced degeneration in glutamatergic neurons and cholinergic motor neurons. We are undertaking an unbiased forward genetic screen to identify suppressors of glutamatergic neurodegeneration in *C. elegans*. Over 50 suppressor lines have been identified; the next step is identification of suppressor genes. To complement the genetic screen, we conducted a comprehensive literature search for previously identified genetic modifiers of ALS-associated genes. We are using bioinformatic approaches to organize genetic modifiers into common pathways relevant to ALS. Our findings will be integrated with results from other ALS studies to understand how motor neurons die and to determine therapeutic pathways.

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Nanosymposium

546. Models, Mechanisms, and Modifiers of Amyotrophic Lateral Sclerosis (ALS)

Location: 146C

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 2:30 PM

**Presentation Number: ***546.05

**Topic: ***C.05. Neuromuscular Diseases

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ALS Association
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NIH Grant P20GM104937

Title: Protein-protein interactions in RNP granules are disrupted by the motor neuron degeneration-associated mutation in hnRNPA2

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Abstract: The RNA-binding protein heterogeneous nuclear ribonucleoprotein (hnRNP) A2 has essential roles in RNA processing and transport in neurons and oligodendocytes. A disease mutation in hnRNPA2 identified in multisystem proteinopathy, a degenerative disease with motor neuron involvement, causes hnRNPA2 to form TDP-43-positive inclusions in patient tissue. While this mutation increases the aggregation propensity of the low complexity (LC) domain of hnRNPA2, the mechanism of self-assembly and the cellular modifications and interactions that direct granule formation and discourage aberrant aggregation remain unknown. Using nuclear magnetic resonance spectroscopy and microscopy, we show that the disease mutation alters hnRNPA2 self-interactions and liquid-liquid phase separation into structures recapitulating key features of neuronal and oligodendroglial RNP granules. We also map the structural interaction with TDP-43 and the proline isomerase cyclophilin A and examine their effect on hnRNPA2 phase separation. Additionally, we find that posttranslational modifications in the LC alter hnRNPA2 phase separation. In summary, hnRNPA2 granule formation is a complex process that can be altered by the disease mutation, interacting proteins, or posttranslational modifications.

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Nanosymposium

546. Models, Mechanisms, and Modifiers of Amyotrophic Lateral Sclerosis (ALS)

Location: 146C

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 2:30 PM

**Presentation Number: ***546.06

**Topic: ***C.05. Neuromuscular Diseases

Support: Finding A Cure and the Leandro P. Rizzuto Foundation

Title: Automated continuous behavioral monitoring reveals early phenotypes in a novel TDP-43 knock-in mouse model of ALS-FTD

Authors: *A. M. DUFFY[1], M. WHITE[3], Y. BARHOMI[4], T. SERRE[1,2,5], R. H. BROWN, Jr[6], J. SREEDHARAN[3], J. R. FALLON[1]
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Abstract: Mutations in the RNA binding protein TDP-43 can cause familial ALS-FTD. However, the mechanisms by which these mutations cause disease are poorly understood. Elucidating the role of TDP-43 in ALS-FTD would be greatly benefited by animal models expressing mutant alleles under the control of endogenous regulatory machinery. It is also of particular interest to characterize early phenotypes that are more likely to reflect the initial events in disease progression - the preferred targets for therapeutic interventions. Here we have characterized a novel knock-in mouse model of ALS-FTD that harbors the human disease mutation TDP-43^{Q331K} using automated continuous behavioral monitoring (ACBM; Jhuang et al., 2010). In ACBM mice are video-recorded continuously at 30 frames/sec in their home cages for 5 days (total of ~1.3 x 10^7 frames/mouse/session). Behavioral assessment is then performed using a supervised, machine learning-based, computer algorithm to assign 1 of 8 designated behaviors to each frame. We assessed walking, hanging, rearing, drinking, eating from hopper, eating by hand (on haunches), grooming and resting in male and female homozygous TDP-43^{Q331K} mice in 5 sessions over 4-12 months of age (each session 5 days). ACBM revealed that mutant mice display deficits in walking and hanging at 4 months of age (repeated measures ANOVA, genotype x hr interaction; $p = 4.6 \times 10^{-5}$ and $p = 0.002$, respectively, n=9 WT and 10 mutant). In contrast, TDP-43^{Q331K} mice showed increased eating by hand and rearing behavior ($p = 0.008$ and $p = 0.04$, genotype and genotype x hr, respectively). The walk deficit was observed in both genders, but was more pronounced in the males, where it was observed in all 5 sessions. The walk deficit was progressive in both genders ($p = 6.9 \times 10^{-23}$, n=10) at 12 months of age. Our results demonstrate that TDP-43^{Q331K} mice exhibit behavioral abnormalities as early as 4 months that progress with age. We propose that ACBM represents a general approach for rigorous,

quantitative and unbiased behavioral assessment of both natural history and therapeutic testing of ALS-FTD and potentially other models for neurological disease.

Disclosures: A.M. Duffy: None. **M. White:** None. **Y. Barhomi:** A. Employment/Salary (full or part-time):; Vium, Inc. **T. Serre:** None. **R.H. Brown:** None. **J. Sreedharan:** None. **J.R. Fallon:** None.

Nanosymposium

547. Tautopathies: Mechanisms

Location: 140A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***547.01

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant NS073899
NIH Grant MH103848
VA Grant BX001637
VA Grant BX002475

Title: Aha1 stimulates tau fibrilization

Authors: *L. B. SHELTON, J. D. BAKER, D. ZHENG, J. KOREN, III, C. A. DICKEY, L. J. BLAIR
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Abstract: Pathogenic tau is the hallmark protein in diseases known as tauopathies, the most common one being Alzheimer's disease (AD). Previous studies have shown that Hsp90 and its co-chaperones can regulate tau pathogenicity. The activator of Hsp90 ATPase homolog 1 (Aha1) is a co-chaperone of Hsp90 that stimulates its ATPase activity. Our lab has shown that Aha1 is able to dramatically increase the production of aggregated, toxic tau species. Aha1 co-localized with tau pathology in human brain tissue and this association positively correlated with AD progression. Overexpression of Aha1 in the rTg4510 tau transgenic mouse model promoted the formation of both insoluble and oligomeric tau, which led to a neuronal loss and cognitive deficits. Drugs targeted at inhibiting Hsp90 have been a popular therapeutic treatment in tauopathies recently, and while these inhibitors do lead to reductions in toxic tau species, most Hsp90 inhibitors are not blood-brain barrier permeable and can present associated toxicities. We hypothesized that targeting Aha1, which stimulates the ATPase activity of Hsp90, could be a more direct way of reducing pathogenic tau. Therefore, we screened several novel, Aha1 inhibitors and found that some were able to reduce insoluble tau *in vitro*. Overall, these data

suggest that Aha1 is able to modulate pathogenic tau species through its interaction with Hsp90 and could offer an excellent therapeutic target for Alzheimer's disease and other tauopathies.

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Nanosymposium

547. Tautopathies: Mechanisms

Location: 140A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***547.02

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Alzheimer's Association MCDN-15-370051
NIH Grant NS0738899
NIH Grant MH103848
VA Grant BX001637
VA Grant BX002475

Title: Human Cyclophilin 40 dissolves neurotoxic amyloid fibrils

Authors: *J. D. BAKER, L. B. SHELTON, D. ZHENG, J. KOREN, III, C. A. DICKEY, L. J. BLAIR
Col. of Med., Univ. of South Florida, Tampa, FL

Abstract: Aggregation of amyloid forming proteins plays a key role in the pathogenic processes underlying several neurodegenerative diseases including Alzheimer's and Parkinson's diseases. Here we show that a human peptidyl prolyl-isomerase (PPIase), cyclophilin 40 (CyP40), dissolves fibrils in recombinant protein assays, in a human cell model, and in a mouse brain overexpressing human tau. PPIases play an important role in normal cell physiology as catalysts of protein folding at structurally important proline residues for both newly synthesized proteins and in conformational changes for molecular switches. Intrinsically disordered amyloid-forming proteins like tau have proline-rich regions which may regulate aggregation propensity. Our work reveals human CyP40 protein, on its own, possesses remarkable disaggregase activity towards amyloidogenic tau and α-synuclein through interaction with proline residues. CyP40 mediated disaggregation requires PPIase activity and is ATP-independent. CyP40 decreases both tau fibril and oligomer accumulation in a tauopathic brain and improves learning and memory as assessed by radial arm water maze and fear conditioning paradigms. This work identified CyP40 as a novel human amyloid disaggregase and demonstrated a role for it in maintaining the cellular proteome in neurodegenerative disease.

Disclosures: **J.D. Baker:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); U.S. Provisional Application Serial No. 62/329,317, filed April 29, 2016. **L.B. Shelton:** None. **D. Zheng:** None. **J. Koren:** None. **C.A. Dickey:** None. **L.J. Blair:** None.

Nanosymposium

547. Tautopathies: Mechanisms

Location: 140A

Time: *Tuesday, November 14, 2017, 1:00 PM - 4:15 PM

Presentation Number: *547.03

Topic: *C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant 1R21NS090160
NIH Grant 5R01NS073899

Title: Palmitoylated DNAJC5 recruits tau to endosomes and promotes tau release from cells

Authors: ***D. ZHENG**, Z. SUN, D. POLANCO, Y. YAN, L. SULLIVAN, A. DARLING, B. NORDHUES, J. WEBSTER, L. BLAIR, C. DICKEY, R. DESCHENES
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Abstract: Accumulation of the microtubule-associated protein tau in the neurons has been linked to cognitive deficits and neurotoxicity in Alzheimer's disease (AD) and other neurodegenerative diseases. Extracellular tau is present in the cerebrospinal fluid in AD, which has been shown to correlate with neuronal cell death. However, the mechanism of cellular secretion of tau has not been clearly established. We recently reported that DNAJC5/CSPα, a protein known to promote exocytosis, increased tau release from cultured cells, primary neurons and brain tissue. In the present study, we sought to explore the underlying mechanism of DNAJC5-mediated tau secretion. Membrane bound subcellular compartments were separated on a discontinuous gradient from tau and DNAJC5 overexpressing HEK293T cell homogenates; we found that DNAJC5 increased tau enrichment in EEA1 and Rab5 positive fractions. Immunocytochemistry showed that DNAJC5 increased the colocalization of tau with the endosome markers Rho B and Rab11a in both HEK293T cells and mouse primary neurons. DNAJC5 is palmitoylated in the cells. 2-bromopalmitate (2BP), a non-metabolizable palmitate analog that blocks palmitate incorporation into proteins, significantly inhibited the formation of the upper DNAJC5 band as well as DNAJC5-mediated tau secretion in a dose-dependent manner. The palmitoylation deficient mutant form of DNAJC5 protein showed a lower capacity to promote tau secretion. Our data show that palmitoylated DNAJC5 can recruit aggregated tau to endosomes and promote tau secretion.

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Nanosymposium

547. Tautopathies: Mechanisms

Location: 140A

Time: *Tuesday, November 14, 2017, 1:00 PM - 4:15 PM

Presentation Number: *547.04

Topic: *C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant R01AG053960
NIH Grant U01AG046161

Title: Tau-mediated disruption of the spliceosome in Alzheimer's disease models

Authors: ***Y.-C. HSIEH**, C. GUO, H. K. YALAMANCHILI, Y. LI, C. A. LASAGNA-REEVES, Y. XU, H. ZHENG, Z. LIU, J. M. SHULMAN
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Abstract: In Alzheimer's disease (AD), studies of human brain tissue have previously revealed that core components of the U1 spliceosome, including U1A, U1-70K and SNRPN/SmN, are abnormally enriched in insoluble protein fractions and co-aggregate with Tau neurofibrillary tangles, leading to splicing errors. We hypothesize that Tau-induced dysregulation of U1 spliceosomal components leads to global disruptions in the neuronal transcriptome, and ultimately, neurodegeneration. We explored potential genetic and biochemical interactions between human Tau (hTau) and the core spliceosomal components, using *Drosophila* as an experimental model. Following RNAi knockdown, numerous core spliceosomal components, including SmB (ortholog of human SmN), U1-70K, and U1C, enhanced hTau-mediated retinal neurodegeneration in transgenic flies. In addition, we found that core and U1-specific spliceosomal components were sharply reduced in the brains of aged flies following pan-neuronal hTau expression (*elav>hTau*^{R406W}). Following expression of hTau in *Drosophila* glia (*repo>hTau*^{WT}), SmB co-localized with phosphorylated-hTau aggregates and was also detected in insoluble fractions. In agreement with these findings, studies of hTau transgenic mice (rTg4510) revealed evidence of reduced SNRPN brain levels and solubility in aged animals. Lastly, transcriptomic profiles from RNA-sequencing reveal evidence of intron retention, consistent with splicing failure in the brains of hTau transgenic flies. Our results suggest that Tau-mediated toxicity is associated with functional disruption of the spliceosome. In further support of this, we have generated and characterized a novel, viable *SmB* hypomorphic allele, which causes reduced survival, progressive locomotor phenotypes, and neurodegeneration

(independent of Tau expression). In sum, our results support a model in which Tau-induced neurodegeneration is mediated by disruption of the spliceosome and resulting perturbations in the neuronal transcriptome.

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Nanosymposium

547. Tautopathies: Mechanisms

Location: 140A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***547.05

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: VA BX000877
NIA AG055474

Title: Preventing tauopathy by targeting MSUT2

Authors: *B. C. KRAEMER[1], J. M. WHEELER[2], P. MCMILLAN[3], T. STROVAS[2]
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Abstract: In Alzheimer's disease and related tauopathy disorders, tau neuropathology correlates with severity of dementia. Interventions for Alzheimer's disease and related dementias are limited to treatment of symptoms without directly altering tau pathology or the resultant neurodegeneration, underscoring the need for tau-targeted disease modifying therapeutics. To study tauopathy disorders in a genetically tractable model system, we developed a transgenic *C. elegans* model. This model recapitulates several hallmarks of human tauopathies including altered behavior, accumulation of abnormal tau protein, and neurodegeneration. To identify genes required for tau pathology, we conducted a genetic screen for mutations suppressing pathological tau phenotypes in *C. elegans*. We ultimately cloned the *sut-2* gene, mutations in which alleviate tauopathy phenotypes in *C. elegans*. The *sut-2* gene encodes distinct sub-type of RNA binding CCCH zinc finger protein conserved across animal phyla. *C. elegans* SUT-2 shares significant identity with the mammalian SUT-2 (MSUT2) homolog in both humans and mice. To study the translational relevance of MSUT2 to tauopathy, we knocked out the MSUT2 encoding gene in mice and crossed these knockout mice to the PS19 transgenic mouse model of tauopathy. Knockout of MSUT2 in the PS19 mouse model of tauopathy ameliorates tau related neurodegenerative changes including decreased accumulation of abnormal tau, reduced neuronal loss, and reduced cognitive dysfunction. The CCCH type zinc finger domains of SUT-2 and

MSUT2 have been implicated in RNA binding. Human MSUT2 CCCH domains bind to poly adenosine stretches in mRNA as well as the nuclear poly(A) binding protein PABPN1. MSUT2 and PABPN1 have been previously reported to have reciprocal effects on poly(A) tail length (PMID 4671764). We have shown depletion of MSUT2 ameliorates tau oligomer and aggregate formation in a human cellular model of tau aggregation while depletion of PABPN1 has the reciprocal effect driving increased tau oligomerization or aggregation. Furthermore, decreasing poly(A) tail length exacerbates tauopathy in human cells. Taken together these findings suggest MSUT2 modulates tau toxicity through binding to and/or regulation of RNA poly(A) tails. Ablating MSUT2 activity decreases pathological tau accumulation in multiple model systems supporting further translational studies of human MSUT2 as a candidate target for therapeutic intervention in diseases with tau pathology.

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Nanosymposium

547. Tautopathies: Mechanisms

Location: 140A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***547.06

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Alzheimer's Association (MNIRDG)
Cure PSP
Ed & Ethel Moore Alzheimer's disease Research Program (Florida Health)
BrightFocus Foundation

Title: Tau-dependent polyamine dysregulation promotes feed-forward cycle of disease progression

Authors: *L. A. SANDUSKY[1], A. KOVALENKO[1], J. HUNT[1], D. PLACIDES[1], S. N. FONTAINE[4], C. A. DICKEY[2], M. FAHNESTOCK[5], M.-L. B. SELENICA[1], K. R. NASH[3], M. N. GORDON[3], D. G. MORGAN[3], D. C. LEE[1]
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Abstract: Tau stabilizes microtubules; however, in Alzheimer's disease (AD) and tauopathies, tau becomes hyperphosphorylated, aggregates, and results in neuronal death. Our group recently uncovered a unique interaction between polyamines and tau fate. Polyamines exert an array of

physiological effects that support neuronal function and cognitive processing. Specific stimuli can elicit a polyamine stress response (PSR), resulting in altered central polyamine homeostasis. Evidence suggests that elevations in polyamines following a short-term stressor are beneficial; however, persistent stress and subsequent PSR activation may lead to maladaptive polyamine dysregulation, which occurs in numerous disease states, and may contribute to neuropathology and cognitive impairment in AD.
We show polyamine dysregulation in human AD brains and four independent mouse models of tauopathy. Significant alterations in spermidine/spermine-N(1)-acetyltransferase (SSAT) expression and SSAT-dependent acetylated byproducts, are common across AD brains and mouse models of tauopathy, identifying a unique tau-dependent polyamine stress response (tau-PSR). Targeting the tau-PSR through genetic deletion of SSAT prevents the tau-dependent (1) induction of SSAT expression, (2) increase in putrescine and acetylated spermidine, and (3) aggregation of monomeric and high-molecular weight tau. Conversely, inducing the tau-PSR through overexpression of antizyme inhibitor 2 (AZIN2), exacerbates the tau-dependent (1) increase in putrescine, (2) aggregation of monomeric and high-molecular weight tau, and (3) impairs working and fear-associated memory. Lastly, we demonstrate the relationship between tau and polyamine dysregulation as being direct, and show that incubation of recombinant tau with polyamines prevents fibrillization, while acetylated forms produced by SSAT catabolism promote tau fibrillization.
Taken together, our central hypothesis states that accumulated hyperphosphorylated tau acts as physiological stressor that induces SSAT to elicit a tau-PSR, which mediates the neuropathology and cognitive impairment seen in tauopathies, including AD. Further, we hypothesize that strategies aimed at circumventing the tau-PSR may serve to reduce neuropathology and ameliorate cognitive impairments. Future studies will investigate the role of the tau-PSR in hyper-network excitability and trans-synaptic spreading of tau, which will determine whether tau efflux is directly modulated by polyamine dysfunction. These data represent a novel paradigm and mechanism linking tau pathology and polyamine dysfunction.

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Nanosymposium

547. Tautopathies: Mechanisms

Location: 140A

Time: *Tuesday, November 14, 2017, 1:00 PM - 4:15 PM

Presentation Number: *547.07

Topic: *C.10.Tauopathies, Tau-dementias, and Prion diseases

Title: Postnatal changes in isoforms and phosphorylation of tau are independently regulated in mouse brains

Authors: *D. TUERDE[1], T. KIMURA[1,2], T. MIYASAKA[2], K. ANDO[1,3], M. HASEGAWA[3], S.-I. HISANAGA[1]
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Abstract: The microtubule-associated protein tau is a principal component of NFTs found in brains of Alzheimer's disease (AD). Tau aggregates are also found in other neurodegenerative disease, which are collectively called Tauopathy. Tau in NFTs is hyperphosphorylated, but it is not known why and how those tau are hyperphosphorylated. There are 6 isoforms in tau, which are produced by alternative splicing. The isoforms of tau in aggregates are different depending on tauopathies. Interestingly, both phosphorylation and isoforms of tau are changed during development. Highly phosphorylated 3-repeats (3R) tau in fetal/perinatal stages is replaced by the adult type of 4R tau with a low phosphorylation state. Because phosphorylation levels of fetal tau are similar to the major hyperphosphorylated tau species in AD, it is important to understand the mechanism of high phosphorylation of fetal tau. However, it is not addressed how the isoform and phosphorylation changes are regulated during neuronal development and how it contributes mechanistically to development of AD or tauopathies. Here, we addressed these questions using developing mouse brains.
Detailed analysis of developing brains revealed that the switch from 3R to 4R tau occurred during postnatal days 9 (P9) to P18 under the same time course as the conversion of phosphorylation from high to low. However, hypothyroidism, which is known to delay brain development, delayed the timing of tau dephosphorylation, but not the shift of isoforms, indicating that isoform switching and phosphorylation are not necessarily linked. Furthermore, we confirmed this finding by using mouse brains that expressed a single isoform of human tau. Human tau, either 3R or 4R, reduced phosphorylation levels during development, even though the isoform did not change. We also found that 3R and 4R tau were phosphorylated differently *in vivo* even at the same developmental days. These results show for first time that the phosphorylation and isoform changes of tau are regulated differently during mouse development.

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Nanosymposium

547. Tautopathies: Mechanisms

Location: 140A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***547.08

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Genetic Approaches to Aging T32 Training grant

Title: Pathological phosphorylation of tau and TDP-43 by TTBK1 and TTBK2 drives neurodegeneration

Authors: *L. M. TAYLOR[1], P. J. MCMILLAN[2], N. LIACHKO[4], B. GHETTI[5], T. BIRD[6], D. KEENE[3], B. C. KRAEMER[7]
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Abstract: Progressive neuron loss in the frontal and temporal lobes of the cerebral cortex typifies frontotemporal lobar degeneration (FTLD). FTLD sub types are classified on the basis of neuronal aggregated protein deposits, typically containing either aberrantly phosphorylated TDP-43 or tau. Our recent work demonstrated that tau tubulin kinases 1 and 2 (TTBK1/2) robustly phosphorylate TDP-43 and co-localize with phosphorylated TDP-43 in human postmortem neurons from FTLD patients. Both TTBK1 and TTBK2 were initially identified as tau kinases and TTBK1 has been shown to phosphorylate tau epitopes commonly observed in Alzheimer's disease and other tauopathies. To further elucidate how TTBK1/2 activity contributes to both TDP-43 and tau phosphorylation in the context of the neurodegeneration seen in FTLD, we examined the consequences of elevated human TTBK1/2 kinase expression in transgenic animal models of disease. We show that C. elegans co-expressing tau/TTBK1, tau/TTBK2, or TDP-43/TTBK1 transgenes in combination exhibit synergistic exacerbation of behavioral abnormalities, protein phosphorylation, aberrant neuronal architecture, and neuron loss. Surprisingly, the TTBK2/TDP-43 transgenic combination showed no exacerbation of TDP-43 proteinopathy related phenotypes. Additionally, we observed elevated TTBK1/2 protein expression in the cortical neurons of FTLD-tau and FTLD-TDP cases relative to normal controls and robust immunostaining of TTBK1 and TTBK2 in both hippocampus and frontal cortex of FTLD cases in comparison to controls. Our findings shed light on the possible etiology of the two most common FTLD subtypes through a kinase activation driven mechanism of neurodegeneration.

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Nanosymposium

547. Tautopathies: Mechanisms

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**Presentation Number: ***547.09

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: AG043053
AG010124
AG17586
Dana Foundation
Penn Institute on Aging

Title: Resilience to alpha-synuclein and TDP-43 co-pathology in primary age-related tauopathy

Authors: *C. MCMILLAN[1], E. B. LEE[2], D. IRWIN[3], M. GROSSMAN[4], J. Q. TROJANOWSKI[5], D. WOLK[3]
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Abstract: Alzheimer's disease (AD) is neuropathologically characterized by amyloid plaques (AB) and neurofibrillary tau tangles (NFTs). In contrast, primary age-related tauopathy (PART) refers to individuals with neuropathological evidence of NFTs with either absent (Definite PART) or minimal (Probable PART) evidence of AB. While it is becoming increasingly recognized that alpha-synuclein (ASYN) or tar-DNA binding protein (TDP-43) co-pathology also occurs in AD, the occurrence of ASYN and TDP-43 has not been evaluated in PART. Thus, to date it is unclear whether AD and PART collectively reflect a continuum of co-pathologies and that, if an individual lives long enough, they would develop all four sources of pathology. Alternatively, AD and PART may reflect distinct conditions with variable degrees of vulnerability for co-pathologies. In the current study we evaluated the frequency of co-pathologies in PART and AD. We performed a retrospective assessment of autopsy cases in the PENN Brain Bank that had semi-quantitative ratings by a neuropathologist for amyloid, NFTs, ASYN, and TDP-43. We identified a total of 298 cases that met neuropathological criteria for Definite PART (N=39; M=72.7±9.8 years), Probable PART (N=14; M=74.1±9.9 years), Intermediate AD (N=33; M=82.9±9.5 years), or High Likelihood AD (N=212; M=75.2±11.2 years). Intermediate AD was significantly older than other groups, but otherwise groups were comparable for age. We then evaluated the frequency of ASYN and TDP-43 pathology in each group. We observed that ASYN co-pathology was often present in High AD (51.9%) but only modestly present in Intermediate AD (33.3%) and rarely present in Probable PART (0%) or Definite PART (7.7%) cases ($X2=38.6$; $p<0.0001$). Likewise, we observed that TDP-43 co-pathology was most frequently present in High AD (44.8%), modestly present in Intermediate

AD (18.2%), and rarely present in Probable PART (0%) or Definite PART (5.1%) ($X2=36.1$; $p<0.0001$). A more detailed inspection of the distribution of ASYN and TDP-43 revealed that, if co-pathology was present, it was predominantly restricted to the amygdala in Definite PART and more diffuse including neocortical regions in High AD. Logistic regression models revealed that age was a significant predictor of ASYN or TDP-43 co-pathology in High AD (all $p<0.05$), but not PART (all $p>0.1$). Together, these findings suggest that ASYN and TDP-43 co-pathology is unique to high probability AD. While additional research is necessary to uncover the mechanisms of PART, we suggest that PART may reflect a distinct condition with resilience to AB, ASYN, and TDP-43 pathology.

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Nanosymposium

547. Tautopathies: Mechanisms

Location: 140A

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**Presentation Number: ***547.10

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH/NIA Grant R01AG050721
CurePSP Foundation Grant 600-6-15

Title: *In vitro* phosphorylated tau allows investigation of aggregation and seeding in the absence of inducers

Authors: *J. DI[1], A. J. MASON[1], C. DESPRES[2], F.-G. KLÄRNER[3], T. SCHRADER[3], C. SMET-NOCCA[2], G. BITAN[1]
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Abstract: Aggregation of hyperphosphorylated tau into paired helical filaments and neurofibrillary tangles is one of the defining pathological hallmarks in Alzheimer's disease and other tauopathies. Tau hyperphosphorylation has been attributed in part to the deregulation of kinase and phosphatase activities. However, how the unfolded tau assembles into oligomers and fibrils, and whether the phosphorylation of tau at any of the stages plays a role in contributing to the aggregation, are unanswered questions. Recombinant tau does not aggregate *in vitro* unless it is induced by polyanions, e.g., heparin. This artificial induction is problematic particularly for testing potential inhibitors of tau self-assembly, because the inducer may interfere with the interaction of the inhibitor with tau itself. To overcome this problem, we compared the

aggregation and seeding activity of heparin-induced tau and *in vitro* phosphorylated tau (p-tau). Tau was phosphorylated *in vitro* by Extracellular signal regulated-kinases 1/2 (ERK1/2), a kinase activated in the first stages of Alzheimer's disease. We used both full-length, 2N4R tau and the F8 fragment [tau(192-324), C291A]. The unphosphorylated form was induced to aggregate by heparin whereas p-tau was incubated without inducers. Aggregation kinetics was followed using the thioflavin-T fluorescence assay. To detect seeding activity, we used a tau monoclonal FRET biosensor cell line, which stably expresses the tau repeat domain (RD) containing the disease-associated P301S substitution fused to either CFP or YFP. In contrast to heparin-induced tau, for which seeding activity depended on aggregation, F8 and full-length p-tau induced a strong seeding response already at t = 0. Native PAGE and Western blots showed that p-tau comprised a mixture of monomer and oligomers. The molecular tweezer, CLR01, was found to inhibit the aggregation and seeding activity of both p-tau and tau aggregates, but the dose-dependence of the inhibition in the presence of heparin was not straightforward. Our data demonstrate that the seeding activity of p-tau is distinct from that of heparin-induced tau aggregates and suggest that testing inhibitors with p-tau is more relevant to therapy development than with heparin-induced tau aggregates. Our study also supports the development of CLR01 as a potential therapeutic agent for Alzheimer’s disease and other tauopathies.

Disclosures: **J. Di:** None. **A.J. Mason:** None. **C. Despres:** None. **F. Klärner:** None. **T. Schrader:** None. **C. Smet-Nocca:** None. **G. Bitan:** None.

Nanosymposium

547. Tautopathies: Mechanisms

Location: 140A

Time: *****Tuesday, November 14, 2017, 1:00 PM - 4:15 PM

Presentation Number: *****547.11

Topic: *****C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant 1RF1AG051684-01A1

Title: Hyper-homocysteinemia modulates tau neuropathology through 5-lipoxygenase in a mouse model of tauopathy

Authors: ***A. DI MECO**[1], J.-G. LI[1], C. BARRERO[2], S. MERALI[2], D. PRATICO[1]
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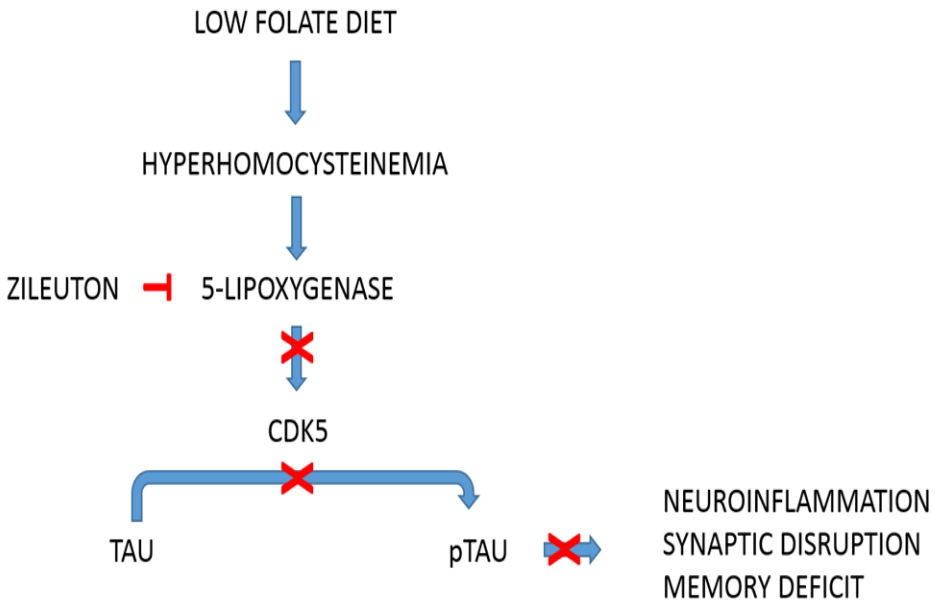
Abstract: BACKGROUND: High circulating level of homocysteine, hyper-homocysteinemia (HHcy), is a recognized risk factor for Alzheimer’s disease (AD). Previous studies showed that HHcy promotes brain amyloidosis and tau pathology in transgenic mouse models of AD.

However, the effect of HHcy on tau pathology has never been investigated in a pure tauopathy model. METHODS: To this aim, human tau transgenic mice (h-tau) were fed a regular chow diet or low folate diet to induce HHcy from 4 to 12 months of age, then assessed for memory, tau pathology, synaptic integrity and neuroinflammation at 8 and 12 months of age. RESULTS: Compared with controls, 12 month old h-tau mice fed low folate diet, had a significant increase in homocysteine (Hcy) level and worsening of behavioral deficits in the Morris Water Maze paradigms. Brains of these mice had a significant increase in 5-lipoxygenase (5LO), tau phosphorylation at specific epitopes, cdk5 activation, biochemical markers of synaptic pathology and astrocytes activation. At 8 months of age, 5LO enzyme was upregulated in the brain of the same mice but no changes in cognition and tau metabolism were detected. In vitro studies demonstrated that HHcy effect on tau phosphorylation was mediated by 5LO activation via the cdk5 pathway and that 5LO pharmacological inhibition was sufficient to rescue Hcy induced tau phosphorylation. CONCLUSION: HHcy induces tau pathology, synaptic dysfunction and neuroinflammation by up-regulating 5LO expression in a mouse model of tauopathy. 5LO upregulation precedes tau hyper-phosphorylation and cognitive decline upon HHcy. Future studies will establish whether 5LO pharmacological inhibition could prevent and/or reverse HHcy induced tau pathology.



Disclosures: **A. Di Meco:** None. **J. Li:** None. **C. Barrero:** None. **S. Merali:** None. **D. Pratico:** None.

Nanosymposium

547. Tautopathies: Mechanisms

Location: 140A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***547.12

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Title: Tau-dependent suppression of adult neurogenesis in the stressed hippocampus

Authors: *I. SOTIROPOULOS[1,2], C. DIOLI[1,2], P. PATRÍCIO[1,2], J. SILVA[1,2], E. FERREIRO[3], A. MATEUS-PINHEIRO[1,2], N. SOUSA[1,2], L. PINTO[1,2]
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Abstract: Chronic stress and excessive glucocorticoid (GC) exposure are suggested to increase susceptibility to brain pathology as they are associated with neuroplastic deficits, impaired cognition as well as mood disorders such as depression. The hippocampus is a well-known target of chronic stress, with previous studies demonstrating structural and functional changes in the hippocampal formation. The dentate gyrus (DG) constitutes the anatomical and functional input of the hippocampus and it suffers from both stress-induced remodeling of the dendritic arbor of its granular cells as well as suppression of neurogenesis and gliogenesis. However, it is mechanistically unclear how stress precipitates the suppression of cytogenesis in the adult DG as well as whether similar stress-driven pathways operate in the reduction of newborn neuronal and glial populations. Previous studies have shown that chronic stress triggers hyperphosphorylation and accumulation of the cytoskeletal protein Tau, a process that may impair the cytoskeleton-regulating role(s) of this protein with impact on neuronal function. Here, we analyzed the role of Tau on stress-driven suppression of neurogenesis in the adult DG using animals lacking Tau (Tau-KO) and wild-type (WT) littermates. Unlike WTs, Tau-KO animals exposed to chronic stress did not exhibit reduction in DG proliferating cells, neuroblasts and newborn neurons; however, newborn astrocytes were similarly decreased in both Tau-KO and WT mice. In addition, chronic stress reduced PI3K/mTOR/GSK3β/β-catenin signaling in the DG, known to regulate cell survival and proliferation in WT, but not in Tau-KO. These data establish Tau as a critical regulator of the cellular cascades underlying stress deficits on hippocampal neurogenesis in the adult brain.

Disclosures: I. Sotiropoulos: None. **C. Dioli:** None. **P. Patrício:** None. **J. Silva:** None. **E. Ferreiro:** None. **A. Mateus-Pinheiro:** None. **N. Sousa:** None. **L. Pinto:** None.

Nanosymposium

547. Tautopathies: Mechanisms

Location: 140A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***547.13

**Topic: ***C.10.Tauopathies, Tau-dementias, and Prion diseases

Support: Mext Grant–in-aid project, Scientific Research on Innovation Area, (Brain Protein Aging and Dementia control
AMED, Reseach and development for dementia

Title: Local somatodendritic translation of tau protein triggered by AMPA and NMDA receptor stimulation

Authors: *A. TAKASHIMA[1], S. KOBAYASHI[2], T. TANAKA[2], Y. SOEDA[3]
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Abstract: Tau is a major component of the neurofibrillary tangles (NFT) that represent a pathological hallmark of Alzheimer's disease (AD). Although generally considered an axonal protein, Tau is found in the somatodendritic compartment of degenerating neurons; recent work has suggested an important role for somatodendritic Tau in triggering neurodegenerative mechanisms, including synaptic dysfunction. This study examined the redistribution and regulation of Tau in dendrites. We demonstrate the presence of tau mRNA in dendritic ribonucleoprotein (RNP), a complex that includes other mRNA species (e.g. CaMKIIα) that are translated locally in dendrites in response to excitatory inputs. We also show that tau mRNA is transported into dendritic spines in mRNP granules after binding to the RNA-binding proteins Staufen1 and FMRP and interactions with the postsynaptic motor protein myosin Va. Further, we report that tau mRNA in the somatodendritic component of primary hippocampal cells is translated and hyperphosphorylated upon stimulation with sub-toxic doses of glutamate; the latter is blocked by the glutamatergic antagonists MK801 and NBQX, indicating NMDA and AMPA receptor involvement in the redistribution of tau to the somato-dendritic region of neurons. In summary, our analysis resolves the question of how tau locates to dendrites to induce neurodegenerative processes, and glutamate stimulation is thought to cause neurodegeneration in AD; memantine, which relieves the aberrant excitation of glutamate on NMDA receptor, has efficacy in AD therapy.

Disclosures: A. Takashima: None. **S. Kobayashi:** None. **T. Tanaka:** None. **Y. Soeda:** None.

Nanosymposium

548. Hair cells

Location: 156

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***548.01

**Topic: ***D.06. Audition

Support: NIH grant 5P20RR018788
Tobacco Settlement Fund from the State of Nebraska

Title: Coordinate roles for Itgα8 and Pcdh15 in the regulation of cilia biogenesis in sensory cells

Authors: *M. ZALLOCCHI, L. CHEUNG
Boys Town Natl. Res. Hosp., Omaha, NE

Abstract: The organism's perception of its surroundings depends on sensory systems and the highly specialized cilia present in the neurosensory cells. Using zebrafish as the experimental model, we described the existence of an integrin alpha8 (Itga8)-protocadherin15a (Pcdh15a) ciliary complex in neuromast hair cells. Depletion of the complex via down-regulation or loss of function mutations leads to a dysregulation of cilia biogenesis and endocytosis. At the molecular level, removal of the complex blocks the access of Rab8a into the cilia as well as normal recruitment of ciliary cargo by centriolar satellites determined by confocal analysis, structured illumination microscopy and western blot studies. These defects can be reversed by the introduction of a constitutively active form of Rhoa, suggesting that Itga8-Pcdh15a complex mediates its effect through the activation of this small-GTPase and the regulation of actin polymerization. Our data points to a novel actin-dependent mechanism involved in the regulation of sensory cilia development, suggesting the existence of an extra layer of complexity evolutionary unique to sensory neuroepithelium. Moreover, since Usher patients suffer from vision loss and a reduction in olfaction activity, our findings may have implications not only for normal hearing and balance functions but for theses sensory systems as well.

Disclosures: M. Zallocchi: None. **L. Cheung:** None.

Nanosymposium

548. Hair cells

Location: 156

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***548.02

**Topic: ***D.06. Audition

Title: Characterization of a new mouse model with a non-sense mutation in loxhd1 dfnb77

Authors: *N. GRILLET, M. CARRARO, A. TROUILLET
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Abstract: We previously identified the gene LOXHD1 as responsible for an autosomal-recessive form of hearing loss in mice and human (Grillet N., AJHG, 2009). The gene LOXHD1 encodes a protein made of 15 PLAT (Polycystin Lipoxygenase Alpha-Toxin) domains and is expressed exclusively by hair cells. The LOXHD1 protein is found in the stereocilia and the cuticular plate, at the junction between membrane and the actin-cytoskeleton. The function of LOXHD1 is unknown. We hypothesize that LOXHD1 is necessary for the function of the hair bundle by forming a physical link between the membrane and the actin-core of the stereocilia.The deaf Samba mutant mouse presents a missense mutation in the PLAT domain #10 of LOXHD1. However the protein is still found in the stereocilia bundle. Even in the adult animal, no major morphological defect is observed in the stereocilia bundle. We asked if truncating the LOXHD1 protein would induce a structural phenotype of the hair bundle. We generated a new mouse model for LOXHD1/DFNB77 where we introduced a non-sense codon and deleted the exons coding for PLAT domain #10. We will present our characterization of the new mutant and its comparison with the Samba strain.

Disclosures: N. Grillet: None. **M. Carraro:** None. **A. Trouillet:** None.

Nanosymposium

548. Hair cells

Location: 156

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***548.03

**Topic: ***D.06. Audition

Support: NIDCD 2R01DC004274

Title: Adaptation to temperature changes at auditory ribbon synapses increases synaptic vesicle exocytosis efficiency

Authors: *M. CHEN[1], H. P. VON GERSDORFF[2]
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Abstract: Frogs adapt to a wide range of body temperature during their normal diurnal and nocturnal activities. To successfully find mating partners their hearing abilities must also be sharp during the warm summer months. *In vivo* single auditory nerve fiber recordings in frogs show a large temperature sensitivity of the afferent fiber spike activity (e.g., tone response threshold, latency of response, spike frequency, vector strength of phase locking). This study aims to understand the underlying mechanisms of the temperature-dependence of synaptic transmission at the hair cell to afferent fiber ribbon-type synapse. We performed *in vitro* patch-clamp recordings of hair cells and/or afferent fibers in bullfrog amphibian papillae under both room (23-25°C) and high (30-33°C) temperature. Temperature was adjusted by heating the bath perfusion with a temperature controller and measured by a miniature thermistor close to the tissue that was recorded. The frequency and amplitude of spontaneous excitatory post-synaptic current (EPSC) increased at higher temperatures. This increase of EPSC frequency may arise from a depolarization of the hair cell at higher temperatures. However, the increase in EPSC frequency was not due to hair cell depolarization, because gramicidine-mediated perforated patch current clamp recordings showed that hair cell resting membrane potential remains the same (around -60 mV at both room and high temperatures). We also observed that the efficiency of exocytosis, defined as the amount of exocytosis per Ca^{2+} ion influx, increased at higher temperatures. We thus suggest that the increase in EPSC frequency is due to a reduction in the energy barrier for vesicle membrane fusion (or exocytosis). High temperature also quickened the activation and decay kinetics of the EPSCs. Excitatory post-synaptic potential (EPSP) and action potential (AP) spikes recorded by current clamp increased in frequency but, surprisingly, not in amplitude for EPSPs. The decay time course of EPSPs was faster at higher temperatures, which could potentially increase the temporal precision of sound detection (e.g., improve phase-locking). A reduction in input resistance of the afferent fiber at higher temperatures may be responsible for the faster decay of the EPSPs. The threshold of the AP also decreased at higher temperatures, which may explain the decreased sound tone response threshold detected by *in vivo* auditory nerve fiber recordings.

Disclosures: **M. Chen:** None. **H.P. von Gersdorff:** None.

Nanosymposium

548. Hair cells

Location: 156

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***548.04

**Topic: ***D.06. Audition

Support: F32DC013477
David M. Rubenstein Fund for Hearing Research
NIH Grant DC011571

Title: Activin signaling instructs hair cell differentiation in the mammalian cochlea

Authors: *A. DOETZLHOFER[1], A. BENITO-GONZALEZ[2], M. PRAJAPATI[2], E. GOLDEN[3]
[1]Neurosci., Johns Hopkins Med. Inst., Baltimore, MD; [2]Neurosci., Johns Hopkins Med. Institutions, Baltimore, MD; [3]Univ. of Colorado, Denver, Denver, CO

Abstract: The mammalian cochlea contains a highly specialized sensory organ tuned to detect and encode sound. Embedded within a two-layered sensory epithelium, mechano-receptor cells, so called hair cells, are arranged in precise rows. To ensure the highly stereotyped pattern of hair cell arrangement, cell cycle withdrawal and differentiation within the auditory sensory epithelium occurs in a spatial and temporally highly coordinated manner. Hair cell (sensory) progenitors exit the cell cycle in an apical-to-basal gradient, which is followed by a reverse, basal-to-apical gradient of differentiation. Here, in this study we examined whether activin A signaling plays a role in controlling these highly stereotyped gradients. Activins are secreted proteins that belong to the large family of TGF-β ligands. The biological activity of activins is limited by follistatin, a secreted protein that binds activins at high affinity. Analyzing activin A and follistatin expression using RNA in situ hybridization, we find that in the developing cochlea activin A and its antagonist follistatin are expressed in opposing gradients; follistatin is highly expressed in the cochlear apex, whereas activin A induction, which coincides with the onset of hair cell differentiation, is confined to the base. Using organotypic cultures, we demonstrate that exogenous activin A induces premature differentiation of cochlear hair cells. Conversely, conditional deletion of the gene *Inhba*, which encodes for activin A, or transgenic overexpression of follistatin, delays the differentiation of cochlear hair cells *in vivo*. Furthermore, we find that exogenous activin A is able to rescue the inhibitory effect of follistatin on hair cell differentiation, suggesting that follistatin inhibits hair cell differentiation through antagonizing activin A activity. Finally, we provide evidence for additional roles for activin signaling in sensory progenitor cell proliferation and patterning. We find that follistatin overexpression or conditional ablation of *Inhba* delays sensory progenitor cell cycle withdrawal and causes an overproduction of inner hair cells. In summary, our study reveals a novel, instructive role for activin signaling in hair cell differentiation, and identifies follistatin as a key

regulator of sensory progenitor maintenance in the mammalian cochlea. The regulatory mechanism described here might be a broadly applied mechanism for controlling progenitor behavior in the central and peripheral nervous system.

Disclosures: A. Doetzlhofer: None. **A. Benito-Gonzalez:** None. **M. Prajapati:** None. **E. Golden:** None.

Nanosymposium

548. Hair cells

Location: 156

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***548.05

**Topic: ***D.08. Vestibular System

Support: NIH Grant R21 DC013181

Title: Inner ear mitochondria exhibit structural features that differ between hair cells, afferents and efferents

Authors: *A. LYSAKOWSKI[1], S. SOBKIV[2], J. LESUS[2], K. ARIAS[2], A. KAMBALYAL[3], M. PATEL[2], S. VAZIRIAN[2], V. BABU[4], L. GHATALAH[2], A. JAYAKUMAR[2], F. PADRON[2], M. H. ELLISMAN[5], G. PERKINS[6]
[1]Dept. of Anat. & Cell Biol., [2]Dept. of Biol., [3]Dept. of Econ., Univ. of Illinois at Chicago, Chicago, IL; [4]Illinois Math and Sci. Acad., Aurora, IL; [5]Dept Neurosci, [6]NCMIR, UCSD BSB 1000, LA Jolla, CA

Abstract: In other organs in the body, the structure of mitochondria and their role in apoptosis and cell death is a topic of intense research interest. Such a framework of structural studies is missing in the inner ear. This study is an attempt to fill that gap by studying hair cell mitochondria for the ultimate purpose of addressing hair cell damage and death in mitochondrial-associated forms of deafness (both non-syndromic and antibiotic-induced). We wanted to know if variations in the physical structure and corresponding molecular composition in various sub-populations of hair-cell mitochondria could cause mitochondria to be affected differently by ototoxic insults, such as aminoglycoside antibiotics and chemotherapeutics. Using electron microscope (EM) tomography and 3D-reconstructions, we have found that mitochondria in vestibular endorgans come in different sizes (large, medium and small) and exhibit different internal structures (lamellar vs. tubular cristae). The mitochondria found in hair cells are mostly medium-sized with lamellar cristae; those found in afferents (both calyces and boutons) are also medium-sized but they have tubular cristae. Efferent boutons are small with tubular cristae. Finally, the largest mitochondria, which have lamellar cristae, are found in the subcuticular plate

region in central type I hair cells. We have analyzed the internal structure of these various types of mitochondria and find differences in the surface areas and volumes of their cristae, which affect their ATPase-carrying capacity. In addition, they appear to be not only tethered to various hair cell organelles and to each other, but also to be arranged in particular orientations in relation to these organelles. As previously shown in mitochondria in the auditory brainstem (Perkins, Spirou, et al., J. Neuroscience, 2010), mitochondrial cristae have openings to the inner mitochondrial membrane termed "crista junctions" and there are 1.5-2x more crista junctions on the side of the mitochondria facing toward structures relevant to hair cell function than on the side away from these structures. These crista junctions may be a way of directing ATP and Ca^{2+} toward energy-requiring organelles, such as ribbon synapses, stereociliar rootlets, striated organelles, etc. We have produced several short animations that illustrate these structural differences and relationships.

Disclosures: **A. Lysakowski:** None. **S. Sobkiv:** None. **J. Lesus:** None. **K. Arias:** None. **A. Kambalyal:** None. **M. Patel:** None. **S. Vazirian:** None. **V. Babu:** None. **L. Ghatalah:** None. **A. Jayakumar:** None. **F. Padron:** None. **M.H. Ellisman:** None. **G. Perkins:** None.

Nanosymposium

548. Hair cells

Location: 156

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Presentation Number: *548.06

Topic: *D.06. Audition

Support: FAG Fonds für Förderung von Lehre und Forschung , Basel (FO140680)
Schweizerische Eidgenossenschaft KTI

Title: New mechanism of auditory hair cell protection from gentamicin toxicity revealed by drugs targeting somatostatin receptors and PPARs

Authors: ***V. PETKOVIC**[1], M. SEKULIC JABLANOVIC[1], K. KUCHARAVA[1], M. B. WRIGHT[2], D. BODMER[1]
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Abstract: The chemotherapy and certain antibiotics such as gentamicin and other aminoglycoside antibiotics damage the hair cells and neurons of the cochlea. Aminoglycoside-induced hair cell stress initiates an influx of calcium ions (Ca^{2+}) and rapid rise in intracellular calcium concentration. Once the inner ear receives these stressful insults, common pathophysiological mechanisms for the cochlea are activated.

Somatostatin receptors (SSTRs) can provide neuroprotection by coupling to voltage-dependent Ca^{2+} channels and mediating the inhibition of Ca^{2+} conductance by SST and its analogues. We previously demonstrated that the somatostatin receptors are expressed in the mammalian inner ear and the somatostatin and its analogues can protect hair cells (HCs) from gentamicin-induced hair cell death in vitro.
We reported that the somatostatin analogue pasireotide with a longer half-life than octreotide, prevents gentamicin-induced HC death in the mouse organ of Corti. By using of Cyanamid a selective antagonist of SSTR2 and BIM selective antagonist for SSTR5 we shown that the protective effect of the pasireotide are mainly due to the involvement of these two receptors. Another indicator of pasireotides protective role was reductions of caspase activities and increases the expression of the protective genes. Direct NFAT inhibition using 11-R VIVIT protects HC from gentamicin-induced toxicity. The full effect of 11-R VIVIT activity was found after 24h of incubation. 11R-VIVIT reversed the effects of gentamicin on the expression of downstream survival targets (NMDA receptor and the regulatory subunit of PI3K).
Pioglitazone is an agonist of peroxisome proliferator – activated receptors, PPARg and PPARa which function as transcriptional regulators of genes controlling glucose and lipid metabolism. We found that the PPARg and PPARa are expressed in cochlea and localized in inner and outer auditory HCs. Gentamicin treatment increased ROS, lipid peroxidation, and altered redox gene expression in mouse OCs. Pioglitazone treatment almost completely prevented the increase in ROS induced by gentamicin, inhibiting subsequent formation of 4-HNE (4-hydroxy-2- nonenal) and by upregulating genes involved in cellular antioxidant pathways including superoxide dismutase (SOD1), glutathione peroxidase (GPX1), catalase (CAT), uncoupling protein 2 (UCP2) and by maintaining gluthatione levels.
Our data in vitro support a highly protective effect of pasireotide, NFAT inhibitor and PPAR agonists to prevent aminoglycoside-dependent hair cell damage and apoptosis therefore represent new therapeutic opportunities for the treatment of hearing loss.

Disclosures: V. Petkovic: None. **M. Sekulic Jablanovic:** None. **K. Kucharava:** None. **M.B. Wright:** None. **D. Bodmer:** None.

Nanosymposium

548. Hair cells

Location: 156

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***548.07

**Topic: ***D.06. Audition

Support: DOD grant W81XWH-15-1-0475
NIH grant R01 DC014441

Title: The Notch ligand Jagged1 is required for the survival of supporting cells in the postnatal mouse cochlea

Authors: *B. C. COX, M. R. RANDLE, K. A. GRAVES, Y. L. DARCY
Pharmacol., Southern Illinois Univ. Sch. of Med., Springfield, IL

Abstract: The highly organized, mosaic pattern of hair cells (HCs) and supporting cells (SCs) in the mammalian cochlea is thought to be the result of Notch-mediated lateral inhibition which occurs during embryonic development. Progenitor cells destined to become HCs express the Notch ligands *Jagged2* and *Delta-like1* which bind to the Notch receptor expressed on neighboring cells to inhibit a HC fate and instead promote a SC fate. Another Notch ligand, *Jagged 1* (*Jag1)*, is expressed by both HCs and SCs, but its role in HC differentiation is not well understood. Many studies have shown that inhibition of the Notch signaling pathway, using either pharmacological agents or genetically altered mice, can produce supernumerary HCs in the intact mammalian cochlea or form new HCs in the damaged cochlea. While *Jagged2* and *Delta-like1* are downregulated in the cochlea during the first postnatal week, *Jag1* expression continues throughout adulthood where its function is not clear. To investigate the role of *Jag1* in the postnatal cochlea, we generated conditional knockout mice using the CreER/loxP system. Specifically, *Jag1* was deleted in HCs and the SC subtypes called pillar cells and Deiters' cells using *FGFR3-iCreER::Jag1*$^{loxP/loxP}$ mice given tamoxifen at postnatal day (P) 0 and P1. Using immunostaining, we observed organized rows of HCs and SC nuclei in both Cre-negative controls and *Fgfr3-iCreER::Jag1*$^{loxP/loxP}$ mice at P7. However quantification of cells showed a significant decrease in the number of SCs in the lateral compartment of the cochlea (pillar cells, Deiters' cells, and Hensen cells), but no change in the number of inner or outer HCs. Further investigation using markers of pillar cells and Deiters' cells show that Hensen cells are missing in *FGFR3-iCreER::Jag1*$^{loxP/loxP}$ mice. At P30, auditory brainstem response (ABR) showed a mild hearing loss in mice lacking *Jag1* expression, with a significant increase in ABR thresholds at 4 kHz, but not at other frequencies. We are currently investigated the morphology of the cochlea at P30, as well as measuring changes in the various Notch target genes after *Jag1* deletion. We also plan to perform ABR in older animals (at P60) to see if the hearing loss is progressive. Taken together our preliminary data suggest that *Jag1* is required for the survival of Hensen cells and loss of these cells leads to hearing loss.

Disclosures: **B.C. Cox:** F. Consulting Fees (e.g., advisory boards); Turner Scientific LLC. **M.R. Randle:** None. **K.A. Graves:** None. **Y.L. Darcy:** None.

Nanosymposium

549. Visually-Guided Reach and Grasp

Location: 152B

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***549.01

**Topic: ***D.09. Visual Sensory-motor Processing

Support: Internal Grant

Title: Study of target interception in a virtual reality setup using deep lstm recurrent neural network

Authors: *K. BINAEE, E. KRUEGER, G. J. DIAZ
Chester F. Carlson Ctr. for Imaging Sci., Rochester Inst. of Technol., Rochester, NY

Abstract: Human visual-motor processing system is known to be extremely efficient in terms of extracting useful information only from retinal images and also being robust to sources of perturbation. We deal with many constraints such as foveated vision and motor delay, yet we compensate for them by predictive and timely redirection of our gaze toward important visual cues. Yet it is not clear whether this prediction is solely based on available visual information or some complicated model of the world. In this study we use a Long Short Term Memory (LSTM) recurrent neural network (RNN) to model human hand-eye coordination in a Virtual Reality setup. We used a VR ball catching paradigm to record 3D gaze of ten subjects as well as their head and hand movements. During data collection we randomized different ball trajectories to create a data set that encompasses variability comparable to the real world scenario, and constrained the available visual information by making the virtual ball disappear for 500 ms. We proposed an LSTM-RNN model that takes only a combination of visual and proprioceptive information as input and generates the next gaze, hand and head position and orientation. The model is trained using successful human performance as ground truth. This approach provides a flexible tool to model/investigate strategies that we pursue at different times.After the training process we verified that the model behaves very similarly to human in terms of gaze, head and hand movements. Then by various perturbation of input and monitoring change in network states we reveal temporal and inter-feature correlation between proprioceptive and visual information. Proposed model captures human characteristics in two different ways. It relies on only a group of available visual information at different portion of the trial. For instance during the blank period the model weights more the contribution of previous target visual information and current proprioceptive signal. Furthermore the quality of model perdition in time leading to success is on average up to the reported value for motor delay in previous studies. For instance the hand prediction positioning error that corresponds to ball interception is only valid up to 150-300 ms.

Disclosures: K. Binaee: A. Employment/Salary (full or part-time):; Rochester Institute of technology. **E. Krueger:** A. Employment/Salary (full or part-time):; Rochester Institute of

technology. **G.J. Diaz:** A. Employment/Salary (full or part-time):; Rochester Institute of technology.

Nanosymposium

549. Visually-Guided Reach and Grasp

Location: 152B

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***549.02

**Topic: ***E.04. Voluntary Movements

Support: German Research Foundation DFG GA1475/4-1 (Research Unit 1847)

Title: Neural encoding of far-located reach goals in motor, premotor, and parietal cortex in a physically unconstrained monkey performing a walk-and-reach task

Authors: *M. BERGER[1,2], A. GAIL[1,2,3]
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Abstract: Goal-directed movements are mostly studied in highly constraining environments to reduce behavioral complexity, and to allow detailed behavioral and physiological measurements, like intracortical recordings in sensorimotor neuroscience. Yet, physical constraints forbid studying goal-directed behavior aiming at targets outside the immediate reach, for example, objects which first need to be approached by locomotion. Psychophysical and neuropsychological studies suggest that motor-related spatial cognitive processing differs between peri- and extrapersonal space. Here, we investigated movement planning and execution while a freely moving monkey was performing a structured goal-directed task. Particularly, we ask if motor goal encoding in reach-related cortical areas exists for motor goals outside of immediate reach, for which the monkey had to relocate its body to reach them (far targets).
For our walk-and-reach task, we developed target devices equipped with touch sensors and LEDs and placed them within a 2 m^3 enclosure in which the monkey could move freely. Target devices served as visual cues, hold buttons, and reach goals. The animal performed a delayed reach task. At trial start two hold buttons had to be touched. Then a visual cue instructed which of eight targets (4x near, 4x far) had to be reached after an instructed delay. Near targets could be directly reached from the starting position. Far targets required the monkey to relocate the body before reaching. We recorded wirelessly from six intracortical 32-channel floating microelectrode arrays (FMAs), two each in the parietal reach region (PRR), dorsal premotor cortex (PMd), and the hand/arm region of the primary motor cortex (M1).
Substantial fractions of neurons in all three areas showed activity selective for target distance

during movement planning. During planning (instructed delay) and target acquisition, fewer neurons were directionally selective for horizontal target position for far targets than for near targets. Several neurons were suppressed during locomotion but regained activity just before target acquisition. In conclusion, our experimental setup proved suitable for recording intracortical brain activity from a freely moving monkey performing a structured goal-directed sensorimotor task. Even though posture and head orientation were not physically constrained, our data for near targets resembles motor-goal encoding obtained from conventional setups. Preliminary results in the walk-and-reach condition suggest that during motor planning prior to relocation of the body, reach motor goals are, if at all, less strongly encoded in reach-related sensorimotor cortex.

Disclosures: M. Berger: None. **A. Gail:** None.

Nanosymposium

549. Visually-Guided Reach and Grasp

Location: 152B

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**Topic: ***E.04. Voluntary Movements

Support: German Research Foundation (DFG) SCHE 1575/1-1, SCHE 1575/3-1

Title: Three categorical subspaces explain population dynamics in the fronto-parietal grasping network

Authors: *B. DANN, J. A. MICHAELS, A. AGUDELO-TORO, H. SCHERBERGER
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Abstract: The fronto-parietal neuronal network is known to be fundamental for higher cognitive functions such as sensory categorization, decision making, movement preparation, and execution. Yet, how this information is encoded and transformed in the system is still a matter of debate. We addressed this question using parallel recordings from many neurons in the fronto-parietal grasping network of the macaque monkey while animals were either visually instructed or freely choosing to grasp a handle with one of two grip types. When we analyzed the neuronal population from the classical representational view, describing activity of individual neurons as a function of various parameters, a large number of neurons were significantly tuned in both the parietal and premotor area of the network (AIP and F5) and during all time points of the task. However, tuning changed dynamically over time and tuning parameters were uniformly distributed across the population, both at odds with the classical view. In contrast, when we considered the whole neuronal population as one strongly interconnected network, in which

neural population activity evolves dynamically through space-space over time and conditions, as suggested by the dynamical system perspective, a clear low dimensional structure became apparent. All task specific single trial activity could be explained by an evolution through just three independent informational subspaces representing visual, preparatory, and movement activity. Interestingly, for free-choice trials, where no specific visual information was given, all task specific activity during the decision process was explained by the preparatory space, suggesting that decision related activity and preparatory activity the same for this task. Also changes of mind, e.g., when enforced by a late visual instruction, were clearly visible in the preparatory space. Crucially, contributions to all three informational spaces were randomly distributed across neurons with no significant category structure. Furthermore, a regularized recurrent neuronal network trained to produce muscle activity for the two grasps could well reproduce the neuronal dynamics both at the single unit and the population level. These results indicate that instead of addressing attributes to individual neurons, neuronal activity can be better understood at the population level, where a neuronal population can encode different processes at different as well as overlapping times, which can be dynamically transformed according to the behavioral demands.

Disclosures: B. Dann: None. **J.A. Michaels:** None. **A. Agudelo-Toro:** None. **H. Scherberger:** None.

Nanosymposium

549. Visually-Guided Reach and Grasp

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**Topic: ***E.04. Voluntary Movements

Support: Deutsche Forschungsgemeinschaft (SCHE 1575/3-1)
Bundesministerium für Bildung und Forschung (BCCN-II, 01GQ1005C)
European Commission (FP7-611687, NEBIAS)

Title: A modular neural network model of the primate grasping circuit

Authors: *J. A. MICHAELS[1], S. SCHAFFELHOFER[2], A. AGUDELO-TORO[1], H. SCHERBERGER[1,3]
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Abstract: Grasping objects is an essential part of primate behavior. In macaque monkeys, the core of the grasping circuit is formed by the interconnected anterior intraparietal area (AIP) in

the parietal lobe, the hand area (F5) of the ventral premotor cortex, and the hand area of the motor cortex (M1). Generating appropriate delayed grasping movements involves many inter-related steps, from identification of visual target identity and spatial location, to the determination and working-memory of the appropriate hand shape, and finally the direct control of muscles during movement. Yet, very few neural network models of this process exist. We hypothesized that the grasping circuit could be effectively modeled by training a recurrent neural network on processed visual images to output muscle length as a linear combination of neural firing rates. The network was composed of three internally recurrent modules sparsely connected to each other: an input module receiving visual information, reciprocally connected with an intermediate module, which was reciprocally connected to an output module controlling muscle velocity. To train and test our model, we recorded from large neural populations of spiking activity simultaneously from AIP, F5, and M1 using floating microelectrode arrays while two macaque monkeys performed a delayed grasping task with a memory component, in which ~50 objects of distinct shape, size, and orientation had to be grasped and lifted. During every trial, 27 degrees of freedom (DOF) kinematics of the arm and hand were recorded using a tracking glove, which were further transformed into a 50 DOF muscle length space using a musculoskeletal model. The network model was successfully trained to produce the observed single-trial muscle velocities during grasping, while withholding movement at all other times. Importantly, biological regularizations were implemented to encourage simplistic solutions (input/output weight penalty, firing rate penalty, complex state trajectory penalty), which resulted in a high similarity between the neural data and the model. Crucially, the AIP data best matched the input module, the F5 data best matched the intermediate module, and the M1 data best matched the output module of our network. Our model therefore provides a simplistic and accurate representation of the primate grasping circuit and suggests that the combined processing of these areas can be well understood as a network optimized to transform object information into the muscle movements required to grasp each object.

Disclosures: **J.A. Michaels:** None. **S. Schaffelhofer:** None. **A. Agudelo-Toro:** None. **H. Scherberger:** None.

Nanosymposium

549. Visually-Guided Reach and Grasp

Location: 152B

Time: *Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

Presentation Number: *549.05

Topic: *D.09. Visual Sensory-motor Processing

Title: Combining choice-related activity measurement and electrical perturbation to probe readout of sensory signals

Authors: *X. YU[1], Y. GU[2]
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Abstract: One frequently applied method for associating neural activity with the animal's perceptual choice is to identify choice realted signals in sensory cortices. In particular, choice related signals describe how neuronal responses covary with perceptual choices on a trial by trial basis. It also quantifies how much an ideal observer can predict the upcoming choice totally based on the preceding responses. Choice related signals so far have been identified among many sensory areas, and have been used as a tool for probing readout. However, this traditional view has now received increasingly arguments as in numerous theoretical works, yet experimental evidence is still missing. In the current study, we combined choice related activity measurement and electrical perturbation technique to probe readout of visual motion signals from multiple sensory cortical areas including MST, MT and VIP. We identified two groups of cells with roughly equal proportion: sensory-choice congruent cells (SCCC) in which choice signals are congruent with respect to the sensory preference, and sensory-choice opposite cells (SCOC) in which choice signals are incongruent with the sensory preference. We found that in areas of MST and MT, microstimulating SCCC generated effects on the animal's behavioral choice that were consistent with the choice-related signals. In contrast, stimulating SCOC generated effects opposite to the choice-related signals. Based on these experimental results, we proposed two points that could underlie this phenomenon. First, SCOC is correlated with SCCC in a way that is unexpected from the normal noise-signal correlation structure.. Second, the readout weight of SCOC should be degraded compared to SCCC. To test this, we constructed a feed-forward network model that implemented the above two conditions. We showed that the model reproduced data pattern similar to that seen in the neurophysiological experiment. Finally, our work also show that although choice related signals in area of VIP is much higher compared to those in MST/MT, microstimulation does not generate any significant effect. Hence, unlike MST/MT, the choice related signals in VIP may not be bottom up in origin, but rather top down. Our work provides a new scenario to deduce decoding process by combining choice-related signal measurements and causal-link techniques such as microstimulation.

Disclosures: X. Yu: None. **Y. Gu:** None.

Nanosymposium

549. Visually-Guided Reach and Grasp

Location: 152B

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**Presentation Number: ***549.06

**Topic: ***D.09. Visual Sensory-motor Processing

Support: NIH Grant NS011862

Title: Parietal cortical responses to grasping actions

Authors: *E. P. GARDNER[1], D. GARDNER[2], J. L. BAKER[3], K. P. PURPURA[3], J.-W. RYOU[3], J. CHEN[1]
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Abstract: To investigate neural mechanisms mediating unimanual and bimanual prehension, we compared actions of the left and right hands in a reach-grasp-and-pull instructed delay task. Neural activity was recorded bilaterally with multiple electrode arrays implanted in the hand area of posterior parietal (PPC) and S1 cortex of macaques when the animal used the left, right or both hands to manipulate objects that differed in shape and location in the workspace. Simultaneous recordings from multiple sites in the parietal lobe allowed us to measure and compare the relative timing, amplitude and synchronization of cortical activity within and between hemispheres as animals skillfully grasped various objects with either hand. Neurons in both hemispheres showed common task-related firing patterns, but actions of the contralateral hand generally evoked stronger responses than those of the ipsilateral hand. S1 neurons (areas 2 and 5) altered their firing rates during reach, hand preshaping, and grasp with the contralateral hand, but rarely with the ipsilateral hand. Peak responses occurred when the hand initially contacted the object; high firing rates continued during grasp and pull, but dropped or were inhibited during static holding. The majority of neurons signaled the release of grasp with another burst as the hand was withdrawn from the object. Few SI neurons responded to the task instructions during the delay period. Simultaneously recorded PPC neurons bordering the IPS responded earlier in the trial when the GO-signal was presented, again with peak activity during contact and grasp. PPC neurons of the IPL (area PFG) generally responded during the cue period, when the rewarded object was signaled, maintained or increased firing rates when reach and grasp occurred, and decreased firing during static hold. IPL neurons responded to similar actions of both hands, showing strong excitation during both planning and execution of goal directed grasping actions. These findings with simultaneous recordings reinforce earlier studies that PPC neurons bordering the IPS are activated before SI cortical cells, and play important cognitive and motor functions in skilled hand actions.

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Nanosymposium

549. Visually-Guided Reach and Grasp

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**Topic: ***D.07. Vision

Support: NIH, 5R01 EY015545-12
Boswell Foundation
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Tianqiao and Chrissy Chen Brain-Machine Interface Center at Caltech

Title: PPC encodes an internal model of arm position in visual coordinates

Authors: *T. AFLALO[1], M. ABBAS[3], C. ZHANG[2], M. JAFARI[2], N. POURATIAN[4], R. A. ANDERSEN[2]
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Abstract: The posterior parietal cortex (PPC) has been hypothesized to encode an internal model of the state of the body. There is little direct neural evidence to support this hypothesis and experiments are complicated as the variables that describe the model are highly correlated with the sensory and motor efference signals that are used to construct the internal estimate. Hypothetically, the ability to measure changes in the internal estimate of limb state in the absence of sensory feedback could provide strong evidence for the internal model hypothesis. Here we adopt this approach in a tetraplegic human.
Motor imagery has been proposed to be the manipulation of an internal model in the absence of overt movement. We recorded single neurons in the PPC of a tetraplegic patient implanted with Utah arrays for a brain-machine interface clinical trial during motor imagery. We asked the patient to perform a center-out imagined reaching task while manipulating the initial imagined arm configuration and point of fixation. Analysis focused on a period when the hand and eye positions were held at this initial configuration, after a dynamic masking stimulus extinguished hand position cues, but before a reach target was presented. We analyzed 431 cells acquired over 4 sessions to characterize unit responses as tuned to eye position independent of hand position (2.3% of tuned cells), hand position independent of eye position (9% of tuned cells; reflecting allocentric or body-centered coding), or tuned to the position of the hand relative to the eye (75% of tuned cells; eye-centered coding of hand position). The large majority of tuned cells (17% of 431, $p<0.05$ uncorrected) were best characterized as encoding the position of the hand relative to the eye.
To ensure that tuning did not reflect global spatial signals (e.g. working memory), we had the participant perform a spatial match-to-sample task (5 sessions, 519 recorded units). The task was

visually identical to begin, however, the participant was instructed to fixate and simply remember the “hand” cue position for a later report. No sustained tuning was found despite its task relevance. From these results we conclude that individual neurons in human AIP encode an internal model of the position of the arm in a visual reference frame.
Previous studies that decode position for use in neural prostheses have implicitly assumed that position is coded in a body centered or allocentric reference frame. While such assumptions may hold for other cortical regions, our results contradict this assumption and may partially account for why velocity/direction based decoding methods have outperformed methods that utilize position.

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Nanosymposium

549. Visually-Guided Reach and Grasp

Location: 152B

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***549.08

**Topic: ***D.09. Visual Sensory-motor Processing

Support: Brain-in-Action NSERC-CREATE
NSERC
Canada Research Chair Program

Title: Transsaccadic updating of object orientation for grasp planning: An fMRIa study

Authors: *B.-R. BALTARETU[1], *B.-R. BALTARETU[1,2], S. MONACO[2,3], J. VELJI-IBRAHIM[1,2], G. N. LUABEYA[1,2], J. CRAWFORD[1,2]
[2]Ctr. for Vision Res., [1]York Univ., North York, ON, Canada; [3]Univ. of Trento, Ctr. for Mind/Brain Sci., Trento, Italy

Abstract: It has been shown that intraparietal cortex is involved in the spatial updating of reach locations (Batista et al., 1999; Medendorp et al., 2003), and that extrastriate and inferior parietal cortex are involved in the transsaccadic perceptual integration object orientation (Dunkley et al., 2016). However, it is not known how object orientation is processed across saccades for planning grasping movements. Here, we used an fMRI-adaptation-inspired paradigm to investigate if saccades produce modulations in cortical areas involved in orientation-specific grasp plans. In each trial, participants (n=13) were instructed to fixate an LED left or right of center, and prepare to grasp an object. A central elongated object (oriented 0° or 135°) was illuminated at center, then the subject either fixated or made a saccade to the opposite side, and then the object was re-

presented at the same (Repeat) or different (Novel) orientation. After the second presentation, participants grasped the object. We analyzed the second illumination period to identify modulations of grasp plans are based on: 1) spatial/gaze parameters (Saccade: Novel + Repeat orientation > Fixation: Novel + Repeat orientation) and 2) orientation (Novel orientation: Saccade + Fixation > Repeat orientation: Saccade + Fixation). During grasp planning, saccades recruited a broad swath of cortex, including: left lingual gyrus (LG), lunate sulcus, middle occipital gyrus, cuneus, posterior intraparietal sulcus (pIPS), and superior parietal lobule, right calcarine sulcus and cingulate gyrus, and bilateral transverse occipital sulcus (i.e., occipital place area, OPA), superior occipital gyrus, anterior precuneus. The orientation specific areas were right inferior temporal gyrus, middle temporal gyrus (MTG), inferior occipital gyrus (IOG), supramarginal gyrus, and post aIPS. To identify the areas that were modulated by both saccade and orientation changes, we took the conjunction between these two contrasts. Activation was found in bilateral superior parietal lobule, left pIPS, superior parieto-occipital cortex, OPA, precuneus, LG, lateral occipitotemporal gyrus, and medial occipitotemporal sulcus. Likewise, an analysis of orientation specificity in saccade-only data revealed modulations in MTG and LG. These data suggest that saccades and orientation changes may interact at an early stage to update grasp plans, but produce widespread modulations of activation through occipital, temporal, and parietal cortex.

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Nanosymposium

549. Visually-Guided Reach and Grasp

Location: 152B

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***549.09

**Topic: ***E.04. Voluntary Movements

Support: European Union's Horizon 2020 research and innovation programme under grant agreement No. 720270

Title: Wide-field imaging of cortical activity in mice performing reach-to-grasp movements

Authors: *E. QUARTA[1,2], A. L. ALLEGRA MASCARO[1,3], C. CAMPAIOLI[1,2], L. SACCONI[1,4], F. S. PAVONE[1,2,4]
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Abstract: Nervous systems can be regarded as machines producing movements (Graziano, 2008). Investigating motor control in rodents allows leveraging on powerful genetic and optic tools for circuits interrogation. The reach-to-grasp task has been recently adapted for head-fixed mice, opening the way for analysis of neurophysiological parameters (Guo et al., 2015). Until now, the cortical activity patterns of mice during learning and execution of these movements have not been elucidated. To fill this gap, we developed a setup for concurrent kinematics analysis of grasping movements and neural activity in head-fixed mice.
Our experimental subjects are mice expressing a fluorescent calcium indicator of neural activity (GCaMP6f) selectively in excitatory neurons. Two high-speed (HS) cameras allow recording of limb movements with high precision. Fluorescent calcium imaging of cortical activation over both hemispheres is performed via wide-field microscopy. Pellets are delivered on a turntable mounted on a servomotor, which is controlled by an Arduino board via an ad-hoc program. During the behavioral task mice have to reach and grasp for pellet placed in front of them. The HS cameras, the camera for calcium imaging, and the Arduino board are synchronized to each other.
We follow the time course of cortical activity as the mice learn to grasp for pellets. Using an ad-hoc software, the recorded forepaw movements are tracked to extract trajectories. Spatio-temporal aspects of grasping are confronted to the patterns of neural activity to dissect the relations between movement and cortical functionality. Cortical activation patterns during the shaping and consolidation phase of learning are dissected to find neuronal correlates of motor performance refinement. Perturbation of the sensory-motor integration process via injury or neuronal modulation allow assessing the robustness of the learned skill.
To our best knowledge, this is the first study that unifies wide-field imaging of cortical activity with the analysis of grasping movements. This combination will be instrumental for advancing our knowledge on the neural correlates of motor control.

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Nanosymposium

549. Visually-Guided Reach and Grasp

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**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***549.10

**Topic: ***D.09. Visual Sensory-motor Processing

Support: USC ASPIRE Postdoctoral Award

Title: Interference between oculomotor and limb motor movements in stroke survivors

Authors: *T. SINGH[1,2], C. M. PERRY[2], T. M. HERTER[2]
[1]Exercise Sci., Med. Univ. of South Carolina, Charleston, SC; [2]Dept. of Exercise Sci., Univ. of South Carolina, Columbia, SC

Abstract: *Background.* Activities of daily living, such as driving and walking, require fast oculomotor movements (saccades) to gather visual information that guides motor planning and execution. Most stroke survivors experience chronic difficulties performing these daily activities. We have previously shown that stroke survivors with mild motor impairments and no visuospatial neglect make a greater number of saccades than age-matched controls during planning and initiating arm movements (reaching). The excessive number of saccades result in relatively worse overall motor performance by the stroke survivors. However, the precise nature of the interaction between the oculomotor and limb motor processes relationship remain unclear. *Objective.* Here, using robotics and eye-tracking, we investigate whether saccades interfere with speed and smoothness of reaching movements in stroke survivors. *Methods.* We examined saccades and reaching in stroke survivors and healthy controls who performed the Trail Making Test (TMT), a neuropsychological test of visuomotor processing and executive function that relies on organized patterns of saccades to guide reaching movements. *Results.* Compared to age-matched controls, stroke survivors made a greater number of saccades during reaching movements. In both controls as well as stroke survivors, most of these saccades were closely followed by a transient decrease in reaching speed. Furthermore, in stroke survivors, the number of saccades made during reaching were strongly associated with reduced speed and smoothness of reaching movements and with greater difficulty performing daily activities (measured using Stroke Impact Scale). *Conclusions.* These results indicate that post-stroke neural damage produces interference between eye and limb movements that may cause deficits performing motor skills. This also suggests that clinical assessments and treatments for post-stroke impairments of visual search could facilitate improvements in motor performance.

Disclosures: T. Singh: None. **C.M. Perry:** None. **T.M. Herter:** None.

Nanosymposium

549. Visually-Guided Reach and Grasp

Location: 152B

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:45 PM

**Presentation Number: ***549.11

**Topic: ***E.05. Brain-Machine Interface

Support: H2020 SME Phase 2 recoveriX

Title: RecoveriX - A clinical study for improvement motor functions of stroke patients with a brain-computer interface that control and avatar and functional electrical stimulation

Authors: *G. EDLINGER[1], W. CHO[2], R. ORTNER[2], J. SWIFT[3], S. DIMOV[2], C. GUGER[2]
[1]G.Tec Med. Engin. Gmbh, Schiedlberg, Austria; [2]g.tec medical engineering GmbH, Schiedlberg, Austria; [3]g.tec neurotechnology USA Inc., Albany, NY

Abstract: A BCI detects the neuronal activity of patients' motor intention and controls external devices to provide appropriate sensory feedback via peripheral nervous system to central nervous system (CNS). When the feedback is timely sent to CNS according to the motor intention with multiple training sessions, the neuronal network in the brain is reorganized due to the neuroplasticity. In this current study, a BCI controlled an avatar and functional electrical stimulation (FES) to provide the visual and proprioceptive feedback respectively. The expected task was to imagine either left or right wrist dorsiflexion according to the instructions in randomized sequences. Then, the linear discriminant analysis and common spatial filter classified the brain activity acquired by EEG. The avatar and FES were triggered only upon correct classification. The avatar of forearms was presented to patients in the first-person point of view, and FES produced a smooth passive dorsiflexion of the patient's wrist. The training was designed to have 25 sessions (240 trials of either left or right motor imagery) of BCI feedback sessions over 13 weeks. Two days before and two days after the BCI training intervention, five clinical measures were used to observe any motor improvement. The primary measure was upper extremity Fugl Meyer assessment (UE-FMA) which evaluates the motor impairment. Four secondary measures were also performed to exam the spasm (modified Ashworth scale, MAS), tremor (Fahn tremor rating scale, FTRS), level of daily activity (Barthel index, BI), and finger dexterity (9 hole peg test, 9HPT). One male stroke patient (53 years old, 11 months since stroke onset, and paralysis in his right upper limb) participated in the training. He quickly learned to use the BCI system and the average of maximal classification accuracy was over 90% after the 5th session. The UE-FMA jumped from 25 to 46 points after the intervention and his behavioral improvement was also detected in the secondary measures. The BI increased from 90 to 95 points, meaning that he could be more independent in his daily activity. MAS and FTRS decreased from 2 to 1 and from 4 to 3 points respectively, implying less spasticity and tremor in his hand. Although he could not conduct the 9HPT until 18th training session, he was able to complete the test from 19th session in 10 mins 22 secs and the time was reduced to 2 mins 53 secs after 25th session. The system is currently validated with 10 validation partners in Japan, USA, Austria, Spain and China and a group study with 50 patients including a control group with only FES will be finished soon.

Disclosures: **G. Edlinger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); g.tec medical engineering GmbH. **W. Cho:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **R. Ortner:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **J. Swift:** A. Employment/Salary (full or part-time):; g.tec neurotechnology USA Inc. **S. Dimov:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **C. Guger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); g.tec medical engineering GmbH.

Nanosymposium

550. Motor Control and Internal Representations

Location: 147A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***550.01

**Topic: ***E.04. Voluntary Movements

Title: Movement-related dynamics of thalamocortical oscillatory activity in Essential tremor

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Abstract: Objective: Recent Electrocorticography (ECoG) data from sensorimotor cortices in essential tremor (ET) patients have demonstrated movement related desynchronization of α and β oscillatory activity. Despite our current understanding about regulatory role of basal ganglia in movement related β desynchronization, the origin of movement related α oscillations is not yet fully understood. According to the role of thalamus in modulating the resting state thalamocortical α rhythm, investigating such oscillatory activity in the thalamocortical network may provide insight into the origin of movement related α suppression in cortex.
Methods: ECoG signals were recorded from a non-penetrating subdural strip implanted over the hand area of the right sensory motor cortex. Concurrent LFP recordings were obtained from the DBS lead implanted in the Ventral intermediate (ViM) nucleus of the thalamus. Signals were recorded during 30 seconds blocks of rest and contraletral hand finger tapping. No action tremor was observed during recordings. Bipolar signals from most ventral DBS contact pair and cortical signals extending over pre and post central sulci were selected for analysis. Signals were band passed filtered (2-600Hz). Power spectral density was calculated using multitaper method. Connectivity between ViM and cortical nodes were measured using debiased weighted phase lag indices (dwPLI). This method was specifically chosen to exclude effects of volume condition. A two group permutation test was used to assess statistical significance of differences between rest and movement power and connectivity ($P<0.05$, corrected).
Results: Our findings verified the movement related α and β desyncrhonization in sensorimotor cortices. We found similar behavior in the ViM in α and low β bands. The ViM high β oscillation however, did not show any significant movement-related modulation. ViM-sensorimotor cortices were significantly coupled at α and low β frequencies during rest. Movement affected thalamocortical coupling by: (1) suppression of α and low β coupling between the ViM and cortex, (2) increase in high β coupling between the ViM and motor cortex.
Conclusions: Our results provide evidence for local and interregional α/low β synchrony in thalamocortical network in ET. Successful execution of movement suppressed such coupling both locally and inter-regionally. Opposite direction of change in α/low β and high β synchrony between thalamus and cortex also points to the differential role of these two bands in thalamicortical network.

Disclosures: **S. Niketeghad:** None. **M. Malekmohammadi:** None. **N. Pouratian:** None.

Nanosymposium

550. Motor Control and Internal Representations

Location: 147A

Time: *Tuesday, November 14, 2017, 1:00 PM - 3:15 PM

Presentation Number: *550.02

Topic: *E.04. Voluntary Movements

Support: ONR Global (N62909-15-1-2002)
Fondazione Roma (NCDS-2013-00000349)
D1 Funds Università Cattolica

Title: Anodal transcranial direct current stimulation modulates motor cortex plasticity and enhances motor performances in healthy and stroked mice

Authors: M. V. PODDA, S. COCCO, S. A. BARBATI, V. LONGO, K. GIRONI, L. LEONE, M. MAINARDI, *C. GRASSI
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Abstract: Several studies have demonstrated that anodal transcranial direct current stimulation (tDCS) over the motor cortex facilitates motor learning in healthy subjects and promotes motor recovery after stroke. However, more in-depth understanding of cellular and molecular mechanisms underlying tDCS action is needed for a rational use of this technique in clinical settings.
Aim of the present study was to investigate the effects of tDCS on synaptic transmission and plasticity in the mouse primary motor cortex (M1). Electrophysiological, behavioral and molecular analyses were performed following 20-min single (1×) or repeated (3×, delivered once a day) anodal tDCS sessions (current density 40-56 $\mu A/mm^2$).
Results showed that long-term potentiation (LTP) at layer II/III horizontal connections was enhanced in 3×tDCS mice compared to sham-stimulated controls (66.5 ± 11.4 *vs.* 38.5 ± 5.8%, respectively; $P<0.05$). Instead, 1×tDCS did not affect LTP. Input-output curves as well as amplitude and frequency of mEPSCs in M1 pyramidal neurons were significantly modified in tDCS mice, thus suggesting that basal synaptic transmission is also affected by tDCS. Molecular analyses showed that tDCS induced: i) increased levels of $pCREB^{133}$ and $pCaMKIIThr^{286}$, 3 h after stimulation; ii) enhanced mRNA levels of the transcription factor Mef2c and of Bdnf exon IX, 24 h after stimulation.
Analysis of skilled motor behavior by "single pellet reaching task" showed that success rate in pellet retrieval was enhanced in tDCS mice (successful reaches/total attempts: 26.5 ± 7.7 *vs.* 9.2 ± 1.2%; $P<0.05$). The speed of success was similarly increased in tDCS mice (successful

attempts/min: 0.98 ± 0.04 vs. 0.24 ± 0.06; P<0.01). No changes of these parameters were observed in control mice.
In mice subjected to Rose Bengal photothrombotic stroke, tDCS enhanced motor performance of the paretic limb in the pellet retrieval (success rate 1 week after stroke: 11.33 ± 1.96 in 3×tDCS stroked-mice *vs.* 4.58 ± 2.31% in sham stimulated stroked-mice; P<0.05; speed of success 1 week after stroke: 0.76 ± 0.11 in 3×tDCS stroked-mice *vs.* 0.31 ± 0.17 in sham-stimulated stroked-mice; P<0.05). In addition, grip-strength test revealed an enhancement of neuromuscular strength in stroked-mice subjected to tDCS (strength/weight 1 week after stroke: 3.2 ± 0.2 in 3×tDCS stroked-mice *vs.* 2.5 ± 0.2 in sham stimulated stroked-mice; P<0.05).
Collectively, these data indicate that tDCS improves motor functions both under physiological conditions and after stroke, probably via increased plasticity of the motor cortex relying on CREB/CaMKII phosphorylation and Bdnf/Mef2c expression.

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Nanosymposium

550. Motor Control and Internal Representations

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Presentation Number: *550.03

Topic: *E.04. Voluntary Movements

Support: BOF/BILA Grant from the Flemish Government

Title: Enhancing bimanual motor coordination in healthy young and older adults using EEG and transcranial direct current stimulation (tDCS)

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Abstract: Introduction: Accompanying the natural advancing of age is a decline in cognitive and motor functions, which can significantly impact the daily life activities in the elderly (>65 y). Such declines may involve altered neuroplasticity, due to changes in synaptic function and neurotransmission. Successful performance of complex motor tasks may also involve specialized functionally connected networks, which may also be subject to age related changes. Recent work has shown that transcranial direct current stimulation (tDCS) may be a useful tool to restitute

these altered mechanisms, and improve performance of motor skills.
Objectives: This study first seeks to identify physiological markers of age-related differences during acquisition of new bimanual motor movements, based on motor cortical functional connectivity, using EEG. Second, the study assesses whether performance of complex bimanual motor skills can be enhanced using tDCS.
Methods: *Experiment 1*: 43 healthy subjects (22 young/21 elderly) were recruited. Subjects performed the bimanual tracking task (BTT), which is a complex task requiring the skilled use of in-phase and anti-phase movements, at various frequencies. The task were performed while EEG was recorded.
Experiment 2: An additional 40 subjects (20 young/20 elderly) were recruited for evaluating whether right M1 anodal tDCS (1.0 mA, 20 min) may improve performance in the task, particularly in the non-dominant left hand. The study was double-blinded, sham-controlled, and used a randomized crossover design in order to assess tDCS-induced performance and functional connectivity differences between young and elderly groups.
Results: Experiment 1: Task performance in younger subjects was more accurate than in elderly; young subjects showed significantly stronger functional connectivity in the theta power band, which was a good predictor for task accuracy.
Experiment 2: ANOVA revealed a main effect of stimulation, which was significant between sessions in the elderly but not in young. Further analyses revealed significant improvements in both left and right hand coordination in real stimulation conditions in both groups of subjects.
Conclusion: Both functional connectivity and inter-limb kinematics underlying bimanual motor coordination are different between the young and elderly. Moreover, a single session of tDCS applied to the motor cortex significantly improved bimanual performance in both young and elderly. Although further studies are needed to optimize tDCS parameters for prolonged effects, this non-invasive technique may be a viable tool in restituting the learning of complex motor functions in the aging population.

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Nanosymposium

550. Motor Control and Internal Representations

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**Topic: ***E.04. Voluntary Movements

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Title: Spontaneous emergence of behaviorally relevant motifs in human motor cortex

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Abstract: The goal of the study was to investigate whether spontaneous neural activity in the human motor cortex represents behaviorally relevant motor neural patterns. To this end we scanned a group of healthy participants (N=15) while they were not performing any task (resting-state scan), and while they performed simple motor tasks differing by their daily life relevance (multiple scans of each scan type). Based on previous work (Ingram et al, 2008) we chose two canonical hand movements as representing the most common hand movements in daily life. Two control movements were included, one not corresponding to the canonical movements, and one sharing a certain amount of similarity with them. We defined a motor ROI by performing a glm analysis contrasting motor performance with baseline activity (four movements combined to avoid biasing the ROI selection to a specific movement). We then defined a central-sulcus cluster on the surface of each participant in which this contrast was significant. To keep the size of the ROIs similar across participants we adjusted the p-level of the contrast until we ended up with an ROI size of 2187 vertices ±7%. We then verified that the BOLD patterns in this ROIs contain task relevant information. To do so we tested whether we could discriminate between the different hand movements using the BOLD pattern in the ROI with linear discriminant analysis (LDA) and a cross-validation leave-run-out method. In each participant, the classification was above chance (one-sample ttest $p<0.00001$). To test our hypothesis, we constructed a mean pattern for each hand movement in each participant (combining all task runs) and compared it to the spontaneous pattern in each resting state frame of that participant, recorded prior to performing the task scans. Similarity between task and rest patterns was evaluated using Pearson correlation. We computed the cumulative distribution function (CDF) of the r^2 values and identified a cut-off value that represents the cumulative 90% point for each movement and in each participant. The higher this value is the more similar the pattern is to the rest activation. By comparing the cut-off values of the different hand movements, we found a main effect of hand movement (rm-ANOVA $p=0.0029$), and a post-hoc ttest indicated that the BOLD patterns of the hand movement most relevant for daily life were significantly more similar to the resting state patterns than a less relevant hand movement ($p=0.0036$). This finding supports the hypothesis that spontaneous neural activity in the human cortex represents, at least in part, behaviorally relevant information.

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Nanosymposium

550. Motor Control and Internal Representations

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**Topic: ***E.04. Voluntary Movements

Support: National Science Foundation
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Title: Brain-machine interface guided movements share a common neural substrate with overt movements

Authors: *S. VYAS[1], N. EVEN-CHEN[1], S. D. STAVISKY[1], S. RYU[2], P. NUYUJUKIAN[1], K. V. SHENOY[3]
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Abstract: Mental rehearsal is hypothesized to derive from a similar physiological substrate as overt movement. Understanding whether population-level neural activity is shared between overt movements and internal motor-related mental processes (such as imagined or intended movements) could facilitate efforts to use such internal behavior, with appropriate feedback, to guide motor learning. Here we address this question by having monkeys perform the same cursor movement task either with natural arm reaches, or directly with neural activity (without arm movements) via a closed-loop brain-machine interface (BMI). The BMI context allowed us to observe what would otherwise be a covert and open-loop mental process related to the task. During BMI use, we introduced a visuomotor rotation (VMR) such that monkeys had to direct the cursor at an angle in order to make direct movements to the target. After adaptation, the context was switched to arm reaches without the rotation. Surprisingly, we found that reaches were biased in the direction opposite to the VMR, suggesting that adaptation did transfer from the BMI to the arm context ($p < 1e\text{-}5$). This adaptation was reflected in population-level motor cortical planning activity. After adaptation, the preparatory neural state resembled the state corresponding to preparing movements oriented in the opposite direction of the VMR. During the washout, this activity gradually rotated back to align with preparing movement towards the original target. We also found that these preparatory states were well aligned between BMI and overt movements (*Bhattacharya coefficient* < 0.05). Since motor preparation is believed to serve

as an initial state from which a movement-period neural dynamical system evolves, this provides a potential explanation for why the VMR transferred between contexts. Operationalizing these results, we demonstrated that monkeys adapted to VMRs faster during overt movements if they had first "rehearsed" the VMR using a BMI (p < 1e-3). These findings open the door to probing if BMI-mediated mental rehearsal can serve as a guided rehabilitation tool, especially when overt practice is not possible.

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Nanosymposium

550. Motor Control and Internal Representations

Location: 147A

Time: *Tuesday, November 14, 2017, 1:00 PM - 3:15 PM

Presentation Number: *550.06

Topic: *E.04. Voluntary Movements

Support: Wellcome Fellowship 110257/Z/15/Z

Title: A normative theory of motor plan representation for optimized neural encoding

Authors: ***D. MCNAMEE**[1], M. LENGYEL[2], D. M. WOLPERT[2]
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Abstract: A normative measure of the relative accuracy with which a population of neurons can encode a variable is normalized mutual information (NMI), the mutual information (MI) between the neural response and the variable divided by the entropy (H) of the target variable. Typically, in the sensory domain, NMI(S;R) is measured between the population response R and a stimulus S. In the motor control, we propose that the objective of a population of motor neurons is to maximize the mutual information NMI(U;R) between the population activity R and actuation variables U. A key distinction between the sensory and motor domains is the degree to which the entropy can be minimized. For example, in vision, one has limited control over incoming natural image statistics beyond effortful and transient attentional mechanisms and eye movements. In contrast, as motor plans are internally generated, the motor system has the option to optimize internal representations of motor plans which can dramatically impact the distribution of control variables U. As NMI(U;R) is inversely proportional to H(U), this implies that the nervous system should organise its motor plans in order to minimize H(U) throughout a movement. From a computational perspective, this leads to a trade-off between motor trajectory entropy (i.e. the variability of movement states) and the degree to which feedback gains alter the movement

dynamics (i.e. transform the distribution of the state-space). This trade-off makes quantitative predictions as to how the maximization of NMI requires some movements to be planned holistically and others to be chunked into separate plans. We test these predictions experimentally in human reaching by examining via-point movement in which we vary the relative direction of the movement components. Using a combination of model-based and model-free methods, we found that, over the course of motor adaptation, humans shifted their motor trajectories towards an optimal chunked representation for movement sequences with higher coherence (i.e. relatively little directional change) and toward optimal elemental representations for movement sequences with lower coherence (and sharper directional changes). These results support the notion of optimized neural encoding of motor plans.

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Nanosymposium

550. Motor Control and Internal Representations

Location: 147A

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***550.07

**Topic: ***E.04. Voluntary Movements

Support: Faculty Research Grant Program

Title: Spatial bias versus variance in pointing to visual and proprioceptive representations of hand position

Authors: *H. J. BLOCK, Y. LIU, B. M. SEXTON
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Abstract: BACKGROUND: When people point with an unseen hand to a visual or proprioceptive target, they make both variable and systematic (bias) errors. The role of variance in position estimation has been well studied, but less is known about spatial bias. We compiled data from over 80 healthy adults who pointed with their unseen right index finger at proprioceptive (left index finger), visual, and combined targets with no knowledge of results or performance feedback. We tested whether spatial bias is related to target modality, whether bias errors are related to spatial properties of variable errors, and whether the more variable sensory modality is also the more biased. We took advantage of subjects' natural spatial biases to compute an experimental weight of vision vs. proprioception on trials with both modalities, asking whether this parameter was related to either bias or variable errors. Finally, we tested the stability of pointing bias and variability, and weight of vision vs. proprioception, over time. RESULTS: Bias errors were related to target modality, with subjects estimating visual and

proprioceptive targets about 20 mm apart. Bias direction was closely related to the angle of the major axis of the confidence ellipse ($p < 0.001$), supporting the idea that bias occurs in the dimension that is most difficult for the brain to discriminate. Thus, spatial bias in position estimation appears dependent on both target modality and the spatial structure of pointing variance. For most subjects, the target modality that yielded greater spatial bias was also estimated with greater variance, suggesting that a minimum variance strategy of multisensory integration is unlikely to worsen spatial bias. Pointing variance, but not spatial bias, was correlated with experimental weight of vision vs. proprioception. This further supports a multisensory integration that minimizes variance rather than bias. Despite the lack of performance feedback, in a second session subjects improved their pointing variance, but not bias, for both target modalities. Pointing variance and bias and weight of vision vs. proprioception were each strongly correlated across sessions, suggesting these parameters are idiosyncratic but fairly stable. These results add to our understanding of the properties, origin, and stability of spatial biases in estimating the position of visual and proprioceptive targets.

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Nanosymposium

550. Motor Control and Internal Representations

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**Presentation Number: ***550.08

**Topic: ***E.04. Voluntary Movements

Support: H2020-MSCA-IF 656262

Title: The influence of social motivation on reaching precision

Authors: *I. COS-AGUILERA[1], G. DECO[2]
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Abstract: A foundation of behaviour is reward prospect: we move to attain valuable states. Moving towards those states implies investing a certain amount of effort and deploying motor strategies requiring specific parameters. To investigate the role of motivation in this choice of parameters and strategies, we performed a decision-making paradigm where healthy human participants, under different movement control conditions, had to make choices between reaching movements. Their goal was to accumulate reward by selecting one of two reaching movements of opposite biomechanical cost, and to perform their selected reaching towards the target. Maximum reward was contingent on aiming precision.
We manipulated the participants' motivated state via social pressure. Each experimental session

was composed of six blocks, during which subjects could either play alone or accompanied by another simulated player. Within this illusion, the amount of reward obtained by the participant and by his/her companion was reported at the end of each trial. The ranking for the two players was shown briefly every nine trials.
The results show that the subjects aiming improved proportionally to the skill of the accompanying player, meaning that subjects cared about their own performance. The main behavioural result was an increase of movement time when playing accompanied. Although this could be viewed as a simple adaptive process of trade-off between precision and time, we also recorded a reduction of velocity when the skill of the companion player was clearly unattainable. Such as a reduction of the amplitude escapes the traditional context of a speed-accuracy trade-off.
To further investigate the dynamics of adaptation under baseline and motivated conditions, we developed a generative computational model of decision-making and motor control, based on the optimization of the trade-off between the benefits and costs associated to a movement. Remarkably, the predictions of this model show that this optimization depends on the motivational context where the movements and the choices between them are performed. Although further research remains to be performed to understand the specific intricacies of this relationship between motor control theory and motivated states, this suggests that this inter-relation between internal physiological dynamics and motor behaviour is more than a simple modulation of the vigour of movement.

Disclosures: I. Cos-Aguilera: None. **G. Deco:** None.

Nanosymposium

550. Motor Control and Internal Representations

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**Topic: ***E.04. Voluntary Movements

Support: MIUR Grant PRIN 2015AWSW2Y
Fondazione del Monte di Bologna e Ravenna FdM/2313

Title: Visual and somatosensory properties of the caudal aspect of the macaque superior parietal lobule

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Abstract: In the superior parietal lobule (SPL), the anterior part (area PE) is known to process somatosensory information while the caudalmost part (area V6) visual information. Here, we studied the visual and somatosensory properties of neurons of the SPL areas that are located in between somatosensory and visual domains namely area PEc and V6Ad. About 1500 neurons were extracellularly recorded in 19 hemispheres of 12 awake, behaving monkeys (*Macaca fascicularis)*. Cells were attributed to areas PEc or V6A on the basis of cytoarchitectonic criteria. The location of each recorded cell and of cytoarchitectonic borders were reported on two-dimensional maps representing the cortex of the caudal SPL of single hemispheres. An averaged flattened cortical map of the region of interest was obtained by the superimposition of the maps of all studied animals. On this summary map, the entire population of recorded cells was reported. We studied in particular the visual and somatosensory properties of neurons of the nearby areas PEc and V6Ad, and compared their distribution and frequency in these two cytoarchitectonic fields (Chi-square test, $p<0.05$). Usually, visual and somatosensory properties of single neurons were studied separately (visually tested N=1208; somatically tested N=610), but in a subpopulation of neurons (N=334) both sensory properties were tested. Results showed that the two SPL areas contained a mix of visual and somatosensory neurons, with visual neurons more represented in V6Ad (56% vs 40%) and somatosensory neurons more represented in PEc (67% vs 43%). The visual neurons of the two areas showed similar properties and represented large part of the contralateral visual field, mostly the lower part, from the center to the far periphery. In contrast, the somatosensory neurons showed remarkable differences in the two areas. In both areas there was an overrepresentation of the arms, more pronounced in V6Ad (V6Ad, 90%; PEc, 66%). However, V6Ad represented only the upper limbs whereas PEc both the upper and the lower limbs. Interestingly, we found that bimodal visual-somatosensory cells represented in both areas the proximal portion of the arms and, much less, the trunk near the arms; they did not represent the hands, or the legs either the head. Present results strongly support the view that PEc is involved in locomotion and in the control of hand/foot interaction with objects in the environment, while V6Ad in the control of object prehension specifically performed with the upper limbs.

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Nanosymposium

551. Animal Models for Depression: Behavioral and Chemical Approaches

Location: 147B

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***551.01

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH-MH099851
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Huck Graduate Innovation Award

Title: Chronic high fat diet leads to increased neural excitability and cognitive deficits

Authors: *M. FENG[1], N. A. CROWLEY[1], A. PATEL[1], B. LUSCHER[2]
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Abstract: Excessive consumption of fat-rich diet and obesity are associated with increased vulnerability to psychiatric disorders including anxiety and depression. Rodents fed with a high fat diet (HFD) display significant weight gain, glucose intolerance, increased expression of inflammatory cytokines and behavioral signs of depressive-states. In order to elucidate the neural mechanisms underlying HFD induced changes in brain state, we exposed C57BL/6J male mice to HFD for 18 weeks followed by behavioral analyses in a number of depression related behavioral and cognitive tests thought to be insensitive to changes in locomotion and feeding. HFD exposure of male mice resulted in glucose intolerance, diabetic-like hyperglycemia and elevated expression of the inflammatory cytokines TNFα and IL-6. Similar but insignificant trends were evident in female mice. The HFD induced metabolic changes of male mice resulted in anhedonia-like behavior in the female urine sniffing test and sucrose splash test. Curiously, these phenotypes were insensitive to treatment with the antidepressant ketamine, although HFD treated animals showed increased sensitivity to the antidepressant-like effects of ketamine (6mg/kg) in the forced swim test. Slice recordings of HFD-treated animals revealed increased intrinsic excitability of pyramidal neurons in the medial prefrontal cortex (mPFC), along with increased currents mediated by hyperpolarization-activated cation channels (I_h). This cellular phenotype was reversible by systemic treatment of mice with retigabine (1mg/kg/day, 8 days), a voltage-gated K^+ channel opener that increases outward K^+ currents and thereby reduces neural excitability. Moreover, preliminary evidence indicates that HFD-induced behavioral and cognitive deficits may be reversible by retigabine. Our study suggests that HFD induced inflammation leads to increased intrinsic excitability of pyramidal neurons that underlie obesity and diabetes-associated behavioral and cognitive abnormalities and can be normalized pharmacologically by agents that reduce neural excitability.

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Nanosymposium

551. Animal Models for Depression: Behavioral and Chemical Approaches

Location: 147B

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**Presentation Number: ***551.02

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

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Title: Glutamatergic markers in the lateral habenula and caudal dorsal raphe are associated with neurocircuitry of depressive-like behavior

Authors: *M. M. MIRRIONE[1], A. S. ALHARBI[2], J. WILLIAMS[3], C. E. LARKIN[4], C. M. MERCUGLIANO[5], J. S. MEARS[6], M. A. MUCCI[4], F. HENN[7]
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Abstract: Improving treatment of patients with major depressive disorder requires detailed molecular and cellular analysis of dysfunctional neural circuits and identification of novel drug targets. Validated animal models of depressive-like behavior, such as learned helplessness, are crucial in elucidating molecular and cellular pathways that may be exploited for new treatments. Previously, we measured whole-brain c-Fos and metabolic neuronal activity with positron emission tomography revealing dysfunction in key regions of helpless animals including the lateral habenula (LHb), dorsal raphe, rostromedial tegmental nucleus (RMTg) and ventral tegmental area (VTA). Here, we identify cell type of functionally activated (c-Fos positive) neurons in these same key brain regions. Twenty wild type male Sprague Dawley rats underwent 120 inescapable, unpredictable foot-shocks followed the next day by 15 escapable, predictable foot-shocks for the learned helplessness paradigm (n=10 helpless, n=6 resilient). Brain tissue was collected 90 minutes following the behavioral test and processed for microscopy. Activation of cells expressing the glutamate receptor subunit GluR2, GABAergic marker GAD67, vesicular glutamate transporter-3 (VGluT3), serotonin, and dopaminergic marker tyrosine hydroxylase were evaluated using immunofluorescence and confocal microscopy. Quantitative statistical analysis of neuronal activity was performed using MatLab and Image J. We found the number of activated neurons expressing GluR2 receptors is significantly increased in the medial sub-region of the LHb in learned helpless animals compared to resilience, which is consistent with our previous findings implicating the habenula in depression circuitry. Furthermore, we found that serotonin neurons co-expressing VGluT3 in the caudal dorsal raphe show significantly enhanced activity in helplessness, suggesting increased serotonergic vesicular packaging may be linked to stress. Preliminary observations in the RMTg and VTA have not revealed significant changes in c-Fos activation, though activated neurons co-localized with dopaminergic and GABAergic markers are ongoing. Overall, our data supports a working model of excessive glutamatergic activity through the LHb associated with helplessness, which may be linked to increased neuronal activity in VGluT3 co-expressing serotoninergic neurons in the caudal raphe. Blockade of glutamatergic activity in the habenula and/or VGluT3 activity in the dorsal raphe may attenuate the overactive stress response leading to depressive behavior.

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Nanosymposium

551. Animal Models for Depression: Behavioral and Chemical Approaches

Location: 147B

Time: *Tuesday, November 14, 2017, 1:00 PM - 3:00 PM

Presentation Number: *551.03

Topic: *G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH R01MH105447
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T90DE022736

Title: Perinatal exposure to the SSRI paroxetine increases offspring's depression-like behavior through changes in hippocampal DNA methylation

Authors: ***M. E. GLOVER**[1], C. R. MCCOY[1], N. L. JACKSON[2], S. M. CLINTON[1]
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Abstract: Selective Serotonin Reuptake Inhibitors (SSRIs) are the mainstay treatment of pregnant women suffering from depression. While maternal antidepressant use is associated with low risk for major birth complications or teratogenic effects, *in utero* exposure may elicit lifelong effects on neurodevelopment and emotional health on the offspring. Both clinical and basic research suggests early life SSRI exposure may lead to increased risk of adulthood depression. Rodent studies have found SSRI exposure increases behavioral despair in the Forced Swim Test (FST), enhances anxiety-like behavior, and reduces sexual behavior. Furthermore, there is evidence in both fields suggesting certain individuals may be more susceptible to the adverse effects of SSRI exposure on emotional health. Our group recently demonstrated early life SSRI exposure increases depression-like behavior in Low Novelty Responder (LR) rats, but not in High Novelty Responder (HR) rats. Transcriptome profiling revealed robust gene expression changes in the neonatal hippocampus (HPC) of LR rats, including reduced expression of the DNA methylating enzyme, *Dnmt3a*. Our new experiments test the working hypothesis that perturbed DNA methylation in the neonatal HPC mediates the adverse behavioral consequences of perinatal SSRI exposure. We hypothesize that perinatal SSRI exposure downregulates DNA methylation in the neonatal HPC and that this may provide a molecular switch that triggers adverse downstream effects on neurodevelopment and emotional behavior. To test this, the present study examined global DNA methylation (5-methylcytosine) levels in brains of SSRI-exposed neonatal rats. Because we previously showed that LR rats are susceptible to behavioral

effects of perinatal SSRI exposure while HRs are resistant, we predicted and indeed found that SSRI exposure selectively affected DNA methylation in brains of LR offspring. Using next-generation sequencing, we interrogated gene-specific methylation changes in the HPC of perinatal SSRI-exposed LR offspring. Our final experiment tested the hypothesis that siRNA-mediated suppression of *Dnmt3a* expression in the HPC of early postnatal rats would elicit adverse behavioral consequences akin to what occurs following perinatal SSRI exposure. Our results may have important implications on the use of SSRIs during pregnancy and on the etiology of depression in general, as early-life changes in epigenetic mechanisms disrupt normal hippocampal development, leading to an increased risk for depression in adulthood.

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551. Animal Models for Depression: Behavioral and Chemical Approaches

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**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:00 PM

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Brain and Behavior Research Foundation NARSAD young investigator award

Title: Social stress induces neurovascular pathology promoting depression

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Abstract: Clinical studies suggest that heightened peripheral inflammation contributes to the pathogenesis of major depressive disorder. We investigated the effect of chronic social defeat stress, a mouse model of depression, on blood-brain barrier (BBB) permeability and infiltration of peripheral immune signals. We found reduced expression of endothelial cell-specific tight junction protein claudin-5 (cldn5) and abnormal blood vessel morphology in the nucleus accumbens (NAc) of stress-susceptible but not resilient mice. *CLDN5* expression was also decreased in postmortem NAc of depressed patients. *Cldn5* down-regulation was sufficient to induce depression-like behaviors while chronic antidepressant treatment rescued cldn5 loss and promoted resilience. Reduced BBB integrity in NAc of stress-susceptible mice resulted in direct passage of peripheral cytokine interleukin-6 (IL-6) and subsequent expression of depression-like behaviors. These findings suggest that chronic social stress alters BBB integrity through loss of tight junction protein cldn5, promoting peripheral IL-6 passage across the BBB and depression.

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Nanosymposium

551. Animal Models for Depression: Behavioral and Chemical Approaches

Location: 147B

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:00 PM

**Presentation Number: ***551.05

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Longterm isolation elicited depression and anxiety-related behaviors by modulating oxytocinergic systems

Authors: *T. HAN[1], E.-H. PARK[2], J. LEE[2], H. KIM[2], S. BACK[3], Y. KIM[2], H. NA[2]
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Abstract: Oxytocin is a neuropeptide produced in the paraventricular nucleus (PVN) of the hypothalamus and associated with social behaviors. Long-term deprivation of social interactions impairs mood stability and evokes comorbid anxiety. To date, neural mechanisms of chronic social isolation-induced depression and anxiety are undetermined. In the present study, we aimed to investigate whether chronic isolation-induced depression and anxiety is attributed to

dysfunction of oxytocinergic circuit. Herein, we demonstrated that social isolation increased 1) depressive-like behaviors in the forced swimming test and the sucrose preference test,2) anxiety-related behaviors in the open field test, and the zero maze for 5 weeks. Intra-amygdala injection of oxytocin ameliorated the chronic isolation-induced depression and anxiety-associated behaviors. Fluorescent microscopic findings showed that neurons in PVN made synaptic connections with oxytocin receptor-expressing neurons in central amygdala (CeA), which also expressed glutamic acid decarboxylase 67, a marker for γ-Aminobutyric acid neurons. Quantification analysis of mRNA of oxytocin receptor in the neurons of CeA demonstrated that long-term isolation significantly decreased oxytocin receptor expression in the neurons of CeA. Taken together, our results suggested that chronic social isolation induced depressive and anxiety-related behaviors by weakening circuit from PVN to CeA.

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Nanosymposium

551. Animal Models for Depression: Behavioral and Chemical Approaches

Location: 147B

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**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

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T32MH065215
NARSAD Distinguished Investigator Award Grant: 21809

Title: Ketamine inoculation immediately after forced ethanol abstinence inhibits the development of time-dependent affective disturbances

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Abstract: Withdrawal from chronic alcohol administration produces affective disturbances that may promote alcohol use disorders. Previous studies have demonstrated the development of negative affective behavior following forced abstinence (FA) from non-contingent paradigms such as chronic intermittent ethanol vapor inhalation (CIE). More recently, studies have shown that depressive-like, but not anxiety-like behaviors are observed two-weeks after FA from chronic two-bottle ethanol drinking paradigms. We previously reported that female C57BL/6J mice undergoing six-week chronic ethanol drinking followed by forced abstinence (CDFA)

develop significant affective disturbances after two-weeks of FA that can be acutely reversed by the antidepressant ketamine (3.0mg/kg i.p.). Here we show 1) that the reversal via ketamine is prevented by pretreatment with the CB1 receptor antagonist rimonabant (1mg/kg i.p.), and 2) that anxiety-like behaviors on the elevated plus maze (EPM) are observed within the early phase of forced abstinence. Moreover, to further explore ketamine regulation of affective disturbances in CDFA, we administered either ketamine or saline at one of three different time points: the onset of forced abstinence, two days-, or six days- post-abstinence and observed its impact on affective behavior in the EPM, the Novelty Suppressed Feeding Test (NSFT), and the Forced Swim Test (FST). We found that ketamine administered at the onset of FA not only prevented early anxiety in the EPM, but also inoculated the mice from developing late depressive-like phenotypes as assessed by the NSFT and FST paradigms. Interestingly, these actions were time-sensitive since ketamine administration at either two or six days post-abstinence failed to prevent the CDFA dependent depressive-like phenotypes. Studies have demonstrated that withdrawal from CIE alters NMDA receptor function within the bed nucleus of the stria terminalis (BNST), a critical brain region for stress-related affective dysfunction. Given that the NMDA receptor is a known target of ketamine, we used field potential experiments to assess the impact of ketamine in FA on LTP in this region. We find that a single ketamine delivery at the onset of FA enhanced BNST plasticity in animals after two weeks of forced abstinence. This suggests a potential critical period at the initiation of FA in which ketamine inoculation can produce lasting impact on affective state, by enhancing, in part, neuronal excitability within the BNST. The present research aims to uncover the neurobiological bases of alcohol related affective disorders, and aid in the development of more effective and longer lasting therapeutics.

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Nanosymposium

551. Animal Models for Depression: Behavioral and Chemical Approaches

Location: 147B

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**Presentation Number: ***551.07

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Human experimenter gender modulates mouse behavioral responses to stress and to the antidepressant ketamine

Authors: *P. GEORGIOU[1], P. ZANOS[2], C. JENNE[3], J. N. HIGHLAND[4], D. GERHARD[6], R. S. DUMAN[7], T. D. GOULD[5]
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Abstract: Lack of replicability of experimental results may be due to unexpected experimental variables that are not appropriately controlled for in experimental designs. Rodents can differentiate the gender of human experimenters, which may affect their physiological and behavioral responses. We investigated experimenter gender effects on stress-induced behaviors in male CD-1 mice, and the reversal of such behaviors by the antidepressant drug ketamine. We showed that a female experimenter conducting procedures induced a less severe anhedonia phenotype following chronic social defeat stress (CSDS), decreased development of helpless behavior following inescapable shocks, and resulted in a decrease in immobility time in the forced-swim test (FST) compared to male experimenters. Consistent with the published literature, ketamine reversed CSDS-induced anhedonia in male C57BL/6J mice, reduced escape failures following inescapable shock training in male CD-1 and CFW mice and decreased immobility time in the FST in male and female CD-1 mice when administered by a male experimenter, while antidepressant responses of ketamine were absent when it was administered by a female experimenter. Non-antidepressant behavioral actions of ketamine were present regardless of the gender of the experimenter. Ketamine administration induced a similar increase in gamma power EEG regardless of experimenter gender. Similar experimenter gender-dependent effects were identified with ketamine's active metabolite (*2R,6R*)-hydroxynorketamine, but not with other classical or fast-acting antidepressant drugs and another NMDAR antagonist. The nearby presence of a female experimenter was sufficient to block antidepressant actions of male-administered ketamine. We also showed that ketamine injected under the hood, thus eliminating experimenter scents, did not result in antidepressant actions regardless of experimenter gender. Overall, these findings demonstrate the importance of experimenter gender to the outcome of behavioral assessments and antidepressant response to ketamine. Our data argue that experimenter gender may affect replicability, and that experiment gender should be considered as an important experimental variable.

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Nanosymposium

551. Animal Models for Depression: Behavioral and Chemical Approaches

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**Presentation Number: ***551.08

**Topic: ***G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH R01 MH108562
Silvio O. Conte Center for Neuroscience Research Vanderbilt University
1P50MH096972

Title: Evaluating sensitive developmental periods necessary for photoperiodic effects on the serotonin system

Authors: *J. K. SIEMANN[1], N. H. GREEN[1], N. REDDY[2], D. G. MCMAHON[1]
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Abstract: Studies have shown seasonally varying risks for mood disorders with higher rates occurring during the fall or winter months when daylight is lowest in the year. The serotonergic system is known to be impacted by the duration of light exposure (i.e. photoperiod) and has been implicated in mood disorders, providing a promising new area of research. Recently, our lab has shown that mice exposed during development to long summer-like photoperiods of 16 hours of light and 8 hours of darkness each day (LD 16:8) demonstrate a greater neuronal firing rate of dorsal raphe serotonin neurons in isolated brain slices and higher levels of monoamines (i.e. serotonin and norepinephrine) in the midbrain along with more anxiolytic and anti-depressive behavioral effects compared to animals exposed to short winter-like LD 8:16 photoperiods or equinox LD 12:12 photoperiods. Based on these prior findings that used a developmental photoperiod from E0 to P30, we have now focused on when these photoperiod changes occur in development (i.e. during a sensitive period), resulting in lasting changes in the serotonergic system. Specifically, we found that when animals were exposed only prenatally (E0-P0) to long photoperiods and then switched to a short photoperiod at birth, the average firing rate of dorsal raphe serotonin neurons measured in adulthood (P50-P90; 1.18 ± 0.076 Hz) resembled the firing rate for animals which continued to develop under a long photoperiod (1.24 ± 0.084 Hz). Interestingly, raphe neurons from animals that were prenatally exposed to a short photoperiod and then switched to a long photoperiod at birth, displayed an intermediate firing rate (0.99 ± 0.083 Hz) compared to those that were continuously exposed to either a long (1.24 ± 0.084 Hz) or short photoperiod (0.69 ± 0.024 Hz) throughout development. In addition, we found that animals switched from the short to long photoperiod at birth displayed an increased concentration of serotonin and its main metabolite 5-hydroxyindoleacetic acid compared to animals raised under an equinox photoperiod or switched from the long to short photoperiod at birth. Lastly, we have preliminary evidence that animals switched from the short to long photoperiod demonstrate an anti-depressive like phenotype in the tail suspension test compared to animals switched from the long to short photoperiod at birth. In addition, it appears that these effects may be driven by sex differences where the switching from a short to long photoperiod at birth may have protective effects when evaluating depression and anxiety relevant behavioral tests.

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Nanosymposium

552. Functional Basis of Attention

Location: 150B

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***552.01

**Topic: ***H.02. Human Cognition and Behavior

Title: Deep neural network activity decoded from fMRI responses to scenes predicts eye movements

Authors: *T. P. O'CONNELL, M. M. CHUN
Yale Univ., New Haven, CT

Abstract: Goal-directed deep convolutional neural networks (CNNs) have recently shown human-level performance on naturalistic visual categorization tasks (Krizhevsky, Sutskever, & Hinton, 2012; Simonyan & Zisserman, 2015; Zhou, Khosla, Lapedriza, Torralba, & Oliva, 2016). Activity in CNN units predicts neural and BOLD activity in visually responsive brain regions (Khaligh-Razavi & Kriegeskorte, 2014; Yamins & DiCarlo, 2016; Yamins et al., 2014), while computational spatial attention models derived from CNNs trained for visual categorization produce state-of-the-art prediction of human eye movement behavior in natural images (Bylinski et al., 2016; Kümmerer, Theis, & Bethge, 2015; Kümmerer, Wallis, & Bethge, 2016). Thus, we test whether features captured by CNN unit activity support representation of spatial attention priority in the human brain. To this end, we decode CNN unit activity from BOLD activity measured with functional Magnetic Resonance Imaging (fMRI), reconstruct spatial priority maps from fMRI-decoded CNN activity, and use the reconstructed spatial priority maps to predict eye movement behavior within and across individuals. We measured BOLD activity with fMRI while participants (N=11) viewed images of natural scenes and completed an old/new recognition task. Participants' fixation patterns on the same images were measured in a separate eye tracking session. Partial least squares regression was used to decode CNN unit activity from the five pooling layers of the VGG-16 CNN trained for scene categorization (Simonyan & Zisserman, 2015; Zhou et al., 2016). fMRI-decoded CNN activity was averaged across channels (filters) within each layer and across layers to reconstruct spatial priority maps for each image. Reconstructed spatial priority maps from V2, V3, and hV4 predicted fixation patterns within individuals ($p<0.005$ bonferroni corrected). In addition, demonstrating the stability of spatial attention priority maps between individuals, group-average reconstructed spatial priority maps from V1, V2, V3, hV4, LOC, and FEF ($p<0.001$) predicted fixation patterns from participants in an independent external validation data set (O'Connell & Walther, 2015). Taken together, these results show that spatial attention priority maps can be reconstructed from fMRI activity evoked by natural scenes and that such reconstructed spatial priority maps are predictive of eye movement behavior within and across individuals. Overall, showing their

biological validity, features captured by CNN unit activity support the representation of spatial attention priority in the human brain.

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Nanosymposium

552. Functional Basis of Attention

Location: 150B

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***552.02

**Topic: ***H.02. Human Cognition and Behavior

Title: Face processing is attenuated during mind wandering: An ERP investigation

Authors: E. DENKOVA, E. BRUDNER, K. ZAYAN, J. DUNN, *A. P. JHA
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Abstract: How do you perceive a face when your mind wanders? Mind wandering (MW), defined as self-generated thinking that is unrelated to the task at hand, has been recently investigated in an escalating number of studies. It has been suggested that, during MW, processing of external stimuli is diminished in favor of internal thoughts. This phenomenon has been referred to as perceptual decoupling and has been investigated in event-related potential (ERP) studies, which have good temporal resolution that allow for the examination of the temporal dynamics of MW. Yet, perceptual decoupling during MW has never been investigated in a task involving attention to faces, nor has it been examined using the early ERP component associated with face processing, the N170. Here, we investigated the modulation of the N170 as a function of subjective reports of MW to tackle perceptual decoupling in the context of faces. We collected ERP data from 36 participants while they completed a sustained attention to response task with faces. Participants were instructed to respond to upright faces (non-targets, 90% of trials) and to withhold their response to inverted faces (targets, 5% of trials). Two questions related to mind wandering and metacognition were presented in succession on 5% of trials. The first question assessed participants' experience of task engagement *vs.* mind wandering using a dichotomous judgment of 'on task' *vs.* 'off task'. The second question assessed participants' level of confidence in their 'on task' and 'off task' reports using a 3-point Likert scale. The behavioral (intra-individual coefficient of variation in reaction time, ICV) and ERP (N170 amplitude) responses to the 6 non-targets preceding the first question were examined as a function of 'on task' *vs.* 'off task' reports. Behavioral results revealed greater ICV for periods preceding 'off task' *vs.* 'on task' reports ($p < .01$), suggesting less stable attentional performance during MW. ERP results revealed attenuated N170 amplitude to faces preceding 'off task' *vs.* 'on task' reports ($p < .05$). The latter findings are in line with perceptual decoupling

literature and suggest attenuated visual processing of faces during MW, which may have implications for social neuroscience research.

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Nanosymposium

552. Functional Basis of Attention

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Time: *Tuesday, November 14, 2017, 1:00 PM - 3:15 PM

Presentation Number: *552.03

Topic: *H.02. Human Cognition and Behavior

Support: NSF grant BCS-1534823

Title: Spatial uncertainty modulates object and spatial representations in IPS

Authors: ***A. J. COLLEGIO**[1], S. L. SHEREMATA[2], D. J. KRAVITZ[1], S. SHOMSTEIN[1]
[1]Dept. of Psychology, The George Washington Univ., Washington, DC; [2]Dept. of Psychology, Florida Atlantic Univ., Boca Raton, FL

Abstract: Recent behavioral evidence suggests that object representations constrain attention only when the location of the upcoming target is uncertain (Drummond & Shomstein, 2010). These findings make the surprising prediction that the strength of object representations should be greater under conditions of spatial uncertainty, despite participants being unable to allocate their attention to a particular object location. Here, we focused on changes in neural activity in object-selective lateral occipital complex (LOC), spatial-selective intraparietal sulcus (IPS), and early visual cortex (EVC), under different levels of spatial uncertainty. Using multivoxel pattern analysis (MVPA), we examined the strength of object identity and spatial attention information in LOC, IPS, and EVC during an attention task with two levels of spatial uncertainty. Two different real-world objects were presented to the left and right of fixation. Two target Gabor patches oriented either 45° left or right were presented, one over fixation, and one on either of the two objects. Participants reported whether their orientations matched. A third, neutral distractor Gabor was presented on the object without a target. Uncertainty was manipulated in two ways: (1) uncertain - target appeared 50% on either of the two objects; (2) certain left or certain right - target appeared 75% on the corresponding side. Consistent with our hypothesis, stronger spatial decoding was observed in contralateral EVC and IPS when a specific spatial location was more likely to contain a target (certain left or right). In contrast, object identity information was more strongly decoded in contralateral EVC and IPS during the uncertain condition, reflecting an increase in strength of object representation in the absence of a spatial

bias. While surprising to observe increased object decoding in IPS, these findings are consistent with prior evidence suggesting that object information is available in the dorsal stream (Freud et al., 2016). Critically, our findings run counter to theories positing that spatial attention facilitates object representations (i.e., binding), and suggest that current models of attention that fail to account for spatial uncertainty must be reconsidered.

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Nanosymposium

552. Functional Basis of Attention

Location: 150B

Time: *Tuesday, November 14, 2017, 1:00 PM - 3:15 PM

Presentation Number: *552.04

Topic: *H.02. Human Cognition and Behavior

Title: Attention to breathing modulates anterior cingulate cortex responses and its coherence to prefrontal cortex

Authors: ***J. L. HERRERO**[1], A. LUTZ[3], S. KHUVIS[2], E. M. YEAGLE[4], A. D. MEHTA, 11549[2]
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Abstract: Recent studies have shown that brain areas above the brainstem such as the hippocampus and the olfactory cortex are involved in respiration. Respiration-locked activity in these areas is prominent during natural breathing. However, how paying attention to the breathing itself modulates respiration-locked oscillations is not known. We performed invasive recordings from epilepsy patients with electrodes implanted in deep and surface areas that have been trained to attend to their breathing. We found that respiration-locked oscillations increase in the anterior cingulate cortex (ACC) and the hippocampus when patients attend to their breathing compared to control conditions. The ACC did not show respiration-locked oscillations at rest or during exteroceptive attention tasks but it did so during breath awareness. Breathing patterns also changed, with reduced speed and breathing volume and increase heart rate variability (HRV). In addition, synchronous oscillatory activity in the theta band between the ACC and the prefrontal (PFC) was also increased when the patient efficiently attended to the breath compared to poor or intermittent attention. Ongoing research using close-loop electrical stimulation is underway to prove a mechanist role of the ACC and ACC-PFC coherence in interoceptive attention. Findings

have implications for cognitive therapy of diseases involving abnormal breathing patterns such as anxiety and for meditative practices.

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Topic: *H.02. Human Cognition and Behavior

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NEI R21-EY024733
James S McDonnell Foundation Scholar Award

Title: The joint impact of alpha amplitude and frequency on visual detection

Authors: ***S. NELLI**[1], A. MALPANI[2], M. BOONJINDASUP[2], J. SERENCES[3]
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Abstract: Rhythmic neural activity in the alpha band (8-13 Hz) plays a role in the selective processing of visual information. Specifically, posterior alpha amplitude is thought to reflect an increase in inhibitory mechanisms that lead to decreased perceptual sensitivity (Klimesch et al 2007 for review). Additionally, increases in alpha frequency have been associated with heightened perceptual sensitivity (Samaha & Postle 2016). However, little is known about how these observations interact to influence behavioral performance.
First, we recorded electroencephalography (EEG) while subjects performed a simple visual detection task in which subjects reported the orientation of a faint and brief (~8.3 ms) target stimulus appearing to the left or right of fixation with 50% probability. We then replicated previous effects associating increased frequency and decreased amplitude with better performance. Furthermore, we found that changes in frequency and amplitude were correlated on a timepoint-by-timepoint basis, indicating that alpha amplitude and frequency jointly impact perception.
To further explore this relationship, we then manipulated the amplitude of alpha oscillations at specific alpha frequencies by entraining neural populations using a checkboard stimulus flickering at one of 8 frequencies in the alpha range (steady-state visual evoked potentials, SSVEP). While recording EEG, subjects were asked to detect a brief (~16 ms) increase in the

luminance of a central black fixation dot that was presented on top of the flickering checkerboard. During this recording session, we also estimated each subject's peak alpha frequency by recording EEG while subjects rested. We confirmed that subjects showed significant entrainment at each alpha frequency in posterior electrodes. We also found a linear effect of flicker frequency on detection performance, as well as localized effects of perturbing the amplitude of modulations around each subject's peak alpha frequency. Our results argue against a purely inhibitory account for the alpha oscillation. Instead, they suggest a nuanced relationship between alpha amplitude and frequency in determining the efficacy of visual information processing.

Disclosures: S. Nelli: None. **A. Malpani:** None. **M. Boonjindasup:** None. **J. Serences:** None.

Nanosymposium

552. Functional Basis of Attention

Location: 150B

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***552.06

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH grant R21-EY021644
NSF Grant BCS-1534823

Title: Task-irrelevant semantic properties of objects modulate early visual cortical activity

Authors: *J. C. NAH[1], G. L. MALCOLM[2], S. SHOMSTEIN[1]
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Abstract: Every object can be described as consisting of a set of low-level (e.g., color) and high-level properties (e.g., semantic information). Decades of research provided evidence that semantic information guides attention when task-relevant (Moores et al., 2003). However, whether semantic information guides attentional allocation independent of task is poorly understood. Recently, Malcolm et al., (2016) demonstrated that task-irrelevant semantic information influences attentional allocation. Here, in a set of two experiments, we investigated the extent to which task-irrelevant semantic-based information modulates processing in the early visual cortex (EVC), object-selective lateral occipital cortex (LOC), and inferior parietal sulcus (IPS) by utilizing univariate and multivariate fMRI methods. We directly tested whether task-irrelevant semantic relationships modulate neural activity in the EVC through facilitation of object representations in object-selective LOC or through the facilitation of spatial representations of objects in spatially-selective IPS. Additionally, decoding of object identity

was investigated in the EVC, LOC, and IPS with the prediction that increased attentional allocation from task-irrelevant semantic information would lead to subsequent increases in strength of object representations (leading to higher classification accuracy). In Experiment 1, participants viewed three objects, one above the central fixation and one in each periphery below the midline. One of the peripheral objects was always semantically related to the central object. Following object presentation, a target and two distractors were superimposed on top of each object. Critically, the target appeared on all three objects equally, rendering semantic relatedness task-irrelevant. In Experiment 2, participants viewed two objects appearing on either side of fixation. Afterwards, a Gabor patch was overlaid on top of each object and participants reported whether the patches were identical in orientation. The objects were either semantically related or unrelated. Behavioral performance demonstrated that task-irrelevant semantic relatedness influenced attentional allocation. Semantic-based modulation throughout the EVC as well as IPS was observed, supporting facilitation of spatial attention hypothesis. Additionally, EVC showed significantly higher object identity decoding accuracy when semantically related. Combined, these results show that task-irrelevant semantic relationships between objects modulate early visual cortical activity by influencing attentional priority maps in IPS.

Disclosures: **J.C. Nah:** None. **G.L. Malcolm:** None. **S. Shomstein:** None.

Nanosymposium

552. Functional Basis of Attention

Location: 150B

Time: *Tuesday, November 14, 2017, 1:00 PM - 3:15 PM

Presentation Number: *552.07

Topic: *H.02. Human Cognition and Behavior

Support: This research was supported by a PhD studentship from the College of Science and Engineering at the University of Glasgow

Title: Interfering with dorsal and ventral parietal network nodes during endogenous and exogenous visuospatial attention: A TMS study

Authors: ***M. M. AHRENS**[1,2], D. VENIERO[1], M. HARVEY[2], G. THUT[1]
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Abstract: Neuroimaging and transcranial magnetic stimulation (TMS) studies have shown that partially segregated large-scale dorsal and ventral fronto-parietal networks play a crucial role in endogenous and exogenous visuospatial attention [1,2]. However, to what extend and under which circumstances these networks interact and/or overlap remains under debate [3]. In

particular, the experimental designs of previous findings may have been confounded by endogenous attentional engagement during exogenous orienting. Here, we addressed this issue by combining a visuospatial attention paradigm, previously shown to behaviourally isolate endogenous from exogenous orienting [4], with neuronavigated double-pulse TMS over right intraparietal-sulcus (rIPS), right temporo-parietal-junction (rTPJ) and sham-TMS. In a within-subject design, participants were asked to perform a visual discrimination task, preceded by predictive symbolic cues engaging endogenous orienting to target positions (left vs. right). Simultaneously non-predictive, task-irrelevant apparent motion cues were presented in the background to trigger exogenous shifts of attention (leftward vs. rightward) to the same positions. Our preliminary results (n=14 participants) reveal that during sham-TMS, endogenous and exogenous cueing both facilitated performance accuracy at validly vs. invalidly cued target locations. Importantly, there was no interaction between endogenous and exogenous cueing. Thus our design effectively avoided endogenous engagement during exogenous orienting, successfully replicating our previous findings [4]. Interestingly, while endogenous cueing benefits were unaffected by TMS (relative to sham), both rIPS- and rTPJ-TMS abolished exogenous orienting. In conclusion, our findings indicate dissociated effects of TMS on endogenous and exogenous processes, and an involvement of both dorsal and ventral nodes (i.e. rIPS and rTPJ) in exogenous orienting. References: [1] Corbetta&Shulman 2002. Nature Reviews 3,201-2015; [2] Chica et al. 2011. Jour of Neurosci. 31(22):8143-8149; [3] Vossel et al. 2014. The Neuroscientist. 20(2) 150-159; [4] Ahrens et al. 2015. Plos One. 10(12):e0144082

Disclosures: M.M. Ahrens: None. **D. Veniero:** None. **M. Harvey:** None. **G. Thut:** None.

Nanosymposium

552. Functional Basis of Attention

Location: 150B

**Time: ***Tuesday, November 14, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***552.08

**Topic: ***H.02. Human Cognition and Behavior

Support: National Natural Science Foundation of China (31371129)

Title: Perception of illusory contour is interfered by a task-irrelevant distractor

Authors: *J. YANG, H. WU, Q. WU, X. WU
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Abstract: A fundamental question in visual cognition is how people recognize objects when the object information is widely separated in space, as demonstrated by the well-known Kanizsa-type illusory contours. Whether and how illusory contour perception is modulated by attention

remain unclear, which was examined in the present study by centrally presenting a task-irrelevant distractor (a dynamic patch) while the subjects performed a peripheral discrimination task. The task involved four types of discrimination, between shapes of illusory contours, between shapes of real contours, between colors of squares, or between orientations of bars. There were three levels of task difficulty (easy, medium, and hard), which was indicated by the difference in contour shapes, bar orientations, or square colors. The results revealed that the discrimination performance was interfered by the dynamic patch, and that this distractor interference effect depended on the task type and task difficulty. The distractor interference effect was observed in the easy task for illusory contours; in all levels of task difficulty for real contours; in all levels of task difficulty for square colors, and in the hard difficulty for bar orientations. The results demonstrate that illusory contour perception is distracted by a task-irrelevant and spatially separated distractor. The findings also suggest the dependence of such distracting effects on the task type and task difficulty, which may indicate different distracting mechanisms in low- to high-level visual areas.

Disclosures: **J. Yang:** None. **H. Wu:** None. **Q. Wu:** None. **X. Wu:** None.

Nanosymposium

552. Functional Basis of Attention

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Presentation Number: *552.09

Topic: *H.02. Human Cognition and Behavior

Support: UWM Research Growth Initiative
US-Israel Binational Science Foundation Grant No. 2013400

Title: Object-based attentional selection emerges late in visual cortex for object percepts of varying strength

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Abstract: Object-based attention (OBA) can - in addition to acting upon explicit object representations - act upon occluded objects and those defined by subjective contours. It remains unknown, however, whether or not the selection of such object representations (both degraded and preserved) is detectable at the same level within the visual cortical hierarchy. This study, therefore, sought to ascertain the level within visual cortex (V1-V3, and LOC) at which object-based selection is first observed for preserved versus degraded (occluded, illusory) objects.

During fMRI acquisition, participants identified a target preceded by a predictive central arrow cue in the double-rectangle cueing paradigm. As anticipated, participants identified the target faster when it appeared at the invalid-same versus invalid-different object location. This same-object advantage emerged regardless of object structure, but, commensurate with recent data, was present only when objects were oriented horizontally. We independently localized retinotopically-specific regions of cortex corresponding to all possible target locations to examine neural fluctuations at each level of the visual cortical hierarchy. We found that activation in V3 following cue onset transiently increased within representations of the invalid-same versus invalid-different object location, which may indicate prioritization of the same object location over and above the different object location. This effect emerged regardless of object type and orientation. No such cue-evoked OBA effects were present in V1/V2. Additionally, activation in V3 following target onset transiently increased when targets appeared in the invalid-different versus invalid-same object location. This effect, which was also detectable further upstream in LOC, may indicate a mismatch between where participants expected the target to appear (on the cued object) and the location in which it actually appeared (on the uncued object). No such target-evoked OBA effects were present in V1/V2. Our results indicate that object-based selection is evident in late stages of the visual cortical hierarchy (V3, LOC), and does not depend on explicit object representations. This finding, therefore, suggests that object-based, akin to space-based, information, is gated in visual cortex.

Disclosures: S. Al-Janabi: None. **N. Strommer-Davidovich:** None. **S. Gabay:** None. **A.S. Greenberg:** None.

Nanosymposium

637. Brain Evolution

Location: 146C

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***637.01

**Topic: ***A.10. Development and Evolution

Title: The course and diameter of cranial nerves in the head of a foetal Risso's dolphin

Authors: *S. HUGGENBERGER[1], G. BARTHELMESS[1], H. SCHRODER[2], H. H. A. OELSCHLÄGER[3]
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Abstract: There is no detailed description of the cranial nerves in cetaceans. For the first time, their topographic anatomy was investigated in detail in a 76 cm long (late-term) formalin-fixed

foetus of the Risso's dolphin (Grampus griseus), a marine delphinid species of about the same size as the well-investigated bottlenose dolphin (Tursiops truncatus). Macroscopical dissection revealed the course of cranial nerves from their origin inside the cranial cavity to the respective periphery. As in adult dolphins, the olfactory nerve (N. I) was not present in the dissected foetus. The course of the other cranial nerves (Nn. II to XII) reflects the mammalian bauplan. The optic, trigeminal, facial, and vestibulocochlear nerves (Nn. II, V, VII, VIII) of the Risso's dolphin show diameters of 1.5 mm, 5 mm, 2 mm, and 2.5 mm, respectively. This is in contrast to the situation in adult dolphins (Tursiops truncatus) where the optic nerve (N. II) equals the dimensions of the trigeminal nerve (N. V). Remarkably, in the Risso's dolphin foetus, the comparatively large diameters of the nerves involved in the nasal generation of sound and ultrasound (Nn. V, VII) and in hearing (N. VIII) reflect the precocial nature of the echolocation system in dolphins.

Disclosures: S. Huggenberger: None. **G. Barthelmess:** None. **H. Schroder:** None. **H.H.A. Oelschläger:** None.

Nanosymposium

637. Brain Evolution

Location: 146C

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***637.02

**Topic: ***A.10. Development and Evolution

Title: Universality in human cortical folding: Heterogeneity, aging, health and disease

Authors: *B. MOTA[1], Y. WANG[2]
[1]Univ. Federal Do Rio De Janeiro, Rio de Janeiro, Brazil; [2]Sch. of Computing Sci., Newcastle Univ., Newcastle, United Kingdom

Abstract: We have previously shown [1] that the folding of the cortex in mammalian brains follows a universal scaling law that can be derived from a simple physics model. Remarkably, this relation is quite successful in predicting the scaling between morphological variables for a diverse data set of 54 species, both gyrencephalic and lissencephalic, varying over four orders of magnitude in size.
Using human cortical surfaces reconstructed from MRI data of over 1000 healthy subjects from three independent public databases, we show that the same scaling law also applies across humans, irrespective of gender. Over healthy aging a systematic reduction occurs in an offset parameter (unconstrained by the theory) related to the mechanical properties of the white matter. Alzheimer's subjects, however, show a much greater decrease in offset, suggesting that from our morphological point of view, Alzheimer's disease can be regarded as a form of premature cortical aging [2].

We also developed a generalization of this model to sub-divisions of the cortical surface. It is known that different parts of cortex have different average thicknesses and degrees of gyrification, and it is worth investigating whether they can be studied separately in the context of a single universal gyrification mechanism. In principle, it is possible to measure the same morphological variables for each (say) cortical lobe as for the complete cortical hemisphere. However, since these quantities depend on the size of each segment, a direct comparison is not able to specify whether each segment follows separately a universal folding rule. However, it is possible to reconstruct a complete hemisphere from each patch so that it has the same gyrification index and average thickness, by using the Gaussian curvature distribution. In this way, our results suggest different brain lobes vary in their degrees of gyrification while at the same time following the same universal rule. We seek to extend this method to study how different lobes age morphologically at different rates, and may potentially be affected by neuro-degenerative conditions by different degrees.
Finally, it has recently been shown that the human cortex is self-similar, with a measured fractal dimension of 2.49 [3]. This independently confirms the value of 2.5 predicted by our theory and empirical analyses [1,2]. Using a different method of estimating fractal dimension, we compare how measures of cortical self-similarity relate across species, individuals, and length scales at each cortex.
[1] Mota B, Herculano-Houzel, S (2015) *Science*, 349 (6243) 74
[2] Wang Y, Necus J, Kaiser M, Mota B (2016) PNAS 113 (45) 12820
[3] Madan C, Kensiger E (2016) Neuroimage 134 617

Disclosures: B. Mota: None. **Y. Wang:** None.

Nanosymposium

637. Brain Evolution

Location: 146C

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***637.03

**Topic: ***H.01. Animal Cognition and Behavior

Support: NSF IOS 1457291

Title: Neuroanatomical correlates of domestication in the russian fox farm experiment

Authors: *E. E. HECHT[1], D. GUTMAN[2], L. COOPER[3], D. OBATUSIN[3], A. KUKEKOVA[5], L. TRUT[6], T. M. PREUSS[4]
[1]Ctr. for Behavioral Neuroscience, Neurosci. Inst., Georgia State Univ., Atlanta, GA; [2]Dept. of Neurol., [3]Dept. of Biomed. Informatics, [4]Yerkes Natl. Primate Res. Ctr., Emory Univ., Atlanta,

GA; [5]Dept. of Animal Sci., Univ. of Illinois at Urbana-Champaign, Urbana-Champaign, IL; [6]Inst. of Cytology and Genet., Russian Acad. of Sci., Novosibirsk, Russian Federation

Abstract: A major goal of modern evolutionary neuroscience is to understand how selection pressure for behavior results in adaptations in the brain. Domestication offers a unique window into this question because it involves strong, sometimes intentionally-applied selection pressure on a focused set of behaviors. A landmark study on experimental domestication has been ongoing for over 50 years at the Institute of Cytology and Genetics at Novosibirsk, Russian Academy of Sciences. In this selective breeding program, farm-raised red foxes (*Vulpes vulpes*) are bred based solely on flight distance, or the distance to which a human can approach before the fox will flee. Selection for low flight distance (i.e., social approach) has produced a strain of dog-like tame foxes that seek out human contact. They display prosocial behavior toward humans, including licking, whining, barking, and tail wagging. Foxes from this strain are so tame that they can be kept as pets. Conversely, selection for high flight distance (i.e., social avoidance) has produced an avoidant/aggressive strain that avoids human contact. Aggressive behavior in this strain is a defensive response to forced contact; when given the option, they flee and avoid contact entirely. An additional strain is bred non-selectively in the same environment. A number of behavioral, endocrine, and genetic correlates of this selection paradigm have been identified, particularly in the HPA axis. Surprisingly, though, no work has yet addressed questions about systems neuroscience. In the current study, fixed left hemispheres of 10 tame, 10 aggressive, and 10 unselected foxes underwent high-resolution ex vivo T1, T2, and DTI imaging at a resolution of 300 cubic microns using a 9.4T Bruker MRI scanner. These animals had previously undergone detailed behavioral assays of social approach-avoidance behavior toward a human. Cortical myelination maps were computed from T1/T2 images. A novel computational approach was used to apply general linear modeling to whole-brain DTI connectomes. This revealed connectivity changes in the HPA axis and in several cortical-subcortical networks. Correlations between neuroanatomical measures and behavior are presented. These results are relevant for understanding general mechanisms of brain-behavior evolution and the specific mechanisms underlying evolved changes in social behavior. Additionally, results may be relevant for understanding evolved changes to, and clinical disruption of, social approach-avoidance processing in our own species.

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Nanosymposium

637. Brain Evolution

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Time: *Wednesday, November 15, 2017, 8:00 AM - 9:45 AM

Presentation Number: *637.04

**Topic: ***A.10. Development and Evolution

Support: Australian Research Council DP160103958
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National Health and Medical Research Council 1005751
Australian Postgraduate Award
UQ-QBI Doctoral Scholarship

Title: Interhemispheric homotopy, and bilateral hubs in medial and lateral isocortical borders predate the evolution of the corpus callosum

Authors: *R. SUAREZ[1], A. PAOLINO[1], L. MORCOM[1], P. KOZULIN[1], L. R. FENLON[1], L. J. RICHARDS[1,2]
[1]Queensland Brain Inst., The Univ. of Queensland, Brisbane, Australia; [2]The Univ. of Queensland, Sch. of Biomed. Sci., Brisbane, Australia

Abstract: The cerebral cortex is a prominent feature of the mammalian brain involved in sensory, motor and higher-order associative processes. While, interhemispheric pallial connections are largely unidirectional and heterotopic in non-mammalian amniotes such as birds, in mammals both cortical hemispheres are highly interconnected between homotopic and heterotopic regions. Notably, these connections course through the anterior commissure in non-eutherian mammals, such as monotremes and marsupials, while eutherians evolved the corpus callosum, the largest tract in the human brain. Whether callosal origin resulted in the eutherian bilateral connectome, or instead a pre-existent interhemispheric map predated callosal evolution remains unknown. Here we combined retrograde and anterograde interhemispheric circuit mapping in marsupials *in vivo* and found that commissural circuits include homotopic and heterotopic connections that resemble the eutherian bilateral connectome. For example, while there is a general homotopy between isocortical regions, specific medial (cingulate, motor) and lateral (insular, perirhinal) cortices connect with their contralateral homotopic regions as well as with a wide range of areas, suggesting they act as hyperconnected hubs. Moreover, the claustrum, a subplate derivative at the lateral border of the allocortex and isocortex, sends more heterotopic projections to the contralateral hemisphere (mostly to medial targets) than to the contralateral claustrum, suggesting it plays a critical role in interhemispheric integration. Taken together, our results suggest that a mesoscale bilateral connectome, including homotopic isocortical connections and hyperconnected hubs at the medial and lateral borders of the isocortex, predated the origin of the corpus callosum. As a consequence, we speculate that callosal evolution involved axonal re-routing through a novel substrate without altering the overall patterns of interhemispheric connections.

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Nanosymposium

637. Brain Evolution

Location: 146C

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***637.05

**Topic: ***A.10. Development and Evolution

Title: The relative size and organization of thalamic nuclei in primates, carnivores, and rodents

Authors: *A. C. HALLEY[1], M. K. BALDWIN[1], S. M. SHERMAN[2], L. A. KRUBITZER[3]
[1]Ctr. for Neurosci., Univ. of California, Davis, Davis, CA; [2]Dept. of Neurobio., Univ. of Chicago, Chicago, IL; [3]Ctr. for Neurosci., Univ. of California Davis, Davis, CA

Abstract: The thalamus plays a central role in both providing input from the sensory periphery to the neocortex as well as relaying information between cortical areas. Species differ widely in the organization of peripheral morphology, sensory mediated behaviors and in the functional organization of the neocortex, but relatively little is known about the evolution of individual thalamic nuclei and how they may have been modified to reflect these species differences. Here we quantify differences in the relative size of thalamic nuclei between different mammalian radiations, with a particular focus on primates (e.g. New World titi monkeys, Old World rhesus macaques), carnivores (e.g. grizzly bears, cats), and rodents (e.g. ground squirrels, rats). Tissue was sectioned coronally and stained in series for cytochrome oxidase, Nissl, AChE, VGLUT2, and/or myelin. Volumetric measurements were calculated for eight distinct thalamic nuclei, including both "primary" first-order sensory nuclei (e.g. dLGN, VPm/l, MGv) as well as higher-order nuclei (e.g. pulvinar). We use a combination of histology and volumetric allometry to describe the variation between taxa in the size, position, and internal organization of different thalamic nuclei, and we also describe differences according to variation in the size of the whole brain and the whole dorsal thalamus (i.e. allometric effects). Preliminary results indicate that thalamic nuclei scale at differing rates, with some nuclei taking up higher proportions of the total thalamus in larger brains (positive allometry; e.g. the medial dorsal nucleus, MD) while others take up smaller proportions (negative allometry; e.g. dLGN, VPm/l). We discuss these basic trends relative to several theories on the scaling of brain areas, including developmental and evolutionary considerations, and compare the new data described here to previously published data on the pulvinar and dLGN. We also present several case studies of thalamic nuclei in novel species, such as VPm/l of the grizzly bear, which exhibits a unique morphology relative to other carnivores and large-brained mammals.

Disclosures: A.C. Halley: None. **M.K. Baldwin:** None. **S.M. Sherman:** None. **L.A. Krubitzer:** None.

Nanosymposium

637. Brain Evolution

Location: 146C

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***637.06

**Topic: ***A.10. Development and Evolution

Title: Highly connected regions in macaque cortex show increased cortical expansion towards human

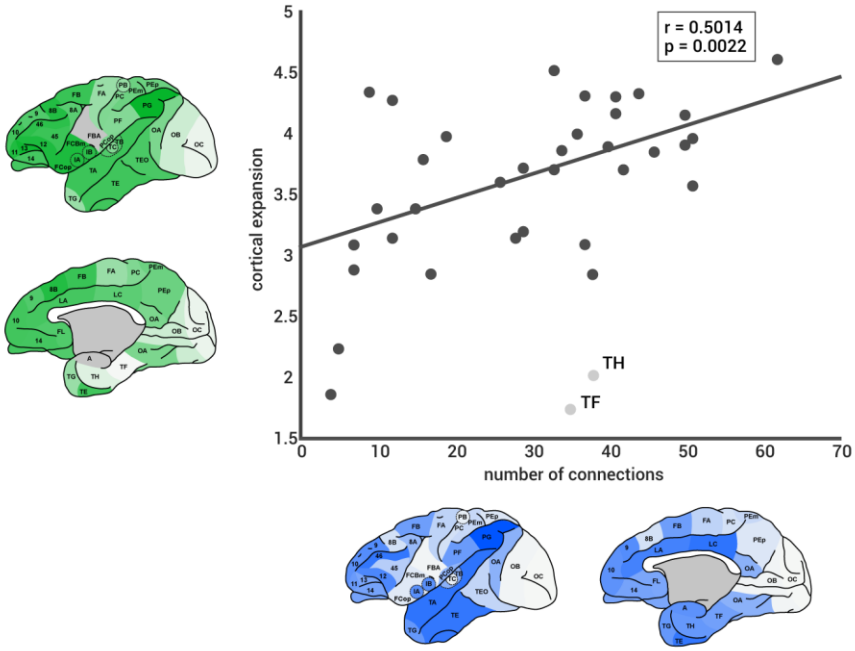
Authors: *L. H. SCHOLTENS, M. P. VAN DEN HEUVEL
Brain Ctr. Rudolf Magnus, UMC Utrecht, Utrecht, Netherlands

Abstract: The brain has been shown to have an efficient network structure, with highly connected hub regions facilitating integration of information between modalities. Across mammals with different brain sizes, cortical hubs have been consistently found to be situated in association areas of the superior frontal, parietal and temporal lobe, together with insular and cingulate cortex (van den Heuvel et al., 2016). In parallel, relative size of primary brain regions stays mostly consistent with increasing brain size, while more complex association areas expand non-linearly (Krubitzer, 2009). However, the evolutionary path of central hub regions remains largely unknown.

Connectivity and expansion data were analyzed using the combined Walker-von Bonin & Bailey atlas (Fig 1). For each region, information on presence and absence of structural corticocortical connections was extracted from the CoCoMac database of tract tracing studies (Stephan et al., 2001), including tracts examined in at least 5 studies and reported to exist in at least 50% of these studies. Macaque-to-human cortical area expansion was computed using CARET landmark-based registration procedures (Van Essen et al., 2001). Cross technique examination of connectivity and cortical expansion was performed using correlation analysis.

Within the macaque cortex, region-wise number of corticocortical connections was found to be associated with level of cortical expansion from macaque to human brain ($r=0.3593$, $p=0.0289$). Temporal regions BB47-TH and BB47-TF deviated from this relationship, excluding these regions from the comparison highlighted a stronger association between regional number of corticocortical connections and cortical macaque-to-human expansion ($r=0.5014$, $p=0.0022$; Fig 1).

Relating regional cortical connectivity in the macaque monkey to macaque-to-human cortical expansion shows a larger number of connections to go hand in hand with a larger increase in surface area towards the human brain, suggesting evolutionary cortical expansion may favor highly connected cortical regions.



Disclosures: **L.H. Scholtens:** None. **M.P. Van den Heuvel:** None.

Nanosymposium

637. Brain Evolution

Location: 146C

Time: *Wednesday, November 15, 2017, 8:00 AM - 9:45 AM

Presentation Number: *637.07

Topic: *E.07. Rhythmic Motor Pattern Generation

Title: The anterior cingulate cortex-midbrain periaqueductal gray pathway constitutes the context-specific aversive emotional connectome in mammals

Authors: ***H. H. SUBRAMANIAN**[1], M. ARUN[2], P. A. SILBURN[2], G. HOLSTEGE[1]
[2]Queensland Brain Inst., [1]The Univ. of Queensland, Brisbane, Australia

Abstract: The midbrain periaqueductal gray (PAG) functions as the central pattern generator (CPG) for emotional expression in mammals[1]. Limbic brain regions use the PAG to modulate autonomic bodily functions to reflect emotional expression such as laughter, stress, fear, anxiety, vocalization and speech (in humans). Of the limbic regions, the anterior cingulate cortex (ACC) is involved in a range of emotional processing particularly behaviours as stress and anxiety.

Thus, the ACC-PAG pathway could contribute to context-specific autonomic modulation of bodily states to regulate efferent drives integral to stress and anxiety. However, the structural and functional basis of the ACC-PAG connectome is unknown. We investigated cat and rat ACC projections to the PAG via neuroanatomical tract-tracing and fixed brain tissue 16.4T diffusion weighted imaging (DWI) tractography. We also investigated motor and autonomic behaviours produced via chemical microstimulation of specific regions/mircocircuits of the PAG innervated by ACC (If so). Neuroanatomical tract-tracing tracing shows that ACC projects densely to central PAG with sparse projections to the caudal ventrolateral PAG. DWI tractography showed similar projections from the ACC to PAG with comparable density of the projections. Chemical stimulation of central PAG produced a variety of autonomic responses inlcuding dyspnea, ataxic breathing and hypotension in both the cat and the rat. Stimulation of the caudal ventrolateral PAG produced 22KHz ultrasonic vocalization calls in the rat (while crying behavior in the cat was shown before[2]). Given that these autonomic responses are often seen as an index of stress and anxiety, these results provide further evidence that the ACC-PAG pathway may constitute the primary context-specific aversive limbic-autonomic emotional connectome in mammals.

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2. **Subramanian HH**, Arun M, Silburn PA and Holstege G (2016). Motor organization of positive and negative emotional vocalization in the cat midbrain periaqueductal gray. *J.Comp. Neurol.* 524(8):1540-57

Disclosures: H.H. Subramanian: None. **M. Arun:** None. **P.A. Silburn:** None. **G. Holstege:** None.

Nanosymposium

638. Preclinical Therapeutic Strategies for Neurodegenerative Disease II

Location: 140A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***638.01

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

Support: The Botsford Foundation
Radiation Oncology, William Beaumont Hospital
Michigan Head & Spine Institute

Title: External radiation and Amyvid treatment is associated with reduction of aβ plaque burden

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Abstract: Alzheimer's Disease (AD) represents the most frequent form of dementia and is characterized by brain extra cellular beta-amyloid (Aβ) plaques and Tau neurofibrillary tangles. A progressive degradation in episodic memory is the clinical hallmark of AD. Our group has previously reported radiation therapy (RT), in doses used to cure children of acute lymphocytic leukemia, results in a significant reduction in Aβ plaques in a hemibrain irradiated mouse model, while whole brain RT results in improved Morris Water Maze performance.[1] This study tests the hypothesis that whole brain RT (5 fractions of 2 Gy) and treatment with Amyvid (500μCi), a radiopharmaceutical used to image Aβ plaques leads to reduction in Aβ plaque in a murine AD model. 10-11month old APPswe, PSEN1dE9)85Dbo/J mice were randomized into 4 groups 1) no-RT or Amyvid (n=3), 2) hemi-brain RT with no Amyvid (n=4), 3) hemi-brain RT with "cold" Amyvid (n=4) and 4) hemi-brain RT with "hot" Amyvid (n=4) or groups. Animals were maintained in accordance with SFN animal housing standards. Eight weeks after RT treatment, animals were injected with "hot" or "cold" (allowed to decay 24 hours) and the animals sacrificed 5 to 6 days post injection. Brains were rapidly dissected and fixed in formalin hen immunostained for the presence of Aβ plaques using standard methods. Images were captured using an Aperio Slidescanner and analyzed both manually by three independent people and by Dinfiniens© Tissue Studio image processing software. Plaque counts were compared using Student's T test. The unirradiated brains had equal plaque counts in the right and left hemisphere (191±13 vs 196±14) whilst the hemi-brain irradiated animals without Amyvid showed an 18% reduction in plaques on the irradiated hemisphere. Addition of "hot" or "cold" Amyvid to hemi-brain irradiation reduced the overall plaque burden and eliminated the differential between right and left hemisphere. Of particular interest, the combination of hemi-brain RT and "hot" Amyvid reduced the total plaque counts from 357±23 in the whole brain of control animals to 239±14 in the combined RT and "hot" Amyvid animals (p=0.00038). These data suggest that external and radionuclide delivered radiation therapy may benefit AD patients by reducing Aβ plaque burden.
1. Marples B, et al. Radiotherapy and Oncology 118(1) 43-51 · November 2015

Disclosures: **D.B. Michael:** A. Employment/Salary (full or part-time):; William Beaumont Hospital, Michigan Head and Spine Institute. **A. Hanna:** None. **T.G. Wilson:** None. **G. Fontanesi:** None. **K. Buelow:** None. **A. Martinez:** A. Employment/Salary (full or part-time):; 21st Century Oncology. **M. Maddens:** A. Employment/Salary (full or part-time):; William Beaumont Hospital. **P. Chinaiyan:** A. Employment/Salary (full or part-time):; William Beaumont Hospital. **J. Fontanesi:** None. **B. Marples:** None. **G.D. Wilson:** A. Employment/Salary (full or part-time):; William Beaumont Hospital.

Nanosymposium

638. Preclinical Therapeutic Strategies for Neurodegenerative Disease II

Location: 140A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***638.02

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

Support: Florida State
Bright Focus Foundation

Title: Functionalized intrabodies as novel therapeutics for Alzheimer's disease and tauopathies

Authors: *M. GOODWIN[1], Z. WANG[2], P. TRUONG[2], J. PEVNER[2], P. CRUZ[1], Y. LEVITES[1], T. E. GOLDE[3]
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Abstract: Many neurodegenerative diseases are characterized by the pathological accumulation of misfolded proteins within intracellular aggregates, including Alzheimer's Disease and Parkinson's Disease. While there are currently no cures for these debilitating diseases, novel antibody-based therapies targeting disease specific proteins such as tau and alpha synuclein are currently under development. However, these therapies may be limited by the ability of extracellular antibodies to cross the blood brain barrier and enter the cytoplasm to engage intracellular proteins. This potentially limiting factor can be avoided by utilizing intracellular antibody technology to target misfolded proteins directly within the cytoplasm. The intracellular expression of antibody fragments known as intrabodies is emerging as a novel strategy to alter the folding, interaction, localization, and degradation of cytoplasmic proteins. Intrabodies specific for alpha synuclein and huntingtin have shown efficacy in preclinical trials, yet there has been little effort to target intrabodies against the microtubule associated protein tau which is the main component of aggregates found in Alzheimer's Disease and other tauopathies. We have generated several tau-specific intrabodies which were found to reduce tau pathology in vitro and in mouse models. We hypothesized that this reduction may be improved by fusing intrabodies to functional domains which will target tau for proteasomal or lysosomal degradation. Our data suggests that targeting tau for proteasomal degradation dramatically reduces tau aggregation in several cell culture models. Future studies expressing functionalized intrabodies in animal models are currently underway.

Disclosures: M. Goodwin: None. **Z. Wang:** None. **P. Truong:** None. **J. Pevner:** None. **P. Cruz:** None. **Y. Levites:** None. **T.E. Golde:** None.

Nanosymposium

638. Preclinical Therapeutic Strategies for Neurodegenerative Disease II

Location: 140A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***638.03

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

Support: HTS Screening Award: HTS-025

Title: Tissue-specific ABCA1 agonists to target lipidation of apoE4 in the CNS as an effective and tolerated therapy for Alzheimer's Disease

Authors: *M. BEN AISSA[1], S. H. LEE[1], B. KARUMUDI[1], M. LADU[2], G. R. J. THATCHER[1]
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Abstract: Cases of AD caused by mutations to a single human gene are extremely rare (1%) and the only major confirmed genetic risk factor for AD is the APOE4 allele. However, the failure of a dozen AD drugs in late stage clinical trials is not caused solely by preclinical AD-Tg mouse models of rare genetic forms of the disease; such preclinical models, but incorporating human APOE4, remain an important drug discovery tool. Similarly, acceptance that AD is a multifactorial disease often with mixed pathology, must inform therapeutic approaches. Recent genome-wide association studies (GWAS) have identified AD-associated single nucleotide polymorphisms (SNPs) within genes involved in cholesterol homeostasis, including: ABCA1, ABCA7 and ApoJ (CLU). One mechanism linking cholesterol mobilization to ApoE4 risk in AD, is defective clearance of neurotoxic amyloid-β peptide (Aβ), by poorly lipidated and unstable ApoE4 lioproteins particles. In the brain, astrocytes secrete the majority of ApoE in HDL-like lipoprotein particles and astrocytes lacking ABCA1 lead to poorly lipidated ApoE particles, which in AD-Tg mice can be mitigated by ABCA1 overexpression. ABCA1 is transcriptionally regulated via liganded nuclear receptor heterodimers, which could also regulate lipogenic genes leading to hepatotoxicity and liver steatosis. Bexarotene, an RXR agonist, increases ABCA1-induced ApoE lipidation, improves memory, and reduces Aβ pathology in AD-Tg mice, at the cost of adverse effects in the liver. **The objective is to develop an effective and well-tolerated tissue-selective ABCA1 agonist (TSAAg) strategy that will be effective in the APOE4 carrier population.** We have used a cell-based HTS screen to identify hits from a high value small molecule library, which elevate ABCA1 in an "astrocyte" cell line without increasing SREBP1c in an "hepatocyte" cell line counterscreen, essentialy TSAAgs. Screening conditions have been optimized to obtain an average Z' factors > 0.8. From initial 10,000-compounds, 5 Chemotypes were selected for SAR and probed in primary astrocytes for regulation of cholesterol efflux and genes associated with neuroinflammation, energy utilization, insulin sensitivity, and cholesterol metabolism e.g. ABCA1, PGC-1, GLUT1 for hit-to-lead

optimization. Preliminary PK/PD and target engagement validated the ability of TSAAgs to engage targets in vivo predicted from in vitro assays for liver steatosis, plasma and brain biomarkers: FAS/Cholesterol and TG levels/HDL/LDL/ABCA1/ApoE. In Conclusion, we propose that this phenotypic approach has potential to impact multiple factors that contribute to AD, both associated with and not directly associated with Aβ.

Disclosures: M. Ben Aissa: None. **S.H. Lee:** None. **B. Karumudi:** None. **M. LaDu:** None. **G.R.J. Thatcher:** None.

Nanosymposium

638. Preclinical Therapeutic Strategies for Neurodegenerative Disease II

Location: 140A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***638.04

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

Title: MH84 - a γ-secretase modulator with PPARγ activity improves mitochondrial dysfunction in a mouse model of early Alzheimer's disease

Authors: *G. P. ECKERT[1,2], M. POHLAND[2], H. ASSEBURG[2,1], S. HAGL[2], M. REUTZEL[1,2], M. WURGLICS[3], M. SCHUBERT-ZSILAVECZ[3]
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Abstract: Today the pathogenesis of Alzheimer`s disease (AD) with late onset (LOAD) is understood as a result of multiple factors. Neuropathological features are extracellular senile plaques, containing beta-amyloid peptides (Aβ) and intracellular neurofibrillary tangles composed of paired helical tau proteins. Both proteins have been associated with neuronal loss and atrophy of the cerebral cortex. Thus, misfolded proteins seem to contribute to the pathogenesis, but are not the only players. It`s becoming clearer that mitochondrial dysfunction occurs early in the disease process and may represent the missing link between ageing and LOAD. Currently approved drugs only attenuate symptoms, but do not cure the disease. Research into AD had several failures in terms of developing disease-modifying therapies and thus new targets in order to develop a causal therapy are desperately needed. The pirinixic adic derivate MH84, which represents a dual γ-secretase /PPARγ modulator is orally active in mice and possesses good pharmacokinetic properties. We recently demonstrated that MH84 improved mitochondrial dysfunction in a cellular model of AD. In the present study, we tested MH84 in Thy-1 APP_{SL} mice a model of early AD, which show enhanced cerebral APP processing and mitochondrial dysfunction at an age of 3 months. MH84 reduced cerebral levels of Aβ40 and C99 and ameliorated mitochondrial dysfunction by restoring complex IV respiration,

mitochondrial membrane potential and levels of ATP. Induction of PGC1α gene expression was identified as possible mode of action that leads to increased mitochondrial mass as indicated by enhanced citrate synthase activity and complex IV & V protein levels. Thus, MH84 may represents a new potential disease-modifying agent against AD.

Disclosures: G.P. Eckert: None. **M. Pohland:** None. **H. Asseburg:** None. **S. Hagl:** None. **M. Reutzel:** None. **M. Wurglics:** None. **M. Schubert-Zsilavecz:** None.

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638. Preclinical Therapeutic Strategies for Neurodegenerative Disease II

Location: 140A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***638.05

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

Title: Metformin reduces protein load and improves disease phenotype in early Huntington's Disease

Authors: M. WILLAM[1], N. GRIESCHE[2], J. KRUMMEICH[1], N. OFFERMANN[2], S. WEBER[2], I. ARNOUX[3], A. METHNER[4], C. CHEN[5], O. MONTEIRO[5], S. BUETTNER[2], K. MEYER[2], D. BANO[2], K. RADYUSHKIN[6], R. LANGSTON[5], J. LAMBERT[5], E. WANKER[7], *S. KRAUSS[2], S. SCHWEIGER[1]
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Abstract: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that is caused by an unstable glutamine (CAG) trinucleotide repeat expansion within the exon 1 of the Huntingtin gene and leads to cognitive impairment and motor dysfunctions. It has an extended preclinical phase with subtle, mostly behavioral symptoms like mood swings and personality changes far before neuronal loss is detected. So far no cure is available. Small homeostatic network changes seem to occur even earlier, opening up critical windows of vulnerability and opportunities for novel therapeutic interventions. Reduction of the disease-causing mutant Htt protein during this early phase, is a promising therapeutic approach.
We have shown previously that translation of mRNA carrying expanded CAG repeats is elevated in HD patients, mediated through mTOR signaling (Krauss et al., 2013). Additionally, the biguanid Metformin, commonly used as an anti-diabetic drug, antagonizes mTOR signaling in neurons in-vitro and in-vivo (Kickstein et al., 2010).

We show here that Metformin reduces protein translation of Htt and thereby reduces Htt protein load in vitro and in vivo. Metformin treatment leads to a reduction of protein-aggregates and improves motility in a C. elegans model of polyglutamine-expansion disorders.
Furthermore, we have analysed a knock-in mouse model that carries 150 CAG repeats and the human exon 1 in the 5' end of the murine huntingtin gene. By using a novel object recognition test with a 24 h interval between sample and test phase we have found an extensive deficiency of long-term memory in heterozygous transgenics. This phenotype was detected as early as 12 weeks of age and is supplementary to deficits which we have identified in the HdhCAG111 mouse model previously. Intranuclear aggregates as well as motor deficits are described at much later stages in both of these models. Metformin sufficiently rescues this early cognitive phenotype of the disease in the aforementioned mouse model.
This data suggests that Metformin is a suppressant of mutant Htt protein and a promising therapeutic compound for chronic treatment commencing early and covering critical windows of vulnerability in HD.

Disclosures: **M. Willam:** None. **N. Griesche:** None. **J. Krummeich:** None. **N. Offermann:** None. **S. Weber:** None. **I. Arnoux:** None. **A. Methner:** None. **C. Chen:** None. **O. Monteiro:** None. **S. Buettner:** None. **K. Meyer:** None. **D. Bano:** None. **K. Radyushkin:** None. **R. Langston:** None. **J. Lambert:** None. **E. Wanker:** None. **S. Krauss:** None. **S. Schweiger:** None.

Nanosymposium

638. Preclinical Therapeutic Strategies for Neurodegenerative Disease II

Location: 140A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***638.06

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

Support: R01 AG032611
R01 NS077239

Title: Live time-lapse imaging in a human neuron like model to clarify the mechanisms of intracellular antibody-mediated neutralization/clearance of human brain derived tau protein

Authors: *D. B. SHAMIR[1], Y. DENG[2], E. M. SIGURDSSON[3]
[1]Neurosci. and Physiol., [3]Neurosci. and Physiology, and Psychiatry, [2]New York Univ. Sch. of Med., New York, NY

Abstract: Our laboratory has pioneered targeting pathological tau proteins using active and passive immunotherapies in models of Alzheimer's disease and other tauopathies. Previously, we double differentiated naïve SH-SY5Y cells with retinoic acid and BDNF to create a more

neuronal-physiological system.This model showed increased tau levels, decreased tau antibody (Ab) internalization, and greater efficacy of tau Abs to clear pathological tau, compared to non-differentiated cells. Time-lapse live imaging is a very sensitive approach, which allows monitoring in real time the internalization, interaction, and dynamics of both Ab and pathological tau within endocytic cellular compartments. The neuron-like cells were pre-treated for 16 h with 50 µg/mL of paired helical filament (PHF) enriched fluorescently-tagged tau and subsequently incubated for 2.5 h with 20 µg/mL CypHer5E-tagged 4E6 tau Ab, which was generated against a P-S396,404 tau immunogen, or non-specific isotype control IgG1. CypHer5E is a pH sensitive dye, which only fluoresces within acidic compartments, like the endosome-lysosome (E-L) system. Ab signal increased over time, and plateaued at 2 h for both antibodies, while the PHF signal was constant during the 2.5 h experiment. Furthermore, 4E6 signal was on average 1.5 to 3-fold greater than IgG1 over this duration. Intracellular PHF-4E6 co-localization increased over time and was confirmed by intensity correlation analysis (r^2= -0.050 to 0.232, p= 0.0157), while PHF and IgG1 did not colocalize over time (r^2 = -0.047 to -0.046, p= 0.9560). 4E6 binding to PHF mainly occurred within the soma, while IgG1 internalization was primarily detected in the neurites/processes with very limited PHF colocalization. Our laboratory has shown in various models that several tau Abs interact with pathological tau both extra- and intracellularly.In this study we focused on their fast intracellular interaction within the E-L system. In these pre-treated cells, PHF gradually finds its way into the soma, and 4E6 binds to it there, while control IgG1 does not. This approach may clarify within a short timeframe the dynamics and mechanisms of intracellular Ab-mediated clearance of pathological tau, and thereby facilitate identifying clinical Ab candidates.

Disclosures: D.B. Shamir: None. **Y. Deng:** None. **E.M. Sigurdsson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EMS is an inventor on patents on tau immunotherapy and related diagnostics that are assigned to New York University and licensed to H. Lundbeck A/S.. F. Consulting Fees (e.g., advisory boards); H. Lundbeck A/S (within the last year), GlaxoSmithKline (within the last year).

Nanosymposium

638. Preclinical Therapeutic Strategies for Neurodegenerative Disease II

Location: 140A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***638.07

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

Support: a Grant-in-Aid for the Cooperative Research Project from Joint Usage/Research Center (Joint Usage/Research Center for Science-Based Natural Medicine) Institute of

Natural Medicine, University of Toyama in 2011
Discretionary Funds of the President and Budget for Functional Enhancement by University of Toyama in 2015-2017

Title: Cognitive enhancement by diosgenin treatment

Authors: *C. TOHDA[1], X. YANG[2]
[1]Inst. of Natural Medicine, Univ. of Toyama, Toyama, Japan; [2]Inst. of Natural Med., Univ. of Toyama, Toyama, Japan

Abstract: Our previous study showed that diosgenin, a plant-derived steroidal sapogenin, improved memory and reduced axonal and presynaptic degenerations in an Alzheimer's disease model 5XFAD mice. We also found that diosgenin may work as an exogenous stimulator of 1,25D_3-MARRS and induces axonal growth and regrowth even in Aβ-induced damaging condition. Here, we aimed to obtain evidence showing that diosgenin facilitates memory ability also in normal mice. Diosgenin treatment in normal mice enhanced object recognition memory and spike firing and cross-correlation in the medial prefrontal cortex and hippocampal CA1. In diosgenin-treated mice, axonal density and c-Fos expression was increased in the medial prefrontal and perirhinal cortices, suggesting that neuronal network activation may be enhanced. The diosgenin-induced memory enhancement and axonal growth were completely inhibited by i.c.v. injection of a neutralizing antibody for 1,25D_3-MARRS. Our *in vivo* data indicate that diosgenin is a memory-enhancing drug and that enhancement by diosgenin is mediated by 1,25D_3-MARRS-triggered axonal growth. Furthermore, we performed a clinical study to investigate effects of diosgenin-rich extract on cognitive ability in healthy subjects.

Disclosures: C. Tohda: None. **X. Yang:** None.

Nanosymposium

638. Preclinical Therapeutic Strategies for Neurodegenerative Disease II

Location: 140A

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**Presentation Number: ***638.08

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

Support: NSFC 81671259
NSFC81470057

Title: Treadmill running exercise protects hippocampal neurons in middle-aged App/PS1 transgenic AD mice

Authors: *Y. TANG, F. L. CHAO, C. N. ZHOU, Y. ZHANG, L. JIANG, L. ZHANG, J. MA
Chongqing Med. Univ., Chongqing, China

Abstract: The risk of cognitive decline during Alzheimer's disease (AD) can be reduced if physical activity is maintained; however, the specific neural events underlying this beneficial effect are still uncertain. To investigate the neural events underlying the effect of running exercise on middle-aged AD subjects, 12-month-old male APP/PS1 mice were randomly assigned to a control group (AD control) or running group (AD runner), and age-matched non-transgenic littermates were used as a wild-type group (WT control). AD runner mice were subjected to a treadmill running protocol (regular and moderate intensity) for four months. Spatial learning and memory abilities were assessed using the Morris water maze. Hippocampal amyloid plaques were observed using Thioflavin S staining and immunohistochemistry. Hippocampal volume, number of neurons and number of newborn cells ($BrdU^+$ cells) in the hippocampus were estimated using stereological techniques, and newborn neurons were observed using double-labelling immunofluorescence. The spatial learning and memory abilities of AD runner mice were significantly better than those of AD control mice. Although there were no significant differences in the hippocampal volume and total volume of the hippocampal subregions among the three groups, hippocampal amyloid plaques were decreased in AD runner mice compared with those in AD control mice. In addition, neuronal numbers in both the CA1 field and dentate gyrus (DG) of AD control mice were significantly reduced compared with those of WT control mice. Compared with AD control mice, AD runner mice had more neurons in the DG. The total number of newborn cells and the density of the newborn neurons in the DG of AD control mice were significantly reduced compared with those of WT control mice, and AD runner mice had more newborn cells and newborn neurons in the DG than AD control mice. Our results indicate that regular and moderate-intensity running exercise cannot rescue hippocampal atrophy but can reduce amyloid plaques in the hippocampi of middle-aged APP/PS1 mice. Marked neuronal loss in both the CA1 field and DG and deficits in both the neurogenesis and survival of new neurons in the DG of middle-aged APP/PS1 mice were observed. Regular and moderate intensity running exercise can delay neuronal loss, induce neurogenesis and promote the survival of newborn neurons in the DG of middle-aged APP/PS1 mice. Exercise-induced protection of neurons and adult neurogenesis within the DG might be part of the important structural bases of the exercise-induced improvement of spatial learning and memory abilities observed in AD mice.

Disclosures: **Y. Tang:** A. Employment/Salary (full or part-time):; Dept. of Histology and Embryology, Chongqing Med. Univ., Chongqing, P. R. China. **F.L. Chao:** None. **C.N. Zhou:** None. **Y. Zhang:** None. **L. Jiang:** None. **L. Zhang:** None. **J. Ma:** None.

Nanosymposium

638. Preclinical Therapeutic Strategies for Neurodegenerative Disease II

Location: 140A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***638.09

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

Support: a Grant-in-Aid for the Cooperative Research Project from Joint Usage/Research Center (Joint Usage/Research Center for Science-Based Natural Medicine) Institute of Natural Medicine, University of Toyama in 2011
Discretionary Funds of the President and Budget for Functional Enhancement by University of Toyama in 2015-2017

Title: Diosgenin restores axonal degeneration via the reduction of HSC70, resulting in improvement of memory function in Alzheimer's disease

Authors: *X. YANG, C. TOHDA
Inst. of Natural Medicine, Univ. of Toyama, Toyama, Japan

Abstract: We previously found that diosgenin, a constituent of Dioscorea Rhizoma, restored axonal degeneration and improved memory function in a mouse model of Alzheimer's disease (AD), 5XFAD. In this study, we aimed to investigate diosgenin-elicited expression change of intracellular molecules, which are involved in axonal regrowth and memory recovery. Vehicle solution or diosgenin (0.1 μmol/kg/day, p.o.) was administered to wild-type or 5XFAD mice (male, 24-27 weeks old) for 15 days. The diosgenin-administered 5XFAD mice showed significant improvement in object recognition memory. After the behavioral test, protein expressions in cortical lysates were compared on 2D-PAGE. We focused several proteins showing drastic changes in the expression level and analyzed those by MALDI-TOF/MS. Heat shock cognate 70 (HSC70) was identified as the protein decreased by diosgenin administration in 5XFAD. Next, cultured cortical neurons (ddY, E14) were treated by $A\beta_{25\text{-}35}$. $A\beta_{25\text{-}35}$ treatment for 3 days increased the expression level of HSC70 and decreased the axonal density. Post treatment by diosgenin (0.1, 1 μM) significantly decreased HSC70 expression and increased density of axons. Next, we tried to clarify functions of HSC70 on axon and memory, by exploring a binding partner (client protein) of HSC70. By immunoprecipitation and nano-LC/MS analysis, α-tubulin was identified as a client protein of HSC70. $A\beta_{25\text{-}35}$ treatment for 1 day decreased the expression level of α-tubulin (intensity/μm) on neurites, but post treatment of diosgenin for 4 days restored α-tubulin levels on neurites and promoted axonal regrowth.Our study suggests for the first time that $A\beta_{25\text{-}35}$-induced increase in HSC70 may promote degradation of α-tubulin, which results in axonal degeneration. Also, diosgenin is a promising drug that induces axonal regrowth by reducing expression level of HSC70 and inhibits

degradation of α-tubulin. It is expected that inhibiting HSC70 function may be a new therapeutic target in AD.

Disclosures: X. Yang: None. **C. Tohda:** None.

Nanosymposium

638. Preclinical Therapeutic Strategies for Neurodegenerative Disease II

Location: 140A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***638.10

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

Title: Moderate exercise and lithium prevent amyloid-B-induced hippocampal disruption

Authors: *A. GONZALEZ ISLA, F. PENA-ORTEGA
Univ. Nacional Autónoma De México, Queretaro, Mexico

Abstract: Amyloid B (AB) is responsible for the neuronal network dysfunction (i.e. theta rhythm inhibition) associated to early impairments of learning and memory in Alzheimer's Disease (AD). Lithium (Li^+), a GSK3B inhibitor used to treat bipolar disorder, prevents several pathological effects of AB and is currently under clinical trials for AD treatment. However, Li^+ produces multiple side effects, which are exacerbated by long-term administration and aging, limiting its therapeutic use. We have recently shown that exercise inhibits GSK3B and prevents AB-induced hippocampal activity inhibition. However, exercise is challenging during aging. Thus, we aimed to test whether short-term Li^+ treatment combined with a moderate exercise regime would produce a cumulative protective effect against AB-induced inhibition of hippocampal function. Using behavioral tests, *in vivo* recordings, western blot and immunohistochemistry, we found that 3 weeks of lithium treatment combined with moderate exercise, which do not produce beneficial effects separately, prevents AB-induced disruption on memory and hippocampal theta activity. Our data suggest that a combination of pharmacological and non-pharmacological therapeutic approach would be useful against AD.

Disclosures: A. Gonzalez Isla: None. **F. Pena-Ortega:** None.

Nanosymposium

638. Preclinical Therapeutic Strategies for Neurodegenerative Disease II

Location: 140A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:45 AM

**Presentation Number: ***638.11

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

Title: USP30 inhibitors as mitophagy modulators for treatment of neurodegenerative diseases

Authors: F. WANG[1], I. SOKIRNIY[1], P. ARSENAULT[1], D. STERNER[1], J. WU[1], B. CUNNION[1], J. WEINSTOCK[2], M. MATTERN[1], *T. R. BUTT[3], S. KUMAR[2]
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Abstract: Alzheimer's disease (AD) affects an estimated 21-35 million people worldwide; this number is predicted to double in the next decade. AD results from the degeneration and death of neurons in the hippocampus and the entorhinal cortex regions of the brain, areas that are critical for learning and memory. Ultimately fatal with no cure available, AD is the sixth-leading cause of death in the United States. Current therapeutics, which provide temporary, symptomatic relief only in patients with early stage AD, have serious side effects, and cannot prevent neuronal death and disease progression. Thus, it is necessary to identify novel therapeutics that can actually halt the progression of AD. The mitochondrion is such a target as mitochondrial dysfunction is well reported in AD. The dysfunctional mitochondria are cleared by phosphorylation and the ubiquitin-mediated autophagy (mitophagy) pathway. The ubiquitin pathway component consists of the conjugating enzyme Parkin, which tags proteins within defective mitochondria with ubiquitin for removal, and the mitochondria-localized deubiquitinating enzyme USP30, which deconjugates ubiquitin, preventing the removal of defective mitochondria. In AD patients the ability to clear defective mitochondria is overwhelmed, and supplementation of Parkin function by overexpression can rescue AD symptoms *in vivo*. Moreover, USP30 knockout has been shown to enhance parkin mediated ubiquitination and increase mitochondrial integrity in neurons. These findings lead to the hypothesis that USP30 is a novel target for developing small molecule inhibitors for treatment of AD; USP30 inhibitors are expected to promote mitophagy and prevent neuronal death, thereby hindering progression of AD. Using Progenra's proprietary UbiPro^{TM} HTS platform we have successfully identified small molecule inhibitors of USP30. Here we present the biochemical and cellular characterization of potent and selective USP30 inhibitors that activate PINK1/Parkin-dependent mitophagy pathway. The combination effects of these molecules with Progenra's novel Parkin activators will also be discussed.

Disclosures: F. Wang: A. Employment/Salary (full or part-time):; Progenra Inc. **I. Sokirniy:** A. Employment/Salary (full or part-time):; Progenra Inc. **P. Arsenault:** A. Employment/Salary (full or part-time):; Progenra Inc. **D. Sterner:** A. Employment/Salary (full or part-time):; Progenra Inc. **J. Wu:** A. Employment/Salary (full or part-time):; Progenra Inc. **B. Cunnion:** A.

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Nanosymposium

639. Parkinson's Disease: Cell Biology, Mechanisms, and Targets

Location: 147B

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***639.01

**Topic: ***C.03. Parkinson's Disease

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JPB

Title: Pacemaking and mitochondrial stress drive methamphetamine toxicity

Authors: *S. M. GRAVES[1], S. E. SCHWARZSCHILD[1], R. A. TAI[1], P. T. SCHUMACKER[2], D. J. SURMEIER[1]
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Abstract: Methamphetamine (meth) is a highly addictive psychostimulant abused by ~13 million people in the US (NSDUH). In addition to being a devastating disease, meth abuse also increases the risk for developing Parkinson's disease (PD) (Callaghan RC *et al., Drug Alcohol Depend* 120:35 2012;Curtin *et al., Drug Alcohol Depend* 145:30 2015). The hallmark motor symptoms of PD are largely a result of the degeneration of substantia nigra pars compacta (SNc) dopaminergic (DA) neurons. Pacemaking-induced mitochondrial oxidant stress appears to be a major factor underlying degeneration of these neurons (Sulzer & Surmeier *Mov Disor.* 28:715 2013). We sought to determine whether chronic meth administration caused degeneration of SNc DA neurons through a common mechanism. To this end, SNc DA neurons were examined in chronically treated mice using a combination of patch clamp electrophysiology and two-photon laser scanning microscopy in *ex vivo* brain slices. Chronic (14 consecutive days) of 5mg/kg meth but not 1 or 2.5mg/kg induced significant SNc degeneration after a 14 day withdrawal period. This chronic 5mg/kg meth model resulted in accelerated pacemaking frequency measured at 1 and 14 days of withdrawal and was associated with increased somatic mitochondrial oxidant stress. Given that meth increases PD risk but cocaine does not (Callaghan RC *et al., Drug Alcohol Depend* 120:35 2012;Curtin *et al., Drug Alcohol Depend* 145:30 2015), we hypothesized that metabolism of cytosolic DA may be a causal mechanism triggering the changes in pacemaking and mitochondrial oxidant stress. Unpublished work from our lab demonstrates that

monoamine oxidase (MAO) metabolism of DA selectively increases mitochondrial oxidant stress. Kv4.3 channels regulate excitability of SNc DA neurons and are sensitive to oxidant stress (Subramaniam *et al., JNS* 834:13586 2014). Consistent with this, Kv4.3 mRNA was decreased when measured after 1 day withdrawal. If MAO-dependent stress led to the observed suppression of Kv4.3 mRNA then inhibiting MAO enzymes with the inhibitor rasagiline should prevent the above changes and be neuroprotective. To test this, mice were administered rasagiline (30min 1mg/kg) prior to 5mg/kg meth and experiments were repeated. Rasagiline pretreatment prevented changes in pacemaking, mitochondrial oxidant stress, and was neuroprotective. Collectively, our data suggest that MAO metabolism of dopamine leads to a loss of Kv4.3 current causing accelerated pacemaking activity and mitochondrial oxidative stress; these effects result in a progressive degeneration of SNc DA neurons.

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Nanosymposium

639. Parkinson's Disease: Cell Biology, Mechanisms, and Targets

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**Topic: ***C.03. Parkinson’s Disease

Support: Van Andel Institute Graduate School (ETW)
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Title: A novel functional interaction of Parkinson's disease-linked proteins VPS35 and parkin

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Abstract: Parkinson’s disease (PD) is the most common neurodegenerative movement disorder. Mutations in at least twelve genes are known to cause familial forms of PD, including autosomal dominant mutations in the *vacuolar protein sorting 35 ortholog* (*VPS35, PARK17*) gene and autosomal recessive mutations in the *parkin (PARK2)* gene. *VPS35* encodes a core subunit of the retromer complex which functions in the endosome-to-*trans*-Golgi network (TGN) and endosome-to-plasma membrane sorting and recycling of transmembrane protein cargo. Parkin is

an E3 ubiquitin ligase which mediates the ubiquitination and proteasomal degradation of numerous protein substrates and plays a role in mitochondrial turnover/biogenesis, vesicular sorting and cell signaling pathways. In this study, we identify a novel functional interaction between parkin and VPS35. We demonstrate that parkin interacts with and robustly ubiquitinates VPS35 in human SH-SY5Y neural cells. Familial parkin mutations do not alter the interaction with VPS35 but they are impaired in their ability to ubiquitinate VPS35. We find that parkin mediates the addition of an atypical poly-ubiquitin chain to VPS35, and mass spectrometry reveals multiple internal lysine residues within the C-terminal region of VPS35 that are covalently modified by ubiquitination. Parkin-mediated VPS35 ubiquitination does not promote the proteasomal degradation of VPS35. Consistent with this observation, parkin does not influence the steady-state levels or turnover of VPS35 in SH-SY5Y cells whereas VPS35 levels are not altered in the brains of both adult conditional and germline parkin knockout mice. These data suggest that ubiquitination of VPS35 by parkin may serve a non-degradative cellular function potentially by regulating retromer-dependent sorting. We are currently assessing the impact of VPS35 ubiquitination on retromer assembly, protein interactions and cargo sorting as well as evaluating the functional interaction of these two proteins *in vivo*. We find that parkin gene silencing in primary cortical neurons disrupts the vesicular sorting of the autophagy receptor ATG9A, a retromer-dependent cargo, suggesting that parkin can regulate retromer function. We further find that parkin deletion in knockout mice does not alter dopaminergic neurodegeneration induced by the overexpression of human D620N VPS35 in the nigrostriatal pathway. We are now testing whether parkin overexpression can protect from mutant VPS35-induced neurodegeneration in rats. Collectively, our data reveal a novel functional interaction of parkin with VPS35 that may be important for retromer-mediated endosomal sorting and neurodegeneration in PD.

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Nanosymposium

639. Parkinson's Disease: Cell Biology, Mechanisms, and Targets

Location: 147B

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***639.03

**Topic: ***C.03. Parkinson’s Disease

Title: A PD-associated single nucleotide polymorphism in ATP6V0A1 modifies its transcriptional regulation by mutant alpha-synuclein

Authors: *C. CORTI[1], J. OBERGASTEIGER[2], C. ÜBERBACHER[2], V. D´AGOSTINO[3], P. PRAMSTALLER[2], A. HICKS[2], M. VOLTA[2]
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Abstract: Vacuolar-type ATPases (V-ATPases) are ubiquitous, conserved proton pumps in the cellular endomembrane system where they energize transport processes across the membrane or regulate pH (Wieczorek, 1999). These proteins are organized in complexes mediating the acidification of eukaryotic intracellular organelles such as lysosomes, endosomes, trans-Golgi cisternae and secretory granules during cellular autophagy. A gene expression profiling study of substantia nigra dopamine neurons demonstrated that the ATP6V0A1 gene was specifically downregulated in Parkinson´s disease (PD) patients neurons, pointing to a potential link between the deregulation of ATP6V0A1 in PD (Simunovic, 2009). In addition, the ATP6V0A1 genetic locus has been recently implicated in the pathogenesis of sporadic PD by genome wide association (Nalls, 2014), where variations in the gene may change the expression level or activity of ATP6V0A1 ultimately leading to an increased risk for disease.In this study, we have identified the human ATP6V0A1 gene promoter region (ancestral promoter) and examined whether SNP rs9897702 in the promoter region (PD-associated promoter) affects ATP6V0A1 transcription by changing the affinity for specific transcription factors. The ATP6V0A1 transcriptional regulation was evaluated by luciferase reporter gene assay in human neuroblastoma cell lines expressing either human alpha synuclein (aSyn), human LRRK2 or their PD-related mutants. We observed no statistically significant differences in the activity of the two promoters in non-transfected cells. On the contrary, in all three aSyn overexpressing cell lines (WT, A53T, A30P), the activity of the ancestral ATP6V0A1 promoter was higher with respect to the PD-associated one. We also identified *in silico* and confirmed by EMSA that SNP rs9897702 affects binding of the transcription factor GATA-1. We also evaluated by EMSA that SNP rs9897702 clearly affects DNA-binding activity of proteins in cell extracts, presumably involving GATA-1 transcription factor as predicted by *in silico* analysis. This indicates that transcription of ATP6V0A1 could be a critical contributor to the regulation of low pH in intracellular vesicles and organelles, which is essential for various membrane trafficking processes and degradation of proteins. Our study demonstrates a functional effect of the PD-related SNP rs9897702, indicating ATP6V0A1 as a susceptibility and/or co-morbid factor in LRRK2- and aSyn -related PD disease. Modulation of the autophagy pathway through regulation of ATP6V0A1 expression and/or function might represent a novel approach for disease-modifying PD treatments.

Disclosures: C. Corti: None. **J. Obergasteiger:** None. **C. Überbacher:** None. **V. D´Agostino:** None. **P. Pramstaller:** None. **A. Hicks:** None. **M. Volta:** None.

Nanosymposium

639. Parkinson's Disease: Cell Biology, Mechanisms, and Targets

Location: 147B

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**Presentation Number: ***639.04

**Topic: ***C.03. Parkinson’s Disease

Title: The small GTPase Rin modulates alpha-synuclein inclusions: Implications for familial and idiopathic Parkinson´s disease

Authors: *M. VOLTA, J. OBERGASTEIGER, G. FRAPPORTI, C. ÜBERBACHER, C. ASCIONE, P. P. PRAMSTALLER, M. ROSATO-SIRI, A. A. HICKS, C. CORTI
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Abstract: The etiology of Parkinson´s disease (PD) is still undefined, but familial cases linked to specific genetic causes provided hints for possible mechanisms. In particular, aSyn and LRRK2 gene alterations lead to autosomal dominant PD with many commonalities to the idiopathic disorder, such as inclusions of alpha-synuclein (aSyn). These are the neuropathological hallmark of neurodegenerative diseases presenting with parkinsonism as common symptom, such as PD. The mechanisms underlying formation, maintenance and clearance of aggregates are still unclear, but hypothesized to involve autophagy, endosome-lysosome pathway, ubiquitination and the unfolded protein response. Multiple cellular players might be involved and definition of a clear molecular process is critically needed.
The novel PD risk factor *RIT2*, coding for the small GTPase Rin, functions in p38 and ERK MAPK pathways influencing several cellular processes, including the ones above. Interestingly, Rin is enriched in neurons of the rat substantia nigra pars compacta and is reduced in human PD brains.
We confirmed Rin expression pattern in the mouse brain and found that Rin gene and protein expression (but not Rit, coded by *RIT1*) in cell lines is reduced by elevated levels of WT or mutant aSyn and LRRK2. In order to better characterize the role played by Rin, we generated a neuroblastoma cell line stably overexpressing Rin, which shows a strong basal activation of p38 MAPK, but not ERK1/2.
Of note, our LRRK2-G2019S cell line displays inclusions of endogenous aSyn, when immunostained for pSer129-aSyn. Importantly, acute overexpression of Rin reduces the percentage of inclusion-bearing cells. We are investigating the contribution of the autophagy pathway in these phenomena.
To extend these findings, we turned to mouse primary cortical neuron cultures and induced Lewy-like pathology by treatment with synthetic aSyn fibrils. We are currently assessing the consequences of Rin overexpression in this model, concomitantly to assessment of neurophysiology.
Our data suggest that Rin, aSyn and LRRK2 share common cellular mechanisms ultimately

impacting aSyn aggregation. In addition, modulating Rin signaling might constitute an experimental strategy to combat synucleinopathy in both familial (i.e. LRRK2) and idiopathic neuropathology models.

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Nanosymposium

639. Parkinson's Disease: Cell Biology, Mechanisms, and Targets

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**Topic: ***C.03. Parkinson’s Disease

Support: NIH
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Title: Development of potential new drugs targeting brain cyclin dependent kinase 5 (CdK5) for the treatment of Parkinson's disease

Authors: A. BERNARDO[1], H. JOSHI[1], *H. C. PANT[2], K. YUEN[1], P. GUNNING[1], N. AMIN[3], R. MISHRA[1]
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Abstract: Cyclin-dependent kinase 5 (Cdk5) is a multifunctional protein kinase whose role has recently been implicated in Parkinson’s disease (PD). Activation of Cdk5 requires association with one of two neuronal regulatory subunits - p35 or p39. Normal activation of Cdk5 by p35 or p39 is essential for many vital cellular processes. However, oxidative stress increases intracellular calcium levels, activating enzyme calpain, which subsequently cleaves p35 to p25. P25 has a higher affinity for Cdk5. The increased presence, and functionally longer half-life of p25 deregulates and hyperactivates Cdk5 in disease states. Hyperactive Cdk5 phosphorylates a multitude of proteins and transcription factors, ultimately resulting in neurodegeneration. This dysregulated Cdk5 (Cdk5/p25 complex) becomes toxic, causing neuronal death. Thus, hyperactive Cdk5, specifically Cdk5/p25 complex activity, is a crucial target in preventing oxidative stress induced toxicity and apoptosis. In this study, we have developed and evaluated novel peptidomimetics which inhibit hyperactive Cdk5 in the cellular and preclinical models of PD. TP5 is a truncated 24 amino acid modified peptide designed based on the structure and

kinetics of the Cdk5/p25 complex. Peptide A is designed to be the 8-amino acid fragment of TP5 closest to the C-terminus instilling the activity and neuroprotective effects of TP5 to achieve greater permeability through the blood brain barrier. Both TP5 and Peptide A were able to prevent and reverse the PD-like motor abnormalities in 6-OHDA lesioned rat model of hemi-parkinsonism. Additionally, TP5 and Peptide A were able to prevent haloperidol induced catalepsy (rigidity and akinesia). Furthermore, we also investigated the neuroprotective effects of TP5 and Peptide A against paraquat induced cellular toxicity in human neuroblastoma SH-SY5Y cells. Paraquat's mechanism of action to induce oxidative stress is very similar to that of MPTP, mitochondrial toxin and has been shown to cause PD-like symptoms similar to those caused by MPTP. Both TP5 and Peptide A were able to prevent paraquat induced cellular toxicity in SH-SY5Y cells. The results of these studies implicate TP5 and its peptidomimetic analogues for the treatment of PD and other neurodegenerative diseases.

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Nanosymposium

639. Parkinson's Disease: Cell Biology, Mechanisms, and Targets

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**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:30 AM

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**Topic: ***C.03. Parkinson's Disease

Support: Michael J Fox Foundation
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Department of Medicine, BUSM

Title: AAV-driven expression of functional PLA2g6(L) protects against progressive loss of DA neurons and motor dysfunction in a new mouse model of PD

Authors: *A. YEN[1], J. W. SHIM[1], F. NIPA[1], M. M. BACHSCHMID[1], S. PIROT[2], C. MANNOURY LA COUR[2], M. J. MILLAN[2], V. M. BOLOTINA[1]
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Abstract: We have recently demonstrated that impairment of PARK14/PLA2g6-dependent Ca^{2+} signaling can be a new determinant of idiopathic Parkinson's disease (idPD). We created a transgenic mouse model (B6.Cg-Pla2g6$^{\Delta Ex2\text{-}VB}$, or PLA2g6ex2^{KO}) that has significant autophagic dysfunction, develops progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc), and age-dependent motor dysfunction that closely mimics idPD in humans. Restoration of PLA2g6 function (by expression of PLA2g6(L) variant) was able to rescue Ca^{2+}

signaling and restore autophagy in cells from idPD patients as well as in iPSC-derived A9 DA neurons from PLA2g6ex2^{KO} animals. The goal of this study was to test if *in-vivo* restoration of PLA2g6(L) function in DA neurons of SNc of aged PLA2g6ex2^{KO} mice could prevent the loss of DA neurons, and slow development of PD-like phenotype. A pseudotyped adeno-associated virus (AAV2/5) was constructed with the synapsin1 promoter to target expression of PLA2g6(L) in neurons. This AAV2/5-Syn1-^{myc}PLA2g6(L) (or saline as control) was stereotactically injected into the SNc of two age groups of ex2^{KO} animals that represent preclinical and early clinical stages of PD (10 and 14 m/o, respectively), as well as in their WT littermates. AAV-driven expression of PLA2g6(L) could be detected in TH+ neurons in the SNc and was stable for at least 6 months after injection. Remarkably, AAV-driven expression of PLA2g6(L) prevented the loss of TH+ neurons in the SNc of PLA2g6ex2^{KO} animals: 20 m/o ex2^{KO} animals injected with saline showed almost 50% loss of TH+ neurons, while the number of TH+ neurons in SNc of AAV-injected ex2^{KO} animals was similar to WT littermates. AAV injection also significantly decreased the number of periodic acid-Schiff (PAS)-positive deposits, and restored normal autophagy in DA neurons. Intensity of TH in the caudate putamen of these animals was found to be indistinguishable from WT animals. Importantly, we found that AAV2/5-Syn1-^{myc}PLA2g6(L) injection into SNc of ex2^{KO} animals delayed the onset and slowed progression of PD-like motor dysfunction, while it had no effects in WT littermates. Disease course altering effects of AAV-driven expression of PLA2g6(L) were evident when started in preclinical, as well as early clinical stages of PD development in ex2^{KO} mice. Thus, restoration of PLA2g6(L) function can have a course altering effect on the progression of PD, and pathogenic PLA2g6/Ca^{2+} axis can be a new target for PD therapeutics.

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Nanosymposium

639. Parkinson's Disease: Cell Biology, Mechanisms, and Targets

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Title: Progranulin and cathepsin D - Implications for frontotemporal dementia pathogenesis

Authors: *C. B. VALDEZ, D. KRAINC
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Abstract: Frontotemporal Dementia (FTD) encompasses a group of neurodegenerative disorders characterized by cognitive and behavioral impairments due to progressive degeneration of the frontal and temporal lobes. Heterozygous mutations in the gene encoding progranulin (*PGRN*) account for up to 25% of familial FTD and result in decreased PGRN expression, but the the mechanism by which its decreased expression leads to disease is still unknown. While PGRN has been implicated in a wide array of biological functions, including inflammation and neurite outgrowth, recent literature has shown that complete loss of PGRN due to a homozygous mutation leads to neuronal ceroid lipofuscinosis (NCL), a group of neurodegenerative lysosomal storage disorders. The discovery that patients with homozygous *PGRN* mutations present with a lysosomal storage disorder suggests that the pathogenesis caused by PGRN deficiency could be dose-dependent and that PGRN mutations which lead to FTD may also cause partial lysosomal dysfunction. Our current research has demonstrated that decreased PGRN levels significantly impaired lysosomal proteolysis. To elucidate the mechanism of this impaired lysosomal proteolysis, we examined the relationship between PGRN and the lysosomal enzyme cathepsin D as previous studies have shown that *CTSD* mutations, which result in decreased levels of the lysosomal enzyme cathepsin D, also cause NCL. Our results demonstrated that *PGRN* mutations did not alter expression of cathepsin D but caused decreased cathepsin D activity. Furthermore, we demonstrated that PGRN interacts with cathepsin D and that PGRN and individual granulins can increase its activity *in vitro.* Taken together, these experiments suggest that PGRN, or individual granulins, may act as an activator of cathepsin D. Reduced cathepsin D activity due to decreased PGRN levels may provide a potential mechanism by which PGRN haploinsufficiency leads to lysosomal dysfunction. Importantly, this project will also examine the relationship between lysosomal and neuronal dysfunction by examining the PGRN-cathepsin D interaction in human induced pluripotent stem cell (iPSC)-derived cortical neurons harboring *PGRN* mutations. This analysis will examine if lysosomal dysfunction due to decreased cathepsin D activity contributes to the pathogenesis of human neurons with *PGRN* mutations. Ultimately, this study may provide insight into the mechanism by which *PGRN* mutations cause FTD and contribute to our understanding of how lysosomal dysfunction contributes to neurodegeneration.

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Nanosymposium

639. Parkinson's Disease: Cell Biology, Mechanisms, and Targets

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**Topic: ***C.03. Parkinson's Disease

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Title: Dopamine induces oscillatory activities in human midbrain neurons with parkin mutations

Authors: *J. FENG[1], P. ZHONG[2], Z. HU[2], H. JIANG[1], Z. YAN[1]
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Abstract: Locomotor symptoms in Parkinson's disease (PD) are accompanied by widespread oscillatory neuronal activities in basal ganglia. Here, we show that activation of dopamine D1-class receptors elicits a large rhythmic bursting of spontaneous excitatory postsynaptic currents (EPSCs) in midbrain neurons differentiated from induced pluripotent stem cells (iPSC) of PD patients with parkin mutations, but not normal subjects. Overexpression of wild-type parkin, but not its PD-causing mutant, abolishes the oscillatory activities in patient neurons. Dopamine induces a delayed enhancement in the amplitude of spontaneous but not miniature EPSCs, thus increasing quantal content. The results suggest that presynaptic regulation of glutamatergic transmission by dopamine D1-class receptors is significantly potentiated by parkin mutations. The aberrant dopaminergic regulation of presynaptic glutamatergic transmission in patient-specific iPSC-derived midbrain neurons provides a mechanistic clue to PD pathophysiology and demonstrates the usefulness of this model system in understanding how mutations of parkin cause movement symptoms in Parkinson's disease.

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Nanosymposium

639. Parkinson's Disease: Cell Biology, Mechanisms, and Targets

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**Presentation Number: ***639.09

**Topic: ***C.03. Parkinson's Disease

Title: Altered glutamatergic properties of dopaminergic cells in Lesch-Nyhan syndrome

Authors: *S. C. BELL[1], H. PENG[2], L. CRAPPER[2], J. THEROUX[1], L. MOQUIN[3], D. AVIZONIS[1], G. BRIDON[1], D. SUTCLIFFE[4], A. GRATON[3], G. TURECKI[3], J. E. VISSER[5], T. ROSENBURGER[6], N. MECHAWAR[3], H. A. JINNAH[4], C. ERNST[1]
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Abstract: Lesch-Nyhan syndrome (LNS) is a purine recycling disorder caused by mutations in *HPRT1* and includes features such as dystonia and self-aggressive behaviour. Human studies have repeatedly implicated dopamine dysfunction in the disorder, but it remains unclear how mutations in *HPRT1* lead to dysfunctions in the dopamine system.To address this question we made iPSC-derived forebrain neurons from 3 LNS patients and controls, and iPSC-derived midbrain neurons from 5 LNS patients and controls, all from fibroblasts. We also deleted *HPRT1*from two independent control cells lines and made forebrain and midbrain neurons simultaneously from these and isogenic control cells. We developed a novel methodology to produce midbrain neurons, which resulted in >90% cells becoming tyrosine hydroxylase positive. Metabolite and HPLC measurements showed a 4-fold reduction in dopamine in mature midbrain cells, and 5-fold increases in hypoxanthine in all cells with mutated *HPRT1*, suggesting this cell model recapitulates the disease. We performed gene expression and metabolic profiling across all cell lines at two developmental timepoints, and we provide evidence that dopaminergic cells with *HPRT1* dysfunction take on characteristics of glutamatergic cells in early development, including increases in VGLUT2 and decreased expression of TH. No alterations in glutamatergic markers were observed in forebrain cells. This is the first analysis of iPSC derived dopaminergic cells in LNS, and these data provide new mechanistic insight into LNS and basal ganglia movement disorders.

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Nanosymposium

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Title: Mechanism of TFEB dysfunction by GBA1 mutations in an iPSC model of neuropathic gaucher disease

Authors: R. A. BROWN, A. VOIT, M. SRIKANTH, R. A. FELDMAN, *O. AWAD
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Abstract: Biallelic mutations in the GBA1 gene cause the lysosomal storage disorder Gaucher Disease (GD). GD is characterized by reduced activity of glucocerebrosidase (GCase) enzyme and accumulation of lipid substrates in the cells of the reticuloendothelial and nervous systems. Neuropathic form of GD is associated with neurodegeneration with either slow or progressive course. GBA1 mutation is also the most common risk factor for both familiar and sporadic Parkinson's disease (PD). Although GBA1-asociated neurodegeneration has been linked to dysfunction of the autophagy lysosomal pathway (ALP), the underlying mechanisms remain unknown. Using induced pluripotent stem cells (iPSCs) derived from patients with biallelic GBA1 mutations, we previously showed that ALP alterations in GBA1 mutant neurons is due to dysfunction of the transcription factor EB (TFEB), the master regulator of lysosomal biogenesis and autophagy. Both TFEB levels and stability were reduced in GBA1 mutant neurons, which resulted in lysosomal depletion and autophagy block. To further investigate the mechanism of GBA1-mediated TFEB dysfunction, we examined TFEB regulation by the mammalian target of rapamycin complex 1 (mTORC1) in both control and GBA1 mutant neuronal cells. mTORC1 is known to regulate TFEB activity by modulating its phosphorylation status and nuclear localization. We found that mTORC1 is hyperactive in GBA1 mutant neurons as evident by increased phosphorylation of its downstream effectors. Treatment with mTOR inhibitor (TORIN) upregulated lysosomal biogenesis and enhanced TFEB functions in mutant cells. We also found that pharmacological substrate reduction normalized mTOR activity and enhanced lysosomal biogenesis, suggesting that the abnormal lipid profile in GD affects mTOR activity, which in turn alters TFEB regulation. Our study provides new mechanistic insights into ALP alterations by GBA1 mutations, which is will significantly aid in developing new therapies against GBA1-associated neurodegeneration.

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Nanosymposium

640. Risk Factors for Diseases of the CNS

Location: 150B

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***640.01

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Toxicology Program
Duke University Superfund Research Center (ES010356)
Leon Golberg Postdoctoral Fellowship

Title: Low-level embryonic exposure to organophosphate flame retardants and related compounds causes neurobehavioral impairment in larval and adult zebrafish

Authors: L. GLAZER[1], A. HAWKEY[1], C. WELLS[1], M. DRASTAL[1], K.-A. ODAMAH[1], M. BEHL[2], *E. D. LEVIN[1]
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Abstract: Flame retardants (FRs) are widely used in home furnishings and electronics. FRs are not chemically bound to products, and thus continuously leach out into the surrounding air and dust, resulting in ubiquitous human exposure to low levels in indoor and outdoor environments. Moreover, FR exposure is higher in toddlers and children due to crawling and hand-to-mouth contact. Organophosphate (OP) FRs have recently replaced the neurotoxic brominated FRs in many consumer products and are increasingly detected in human tissue samples. In this study, we examined the larval (early-life) and adult (later-life) behavioral consequences of developmental exposure to low levels of OPFRs. In addition to the target OPFRs, we included in our exposures the OP pesticide chlorpyrifos (CPF), a related compound with known neurotoxicity. Zebrafish embryos were exposed to low concentrations of the test chemicals at 5-120 hours post fertilization (hpf), when they were transferred to non-dosed water. At 144 hpf the larvae were tested for locomotor activity in response to alternating light and dark conditions. This testing serves as an early comparator to the long-term behavioral effects of developmentally exposed zebrafish in adulthood. The adult behavioral battery includes assays for anxiety-related behavior, sensorimotor response and habituation, social interaction, predator avoidance. The results for the larval motility testing indicate that early-life exposure to the OPFRs triphenyl phosphate (TPHP), tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), 3,3',5,5'-tetrabromobisphenol A (TBBPA), tris(2-chloroethyl) phosphate (TCEP), and trimethyl phenyl phosphate (TMPP), as well as CPF cause larval behavioral impairments of either hypo- or hyper-locomotion during specific illumination phases. These effects are manifested in a chemical-specific manner. This will be compared to the results of adult testing to determine how predictive larval testing is for long-term behavioral dysfunction. Recent results following similar exposures to other OPFRs as well as brominated FRs showed that in some cases, at the lower doses of exposure the adult behavioral effects were not predicted by effects on larval motility, thus stressing the importance of life-long behavioral testing of multiple behavioral domains. We will compare our current larval and adult behavioral results for the above set of OP chemicals, with previous results and suggest a way forward for testing the extent of neuro-behavioral toxicity of flame retardants.

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Nanosymposium

640. Risk Factors for Diseases of the CNS

Location: 150B

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**Presentation Number: ***640.02

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIA Grant P01AG012411
UAMS "S.T.O.P. Alzheimer's" Fund
VA Merit grant 5IO1BX001655 (RSR)

Title: Western diet increases protein aggregation and alters membrane tethering of signal transduction proteins in a manner consistent with Alzheimer's disease

Authors: *S. W. BARGER[1], S. AYYADEVARA[3], M. BALASUBRAMANIAM[1], S. Y. AGHDAM[1], R. D. HENDRIX[2], S. T. GRIFFIN[1], R. J. SHMOOKLER REIS[1]
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Abstract: Food abundance has increased with industrial development and large-scale agriculture. This has resulted in a shift from undernourishment to overconsumption and an epidemic of obesity. Epidemiology and prospective animal studies indicate that diets rich in calories-- particularly fats and sugars-- lead to obesity, a key risk factor for many age-related disorders including metabolic syndrome, type-2 diabetes, and neurodegenerative diseases such as Alzheimer's disease (AD). High-fat diets also appear to induce cognitive deficits more acutely. Rodents on such diets have altered insulin signaling and membrane tethering of proteins, and these effects have been implicated in memory loss. Mechanisms by which high-calorie diets promote protein aggregation and alters signal transduction are poorly understood. We found elevated protein aggregation in AD hippocampus and similar increases in brains of mice transgenically overexpressing amyloid β-peptide (Aβ) 1-42 (the BRIAβ42 line). We further compared these mice to wild-type mice maintained on a "western" (high-fat, high-sucrose) diet. Proteomic analyses were conducted, including parsed analysis of proteins in fractions that were aggregated, soluble, membrane-associated, or bound to phosphatidylinositol trisphosphate. Membrane fractions showed overlapping changes in abundance of many components in western-diet-fed mice and BRIAβ42 mice, and many of these changes corresponded to the effects of AD on the human brain. These findings indicate that specific signaling proteins tethered to the membrane are altered by both pathogenic diets and AD pathology, impacting multiple signaling pathways. Confirmation of these findings would imply that protein aggregation in the brain participates in converging neurodegenerative sequelae promoted by lifestyle choices and primary AD pathogenesis. We hypothesize that pathogenic diets alter proteostasis and, by extension,

intracellular signaling intermediates critical to normal brain function, resulting in cognitive impairment that can manifest alone or accelerate the development of AD.

Disclosures: **S.W. Barger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SWB receives royalties from MilliporeSigma for the sales of secreted amyloid precursor protein. **S. Ayyadevara:** None. **M. Balasubramaniam:** None. **S.Y. Aghdam:** None. **R.D. Hendrix:** None. **S.T. Griffin:** None. **R.J. Shmookler Reis:** None.

Nanosymposium

640. Risk Factors for Diseases of the CNS

Location: 150B

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Presentation Number: *640.03

Topic: *C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: MH087332
MH104131
MH105330
DA026306

Title: Methamphetamine and HIV-1 gp120 and Tat proteins affect neural networks *In vivo* through lasting changes in CNS gene expression

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Abstract: Methamphetamine (METH) is a highly addictive psychostimulant drug, the use of which is associated to the risk of contracting or transmitting viral infections such as human inmmunodeficiency virus (HIV) The combination of viral infection and METH in the central nervous system (CNS) is suspected to exacerbate the HIV disease and HIV-associated neurocognitive disorders (HAND). METH abuse alone can lead to irreversible damage in the brain, causing neuroinflammation and compromising several neurotransmitter systems. However, the combined effects of HIV-1 and METH on the brain are incompletely understood at the molecular level. Expression of HIV viral proteins gp120 or Tat in mouse brains mimics some key neuropathological features observed in AIDS brains. Therefore, we treated 3-4 months old HIV-1/gp120 transgenic (gp120tg) and HIV-1/Tat transgenic (iTat-tg) mice and the respective wild type (wt) controls with either a 25 day escalating METH binge or a long-term low-dose regimen. Following abstinence periods we performed of behavioral studies at 10-12 months of

age. HIV-1/gp120tg, iTat-tg and METH-exposed animals showed significant impairment in spatial learning and memory. In order to investigate underlying mechanisms different regions of the animals' brains (cortex, hippocampus and striatum) were analyzed using RT^2 Profiler™ PCR arrays to determine the changes in expression of genes related to the dopaminergic, serotonergic, GABAergic, and glutamatergic neurotransmission systems. Using Ingenuity Pathway Analysis (IPA) we found that the most affected networks were: Cell-to-cell Signaling and Interaction, Nervous System Development and Function, Behavior and Neurological Disease. In summary, METH exposure and HIV-1/gp120 and Tat expression in the brain are all associated with significant, specific and lasting alterations of the four major neurotransmission systems.

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Nanosymposium

640. Risk Factors for Diseases of the CNS

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**Presentation Number: ***640.04

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: JSPS KAKENHI Grant Number JP17K01354
JSPS KAKENHI Grant Number JP2635049
Health Labour Sciences Research Grant of Japan

Title: Recovery effects with bumetanide or oxytocin administration in developing cerebellar cortex of drug-induced autistic model rat

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Abstract: Autism spectrum disorder (ASD), which is a severe neurodevelopmental disorder, is reported to show cerebral and cerebellar abnormalities. In particular, reduction in size and number of Purkinje cells in cerebellum is observed in both postmortem human studies, and drug-administrated adult animals. Some antiepileptic drugs, for example, sodium Valproate (VPA) and organophosphorus agents, for example, chlorpyrifos (CPF) are known as the candidates of inducer of autism. We have observed these drugs made recognizable structural and functional change in developing rat cerebellar cortex. The irregular structure was focused on lobule V - VII, and maintained to adult with Purkinje cell decrease. Recently, it was reported that oxytocin

(OXT), a neuropeptide hormone, or bumetanide (BU), a blocker of the NKCC1 cation-chloride co-transporter, could decrease ASDs repetitive behaviors in human. However, the mechanism of recovery from ASD with OXT or BU hasn't been elucidated, and additionally, the safety of these drugs to young children are uncertain. In this study, we investigated the recovery effects with OXT or BU administration to valproate-induced ASD model rat. Each drug was administrated to embryonic day 16 p.o. (VPA; 600 mg/kg and CPF; 4.3 mg/kg of mother weight, respectively), and after birth, 33μg/kg BU or OXT were administrated p. o. to VPA-treated pups or control pups from postnatal day 3 to 7. OXT or BU administration after birth showed recovery effects about cerebellar development and formation in VPA-induced ADS model rat. Because BU and OXT suppress GABA excitation via intracellular Cl- concentration, our results suggest the autistic disorder would closely correlate with GABA excitation.

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Nanosymposium

640. Risk Factors for Diseases of the CNS

Location: 150B

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***640.05

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant AG-17926
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Title: PS1 FAD mutants affect NMDA-EphB receptor interactions and compromise neuroprotection

Authors: *M. A. RAHIM, Z. SHAO, L. MARTINEZ-MEDINA, Y. YOON, C. DIMOVASILI, J. SHIOI, A. GEORGAKOPOULOS, N. ROBAKIS
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Abstract: It has been proposed that reduced protection from brain toxic insults such as excitotoxicity, ischemia and oxidative stress, is involved in neurodegenerative disorders including AD and Parkinson's disease. It is also known that NMDA receptor (NMDAR) modulates neuronal responses to toxic insults and may interact with brain neurotrophins to protect neurons from excitotoxicity and oxidative stress. Many PS1 mutations are found to cause dominant familial AD (FAD) and we reported that PS1 plays a vital role for the ability of efnB1, a ligand to EphB2 receptor, and brain derived neurotrophic factor (BDNF), to rescue neurons

from excitotoxicity. Importantly, we also found that PS1 FAD mutants (M146V, I213T) block the efnB1- and BDNF-dependent neuroprotection. We found that PS1 is required for the association of EphB2 with NMDAR and that efnB1 stimulates the formation of a ternary complex containing PS1, EphB2 and NMDAR. Thus, PS1 is essential to the efnB1-dependent neuroprotection and stimulation of the EphB2-NMDAR association. Since PS1 FAD mutant-expressing neurons are not rescued by efnB1, we asked whether these mutants affect the efnB1-dependent association of EphB2 and NMDAR. We discovered that efnB1 is unable to increase the EphB2-NMDAR complex in neurons either heterozygous or homozygous for PS1 FAD mutants. Furthermore, PS1 FAD mutants perturb the constitutive interactions between EphB2 and NMDAR, thereby blocking the neuroprotective function of efnB1. These data reveal new functions of PS1 in receptor interactions and neuroprotection, and suggest that the efnB1-induced complex of EphB2 and NMDAR plays pivotal roles in neuronal survival from toxic insults. Importantly, we also obtained data that PS1 FAD mutants have similar effects on the BDNF-TrkB neuroprotective system suggesting our work on the efnB1-EphB2-PS1-NMDAR system may serve as a model for the PS1 FAD effects on other brain neurotrophin systems. In summary, our study reveals that FAD mutations target EphB2-NMDAR interactions and thus may offer a novel druggable target for AD.

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Nanosymposium

640. Risk Factors for Diseases of the CNS

Location: 150B

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**Presentation Number: ***640.06

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

Support: 1R01AG048923
1RF1AG054014

Title: Molecular interplay between gender and ApoE genotype in Alzheimer's disease

Authors: *D. CAI[1,2], B. ZHANG[1], F. EL GAAMOUCH[1], L. ZHU[1], M. WANG[1], E. PARISE[1], A. GOATE[1], V. HAROUTUNIAN[1], E. NESTLER[1]
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Abstract: Background: The Apolipoprotein E4 (ApoE4) is the strongest risk factor for sporadic Alzheimer's Disease (AD). Intriguing, previously published epidemiologic and neuroimaging data suggests that ApoE4 allele has a stronger effect in promoting AD risk in females than in

males. However, an in-depth molecular characterization of these differences has not been established, and in general, sex differences in the effect of the ApoE alleles remain largely underexplored. **Results:** We have assembled a number of large-scale datasets studying gene expression in human postmortem brains from AD patients at various stages and non-demented controls. These datasets include three microarray datasets from seven total brain regions, one proteomics dataset from two brain regions, and three RNA-sequencing datasets in various stages of AD development. We have found that gender difference in AD is region specific with parahippocampal gyrus showing the greatest gender difference. There are more genes differentially expressed in female AD *versus* normal aging controls than those in male AD *versus* controls. Our preliminary weighted interaction network analysis (WINA) has identified several gender specific co-expression modules that are associated with AD and differentially connected in males and females. Further Bayesian network analysis of the AD-associated modules in $ApoE4^+$ males and females has identified top key drivers common and specific to each group, suggesting gender- and ApoE4-specific fingerprints in AD disease development and progression. We have also compared the gender- and ApoE-specific signatures in hippocampal brain tissues of 12-16 months old ApoE4 and ApoE3 knockin (KI) mice. The differentially expressed genes (DEGs) between female and male ApoE4 mouse brains are significantly enriched in some modules of human AD $ApoE4^+$ female and $ApoE4^+$ male coexpression networks. A key driver of the hormone secretion module in the AD $ApoE4^+$ Female network is also differentially expressed between aged $ApoE4^+$ female and $ApoE4^+$ male mouse brains, highly suggestive of its regulatory roles in ApoE4-sex interaction in AD pathogenesis. We will next perform gene perturbation experiments through intraventricular delivery of AAV-containing cDNA into hippocampal brain regions of 3-month old ApoE4 female and male mice. ApoE3 female and male mice will be used as controls. The behavioral and biochemical analysis of these cohorts will be performed at 9-12 months of age. **Conclusions:** Our comprehensive studies of molecular mechanisms underlying the interplay between sex and ApoE genotype in AD pathogenesis, will pave a path towards distinct targeted therapies for AD females and males.

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Nanosymposium

640. Risk Factors for Diseases of the CNS

Location: 150B

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***640.07

**Topic: ***C.01. Brain Wellness and Aging

Support: NIH Grant AG043813

Title: The influence of cognitive, social, and environmental enrichment on physiology, behavior, and pathology in mouse models of healthy aging and cerebral amyloid angiopathy

Authors: *L. S. ROBISON, D. L. POPESCU, S. I. BEIGELMAN, S. M. FITZGERALD, S. SUBZWARI, J. HATFIELD, A. E. KUZMINA, D. A. LITUMA, S. A. AMREIN, W. LIU, F. XU, J. DAVIS, R. KIM, B. J. ANDERSON, W. E. VANNOSTRAND, J. K. ROBINSON
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Abstract: Environmental enrichment (EE) has been shown to have several beneficial effects on the brain and behavior in mouse models of healthy aging and Alzheimer's Disease; however, studies examining the effects of EE on cerebral amyloid angiopathy (CAA) are lacking. While the EE paradigm usually consists of the combination of social, cognitive, and physical enrichment, it is of interest to assess the effects of these three classes of enrichment alone, as well as in combination, to determine their individual contributions. In the current study, we assessed the effects of EE, social enrichment (SOC; group housing) and cognitive enrichment (COG, toys and tunnels replaced and moved twice weekly) compared to a control group that was single housed without enrichment (CON) from 4 to 8 months of age in wild-type mice (WT) and Tg-SwDI mice, a transgenic mouse model of CAA that exhibits cognitive and behavioral deficits associated with vascular amyloid beta (Aβ) pathology. The effects of EE on Tg-SwDI have not yet been tested, and this model may be uniquely susceptible to EE due to the vascular nature of the pathology. Tg-SwDI ate more but weighed less than WT, and SOC and EE reduced food intake and body weight in both genotypes. Tg-SwDI were impaired on some motor and cognitive measures, exhibited reduced activity/exploratory behavior, and were more anxious compared to WT mice, but were no different in strength and several other cognitive measures. EE improved motor function and several cognitive measures, altered activity levels, and reduced anxiety; these changes were generally seen in both WT and Tg-SwDI, though the degree varied by genotype and task. For some measures, SOC produced effects similar to EE, or at least were altered. COG was generally less effective at producing changes, though some effects were observed. EE, and SOC to a lesser degree, increased muscle mass, and both of these conditions increased relative brain mass in both genotypes. While there were no differences under deprived conditions between genotypes, EE and SOC increased relative adrenal mass and serum corticosterone levels in Tg-SwDI only. ELISAs for Aβ species found that housing conditions significantly affected insoluble Aβ (both 40 and 42) levels in Tg-SwDI mice (EE > SOC = COG > CON), but had no effect on soluble Aβ. These results indicate that individual facets of enrichment can produce behavioral and physiological changes, though a "dose-response" effect is suggested (combined EE is generally most effective), and that overall Tg-SwDI mice appear more susceptible to the effects of housing conditions compared to WT mice.

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Nanosymposium

640. Risk Factors for Diseases of the CNS

Location: 150B

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***640.08

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NINDS 09923
The Miami Project to Cure Paralysis

Title: Polyvinylpyrrolidone-based dexamethasone delivery to reduce inflammatory response in neuronal tissue injury

Authors: *R. SAIGAL[1], T. URAKOV[2], S. R. CERQUEIRA[3], M. B. BUNGE[4]
[1]Neurolog. Surgery, UW Neurolog. Surgery, Seattle, WA; [2]Univ. of Miami, Miami, FL; [3]Miami Project to Cure Paralysis, Miami Project To Cure Paralysis, Miami, FL; [4]Miami Project Cure Paralysis, Neurosurg, Cell Biol. and Anat, Univ. of Miami Sch. of Med., Miami, FL

Abstract: Although an area of clinical controversy, administration of steroids after spinal cord injury (SCI) originally gained favor due to their anti-inflammatory and neuroprotective effects in pre-clinical models. Previous pre-clinical delivery methods involved the use of either an indwelling catheter or intraparenchymal implantation of a substrate. In this study, a new polymer-based system for controlled release of dexamethasone has been developed with sustained release over 3 days, which is the ideal treatment window after SCI. Fluorescein-conjugated dexamethasone was incorporated into polyvinylpyrrolidinone (PVP), and gel droplets were formed by UV polymerization. Beta-cyclodextrin was added to extend the drug release over 72 hours. To evaluate the drug release profile, fluorescence levels were quantified from media containing dexamethasone-PVP gels. Dexamethasone was detected at least for 3 days, confirming the sustained release provided by the drug delivery system. Cell toxicity and response to an inflammatory stimulus were studied in primary neuronal cultures. Schwann cells were isolated from rat sciatic nerves and cultured in the presence of the dexamethasone-PVP gels. To evaluate the effect of the gels in the metabolic activity of the cells, the MTS assay was performed. Our results revealed no alterations in the metabolic activity of cells cultured in the presence of dexamethasone-PVP, suggesting that the polymer is not cytotoxic. Microglia cells were isolated from rat pup cortices and stimulated with bacterial lipopolysaccharide (LPS) to model an inflammatory environment *in vitro*. Production of nitric oxide (NO) was measured by the Griess reagent. Addition of LPS to microglia induced a significant increase in the production of NO, which was significantly decreased after addition of 10 ug/mL of the anti-inflammatory corticosteroid dexamethasone. Interestingly, the presence of dexamethasone-PVP gels in culture had a similar effect to the drug itself, significantly decreasing the production of NO due to LPS stimulation. TNFa and reactive oxygen species (ROS) were also measured using ELISA and an

enzymatic conversion assay, respectively, and its levels were lower in cells incubated with dexamethasone-PVP gels. This new PVP-based dexamethasone delivery system was shown to be successfully processed into gel discs and possess a sustained drug delivery profile. Our results also suggest safety and efficacy *in vitro* inflammation models using primary cultures of rat Schwann cells and microglia. Future directions will focus on translation experiments in animal models of spinal cord injury.

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Nanosymposium

640. Risk Factors for Diseases of the CNS

Location: 150B

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:15 AM

**Presentation Number: ***640.09

**Topic: ***C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONACYT FC-251

Title: Role of astrocytes in the effect of vasoinhibins reducing viability of hippocampal neurons

Authors: *R. M. AROÑA[1], E. ARNOLD[2], C. CLAPP[1], G. MARTÍNEZ DE LA ESCALERA[1]
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Abstract: Vasoinhibins (Vi) are a family of peptides derived from the hormone prolactin (PRL) that have been shown to act on endothelial cells inhibiting angiogenesis, vasodilation and vasopermeability. Furthermore, Vi can participate in the modulation of some functions of the central nervous system (CNS) such as promoting anxiety and depression behaviors. These behaviors have been associated with hippocampal neurodegeneration, thus in the present study we explored whether Vi affect hippocampal neurons. To explore the actions of Vi on hippocampal cells, primary hippocampal neurons were isolated from the brain of E16 mice and cultured on plates treated with poli-L-lysine. On DIV2 hippocampal cultures were treated or not with AraC (10 μM, 48 hours) to inhibit the growth of dividing astrocytes, obtaining neuron-enriched and mixed neuron-astrocyte cultures. Then, on DIV5 cultures were treated with increasing concentrations of Vi (5-20nM) for up to 72 hours (DIV5-DIV8). Incubation of neuron-enriched and mixed hippocampal cultures with Vi reduced the metabolic activity evaluated by MTT assay. The effect of Vi was stronger when the astrocytes were present. Moreover, Vi increased the expression of GFAP and pro-apoptotic genes such as CASP3 and BIM in mixed neuron-astrocyte cultures evaluated by qRT-PCR, while these effects were not

observed in the hippocampal neuron-enriched cultures. Altogether these findings show that Vi are capable to affect hippocampal cells, both neurons and astrocytes, suggesting that Vi could exert direct effects on neuronal degeneration, as well as indirect effects through astrocytes activation. This mechanism may be involved in the reported actions of Vi on anxiety and depression.

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Nanosymposium

641. Advances in Pain Neuroimaging

Location: 144A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***641.01

**Topic: ***D.03. Somatosensation: Pain

Support: University of Maryland, Baltimore
NIDCR (1R01DE025946)

Title: Social observational learning and pain modulation: An fMRI approach

Authors: *L. A. SCHENK, N. RAGHURAMAN, L. COLLOCA
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Abstract: Background: Placebo hypoalgesia refers to decreased pain due to the expectancy of pain relief from the psychosocial context around a treatment. Although the psychosocial context plays a critical role in forming placebo effects, the influence of social observation is poorly understood. Recent studies showed that observing pain relief in others leads to placebo hypoalgesia; however, the neural processes behind observational learning remain unclear.
Methods: 38 healthy study participants completed an observation and a test phase during fMRI acquisitions. The observation phase included short videos of a demonstrator with two inert treatments on his forearm that were described as a control and an active analgesic. The demonstrator received painful heat stimulations after one of two visual cues that indicated treatment or control. The demonstrator showed a painful facial expression and reported high pain after the control cue and showed a neutral facial expression and reported low pain after the treatment cue. During the subsequent test phase, the same treatments were applied to the participants and they received medium pain along with both cues to determine observationally-learned pain modulation.
Results: Observing another person receiving an effective treatment induced a robust placebo hypoalgesic effect: during the test phase, participants reported less pain intensity ($F(1,37)=28.0$,

p<0.001) and pain unpleasantness (F(1,37)=18.7, p<0.001) after the treatment cue compared to the control cue. At the neural level, we found a stronger activation of the right and left temporoparietal junction (TPJ) in the treatment compared to the control condition during the observation (T(1,37)=4.9, p<0.05; T(1,37)=4.2, p<0.05) as well as the test phase (T(1,37)=3.9, p<0.05; T(1,37)=4.6, p<0.05).
Conclusion: Our study provides insights into the neural processing of observational learning and pain modulation. The TPJ is involved in social cognition and understanding what other people are experiencing. Our data support that the TPJ is implicated in learning pain from others through observation as well as in mediating observationally-learned placebo hypoalgesia.

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Nanosymposium

641. Advances in Pain Neuroimaging

Location: 144A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***641.02

**Topic: ***D.03. Somatosensation: Pain

Support: CIHR Operating Grant MOP130555
University of Toronto Centre for the Study of Pain
University of Toronto Faculty of Medicine

Title: Diffusivity alterations predict outcome of radiosurgical treatment in trigeminal neuralgia

Authors: *S. TOHYAMA[1,2], P.-P. HUNG[2,1], J. ZHONG[1], M. HODAIE[2,1]
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Abstract: Background & Aims: Radiosurgery is an important treatment modality for trigeminal neuralgia (TN), a severe chronic facial pain disorder. Since treatment outcome is assessed clinically, the current postsurgical care is insufficient in predicting which patients will benefit from treatment. Neuroimaging may be a potential avenue to prognosticate treatment response in TN patients. Determination of long-term clinical outcome at a single, early point of assessment would be especially valuable to promptly optimize individual pain treatment. Using diffusion tensor imaging (DTI), we aimed to determine whether early postsurgical trigeminal nerve diffusivity alterations would prognosticate long-term clinical outcome. **Methods:** Brain imaging data were gathered from 32 TN patients (20 females, mean age 68.8±13.5) at 6 months post-treatment (range: 5-7 months). Diffusivity metrics of fractional anisotropy (FA), axial, radial, and mean diffusivities (AD, RD, and MD, respectively) were extracted from the target location

of the affected trigeminal nerve. The contralateral, unaffected nerve served as the control. Early, 6-month trigeminal nerve diffusivities were compared with long-term treatment response. Based on retrospective chart reviews, patients were identified as responders if they achieved at least 75% reduction in preoperative pain for 12 months or longer following treatment. Patients who did not respond or experienced recurrence of pain within 12 months of treatment were determined as non-responders. **Results:** We identified 17 long-term responders and 15 non-responders. Trigeminal nerve diffusivity at 6 months was predictive of long-term clinical outcome, demonstrating significantly lower FA in responders compared to their unaffected nerve and to non-responders. Responders also revealed significantly higher RD compared to their unaffected nerve, suggesting that the microstructural changes are consistent with demyelination. No significant differences were observed in AD and responders showed a trend towards higher MD compared to their unaffected nerve. **Conclusions:** Assessment of diffusivities at a single, early postsurgical time point successfully predicts long-term treatment response in TN patients. Of the different diffusivities, FA and RD were most significant, indicating that alterations in white matter microstructure that is consistent with demyelination are strong predictors of long-term pain relief. DTI serves as a promising tool to assess the effects and prognosis of radiosurgery on the trigeminal nerve for TN patients.

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Nanosymposium

641. Advances in Pain Neuroimaging

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**Presentation Number: ***641.03

**Topic: ***D.03. Somatosensation: Pain

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FNRS "grands équipements"

Title: EEG frequency tagging to isolate cortical activity associated with sustained burning pain

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Abstract: Although ongoing pain is a common and important feature of many pathological clinical pain conditions, little is known about the brain activity underlying its perception because most studies have focused on the brain responses elicited by short-lasting nociceptive stimuli typically lasting only a few milliseconds or seconds. Here, we present a novel non-invasive

approach using EEG to characterize, in humans, the sustained changes in brain activity associated with the perception of long-lasting burning pain. A temperature-controlled CO2 laser stimulator was used to generate a prolonged (75 s) sinusoidal heat stimulation of the hand dorsum skin, oscillating between baseline and 50°C at a frequency of 0.2 Hz. In a first experiment, we show that when such long-lasting thermal stimuli are applied to the hand dorsum of healthy volunteers, the slow rises and decreases of skin temperature elicit a robust periodic EEG response at 0.2 Hz and upper harmonics, symmetrically distributed over both hemispheres and maximal over frontal-central electrodes. Furthermore, we show that the stimulation also induces a periodic modulation of theta, alpha, and beta band EEG oscillations, maximal over the central and parietal regions contralateral to the stimulated hand. In a second experiment, we demonstrate using an A fiber block that these EEG responses are conveyed by slowly-adapting C fiber thermonociceptors. Finally, in a third experiment performed in patients implanted with depth electrodes for the diagnostic workup of partial intractable epilepsy, we show that sustained periodic EEG responses can be recorded directly from the human insula. Taken together, our results show that EEG "frequency tagging" using periodic heat stimulation of the skin can be used to explore the cortical processes underlying the perception of tonic heat pain in humans.

Disclosures: A. Mouraux: None. **E. Colon:** None. **G. Liberati:** None.

Nanosymposium

641. Advances in Pain Neuroimaging

Location: 144A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***641.04

**Topic: ***D.03. Somatosensation: Pain

Title: Reorganization of shared graph properties in chronic pain

Authors: *D. RECKZIEGEL[1], A. T. BARIA[1], L. HUANG[1], A. APKARIAN[1,2,3]
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Abstract: Despite significant recent advances linking functional connectivity properties of the brain to chronic pain, connectivity architecture (as defined by local graph theory metrics), in the context of pain, remains poorly understood. Here we use voxel-wise graph theory-based similarity to identify clusters of networks across chronic back pain (CBP), chronic osteoarthritis pain (OA) and healthy control (HC) participants.
FMRI and T1 anatomical images were acquired at rest in 110 participants: 36 CBP, 43 OA and 31 HC. Functional images were preprocessed using ICA-AROMA. The Brain Connectivity

Toolbox was used to calculate eight network metrics for each voxel: clustering coefficient, efficiency, degree, betweenness centrality, flow coefficient, eigen vector centrality, participation coefficient and within degree z-score. To determine which voxels exhibit similar network properties, we used k-means clustering with a defined number of clusters ranging from 4 to 6. Mutual information of cluster membership was used to determine clustering similarity between participants in each group (CBP, OA, HC). Within-group consensus clustering was performed to assess functional architecture differences between groups.
Group consensus clusters correspond to well-defined anatomical and functional regions. The clustering patterns present distinctions between all groups, and are consistent across the range of tested number of clusters. A clear feature distinguishing CBP and OA from HC is a segregation of the basal ganglia from the default mode network (DMN). Additionally, CBP patients exhibit a DMN that is uniquely fractionated into frontal and parietal portions. Mutual information of cluster membership indicates higher similarity in functional architecture between subjects in the HC group, relative to OA and CBP.
Foremost, our results show that canonical functional networks exhibit distinct graph architectures. Clustering of graph properties distinguish chronic pain from the healthy state, as well as different chronic pain conditions, primarily in clusters overlapping the DMN. While the segregation of the basal ganglia from the DMN was found to be a characteristic of chronic pain in general, OA and CBP could be distinguished based on the frontal-parietal fragmentation of the DMN seen in CBP. Additionally, results from mutual information analysis suggests that chronic pain subjects may have less similarly organized brains than HC. How these features relate to the perception of pain is still to be elucidated and will be investigated.

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641. Advances in Pain Neuroimaging

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**Presentation Number: ***641.05

**Topic: ***D.03. Somatosensation: Pain

Support: NIDCR1R01DE025946

Title: Placebo and nocebo effects: Neural and behavioral impact of an expectancy and valence mismatch

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Abstract: Background: During treatment, patients often experience a mismatch between what they expected and what actually happens, an effect that decreases treatment compliance. It currently remains unclear how this effect influences endogenous pain modulation such as placebo hypoalgesia and nocebo hyperalgesia. Here, we explored for the first time the influences of mismatch processing on placebo and nocebo effects. Methods: 25 healthy volunteers (12M) received heat pain preceded by 3 cues (red, yellow, green) during a conditioning and test session. On day 1, during conditioning, the cues were followed by three pain levels and a congruent second cue was presented during the pain delivery (red: fearful face-high pain; yellow: neutral face-medium pain; green: happy face-low pain). On day 2, during test, all cues were followed by medium pain and congruent (i.e. red: fearful) or incongruent second cues (i.e. red: neutral or happy) and fMRI measurements were performed. Results: Placebo and nocebo modulated pain in the congruent conditions (placebo: $F(1,24)=30.5$, $p<0.001$; nocebo: $F(1,24)=13.9$, $p<0.005$), while a mismatch between the anticipatory and pain-related cues significantly attenuated placebo and nocebo effects (congruent vs. incongruent placebo: $F(1,24)=9.6$, $p<0.005$; congruent vs. incongruent nocebo: $F(1,24)=12.9$, $p<0.005$). At the neural level, we observed a stronger activation of the inferior parietal lobe during the incongruent compared to the congruent condition. Conclusions: Our data supports that if expectations are not met, placebo and nocebo effects are reduced. Our data further reveals a new mechanism in the inferior parietal cortex underlying placebo and nocebo effects during mismatch processing.

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**Topic: ***D.03. Somatosensation: Pain

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Title: Brain networks reflecting personality in chronic pain; linking pain to the mind

Authors: *E. VACHON-PRESSEAU[1], S. E. BERGER[2], T. B. ABDULLAH[3], T. J. SCHNITZER[1], A. V. APKARIAN[4]
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Abstract: Introduction: A whole body of literature demonstrated that pain characteristics, disability, and response to treatment could be predicted by factors of personality (Gatchel et al., 2007). Yet, personality in chronic pain has generally been ignored by the field of neuroscience and regarded as uncontrollable noise. In this study, we performed a data driven approach that uses personality traits as a phenotype of 63 chronic low back pain from which we derived neuromarkers from resting state functional connectivity (rsfMRI).
Methods: Personality was initially profiled using a series of 37 subscales from 14 validated questionnaires. A principal component analysis was used to generate 4 orthogonal components: *Pain* reflecting high levels of anxiety and catastrophizing; *Psyche* reflecting the big five personality traits; *Awareness* reflecting awareness and emotion regulation and *Neuroticism* reflecting neuroticism and loss aversion. The clinical portrait of chronic pain patient was drawn using seven different pain measurements, anxiety traits, and depressive mood.
We identify connectome-based neuromarker to predict these four components of personality from rsfMRI applying *Shen et al* 2017 protocol. Connections associated with personality were identified by robust regressions performed between each edge of the connectivity matrices with the patients' personality score ($p < 0.05$). Leave-one-out-cross-validation was performed to reduce the number of connections to the one that predicted personality in each iteration. A summary statistic was calculated from the sum of all edges (*z(r)*) positively correlating and negatively correlating with personality separately. These connections were considered as a marker if they were successfully validated in an out of sample testing set.
Results: We observed that only the *Pain* and *Neuroticism* components of personality correlated with pain outcomes, depression, and negative affect. Three neuromarkers of personality were successfully validated: 928 positive links located between the default mode network (DMN) and the other communities predicted *Pain*; 628 negative links located between the sensorimotor (SM), the DMN, the visual, and the ventral attention communities predicted *Pain*; and 708 positive links located between the DMN with the visual and the SM communities predicted *Neuroticism*. The brain connections that predicted *Psyche* (PC2) and *Awareness* (PC3) were not successfully validated in the test set.
Conclusion: We demonstrated that markers of personality could be derived from rsfMRI and that these predictive markers were specific to the psychological characteristics relevant to chronic pain.

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641. Advances in Pain Neuroimaging

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**Topic: ***D.03. Somatosensation: Pain

Title: Abnormal hippocampal connectivity in neuropathic chronic back pain

Authors: *L. J. AYOUB[1], A. LEBOUCHER[2], M. GOLOSKY[2], D. A. SEMINOWICZ[4], M. MCANDREWS[5], M. MOAYEDI[3]
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Abstract: Recent neuroimaging studies provide a role for medial temporal lobe (MTL) structures in pain. The hippocampus (HC), in particular, is consistently activated in response to nociceptive stimuli. Additionally, the HC shows functional abnormalities in some chronic pain conditions, and has been shown to be a predictor of the transition from subacute to chronic back pain. The HC's role in memory formation is well documented; however, its role in pain processing remains to be understood. Here, we aim to identify consistent functional abnormalities of the HC in chronic pain patients. We used the GingerALE software (v2.3.6) to transform brain coordinates of 13 fMRI studies into activation likelihood estimate (ALE) values to generate ALE maps, thresholded at a cluster corrected $p< 0.05$. We report that chronic pain patients had greater activation of the right anterior HC, compared to controls. Next, we used this right antHC region as a seed for resting state functional connectivity in a cohort of chronic low back pain (CLBP) patients of neuropathic etiology (NeuBP). We hypothesize that this region would show greater connectivity with nociceptive-related regions, such as the posterior insula. A previously published CLBP fMRI dataset was obtained, which comprised 34 NeuBP and 34 healthy, age- and sex-matched controls from the cbp_resting dataset on Open Pain Repository (collected by the Apkarian Group). Data underwent standard preprocessing and were analyzed using the CONN v16b toolbox, and Statistical Parametric Mapping 12 tools. We performed a whole brain functional connectivity of the right antHC. A two-sided t-test was used, and maps were thresholded using cluster FDR $p<0.05$ (height $p<0.001$). We found that NeuBP had abnormally increased resting state connectivity between the right antHC and a cluster (peak MNI coordinates: 54,-28, 54) of 131 voxels overlapping the right primary somatosensory cortex (S1) and the right posterior parietal cortex (PPC) compared to healthy controls. This connectivity was significantly related to pain duration ($r=0.49$, $p<0.005$). S1 and the PPC are implicated in nociceptive processing. The PPC is involved in the integration of visual, vestibular and somatosensory information. Furthermore, this region encodes aversive stimuli to the body, and a body schema – a map of the body in egocentric coordinates. These data suggest an abnormal

pain-related body map in NeuBP. Future studies should investigate the behavioural consequence of such abnormal hippocampal-parietal connectivity.

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Nanosymposium

641. Advances in Pain Neuroimaging

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**Time: ***Wednesday, November 15, 2017, 8:00 AM - 11:30 AM

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**Topic: ***D.03. Somatosensation: Pain

Support: MS society
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Title: Abnormal cross-network functional connectivity and regional BOLD fMRI signal oscillations and its association with chronic pain in patients with multiple sclerosis

Authors: *R. BOSMA[1,2], J. A. KIM[3,2,1], A. ROGOCHOV[3,2,1], K. S. HEMINGTON[2,3,1], J. CHENG[2,3,1], N. R. OSBORNE[3,2,1], J. OH[4,3], K. D. DAVIS[2,1,3]
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Abstract: Objectives: Over 50% of patients with MS suffer from chronic pain that significantly impacts their quality of life. The location of brain lesions from MS plaques does not definitively predict pain and so the underlying cause of MS pain is not understood. Previously we found that patients with chronic pain due to ankylosing spondylitis (AS) have altered functional communication between two brain networks that normally show anticorrelated functional connectivity (FC); the salience network (SN) and the default mode network (DMN) (Hemington et al., 2016). These cross-network abnormalities were related to AS pain and disease symptoms. We further reported that measures of brain signal oscillations (BOLD variability, fractional amplitude of low frequency fluctuations; fALFF) within nodes of these networks and the ascending nociceptive pathway are related to pain sensitivity in healthy adults (Rogachov et al., 2016), and are diminished in AS chronic pain (Rogachov et al., HBM abst 2017). The goal of our current study was to examine functional communication within and between brain regions and neuronal oscillations (fALFF) in regions that comprise the SN, DMN and other nodes of the dynamic pain connectome (Kucyi and Davis, 2015) in patients with MS compared to healthy control adults. We hypothesized that MS patients will have functional abnormalities in the dynamic pain connectome that relate to their pain and associated symptoms.

Methods: Patient with MS and age-and sex-matched healthy controls provided informed written consent. All participants underwent 3T MRI including a 10 minute resting state fMRI scan, quantitative sensory testing, and completed pain questionnaires including the brief pain inventory (BPI) and painDETECT to assess static FC and fALFF at three different slow wave frequency in the dynamic pain connectome.
Results: There were no differences between patients and controls in quantitative sensory pain assessments. However, the MS patients showed abnormal cross-network FC between the DMN and SN that was correlated with painDETECT (likelihood of neuropathic pain) and BPI (pain interference) scores. Furthermore, MS patients had significantly different regional brain signal fluctuations across multiple frequency bands.
Conclusions: These findings indicate that the dynamic pain connectome is abnormal in patients with MS, both in terms of cross-network communication and regional oscillations. Given the relationship between imaging abnormalities and pain, these findings likely relate to the pain in MS rather than to non-specific features of MS.

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Title: The neurobiological mechanisms supporting mindfulness-based analgesia: A longitudinal perspective

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Abstract: The experience of pain is mediated by sensory, cognitive, and affective factors, rendering the treatment of chronic pain difficult and often a financial burden. New far-reaching policy guidelines by the Centers for Disease Control have advocated for the utilization of non-pharmacological pain therapies. To this extent, mindfulness meditation, a cognitive practice premised on sustaining non-judgmental awareness of arising sensory events, significantly attenuates experimental and clinical pain. Yet, the neural mechanisms supporting mindfulness-based analgesia remain poorly characterized. This presentation will provide a comprehensive understanding of the brain processes supporting the modulation of pain by mindfulness meditation from a longitudinal perspective.
Novel findings, from our laboratory, reveal that healthy individuals (with no prior meditation experience) exhibiting higher levels of dispositional mindfulness report significantly lower pain ratings in response to noxious heat stimulation (49°C). Employing arterial spin labeling functional magnetic resonance imaging (ASL fMRI), we found that greater trait mindfulness was also associated with greater deactivation of the precuneus/ posterior cingulate cortex during noxious stimulation, brain regions critically involved in facilitating self-referential processes.
In two ASL fMRI studies, mindfulness meditation, after a brief, four-session (20min/session) meditation-training regimen, significantly reduced pain through greater activation of the orbitofrontal cortex, subgenual anterior cingulate cortex, right anterior insula and deactivation of the thalamus. These findings demonstrate that mindfulness meditation reduces pain through unique cortico-thalamo-cortical interactions. We will also discuss findings showing that mindfulness meditation, after brief mental training, does not engage endogenous opioids to attenuate pain, an important consideration for the millions of pain patients seeking a fast-acting, non-opioid pain therapy.
Finally, we will present findings demonstrating that meditation-induced analgesia, after extensive meditation training (> 1000 hours), is associated with greater activation in somatosensory cortices and deactivation of the prefrontal cortex during noxious heat stimulation, likely reflective of a decoupling between sensory and appraisal systems. These findings suggest that mindfulness meditation after brief training engages brain mechanisms supporting unique reappraisal processes, while meditation-based analgesia after long-term training employ non-appraisal mechanisms.

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Trigeminal Neuralgia Association of Canada

Title: Support vector regression of diffusion tensor imaging metrics predicts pain intensity following surgical treatment for trigeminal neuralgia

Authors: *S.-P. HUNG[1,2,3], S. TOHYAMA[1,2,3], E. WHARTON-SHUKSTER[1], M. HODAIE[1,2,3,4]
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Abstract: Introduction: Gamma Knife radiosurgery (GKRS) is a successful treatment strategy for trigeminal neuralgia (TN)—a severe chronic neuropathic facial pain syndrome. No current methods exist for the prediction of GKRS treatment efficacy. Diffusion tensor imaging (DTI) allows *in vivo* assessment of white matter microstructure. We previously showed that GKRS results in acute, focal alterations in fractional anisotropy (FA; white matter integrity) at the radiosurgical target. While radiation-related microstructural alterations are thought to correlate with clinical findings such as pain intensity, a longitudinal assessment has not been performed. We aim to use DTI to 1) characterize the longitudinal relationship between trigeminal nerve microstructure and pain intensity following GKRS for TN and 2) construct a machine learning predictor of pain intensity for GKRS-treated patients. Methods: 48 magnetic resonance (3T diffusion and T1 anatomical) imaging samples were acquired from 18 GKRS-treated TN patients up to 4 years post-surgery. DTI metrics were bilaterally extracted from 4 trigeminal nerve regions—cisternal segment, root entry zone, pontine segment, and radiosurgical target. For metrics at each region, linear mixed effects statistics were obtained across time and between nerve types. Ratings of pain intensity across time were assessed with 1-way ANOVA. Statistical significance was set at $p < 0.05$. To predict pain intensity, a support vector regression (SVR) model was trained on DTI metrics from symptomatic radiosurgical target and number of days post-GKRS. Results: TN-induced pain intensity was significantly reduced at 6-months post-surgery (9 ± 1 to 1 ± 1) and this reduction persisted to the end of available follow-up. Microstructural alterations in the target zone, with significantly decreased FA, appear most pronounced at 12-months post-treatment compared to control. After which, these alterations gradually reversed to pre-GKRS levels. DTI-metrics were statistically similar at all other regions across time. The SVR model achieved a 0.98 leave-one-out-cross-validated R^2 and predicted the intensity of TN pain in GKRS-treated patients within a mean error of 0.52. Conclusion: SVR can successfully predict pain intensity after radiosurgical treatment of TN. Alteration in trigeminal nerve FA has been strongly associated with the pathophysiology of TN. The inclusion of FA and time—the strongest predictors—allowed our model to reliably predict ongoing pain intensity. Ultimately, our model may guide re-treatment decisions following initial GKRS by allowing clinicians to objectively identify patients with subpar clinical pain relief.

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Topic: *D.03. Somatosensation: Pain

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Title: Involvement of anterior cingulate cortex in coding the anticipation of pain

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Abstract: Pain is a multidimensional experience that includes sensory and affective components, modifiable by expectations and other cognitive and affective processes (Bingel et al., 2007; Bingel and Tracey, 2008).
The primary somatosensory cortex (S1) has been thought to be important in the sensory-discriminative aspect of the pain, yet the anterior cingulate cortex (ACC) is known to play a crucial role in the affective-motivational experience of pain. Human imaging studies have identified patterns of activities within key cortical areas that can encode different pain experiences, but it remains unclear how pain can also be encoded reliably at the level of individual neurons or populations of neurons. Therefore, a complete understanding of neural codes for acute pain in physiology remains missing. The anterior cingulate cortex (ACC) has a crucial role in the affective-aversive experience of pain (Lubar, 1964; Foltz and White, 1968; Turnbull, 1972; Talbot et al., 1995; Craig et al., 1996; Rainville et al., 1997; Koyama et al., 2000; Johansen et al., 2001; Koyama et al., 2001; LaGraize et al., 2006; Qu et al., 2011). The ACC receives nociceptive inputs from the medial thalamus as well as from other cortical regions (Vogt and Sikes, 2000; Shyu et al., 2010). Individual ACC neurons can respond to noxious stimuli by increasing firing rates (Sikes and Vogt, 1992; Yamamura et al., 1996; Hutchison et al., 1999; Kung et al., 2003; Iwata et al., 2005; Kuo and Yen, 2005; Zhang et al., 2011) to provide evaluation for the intensity of acute pain (Coghill et al., 1999; Buchel et al., 2002). While previous studies have demonstrated that ACC is necessary and sufficient for the acquisition of stable aversive learning in the chronic pain condition (Johansen et al., 2001; Qu et al., 2011;

Barthas et al., 2015; Navratilova et al.,2015), his role in shaping pain by coding expectation as only been describe through fMRi or human reported studies.
Here we demonstrate how the ACC neurons are coding pain anticipation using *in vivo* electrophysiological recording in freely moving rats during a classical conditioning paradigm, and manipulate this neuronal activity via the use of optogenectics in order to modulate pain.

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Title: Deciphering neuronal population codes for acute thermal pain in rats

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Abstract: Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Few studies have attempted to assess the onset and intensity of pain, partly due to the complex molecular and circuit mechanisms involved in pain processing. To address this issue, we used supervised and unsupervised machine learning methods to detect acute pain onset and to predict pain intensity in rats. We used a laser to provide acute thermal pain of controlled intensity to the hind paws of freely moving rats. Using *in vivo* ensemble neuronal recordings from the rat primary somatosensory cortex (S1) and anterior cingulate cortex (ACC), we investigated neural codes for acute thermal pain at both single-cell and population levels. To detect the onset of acute thermal pain signals, we proposed a latent state-space framework to decipher the ensemble spike activity. This state space analysis allowed us to uncover a latent state process that drives the observed ensemble spike activity, and to further detect the "neuronal threshold" for acute thermal pain on a single-trial basis. Our method achieved good detection performance in sensitivity and specificity. Meanwhile, to decode the intensity of pain, we used two supervised machine learning approaches. Support vector machine (SVM) and nearest neighbor classifiers were used for discriminating high-intensity painful vs

non-painful stimulus or low- vs high-intensity pain stimulus. Our results suggest high accuracy in decoding pain intensity. We will also show how chronic pain, causes generalized enhancement of pain aversion, alters acute pain decoding. Thus, our work demonstrates the feasibility for new methods to detect pain objectively.

Disclosures: Q. Zhang: None. **A. Tong:** None. **T. Manders:** None. **A. Garg:** None. **Z. Chen:** None. **J. Wang:** None.

Nanosymposium

641. Advances in Pain Neuroimaging

Location: 144A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***641.13

**Topic: ***D.03. Somatosensation: Pain

Support: NIH grants K08-GM1026911
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NIH grant R01-NS100065

Title: Chronic pain impairs prefrontal pain regulation of acute pain

Authors: *J. A. DALE, H. ZHOU, Q. ZHANG, J. WANG
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Abstract: Previous studies have suggested decreased activity in the prefrontal cortex (PFC) in the chronic pain state. The expression and impact of this decreased activity, however, has not been investigated *in vivo*. The objective of the study is to elucidate the effect of chronic pain on the prelimbic prefrontal cortex's (PL-PFC) ability to modulate acute pain in rat model. We hypothesized that reduced PFC function leads to impaired pain regulation. Neuronal activity was recorded using tetrode arrays chronically implanted into the PL-PFC. Chronic pain was induced by injection of Complete Freund's Adjuvant (CFA) into the left hind paw and acute pain stimulations were pin pricks applied to the right hind paw. And the aversive quality of pain was quantified using conditioned place aversion (CPA) paradigm. Additionally, we performed Hargreaves and allodynia to assess the sensory component of pain. We found that chronic pain state depresses baseline and stimulus-evoked firing of neurons of the PL-PFC and increases the sensory and affective component of pain. Optogenetic activation at a rate similar to normal baseline firing greatly diminishes pain response. These results highlight the critical role of PL-PFC hypoactivity in chronic pain phenotype. Chronic pain state induced a decrease in the number of pain responsive neurons of the PL-PFC and a decrease in the baseline firing rate.

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641. Advances in Pain Neuroimaging

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Topic: *D.03. Somatosensation: Pain

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Title: Reduced pyramidal neuron activity in frontal association cortex of a mouse model of neuropathic pain

Authors: ***S. TENG**, G. YANG
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Abstract: Neuropathic pain caused by peripheral or central nerve injury is often accompanied by depression or other cognitive changes, implicating the alteration of frontal cortex in chronic pain states. Recent studies suggest that the prefrontal cortex provides a top-down modulation of the sensory and affective aspects of pain. However, the role of frontal circuitry in the chronification of pain remains unclear. Here, using in vivo two-photon microscopy, we examined the Ca^{2+} activity of layer 5 (L5) pyramidal neurons in the frontal association area (FrA) of a spared nerve injury (SNI) model of neuropathic pain. We found that peripheral nerve injury caused a substantial reduction of pyramidal neuron activity in FrA at one week post-injury. Using optogenetic manipulation in freely moving mice, we further showed that activation of FrA neurons in SNI animals restored the pain threshold to mechanical stimuli in Von Frey tests and relieved the aversive quality associated with chronic pain in conditional place preference tests. Together, these results demonstrate hypofunction of FrA pyramidal neurons in neuropathic pain and suggest FrA as a potential therapeutic target for pain management.

Disclosures: **S. Teng:** None. **G. Yang:** None.

Nanosymposium

642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

Location: 150A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***642.01

**Topic: ***E.05. Brain-Machine Interface

Support: NIH CoBRE P20GM109098
the U.S. Army Research Office and the Defense Advanced Research Projects Agency (DARPA) under Cooperative Agreement Number W911NF-15-2-0016 (http://www.darpa.mil).

Title: Decoding motor commands for postural control of a biomimetic myoelectric prosthesis

Authors: *A. SOBINOV[1], M. BOOTS[2], V. GRITSENKO[3], M. MANSOURI[4], C. BERINGER[4], M. L. BONINGER[4], L. E. FISHER[5], J. L. COLLINGER[6], R. A. GAUNT[5], S. YAKOVENKO[3]
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Abstract: Low-level activation of muscles is typically sufficient to maintain a static posture when the arm and hand are unloaded and joints are not near their biomechanical limits. At these low recruitment levels, the signal-to-noise ratio in electromyographic (EMG) signals is also low. Therefore, maintaining static postures could be challenging for biomimetically-inspired prosthetic control algorithms that include real-time simulation of the musculoskeletal dynamics, thus degrading the overall utility of such a control scheme. Using the control signals required to generate stabilizing torques at each joint could solve the problem of maintaining posture in a dynamic physical model of a prosthetic hand.
To achieve this goal, we used a dynamic model of a human hand with 18 degrees of freedom (DOFs) to obtain torques necessary to maintain multiple static postures. We explored these postures by varying 9 DOFs (3 wrist rotations, two movements at the thumb and 1 movement at each remaining finger) within their physiological ranges. Next, we constrained the model using the natural biomechanics of the muscles present in the arm, such as position-dependent muscle moment arms, muscle lengths, and non-linear force-velocity and force-length muscle properties. In the presence of these constraints and using the least-squares method, we extracted activations for 34 musculoskeletal actuators that were sufficient to produce static joint torques. These activations were then approximated with best-fitting functions (Sobinov et al., 2016) to enable real-time performance. Activations generated by these functions drove the musculoskeletal model to produce stabilizing torques with better than 0.01 Nm precision over all hand DOFs. To further stabilize the system, we extended the static torque model by developing a model of co-contraction that relies on muscle intrinsic viscoelasticity. Using co-activation of antagonistic muscles that stiffen each DOF, the model can compensate for brief perturbations from external

loads or EMG noise. We found that muscle activations extracted from the modeled system resemble co-activation observed in experimental intramuscular EMG. These results support the idea that the musculoskeletal system simplifies the control redundancy problem. This method can be used to stabilize biomimetic musculoskeletal models that only have the sparse representation of control signals.

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Nanosymposium

642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

Location: 150A

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**Presentation Number: ***642.02

**Topic: ***E.05. Brain-Machine Interface

Support: Coulter Foundation
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NSF GRFP to P. P. V. & C. S. N.

Title: Extracting regenerative peripheral nerve interface signals from human subjects for neuroprosthetic control

Authors: *P. P. VU[1], Z. T. IRWIN[1], P. T. HENNING[2], C. S. NU[1], D. GATES[3], R. B. GILLESPIE[4], S. W. KEMP[5], T. A. KUNG[5], P. S. CEDERNA[5], C. A. CHESTEK[1]
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Abstract: Peripheral nerves provide a promising source for neuroprosthetic control given their functional selectivity and relative ease of accessibility. However, current interface methods, such as penetrating electrodes, are limited in a clinical setting either by low signal amplitude or interface instability. Here we address these issues by extracting hand level prosthetic control signals from Regenerative Peripheral Nerve Interfaces (RPNI) implanted within 3 human subjects. RPNIs are constructed by suturing a small graft of devascularized, denervated muscle to the residual end of a severed nerve. The graft then revascularizes, regenerates and becomes reinnervated by the transected nerve, creating a stable bioamplifier that produces recordable electromyography (EMG) signals (Kung et al., 2014). In addition, nerves can be surgically subdivided into individual fascicles to construct multiple RPNIs and independent signal sources. Here, 2 distal transradial (P1, P2) and 1 proximal transradial (P3) amputees were implanted with

RPNIs. P1 and P2 were each implanted with 3 RPNIs with a single graft placed on each of the median, ulnar, and dorsal radial sensory nerve. P3 had 9 RPNIs implanted, with the median, ulnar, and radial nerves subdivided into 4, 3, and 2 branches, respectively. During acute recording sessions, we used ultrasound to locate and implant percutaneous fine-wire bipolar electrodes within the RPNIs. When available, relevant finger-related residual muscles were also implanted with electrodes, particularly in P1 and P2. A total of 3-8 electrodes were inserted per recording session. P1 and P2 were able to produce EMG signal within a range of 20-270µVp-p from the median RPNI with a signal-to-noise ratio (SNR) between 2.2-31.4 and 50-140µVp-p from the ulnar RPNI with a SNR between 3.3-11.6. P3's 3 ulnar RPNIs produced signal with a range of 30-50µVp-p and SNR of 1.6-5.6, and the 2 radial RPNIs produced signal with a range of 14.5- 28.3 µVp-p and SNR of 2.0-3.0. Using a combination of RPNI and available residual muscle signals, subjects successfully controlled a virtual prosthesis in real-time. For P1, a Naïve Bayes classifier was able to classify movements as either rest, index, middle, or thumb opposition in a 212-trial session with 96.2% accuracy using temporal features of the EMG waveform within 300-1500Hz and binned at 50ms. Similarly, P2 could control rest, thumb, or index with 100% accuracy in a 115-trial session, while P3 could control between little and fist movements with 87.1% accuracy. Overall, we have demonstrated that RPNIs may provide a clinically viable strategy for producing high amplitude signals from severed nerves for neuroprosthetic control.

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Nanosymposium

642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

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NIH CoBRE P20GM109098
Ruby Fellowship

Title: Scaling of musculoskeletal morphometry for human upper-limb models

Authors: *M. BOOTS[1], A. SOBINOV[1], V. GRITSENKO[2], M. MANSOURI[3], L. E. FISHER[4], J. L. COLLINGER[5], R. A. GAUNT[4], S. YAKOVENKO[2]
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Abstract: One approach to controlling artificial limbs is to use a biomimetic control scheme that relies on accurate internal models representing musculoskeletal anatomy and dynamics. To build such a model, muscle moment arms and physiological cross section areas (PCSAs) must be either estimated or measured to set the model parameters. However, these measurements come from multiple sources and often require additional scaling to create a holistic representation that can be used to model limb force generation. These adjustments are not trivial for realistic models attempting to capture the behavior of human limbs.
In this study, we developed a method to validate and scale muscle parameters using published isometric measurements for whole-limb force generation. Our dynamic model of the human hand was implemented in OpenSim (Delp et al., 2007) and MuJoCo (Todorov at al., 2012). It comprises 18 degrees of freedom (DOFs) and 32 musculotendon actuators with intrinsic Hill-type properties (Yakovenko et al., 2004), that each span on average 4 DOFs. The geometry a muscle takes from origin to insertion is used to model its moment arm and length values. We compared simulated moment arm profiles across the full physiological range of a joint to published experimental data, which were digitized and averaged across 9 studies. The criterion of the validation quality was based on the root-mean-square of the difference between simulated and experimental values normalized to the maximum of the experimental data. The maximum criterion value was 0.33, which ensured that simulated moment arms were within the standard deviation of experimental measurements. Next, we used experimental maximum voluntary contraction measurements, found in literature, for 4 DOFs (wrist flex/ext, wrist pro/sup, thumb abd/add, and thumb flex/ext) to scale isometric maximum forces for each muscle. The initial force values were predicted from PCSAs. Joint torques were produced by forces generated by maximally activated muscles spanning the relevant joint during feedforward dynamic simulations with the model locked in the posture that matched experimental conditions. The isometric maximum forces were adjusted, using ratios defined by the PCSAs, to match the empirical torques. This method allowed us to reduce torque disparity to within 10% across all DOFs. The maximum force value of each simulated muscle was similar yet higher (by less than 20%) than the value predicted by the PCSA. This method may be applicable to other complex musculoskeletal models where sufficient anatomical and physiological measurements are available.

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Nanosymposium

642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

Location: 150A

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**Topic: ***E.05. Brain-Machine Interface

Support: DARPA MTO SPAWAR Pacific Grant/Contract No. N66001-15-C-4017
National Science Foundation (NSF) Grant NSF/NCS-FO ECCS-1533649

Title: High-resolution somatosensory feedback in a human amputee allows sensorimotor discrimination, increases prosthesis embodiment, and reduces phantom pain

Authors: *J. A. GEORGE[1], D. T. KLUGER[1], D. M. PAGE[1], S. M. WENDELKEN[1], T. S. DAVIS[2], C. C. DUNCAN[3], D. T. HUTCHINSON[4], G. A. CLARK[1]
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Abstract: The long-term goal of these studies is to provide rich, biofidelic tactile and proprioceptive feedback from an advanced prosthetic hand after prior amputation in humans. Here we report on S6, our most recent of six human subjects. S6 received two 100-electrode Utah Slanted Electrode Arrays (USEAs; Blackrock Microsystems) implanted chronically (12 months) in residual median and ulnar nerves for stimulating sensory fibers and recording from motor fibers after a long-term (13-y) transradial amputation, as well as an array of intramuscular electrodes for electromyographic (EMG) recordings from residual extrinsic hand muscles (Ripple, LLC). Sensory percepts were mapped by passing increasing current through individual USEA electrodes (biphasic, 200-µs pulses; 100-200 Hz, 200-500 ms trains) until the subject reported a percept (location, type, and intensity), or until stimulation maximum (< 100 µA). Experiments were conducted either in a MuJoCo (Roboti, LLC) virtual reality environment; or with a simple sensorized, motorized physical prosthetic hand (Open Bionics); or with a more advanced, sensorized, motorized prosthetic hand (DEKA) having 6 DOFs and 19 receptive fields. S6 reported up to 119 different primary or secondary USEA-evoked cutaneous (e.g., pressure, vibration) or proprioceptive percepts (e.g., movement or tightening). The evoked percepts covered most of the phantom hand (although representation was sparse for the index finger tip); corresponded to normal afferent fiber distributions; and were typically perceived as enjoyable by S6. Percepts showed within-session stability, and more than half maintained location stability when retested at $\geq$ 1 month. S6 also used sensory feedback evoked by biofidelic afferent fiber stimulation to guide motor control of the DEKA hand (Kluger et al., SFN17). S6 could discriminate between “soft” foam blocks and “hard” plastic blocks in a sensorimotor task using the DEKA hand (15 successes in 18 trials). S6 also showed objective evidence of embodiment of both the Open Bionics and DEKA hands, as measured by proprioceptive shift

from the amputated hand to the prosthetic hand and by responses to survey questions. Stimulation of sensory fibers also resulted in a 23.2% reduction in subjective phantom pain scores for S6 (from 3.75 ± .14 to 2.88 ± .18, $p < 0.005$). The emerging ability to provide a relatively complex repertoire of high-count, high-resolution somatosensory inputs may enhance sensorimotor control, increase prosthesis embodiment, and reduce phantom pain for amputees, ultimately improving the adoption of advanced neuroprostheses.

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Nanosymposium

642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

Location: 150A

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**Topic: ***E.05. Brain-Machine Interface

Support: DARPA MTO SPAWAR Pacific Grant/Contract No. N66001-15-C-4017
National Science Foundation (NSF) Grant NSF/NCS-FO ECCS-1533649.

Title: Performance of tasks with closed-loop control of sensorized prosthetic hands by a transradial amputee with peripheral nerve and intramuscular implants

Authors: *D. T. KLUGER[1], S. M. WENDELKEN[1], J. A. GEORGE[1], T. S. DAVIS[2], C. C. DUNCAN[3], D. T. HUTCHINSON[4], D. J. WARREN[1], G. A. CLARK[1]
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Abstract: The goal of this work is to restore both the motor and sensory functionality of a missing limb back to an amputee. We have progressed towards this goal by granting a human transradial amputee volunteer (S6) closed-loop control of two sensorized, motorized prosthetic hands: a simple 5 degree-of-freedom (DoF) 3D-printed hand (a modified Open Bionics Ada hand), and a more advanced 6 DoF LUKE™ Arm (DEKA Research Corporation).
We implanted a 32-channel intramuscular electromyographic (EMG) array (Ripple, LLC) into S6's residual forearm muscles and two 96-channel Utah Slanted Electrode Arrays (USEAs, Blackrock Microsystems) into the residuum's median and ulnar nerves. The subject performed decodes of up to 10 DoFs using modified Kalman-filter-decoded EMG signals, which exceeded the controllable maximum set by the hands' robotics. We have shown that 3-DoF calibrations remain stable for over a month, and that stability improves over the course of the post-implant period and associated factors, such as training. USEA stimulation mapping sessions revealed a

subset of the implanted USEA electrodes that generated phantom perceptions (George et al., SfN17). We signaled changes in hand sensor activity back to S6 through frequency- and/or amplitude-modulated USEA stimulation, thereby providing sensory feedback through the prostheses.
S6 performed several activities of daily living (ADLs) with the LUKE™ Arm, and performed quantifiable ADL assessment tasks (e.g., box and blocks test) with the 3D-printed hand. Subjective self-reporting indicated that the subject enjoyed the new capabilities. We examined whether sensory feedback through USEA stimulation improved performance of a dexterous motor task. The task required lifting and moving a "mechanical egg" intact from one location to another with the LUKE™ Arm. The egg holds its shape until a threshold compression force is exceeded, resulting in trial failure. Over two days of testing, S6's success rate was better with stimulation on (53/80) than with stimulation off (36/80; Pearson's chi-squared test: $p < 0.01$). For successful trials, he performed the task faster in stimulation-on trials than in stimulation-off trials (Wilcoxon rank-sum test: $p < 0.0001$). This finding held true both for trials for which he was paying full attention to the task (Wilcoxon rank-sum test: $p < 0.005$), and trials for which he was distracted by backward counting (Wilcoxon rank-sum test: $p < 0.0001$).
We have demonstrated a viable strategy to restore partial functionality of a missing hand back to an amputee, and that restored sensory function can improve the performance of motor tasks.

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Nanosymposium

642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

Location: 150A

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**Topic: ***E.05. Brain-Machine Interface

Support: DARPA Grant HR0011-15-2-0008

Title: Osseointegrated Neural Interface (ONI): A novel approach to peripheral nerve interfaces

Authors: *A. M. DINGLE[1], J. NOVELLO[2], J. P. NESS[2], J. S. ISRAEL[1], J. PISANIELLO[2], L. KRUGNER-HIGBY[3], B. NEMKE[3], Y. LU[3], S. BRODNICK[2], M. D. MARKEL[3], A. J. SUMINSKI[4], J. C. WILLIAMS[2], S. O. POORE[1]
[1]Surgery, [2]Biomed. Engin., [3]Vet. Med., [4]Neurosurg., Univ. of Madison, WI, Madison, WI

Abstract: Objective: Todays advanced prosthesis hold great potential for restoring function and improving quality of life. The patient's ability to control these devices with ease and precision is

constantly improving; however, seamless control remains a futuristic goal. Typically, these devices are actuated by myoelectric signals from soft tissue interfaces subject to motion artifact and muscle signal cross talk.We have developed the **Osseointegrated Neuronal Interface (ONI)**; for prosthetic control. The ONI is a based on a common surgical method for preventing amputation neuromas, whereby a mixed sensory-motor nerve end is translocated into bone. Re-directing nerve endings into the medullary cavity of long bones protects the nerve from mechanical and electrical stimuli, in a highly vascular, stem cell-rich environment. This unique environment presents the perfect *in vivo* bioreactor for stable interfacing of severed nerves and electronic prostheses. This study describes the development of the ONI model, and subsequent proof of principal.

Methods: Midshaft femoral amputation was performed in male and female New Zealand white rabbits. Briefly, the sciatic nerve was isolated and severed above the point of bifurcation. The femur was amputated at the midpoint and the nerve passed through a corticotomy. The terminal end of the nerve was sutured into a PDMS sleeve, representing a mock electrode, which was pressed back into the opening of the medullary cavity, forming a seal. The muscle and skin were closed over the femur. Animals were explored at 5 and 12 weeks via histology and electrophysiology.

Results: Histological examination of the ONI limb demonstrates nerve sprouting at 12 weeks by S100+ Schwann cells beyond the PDMS sleeve. Cross sections of distal portions of the nerve demonstrate the ONI nerve contains smaller myelinated axons and substantially more collagen than the healthy control. While substantial axonal loss is evident and expected, qualitative assessment indicates an increased S100+ Schwann cell population at 12 weeks compared to 5 weeks. Electrophysiological assessments are currently being analyzed. No gender differences have been identified.

Conclusions: The terminal nerve is viable and demonstrates signs of regeneration following redirection into the medullary cavity of the femur at 12 weeks. The ONI model is feasible and may facilitate the harnessing of both sensory and motor signals to drive a prosthesis. Ongoing work on the ONI involves development and testing of implantable electrodes.

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Nanosymposium

642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

Location: 150A

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**Topic: ***E.05. Brain-Machine Interface

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Larry and Pamela Garlick
Samuel and Betsy Reeves

Title: Accurate and simultaneous 5.1 degree-of-freedom control of a virtual cursor by a person with paralysis using an intracortical BCI

Authors: *S. D. STAVISKY[1,2], P. NUYUJUKIAN[3,1,2,4,5], C. PANDARINATH[1,2], N. EVEN-CHEN[2,4], B. JAROSIEWICZ[1], P. REZAII[1], L. R. HOCHBERG[7,8,9,10,11], J. M. HENDERSON[1,5,4], K. V. SHENOY[2,5,3,4,6]
[1]Neurosurg., [2]Electrical Engin., [3]Bioengineering, [4]Bio-X Program, [5]Stanford Neurosci. Inst., [6]Neurobio. & Howard Hughes Med. Inst., Stanford Univ., Stanford, CA; [7]Neurol.,, Massachusetts Gen. Hosp., Boston, MA; [8]Ctr. for Neurorestoration and Neurotechnology, Rehab. R&D Service, Dept. of VA Med. Ctr., Providence, RI; [9]Sch. of Engin., [10]Inst. For Brain Sci., Brown Univ., Providence, RI; [11]Neurol., Harvard Med. Sch., Boston, MA

Abstract: Intracortical brain-computer interfaces (BCIs) in pilot clinical trials have shown promise towards providing intuitive control signals for high degree-of-freedom (DOF) effectors. Recent reports of >2 DOF neural control in people with paralysis have focused on functional task performance (e.g., picking up and moving objects), with less emphasis on the quality of the high DOF neural decoding itself. An important part of advancing these systems is to quantify and maximize the quality of high-DOF neural control, which can be obscured when controlling downstream effectors (robotic arms, functional electrical stimulators, etc.) with their own limitations. We therefore measured closed-loop BCI control quality without the added variability inherent to physical effectors by conducting experiments in 3D virtual reality using shuttered glasses. We report performance metrics demonstrating that a person with tetraplegia can accurately command up to 5 DOF, plus a binary 'grasp' state, both simultaneously and individually, using decoded movement imagery.
A BrainGate2 clinical trial participant ('T5') with tetraplegia with two 96-electrode arrays in left motor cortex manipulated a virtual object by attempting right arm movements. He commanded a 'grasp' by attempting to contract his left bicep. The cursor and target objects were rods with 3 DOF of translation and 2 DOF of rotation defined using spherical coordinates. Velocities in all 5 DOF were simultaneously decoded from multiunit spikes using ReFIT-KF. The grasp state was decoded using a Hidden Markov model [1]. Targets were acquired by bringing the cursor center within 2 cm and 13° of the target center and orientation, respectively, and dwelling on it for 500 ms or commanding a grasp.
In a task with 242 possible target locations arranged on a 10 cm / 66° radius 5D hypersphere, T5 acquired 22.2 targets per minute (TPM) with 0.67 path efficiency (PE) using dwell. Using grasp, the metrics were 21.1 TPM and 0.64 PE. Generalizability was demonstrated with a random target location/size task, for which PE was 0.65 using dwell and 0.60 using grasp.

5 DOF performance may have been limited by the somewhat unintuitive nature of spherical coordinates, rather than neural control limitations. We therefore performed further 4 DOF experiments (3D translation and 1D rotation) to better test simultaneous high DOF control. Performance on a 4D hypersphere task in dwell mode was 22.6 TPM, 0.76 PE. These metrics were similar across target subsets requiring position change along 1, 2, 3 or all 4 DOF. This demonstrates distinct and specific control of each DOF, and simultaneous control of all DOF.
[1] Pandirinath*, Nuyujukian* et al. eLife 2017

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Nanosymposium

642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

Location: 150A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***642.08

**Topic: ***E.05. Brain-Machine Interface

Support: DARPA HAPTIX

Title: Bi-directional neural control of an advanced limb prosthesis through an osseointegrated conduit in the context of the Agonist-antagonist Myoneural Interface (AMI)

Authors: *T. R. CLITES[1], M. J. CARTY[2], M. CARNEY[2], S. SRINIVASAN[2], R. O'DONNELL[3], R. BRAANEMARK[3], H. HERR[2]
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Abstract: Background: Despite recent advances in the development of prosthetic devices, current limb prostheses fall short of replicating the control experience afforded by biological limbs. This can be attributed, in large part, to poor treatment of nerves and muscles in the current standard-of-care limb amputation surgical paradigm. A majority of state-of-the-art myoelectric control strategies for prosthetic devices are built on complex pattern-recognition algorithms that seek to decode movement intent from the isometric contraction of residual muscles. However, fundamental biomechanics research has demonstrated a direct, proportional relationship between muscle activation and joint torque (mediated by fascicle length, contraction velocity, and musculoskeletal geometry). The Agonist-antagonist Myoneural Interface (AMI), a novel neural interface technology designed to preserve functional agonist-antagonist muscle relationships,

paves the way for improved myoelectric control of multi-degree-of-freedom prostheses. **Methods:** The AMI architecture enables an array of control strategies that leverage surgical coaptation of natively-innervated agonist-antagonist muscle pairs within the residuum to create a biomimetic control experience. Preservation of the mechanical coupling between agonist contraction and antagonist stretch allows physiologically-relevant muscle state feedback from a prosthesis through mechanical activation of native mechanoreceptors within these linked muscles. An osseointegrated neural conduit provides a stable mechanism of transcutaneous neural signal communication. Herein we present pre-clinical data, as well as preliminary data from early human trials, demonstrating the potential of the AMI to serve as a platform for improved bi-directional neural control of an advanced prosthetic limb. **Results:** Pre-clinical data from animal models demonstrate the capacity of the AMI to replicate the dynamic muscle relationships that exist in the biological limb. Preliminary data from human trials presented herein highlight the impact of the AMI on control of an advanced limb prosthesis in subjects having a unilateral transtibial amputation. Integration of the lessons learned from these experimental models enabled the development of an AMI-driven transfemoral bionic system, capable of replicating biological function in a prosthetic knee, ankle, subtalar, and metatarsophalangeal joints. **Conclusion:** The combination of AMI-driven control architectures, osseointegration, and cutting-edge robotic systems may provide a complete limb replacement system for patients having amputation at the transfemoral level.

Disclosures: T.R. Clites: None. **M.J. Carty:** None. **M. Carney:** None. **S. Srinivasan:** None. **R. O'Donnell:** None. **R. Braanemark:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Integrum, Inc.. F. Consulting Fees (e.g., advisory boards); Integrum, Inc.. **H. Herr:** None.

Nanosymposium

642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

Location: 150A

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**Presentation Number: ***642.09

**Topic: ***E.05. Brain-Machine Interface

Support: Defense Advanced Research Projects Agency (DARPA) Grant No. N66001-15-C-4038.
NIH T32 Grant 5T32EB004314-17

Title: Timing of restored tactile sensation in people with lower limb amputations

Authors: B. P. CHRISTIE[1], *H. CHARKHKAR[3], E. L. GRACZYK[1], D. J. TYLER[1], R. J. TRIOLO[2]

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Abstract: Electrical stimulation applied to the intact sensory nerves of people with amputations can elicit tactile and/or proprioceptive sensations referred to their missing limb. This restoration of sensory feedback can improve prosthesis control and embodiment. To maximize these benefits, stimulation must temporally align with visual cues from the interaction of the prosthesis with objects. We examined the temporal synchrony between visual stimuli and sensations elicited via neural stimulation.

Two people with trans-tibial amputations were chronically implanted with 16-contact cuff electrodes on their tibial, fibular, and distal sciatic nerves. Subjects performed a visuotactile simultaneity judgment task. The "tactile" portion involved suprathreshold stimulation of a single contact. The delay between the two stimuli, referred to as the stimulus onset asynchrony (SOA), was varied between -500 to +500ms. Positive SOA values refer to cases where stimulation occurred before the LED was flashed. The subjects were asked if stimuli were "synchronous" or "asynchronous." PSS was the timing delay at which the stimuli were perceived as maximally "synchronous." JND was the smallest time interval that they could reliably detect.

Table 1 displays the preliminary PSS and JND values. All PSS values were positive, meaning it took longer to process stimulation than visual stimuli. The PSS values were also significantly larger than able-bodied subjects ($p<0.05$) (Harrar & Harris 2005). This could possibly be due to the fact that they are 10+ years post-amputation and may now be biased due to their dependence on vision while operating prostheses. The JNDs are not significantly different than able-bodied subjects (Poliakoff 2006), which indicates that sensitivity to stimulation-induced sensation is similar to that of normal tactile sensation.

We were able to quantitatively examine the temporal synchrony between visual stimuli and sensations elicited via neural stimulation in two people with lower limb amputations. After a prosthesis user sees an object interact with their prosthesis, stimulation should occur within the "synchronous" temporal range. This is an important step towards the development of a neuroprosthesis that provides instantaneous sensory feedback.

Metric	**Subject 1, Ch1**	**Subject 1, Ch2**	**Subject 2, Ch1**	**Subject 2, Ch2**
PSS (ms)	+113 (stim first)	+140 (stim first)	+143 (stim first)	+60 (stim first)
JND (ms)	147	131	78	109

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Nanosymposium

642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

Location: 150A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***642.10

**Topic: ***E.05. Brain-Machine Interface

Support: DARPA HAPTIX
DARPA and NIH SBIR grants

Title: Implantable and wearable neural technologies for take home clinical trials

Authors: *D. MCDONNALL, S. HIATT, B. CROFTS, C. SMITH, A. WILDER, D. MERRILL
Ripple, Salt Lake City, UT

Abstract: Control of prosthetic arms has been limited by the small number of inputs that are used to control multiple degrees of freedom in the limb. Conventional myoprostheses rely on a pair of signals recorded from surface electrodes on the residual limb. We are developing a series of neural technologies to support investigations into improved prosthesis control, including: a myoelectric implant to detect signals from multiple residual muscles for improved control, a neural stimulation and recording implant for selective activation of peripheral nerves to restore sensation, and a wearable processor to implement decoding and encoding algorithms for real-time system control. We report design considerations for system integration and results from *in vitro* performance of the system and an *in vivo* trial to validate device function in an animal model.

The implants are constructed on a ceramic circuit board with a bioamplifier/stimulator ASICs and additional discrete components. Theses implants are inductively powered by an external transceiver, and digitized signal data are sent from the implants by infrared data transmission. Myoelectric implants have 32 independent EMG recording electrodes to be implanted intramuscularly throughout the limb. The neural stimulation implant supports 64 independent channels and can be attached to a number of types of neural electrodes. First-in-human neural implants will include Utah Slanted Electrode Arrays developed by the University of Utah and Blackrock Microsystems.

The myoelectric implant is being validated in an ongoing GLP study in canine subjects in a six-month trial. The 32-channel implant is surgically inserted in the forelimb with intramuscular electrodes implanted in deltoideous and lateral head of triceps. Following implantation, each animal was fitted with a backpack carrying an external transceiver coil and a battery-powered data acquisition system, and the dogs were allowed to freely walk down a hallway. EMG recorded from each animal as it walked down a hallway had very low noise and, in conjunction with recorded video, clearly indicated swing/stance phases of gait.

These technologies will support clinical trials at multiple institutions for year-long take-home

trials as part of the DARPA HAPTIX program. We will also provide implantable and wearable technologies to other neuroscience investigators to provide a research platform for other large animal and human subject studies.

Disclosures: D. McDonnall: A. Employment/Salary (full or part-time):; Ripple. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ripple. **S. Hiatt:** A. Employment/Salary (full or part-time):; Ripple. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ripple. **B. Crofts:** A. Employment/Salary (full or part-time):; Ripple. **C. Smith:** A. Employment/Salary (full or part-time):; Ripple. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ripple. **A. Wilder:** A. Employment/Salary (full or part-time):; Ripple. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ripple. **D. Merrill:** A. Employment/Salary (full or part-time):; Ripple.

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642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

Location: 150A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***642.11

**Topic: ***E.05. Brain-Machine Interface

Support: DARPA W911NF-17-1-0049

Title: Improving myoelectric controller of a soft-synergy based prosthetic hand for feedback-driven grasp force control

Authors: *Q. FU[1], M. SANTELLO[2]
[2]Sch. of Biol. and Hlth. Systems Engin., [1]Arizona State Univ., Tempe, AZ

Abstract: Recent development of soft robotics approaches have brought advances in the mechanical design of prostheses. By merging with the neuroscientific concept of postural synergies of the human hands, a multi degrees of freedom soft prosthetic hand (SoftHand Pro, SHP) was created to provide adaptive and robust functional grasps with only one actuator, which leads to simple and intuitive myoelectric control of hand motion (Godfrey et al., 2013). However, the current myoelectric controller does not allow fine control of grasp forces during hand-object interactions. We addressed this challenge by designing a switching gain hybrid myoelectric controller that uses multiple control gains based on the sensorimotor state of the SHP. This controller was tested against a conventional single-gain controller, as well as against

native hand in able-body subjects. The following tasks were used to evaluate the quality of grasp force control: 1) pick and place object with different size, weight and fragility levels using power or precision grasp, and 2) squeezing and label objects with different stiffness. Sensory feedback of the grasp forces was provided to the user through a non-invasive, modality-matched haptic feedback device mounted on the upper arm (Casini et al., 2015). Kinematics of the hand and objects, as well as grasp forces were recorded. We found that the new hybrid controller improved the speed and accuracy of all experimental tasks. This improvement was mainly due to a better control of force after hand-object contact.

Disclosures: Q. Fu: None. **M. Santello:** None.

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642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

Location: 150A

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**Topic: ***E.05. Brain-Machine Interface

Support: NIH-R01-EB008578
DARPA-W911NF-17-1-0022

Title: Effect of vibrotactile feedback and hand interface compliance on grasp force and hand opening control of a sensorized myoelectric prosthetic hand

Authors: *A. E. PENA[1], L. RINCON GONZALEZ[1], J. J. ABBAS[2], R. JUNG[1]
[1]Biomed. Engin., Florida Intl. Univ., Miami, FL; [2]Ctr. for Adaptive Neural Systems, Arizona State Univ., Tempe, AZ

Abstract: Current myoelectric prosthetic limbs are limited in their ability to provide direct sensory feedback to users, which increases attentional demands and reliance on visual cues. Vibrotactile sensory substitution (VSS), which can be used to provide sensory feedback in a non-invasive manner, has demonstrated only limited improvement in myoelectric hand control. In this work, we use VSS to investigate the effect of vibrotactile paradigms and prosthetic hand interface compliance on the quality of control of grasp force and hand opening that could be achieved using a myoelectric hand. We developed a system that delivers vibratory patterns to the forearm based on sensor readings from an off-the-shelf prosthetic hand instrumented with grasp force and hand-opening sensors. One “C-2” linear actuator (T1) conveyed signal intensity by adjusting the driving tone burst rate and period. A linear array of five coin-shaped tactors (T5) conveyed signal intensity by varying the location of the tactors activated.
We tested the accuracy and repeatability of myoelectric control during virtual target tasks,

monitoring error rates and task durations. The subject's capability to discriminate and maintain a stable perception of the different target levels before and after each myoelectric control experiment was also tested. Able-bodied subjects controlled a prosthetic hand to reach a target value (0, 25, 50, 75, or 100%) of their maximum grasp force or hand opening as shown on a computer display. All tasks were completed with and without visual (display) or vibrotactile feedback. Eight subjects completed the tasks, receiving force feedback (T1) or hand opening feedback (T5). In the absence of visual feedback, the mean absolute error and task duration for force and hand opening were statistically different (12.9±0.9%, 7.4±0.6s and 8.4±0.7%, 5.5±0.3s mean±SEM, respectively). To further test force control, six subjects received T1 or T5 feedback to reach force targets when grasping with a stiff or compliant interface between the prosthetic hand and the object. In the absence of visual feedback, the T1/Stiff and T5/Compliant conditions were statistically different (errors and durations of 13.7±1.1%, 9.5±0.7s and 9.8±0.8%, 7.6±0.7s respectively). These results suggest that in the absence of visual feedback, myoelectric control performance is better when using a compliant interface (for force tasks) and with spatially distributed tactor VSS feedback. Additionally, longer force task durations seen for both VSS paradigms suggest that force outputs are more difficult to control than hand opening.
Supported by NIH-R01-EB008578 and DARPA-W911NF-17-1-0022

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Nanosymposium

642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

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Topic: *E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (P1155R, N9288C, B6453R)
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Doris Duke Charitable Foundation

Title: Advances in mobile wireless signal processing toward intracortical BCI deployment

Authors: *J. D. SIMERAL[1,2,3], C. D. HEELAN[2], J. KOMAR[2], A. V. NURMIKKO[2,3]
[1]VA Ctr. for Neurorestoration and Neurotechnology, Rehab R&D Service, Brown Univ. Sch. of Engin., Providence, RI; [2]Sch. of Engin., [3]Inst. for Brain Sci., Brown Univ., Providence, RI

Abstract: Brain-computer interfaces are being developed to improve independence for people living with tetraplegia and to restore communication for individuals with locked-in syndrome or others whose paralysis further results in the inability to speak. As research extends BCI performance for communication (Jarosiewicz et al., 2015; Pandarinath et al., 2017), upper limb prosthetics (Hochbeg et al., 2012; Collinger et al., 2013) and reanimation of a paralyzed limb (Ajiboye et al., 2017), translation of complex BCI research platforms for practical home use becomes paramount. At-home studies of EEG BCI use by individuals with motor disability (Miralles et al., 2015) are yielding important translational insights. Intracortical BCIs are also addressing the translation challenge. For example, the BrainGate* pilot clinical trial has accumulated over 1,500 in-home study sessions across 13 study participants. To further advance intracortical BCIs toward independent, on-demand use at home without technical oversight, we have recently deployed external, pedestal-mounted broadband wireless transmitters to replace neural signal recording cables that otherwise tether users to a rack of decoding computers. In striving towards a fully mobile BCI system, we report here (1) a compact mobile integrated microwave antenna-receiver device (ARD) that links 96-channel x 20kS/s wireless neural signal transmitters to (2) a high-performance, small-form embedded system ("ESPA"). Importantly, the embedded system can perform both full bandwidth neural signal processing and decoding in one integrated package for mobile BCI. The overall system platform is general and portable to other high data rate wearable medical sensor applications. Up to four ARDs mobile packages connect via HDMI cable to the ESPA device where neural signal processing and decoding algorithms are being implemented in FPGA logic and ARM processor code. Previously (Heelan et al., 2015), we demonstrated the ability to receive, decode and store (over WiFi) intracortical data through the ESPA platform. Both the antenna-receiver and the embedded system are designed in a compact form factor for wheelchair mounting to enable mobile use of the intracortical BCI for tablet or device control throughout the home and, one day, beyond. We describe the architecture of the mobile intracortical BCI, components of the system, functional testing and performance. Together, the antenna-receiver device and the ESPA embedded system are foundational elements of a future mobile intracortical BCI system for in-home independent BCI use by individuals with severe motor disability.

Disclosures: **J.D. Simeral:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ESPA (IP Rights). **C.D. Heelan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ESPA (IP Rights). **J. Komar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BWD (IP Rights. Licensed to Blackrock Microsystems). ESPA (IP Rights). **A.V. Nurmikko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BWD (IP Rights. Licensed to Blackrock Microsystems). ESPA (IP Rights).

Nanosymposium

642. Prosthetics: Peripheral Neural Interfaces for Reach and Grasp

Location: 150A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 11:30 AM

**Presentation Number: ***642.14

**Topic: ***E.05. Brain-Machine Interface

Support: Sponsored by the Defense Advanced Research Projects Agency (DARPA) Biological Technologies Office (BTO) HAPTIX program under the auspices of Dr. Doug Weber through the Space and Naval Warfare Systems Center, Pacific Contract No. N66001-15-C-4016

Title: Dexterous finger control and sensory restoration in partial hand amputees

Authors: *E. W. KEEFER, III[1], C. OVERSTREET[1], J. CHENG[2]
[1]Nerves Inc., Dallas, TX; [2]Plastic Surgery, UTSW Med. Ctr., Dallas, TX

Abstract: As part of the DARPA HAPTIX program, we are developing a prosthetic control/sensory restoration system for partial hand amputees. Our goal is to provide dexterous control of individual prosthetic fingers using data obtained directly from peripheral nerves. We also seek to restore both tactile and proprioceptive sensation through electrical stimulation. Our solution for accomplishing these goals is enabled by surgically targeting individual fascicles of peripheral nerves with novel electrode arrays we have designed and developed. Data acquired to date provide evidence that individual prosthetic finger control and multi-modality, functionally relevant sensations can be implemented using selectively targeted electrode arrays implanted within individual nerve fascicles of the ulnar nerve.

We have implanted partial hand amputees with multiple electrode arrays targeted to individual fascicles of their ulnar nerve. Percept thresholds, percept maps, and percept quality are measured at each lab session. Sensory stimulation can produce a range of percepts, including light pressure, pulsing, squeezing, individual finger movements, and multi-digit grasp sensations. Modulation of sensory stimulation pulses and trains can elicit changes in the quality and location of the percepts, with shorter pulse widths tending to feel more “natural” and shorter pulse trains tending to produce more focal sensations. Stimulation on multiple electrodes can produce discrete or fused percepts with the appropriate choice of parameters. Subjects can reliably discriminate between pulse amplitudes as small as 5 μA, and can detect stimulus trains as short as two pulses. When mapped to subject’s prosthetic hands, percepts can be used by subjects to identify contact events on multiple digits and joint motion during grasping. Recorded data can be decoded to identify imagined movement of specific amputated fingers with high accuracy. We are implementing the decoding algorithms for on-line use to provide real-time, dexterous control of the subjects’ prostheses.

We have shown that surgical targeting of nerve fascicles can allow us to elicit modality specific

percepts in partial hand amputees. The percept maps remain stable for at least ninety days, and can be used by the subjects to enhance the use of their prosthetic hands. The data recorded from the ulnar nerve can be decoded to identify subject's imagined finger movements. When fully implemented in real-time, we believe the decode algorithms and sensory restoration protocols we are developing can provide dexterous control of prosthetic hands with restoration of both tactile and proprioceptive sensations.

Disclosures: E.W. Keefer: A. Employment/Salary (full or part-time):; Nerves Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nerves Incorporated. **C. Overstreet:** A. Employment/Salary (full or part-time):; Nerves Incorporated. **J. Cheng:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nerves Incorporated.

Nanosymposium

643. Hormonal and Neuropeptide Control of Physiology and Behavior

Location: 152A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***643.01

**Topic: ***F.02. Behavioral Neuroendocrinology

Support: NIH Grant Z1A HD000195-22

Title: Single cell analysis reveals electric and genetic heterogeneity of secretory pituitary cells

Authors: *M. ROKIC, R. M. PREVIDE, P. A. FLETCHER, A. SHERMAN, S. S. STOJILKOVIC
NIH, Bethesda, MD

Abstract: Pituitary cells are typically defined by the major hormones they express and secrete: proopiomelanocortin (POMC) synthesizing melanotrophs and corticotrophs, luteinizing (LH) and follicle-stimulating hormone secreting gonadotrophs, thyroid-stimulating hormone (TSH) secreting thyrotrophs, prolactin (PRL) secreting lactotrophs and growth hormone (GH) secreting somatotrophs. However, there is increasing functional evidence that there may be additional pituitary subtypes. We characterized electrical and genetic heterogeneity in adult secretory pituitary cells from male and female rats by measuring both electrical activity and gene expression in single cells. Perforated patch clamp recording with a superfast perfusion system was used to record electrical responses to the hypothalamic regulatory hormones thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), corticotropin-releasing hormone (CRH) and dopamine (DA). After recording, the cell cytosol was sampled and reverse

transcription and pre-amplification of the pituitary target genes was done. Gene expression was measured by q-PCR relative to *Gapdh* expression in each cell. The electrophysiological properties of pituitary cells included spontaneous firing, spontaneous bursting and electrical quiescence. Electrophysiological responses to applied releasing hormones included: 1) CRH+ DA+ GnRH- TRH-; 2) CRH+ DA- GnRH- TRH-; 3) CRH- DA- GnRH- TRH+; 4) CRH- DA+ GnRH- TRH+; 5) CRH- DA- GnRH+ TRH-; and 6) CRH- DA- GnRH- TRH-. Analysis of gene expression was done using hierarchical clustering. Grouping the cells into five clusters showed the presence of known pituitary cell types in terms of their primarily (higher) expression of pituitary target genes, with *Pomc* positive cells (putative corticotrophs and melanotrophs) grouped together. The clustering also revealed that the conventional cell groups could be further subdivided into subtypes based on secondary (lower) expression of other pituitary target genes. The biggest contributors of genetic heterogeneity were found in *Pit-1*-derived cell lineages. All *Tshb* positive cells also expressed *Cga* as well as *Gh* and 50% of them expressed *Prl.* All *Tshb* negative and *Prl* positive cells also contained traces of *Gh*, and 50% of them expressed *Cga*. 80% of *Lhb* and *Gnrhr* positive cells contained traces of *Gh*, 60% contained traces of *Prl* and 20% contained traces of *Tshb*. The expression of secondary pituitary target genes likely reflects the developmental trajectory of the cell, and may be indicative of cell subpopulations with the potential to transdifferentiate in certain physiological circumstances such as estrus cycle or puberty.

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Nanosymposium

643. Hormonal and Neuropeptide Control of Physiology and Behavior

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**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***643.02

**Topic: ***F.02. Behavioral Neuroendocrinology

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PIRG-GA-2009-256413
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Title: The Oxytocin Receptor and the Vasopressin/Vasotocin Receptor 1A appear to be paralogous sister genes explaining their common functions

Authors: *C. THEOFANOPOULOU[1,2], G. GEDMAN[2], C. BOECKX[1,3], E. D. JARVIS[2,4]
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Abstract: The reason why the Oxytocin Receptor (OTR) and the Vasopressin Receptor 1A (AVPR1A; aka Vasotocin 1A) display common properties has been a long-standing question in neuroscience. Both receptors exhibit common expression patterns in the brains across species, with oxytocin (OT) binding to AVPR1A neural receptors with equal affinity as to the OTR. Also, OT manipulations have long lasting effects on AVPR1A receptors, and several behavioral effects of OT have been shown to be mediated by its binding to AVPR1A. Added to that, polymorphisms on the OTR and AVPR1A genes predict overlapping variation in social and sexual behaviors in several species. Here we present evidence using comparative genomics that explains why these two receptors share so many features. We performed sequence identity (BLAT/BLAST) and synteny (CoGe and SynMap) analyses on the OTR and the AVPR1A in the genomes of 26 species that span all major vertebrate lineages. These included newly re-sequenced genomes we and others generated with long-read technology that filled in gaps and corrected errors in previous shorter-read assemblies. We found that OTR and AVPR1A both reside in highly conserved syntenic blocks from humans all the way back to the common ancestor with elephant shark. Going even further back to the lamprey genome, we found one chromosomal block containing an OTR/AVPR1A precursor, suggestive of a duplication event of this ancestor gene that led to paralogous formation of OTR and AVPR1A receptor types. On the basis of a transposable element adjacent to OTR, we hypothesize that OTR was the duplicated gene from the more ancestral AVPR1A. These findings on homology and synteny of these two genes unveil the reason why scientists have been encountering overlapping results when studying them at multiple levels of biological analysis and should thus inform future studies on these two receptor types. According to our findings, the OTR and AVPR1A are ‘sister’-genes, something that has been puzzling scientists so far, just because their sisterhood was not depicted in their nomenclature. Our future efforts we focus on generating a uniform evolution-based nomenclature for these genes and their gene family members.

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Nanosymposium

643. Hormonal and Neuropeptide Control of Physiology and Behavior

Location: 152A

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**Topic: ***F.02. Behavioral Neuroendocrinology

Support: NIH Grant R01MH102456
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Title: Involvement of the vasopressin system in preventing, as well as inducing, sex differences in social behavior: A tale of two brain regions

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Abstract: The vasopressin (AVP) system shows sex differences in the number of cells in the posterior bed nucleus of the stria terminalis and medial amygdala and in the density of AVP fiber projections from these regions to the lateral septum (LS). This sex difference is highly conserved across vertebrate species. Here, we aimed to determine (i) whether the sex differences in AVP fiber density occur prior to puberty, (ii) whether these differences occur in other projection areas, and (iii) what the behavioral implications of these sex differences are. We found that juvenile rats show a similar sex difference in AVP fiber projections compared to adult rats, with denser AVP fibers in the LS of males compared to females. Furthermore, higher AVP fiber density in males versus females was found in additional brain regions, including the ventral pallidum (VP). These sex differences in AVP fiber density likely correspond with sex differences in AVP signaling, which in turn, may have implications for the regulation of social behavior. In support, we found that AVP regulates juvenile social play behavior and adult sociosexual motivation in sex-specific ways. In detail, blocking AVP signaling in the LS induced a sex difference in juvenile social play behavior by enhancing social play in males and reducing social play in females. Furthermore, blocking AVP signaling in the VP eliminated a sex difference in adult sociosexual motivation (as measured by a opposite sex preference) by reducing sociosexual motivation in males, but enhancing it in females. Overall, these findings demonstrate opposing roles of the AVP system in the regulation of social behaviors in males and females and suggest that the AVP system is involved in preventing sex differences in social play behavior by acting on the LS as well as inducing sex differences in sociosexual motivation by acting on the VP.

Disclosures: A.H. Veenema: None. **B.T. Benedictis:** None. **R. Bredewold:** None.

Nanosymposium

643. Hormonal and Neuropeptide Control of Physiology and Behavior

Location: 152A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***643.04

**Topic: ***F.02. Behavioral Neuroendocrinology

Support: NIH

Title: Neuromodulation of parental behavior

Authors: *I. CARCEA[1], N. LOPEZ[2], R. OYAMA[3], R. C. FROEMKE[4]
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Abstract: Long-term plasticity in the cortex is thought to be important for learning and experience-dependent changes in behavior, but when do such changes occur during natural experience? Activation of subcortical neuromodulatory systems is often required to enable mechanisms of synaptic and spiking plasticity, and thus it is important to relate periods of heightened modulation to changes in cortical responses in a behavioral context. Social interactions such as forms of maternal care are likely to involve increased activity of neuromodulatory systems, particularly of the paraventricular nucleus (PVN) oxytocin neurons. However, it has remained unclear when these neurons fire during maternal experience, and what behavioral episodes might drive experience-dependent maternal abilities.
Recently, we examined how oxytocin acts in the mouse left auditory cortex to promote long-term synaptic plasticity, enhance responses to ultrasonic pup distress calls and to enable maternal care towards pups in virgin females co-housed with an experienced mother and her litter (Marlin et al., Nature 2015). To understand when these changes might occur during days of natural maternal experience, we constructed a system for synchronously and continuously recording audio, video and neuronal responses before, during and after co-housing. Using this system, we documented episodes of adult-adult and adult-pup interactions while making single-unit recordings from PVN neurons and/or auditory cortical neurons in freely moving behaving mice. We found that in virgin mice, PVN neurons spiked more frequently during interactions with another female or with a pup, suggesting that the ongoing activity of this neurons would be higher during co-housing compared to single-housing conditions. PVN neurons in virgins also fired robustly when these mice observed a retrieving episode performed by the mother with which they were co-housed. We confirmed that PVN neurons also fire in mothers during the retrieval behavior. Our data indicate that a similar neuronal population is activated in mothers during pup retrieval and in virgins while observing pup retrieval. This system therefore allows us

to determine what environmental conditions or social interactions activate modulatory neurons, gating behaviorally-relevant plasticity in real time.

Disclosures: I. Carcea: None. **N. Lopez:** None. **R. Oyama:** None. **R.C. Froemke:** None.

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643. Hormonal and Neuropeptide Control of Physiology and Behavior

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**Presentation Number: ***643.05

**Topic: ***F.02. Behavioral Neuroendocrinology

Support: NIH

Title: Social modulation of appetite and avoidance by zebrafish oxytocin circuits

Authors: *C. L. WEE[1], E. SONG[1], M. NIKITCHENKO[1], S. WONG[1], S. LUKS-MORGAN[2], A. D. DOUGLASS[2], S. M. KUNES[1], F. ENGERT[1]
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Abstract: The neuropeptide oxytocin (OXT) is known to play multifaceted roles in social behavior, pain, and appetite, yet the mechanisms underlying such diverse functions are not well understood. Here, we leverage the accessible neural circuitry and genetics of the larval zebrafish to explore the evolutionary logic underlying OXT's broad effects on behavior. By using a brain-wide activity mapping approach, we pinpoint hypothalamic OXT neurons as a key hub for controlling defensive responses to pain. We show that a large fraction of OXT neurons integrate multiple noxious stimuli, particularly input from TRPA1 damage-sensing receptors, and are essential for driving pain avoidance behavior. Interestingly, OXT neurons also increase their activity during social isolation, which correlates not only with enhanced pain responses, but also a reduction in food intake. Manipulation of OXT signaling can reverse or mimic the behavioral effects of social isolation. Our results not only recapitulate oxytocin-related phenotypes present in mammals, but also provide mechanistic insights into how oxytocin circuits can represent social context to modulate downstream behaviors in a state-dependent manner.

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Nanosymposium

643. Hormonal and Neuropeptide Control of Physiology and Behavior

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**Topic: ***F.02. Behavioral Neuroendocrinology

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Title: Non-invasive eye tracking for the study of social cognition in monogamous titi monkeys

Authors: *S. M. FREEMAN[1], L. LOYANT[2], M. C. PALUMBO[1], T. MURAI[3], M. D. BAUMAN[1], K. L. BALES[1]
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Abstract: Primates acquire social information primarily through the visual system. Measuring patterns of eye movement gives researchers insight into the cognitive processes that allow individuals to visually navigate their social world. Eye-tracking technology has been used in social neuroscience research with humans and nonhuman primates to determine what individuals pay attention to and what they ignore. For example, rhesus macaques recognize familiar group members and avoid looking at the eyes of dominant animals. Children with autism spectrum disorder, a condition characterized by impairments in social bonding, fixate on the non-social features of pictures and videos of social scenes. To investigate the biology of social attachment, we study the hormones, brains, and behavior of the monogamous coppery titi monkey (*Callicebus cupreus*). Like humans, titi monkeys form enduring adult social attachments after mating. We used non-invasive eye tracking (Tobii Pro TX300) to quantify their social looking behavior. We tested 19 animals (8 juveniles; 11 adults) with photos and videos of other titi monkeys. None of the animals were habituated prior to testing, and the viewing task was voluntary: each monkey was presented with visual stimuli while sitting in a familiar transport box that was modified to include a small window at face height. Fourteen animals (74%) participated and spent an average of 26% of the session looking at the stimuli. The remaining five animals did not spend any time looking at the stimuli. Juveniles spent significantly more time looking at the stimuli than adults ($p<0.03$), and all monkeys spent significantly more time looking at videos compared to photos ($p<0.02$). We found no effect of sex on looking time. We are now using this technology to determine whether pair-bonded mates of this monogamous New World monkey species show preferential looking at the face of their pair-mate compared to unfamiliar faces. Future studies can include manipulations of the oxytocin and vasopressin systems, which are known to influence social attachment and primate visual attention. This work supported by P51 OD011107 and the Good Nature Institute.

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Nanosymposium

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Presentation Number: *643.07

Topic: *F.02. Behavioral Neuroendocrinology

Title: Oxytocin differentially couples the anterior cingulate cortex and amygdala for prosocial and antisocial decisions

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Abstract: In recent years, the neuropeptide oxytocin (OT) has become one of the most studied peptides of the human and animal neuroendocrine system. Research has shown widespread behavioral effects and potential therapeutic benefits. However, little is known about the mechanisms by which OT triggers these effects in the brain. Previous studies have focused on the amygdala as an important target of OT's effects, typically reporting a decrease in BOLD activation in response to emotional stimuli following systemic OT administrations. Furthermore, accumulating evidence suggests that OT plays a role in regulating communications among brain regions involved in social behavior. However, it remains unexplored how local OT signaling within a specific brain region modulates such interactions during social behaviors. Here, we focally infused OT in the basolateral amygdala (BLA) to examine its direct effects on the neuronal coordination between BLA and the reciprocally-connected anterior cingulate gyrus (ACCg), two regions previously investigated for their roles in social decision-making at the single-neuron level. We used a social reward allocation task in which an actor monkey chooses among delivering juice rewards to himself (*Self*), the other monkey (*Other*), both himself and the other monkey (*Both*) or a juice collection bottle (*Neither*). During this task, we recorded local field potential (LFP) activity simultaneously from ACCg and BLA to investigate changes in their coordination following either OT or vehicle (saline) infusions into BLA. The actors preferred to donate juice to the other monkey (*Other)* over a juice bottle (*Neither),* but also preferred *Self* over *Both*, providing the contexts for examining the ACCg-BLA interaction across prosocial (*Other* over *Neither*) and antisocial (*Self* over *Both*) decisions. OT infusions into BLA overall enhanced prosocial behaviors by increasing the number of *Other* and *Both* choices while increasing LFP power across multiple frequency bands in BLA following prosocial relative to

antisocial choices. Notably, OT infusions into BLA resulted in distinct changes in the ACCg-BLA coherence for prosocial and antisocial decisions - OT increased the ACCg-BLA coherence in the gamma band for prosocial choices but in the beta band for antisocial choices. Our results suggest that enhancing local OT processing in the BLA distinctively modulates neuronal synchronization between ACCg and BLA to guide prosocial and antisocial decisions.

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Nanosymposium

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Title: Face recognition ability in male infant monkeys predicts cerebrospinal fluid oxytocin concentrations later in life

Authors: *J. E. MADRID[1,2], O. OZTAN[1], V. SCLAFANI[4,6], L. A. DEL ROSSO[4], L. A. CALONDER[4], K. CHUN[4], J. P. CAPITANIO[4,5], J. P. GARNER[1,3], K. J. PARKER[1,4]
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Abstract: The ability to recognize individuals is a critical skill acquired early in life for group living species. In primates, individual recognition occurs predominantly through face discrimination. Despite the essential adaptive value of this ability, robust individual differences in conspecific face recognition exist, yet its underlying biology remains unknown. Although pharmacological administration of oxytocin has implicated this neuropeptide in face perception and social memory, no prior research has tested the relationship between individual differences in face recognition ability and endogenous oxytocin concentrations. Here we show in a male rhesus monkey cohort (N=60) that infant ability to recognize conspecific faces robustly predicts

cerebrospinal fluid, but not blood, oxytocin concentrations up to five years after behavioral assessment (WLS-GLM: $F_{1,57} = 13.86$; partial r = 0.45; P = 0.0005). These results argue that central oxytocin biology may mediate individual recognition abilities critical for group living, and that these differences are stable traits.

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Nanosymposium

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Title: Oxytocin and vasopressin promote social interaction in male but not female macaque monkeys

Authors: ***Y. JIANG**, M. PLATT
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Abstract: The neuropeptides oxytocin (OT) and arginine-vasopressin (AVP) shape social behavior in a wide array of mammals. In both human and nonhuman primates, OT delivered intranasally increases attention to others and promotes prosocial behavior, though the effects often vary across species and behavioral contexts. Little is known about how either neuropeptide influences unconstrained behavior outside of laboratory tasks, despite strong interest in using these neuropeptides to improve social function of patients with autism and other disorders in the real world. To address these issues, we administrated OT and AVP via aerosolized nebulization as well as intracerebral injection in both male and female rhesus macaques. We monitored behaviors of both monkeys in a pair after treating only one of the animals with OT, AVP, or saline. Intranasal OT treatment relaxed social interactions between males by suppressing aggressive behavior of dominant males and increasing the boldness of submissive males, effectively flattening the social hierarchy. OT also enhanced the effectiveness of social communication by increasing behavioral synchrony within the pair. Notably, OT altered the

behavior of not only the treated monkey but also his non-treated partner. These effects were largely recapitulated when OT was injected focally into the anterior cingulate gyrus (ACCg), a brain area previously linked to vicarious reward, empathy, and other-regarding behavior. These effects were reproduced, with greater efficacy, following AVP inhalation as well as its injection into ACCg. Together, these findings demonstrate that exogenous OT modulates social behavior in males in part via binding with presynaptic OT receptors or with AVP receptors in ACCg. By contrast, intranasal administration of both OT and AVP in female macaques resulted in completely different behavioral patterns. Most notably, both neuropeptides heightened the alertness of females during their interactions with males, but not with other females. OT and AVP both reduced the submissiveness of females when facing males and, simultaneously, decreased aggressive behavior of their untreated male partners. Unlike in male-male interactions, OT and AVP did not alter female behavior by increasing sensitivity to social cues. Both neuropeptides increased the likelihood that females would initiate behaviors such as threats. These findings show that increasing central levels of OT and AVP evoke different behavioral effects in male and female macaques, possibly via different neural pathways. Our results endorse a more careful examination of the neurobiology of these peptides especially in female primates.

Disclosures: Y. Jiang: None. **M. Platt:** None.

Nanosymposium

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**Topic: ***F.02. Behavioral Neuroendocrinology

Support: NSFC 31530032

Title: Sex- and context-dependent effects of oxytocin on social reward processing

Authors: *X. MA, B. BECKER, W. ZHAO, R. LUO, F. ZHOU, Y. GENG, L. XU, Z. GAO, X. ZHENG, K. KENDRICK
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Abstract: We interact socially and form bonds with others because such experiences are rewarding. However, an insecure attachment style or social anxiety can reduce these rewarding effects. The neuropeptide oxytocin (OXT) may facilitate social interactions either by increasing their rewarding experience or by attenuating anxiety, although effects can be sex- and attachment-style dependent[1-2]. We investigated whether OXT modulates the behavioral and

neural effects of shared experiences (with a friend or stranger vs alone) and if they are sex- or attachment style-dependent. We hypothesized that OXT would enhance the impact of sharing positive experiences and this would be associated with either increased reward- or decreased anxiety-related neural activity.
128 pairs of friends of the same sex (n =256) received either intranasal OXT (40IU) or placebo (PLC) in a randomized, double-blind, between-subject design. 45 min after treatment the friends completed the same procedure with one in an MRI scanner and the other in a separate testing room. In a sharing paradigm, subjects viewed pictures with different valence scenes and were told that they were viewing them alone (control condition) or together with a stranger, or their friend (sharing conditions). Subjects rated each picture for valence and arousal on a 1-9 scale. A repeated ANOVA analysis for valence ratings revealed a valence * drug interaction [$F_{(2,474)}$=3.17, P=0.043], with OXT increasing ratings for positive valence pictures. There was also a group (subjects in vs out of the scanner) * treatment * sex * condition * valence interaction [$F_{(2,474)}$=3.13, P=0.045], with OXT increasing ratings for positive valence picture stimuli shared with a friend in women, but not men, particularly in the subjects tested in the scanner. OXT effects in women were modulated by their attachment security. Behavioral OXT effects were accompanied by decreased insula and amygdala activity as well as their functional connectivity in women, but increases in men (P<0.05, FWE-corrected). OXT also uncoupled the positive association between attachment anxiety and amygdala activity when women shared pictures with their friend.
Our findings demonstrate that OXT facilitates the impact of sharing positive experiences with others. Its effects on sharing them with friends occur primarily in females and are modulated by attachment security. OXT effects in females were associated with attenuated activity in core anxiety circuitry hubs and uncoupling of the association between attachment anxiety and amygdala activity.
References
1. Gao S et al (2016) Proc Natl Acad Sci USA 113: 7650-7654.
2. Hurleman R & Scheele D (2017) Biol Psychiatry 79:185-193.

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Nanosymposium

644. Translational Studies With Opioids

Location: 143A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***644.01

**Topic: ***G.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA037344
Pearson Center for Alcoholism and Addiction Research

Title: Impact of prolonged inhibition and genetic deletion of fatty acid amide hydrolase (FAAH) on opioid dependence

Authors: *J. E. SCHLOSBURG[1], L. F. VENDRUSCOLO[2], B. F. CRAVATT[3], M. HEILIG[4], G. F. KOOB[5]
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Abstract: The usage rate of heroin, and subsequent incidence of opiate overdoses, has vastly increased over the past decade in the United States, tripling to quadrupling in the past 5-10 years alone. Based on an underpinning of previous studies examining the role of opiate dependence altering brain stress systems, and that chronic stressors result in upregulation of fatty acid amide hydrolase (FAAH) activity, we present data showing chronic FAAH inhibition by PF-3845 can blunt the escalation of intake and increased motivation for heroin in rat self-administration models. Furthermore, FAAH inhibition reduced corticosterone release during heroin withdrawal, prevented heroin-induced deficits in reward threshold evaluated using intracranial self-stimulation (ICSS), and reversed upregulation of FAAH in the basolateral amygdala in heroin-dependent rats.
To facilitate more efficient examination of the role of FAAH in response to chronic stressors, opiate intake, and prolonged withdrawal, a Wistar rat deficient in FAAH activity was generated using a zinc-finger nuclease targeted deletion around an end region of exon 1. Three founders were generated, and a rat with a stable 65bp deletion was bred successfully. Wild-type, heterozygous, and FAAH knockout Wistar rats are currently being evaluated for basic behavioral phenotypic differences in pain and anxiety response, as well as being bred for biochemical validation of the deletion using Western blot, activity-based protein profiling, and mass spectrometry of fatty acid amide levels.

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Nanosymposium

644. Translational Studies With Opioids

Location: 143A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***644.02

**Topic: ***G.08. Drugs of Abuse and Addiction

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Title: Optogenetic activation of specific gabaergic circuits in the ventral tegmental area

Authors: *K. BARCOMB[1], A. M. POLTER[2], A. C. TSUDA[1], J. A. KAUER[1]
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Abstract: DA cells in the VTA are essential mediators of reward. Drugs of abuse reduce the effectiveness of GABAergic synapses that regulate the excitability of VTA DA neurons. Previous studies generally considered the VTA as a whole; in reality it is a heterogeneous region with segregated populations of DAergic efferents that receive inputs from both locally originating VTA GABAergic cells and long-range GABAergic projections, such as from the rostromedial tegmental nucleus (RMTg). The circuit specificity of GABAergic regulation of DAergic cells in the VTA is largely unknown, both in terms of basic synaptic properties and with respect to the effects of drugs of abuse.

Here we compare GABAergic synapses in the VTA that originate in either the VTA or RMTg. GABAergic afferents were isolated by injecting AAV2-DIO-ChR2-eYFP into the VTA or the RMTg of VGAT-Cre mice. In imaging experiments of RMTg injected animals, cell bodies in the RMTg expressed YFP-ChR2 and displayed positive staining for FoxP1. Conversely, VTA-injected animals expressed YFP-ChR2 in cell bodies within the VTA but showed no fluorescence in the RMTg. Using whole cell electrophysiology, we compared basic synaptic properties of optically activated VTA or RMTg inputs onto VTA dopamine cells (identified by the presence of an I_h). Inhibitory postsynaptic currents (IPSCs) from GABAergic VTA inputs had a faster rise time (VTA: 1.0 ± 0.1 ms, RMTg: 1.3 ± 0.1 ms) and decay time constant than RMTg inputs (VTA: 4.6 ± 0.3 ms; RMTg: 5.6 ± 0.3 ms). GABAergic VTA inputs also had a smaller paired pulse ratio at 20 Hz (VTA: 0.76 ± 0.06, RMTg: 1.42 ± 0.33) and a higher average ratio comparing the last 3 pulses of a 10 pulse train at 5 Hz (VTA: 0.74 ± 0.07; RMTg: 0.47 ± 0.07), suggesting that VTA synapses have a greater initial release probability. Bath application of DNQX indicated that neither GABAergic input co-releases glutamate, though strychnine application indicated that RMTg inputs have a small glycinergic component (PSC amplitude: 70 ± 7 % Baseline). We also tested the two inputs for their capacity to undergo a form of nitric oxide-dependent GABAergic plasticity known as LTP_{GABA} (Polter et al., 2014). Interestingly, only VTA GABAergic inputs expressed LTP_{GABA} (LTP Magnitude: 129 ± 9% baseline), while this plasticity was not observed at RMTg inputs (89 ± 9% baseline). LTP_{GABA} is blocked by drugs of abuse, thus this drug-induced effect must be independent of RMTg synapses, as they lack the capacity for that form of plasticity. Taken together, our results show that GABAergic synapses originating from within the VTA have different basic synaptic properties as compared to those originating from the RMTg.

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644. Translational Studies With Opioids

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Support: Drug Enforcement Administration
National Center for Toxicological Research
University of Arkansas for Medical Sciences

Title: Pharmacological characterization of furanyl fentanyl: Radioligand binding and analgesia

Authors: *T. HIRANITA[1,2], A. J. JANOWSKY[3,4], A. J. ESHLEMAN[3,4], S. FUKUDA[2], K. URQUHART[2], C. PRIOLEAU[5], A. S. BALE[5], S. R. TELLA[5], M. G. PAULE[1], W. E. FANTEGROSSI[2]
[1]Neurotoxicology, NCTR/FDA, Jefferson, AR; [2]Pharmacol. and Toxicology, Univ. of Arkansas for Med. Sci., Little Rock, AR; [3]VA Med. Ctr., Portland, OR; [4]Psychiatry, and Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR; [5]Drug and Chem. Evaluation Section, Drug Enforcement Admin., Springfield, VA

Abstract: Recently the abuse of furanyl fentanyl, a designer drug structurally related to fentanyl, a mu-opioid receptor (MOR) full agonist, has been associated with numerous deaths in the United States. Currently, there is little or no published information regarding its pharmacological properties. Thus, the present study characterized its opioid-like activities *in vitro* and *in vivo*. In a radioligand binding assay using [^{3}H]DAMGO and the rat MOR stably expressed in CHO cells, furanyl fentanyl (Ki = 0.0279 ± 0.008 nM), similar to fentanyl (Ki = 0.15 ± 0.03 nM), had high binding affinity for MOR. Furanyl fentanyl had at least a 1,930-fold higher affinity for the MOR compared to the human kappa ([^{3}H]U69,593; Ki = 59.2 ± 6.4 nM) and delta ([^{3}H]DPDPE; Ki = 54 ± 15 nM) opioid receptors stably expressed in CHO cells. The Emax values for furanyl fentanyl and fentanyl in stimulating [^{35}S]GTPγS binding were 55.5 ± 4.3% and 81.2 ± 7.4% of DAMGO-stimulated activity, respectively. In addition, furanyl fentanyl stimulated [^{35}S]GTPγS binding in kappa opioid receptors with an Emax = 24.9 ± 1.5% at 10 uM but did not stimulate the delta opioid receptors at concentrations up to 10 uM. On the other hand, furanyl fentanyl (0.1-1.0 mg/kg, S.C., N=8 per group) produced dose-dependent increases in tail-flick latency up to a maximum of 10 seconds in Swiss Webster mice using warm water tail withdrawal procedures (55°C) but was approximately two-fold less potent than fentanyl [ED_{50} values (95% confidence limits): 0.246 (-0.284—0.488) and 0.132 (0.199—0.575) mg/kg (S.C.), respectively]. These increases in tail-flick latency were not due to motor disruption because the highest doses of furanyl fentanyl (1.0 mg/kg, S.C.) and fentanyl (0.3 mg/kg, S.C.) increased rather than decreased lcomotor activity above their vehicle-induced activity levels (N=8, each). The

analgesia produced by furanyl fentanyl (1.0 mg/kg, S.C.), similar to fentanyl (0.3 mg/kg, S.C.), was blocked by pretreatment with naltrexone, an opioid antagonist (10 mg/kg, S.C.). Thus, furanyl fentanyl had an analgesic effect and functioned as a full MOR agonist *in vivo*. Supported by the Drug Enforcement Administration, National Center for Toxicological Research (protocol # E0763601) and University of Arkansas for Medical Sciences. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Drug Enforcement Administration or the Food and Drug Administration.

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Nanosymposium

644. Translational Studies With Opioids

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Title: Intravenous heroin induces rapid brain hypoxia and hyperglycemia that precede brain metabolic activation

Authors: *E. SOLIS, JR, K. T. CAMERON-BURR, Y. SHAHAM, E. A. KIYATKIN
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Abstract: Heroin use and overdose have increased in recent years as people transition from abusing prescription opiates to using the cheaper street drug. Despite a long history of research, many physiological effects of heroin and their underlying mechanisms remain unknown. Here, we use high-speed amperometry to examine the effect of intravenous heroin on oxygen and glucose levels in the nucleus accumbens (NAc) in freely-moving rats. Heroin within the dose range of human drug use and rat self-administration (100-200 μg/kg), induced a rapid, strong, but transient drop in oxygen that was followed by a slow and prolonged rise in glucose. By obtaining oxygen and glucose recordings in the subcutaneous space, a densely-vascularized site with no metabolic activity, we confirmed that heroin-induced brain hypoxia results from decreased blood oxygen, presumable due to drug-induced respiratory depression. This effect and the associated rise in CO_2 levels appears to drive tonic increases in NAc glucose via local vasodilation. Heroin-induced changes in oxygen and glucose were rapid and preceded the slow and prolonged increase in brain temperature and were independent of enhanced intra-brain heat production, an

index of metabolic activation. A very high heroin dose (3.2 mg/kg), corresponding to doses used by experienced drug addicts in overdose conditions caused strong and prolonged brain hypoxia and hyperglycemia coupled with robust initial hypothermia that preceded an extended hyperthermic response. Our data suggest heroin-induced respiratory depression as a trigger for brain hypoxia, which leads to hyperglycemia, both of which appear independent of subsequent changes in brain temperature and metabolic neural activity.

Disclosures: E. Solis: None. **K.T. Cameron-Burr:** None. **Y. Shaham:** None. **E.A. Kiyatkin:** None.

Nanosymposium

644. Translational Studies With Opioids

Location: 143A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***644.05

**Topic: ***G.08. Drugs of Abuse and Addiction

Support: CIHR

Title: Expression of connexin-36 gap junctions in the ventral tegmental area is necessary for the development of opiate dependent motivation

Authors: *G. MAAL-BARED[1], M. BERGAMINI[2], M. YEE[3], M. PATEL[4], D. VAN DER KOOY[2]
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Abstract: The ventral tegmental area (VTA) is a midbrain structure that is crucial for adaptive and maladaptive motivated behaviours such as eating and chronic drug-seeking. This region houses a population of GABA neurons that serve as a point of divergence between two dissociable pathways that mediate drug reinforcement in drug-nondependent and drug-dependent animals. Descending projections to the tegmental pedunculopontine nucleus (TPP) are necessary for morphine-conditioned place preferences (mCPP) in opiate-naïve but not opiate-dependent animals, whereas ascending mesoaccumbal dopamine (DA) outputs are necessary for mCPP in opiate-dependent but not opiate-naïve animals. The switch to a dependent motivational state involves a disruption in chloride homeostasis in VTA GABA neurons. Thus, furosemide, a blocker of the chloride exporter KCC2, switches the substrates underlying morphine motivation from TPP to mesolimbic DA in rats with no prior drug exposure. Here, we report that the expression of connexin-36, a gap junction-expressing protein, in the VTA is necessary for the manifestation of opiate-dependent motivation. Injections of the Cx36 blocker, mefloquine, into

the VTA of opiate-dependent rats results in a reversion to an opiate-naïve state such that mCPP is mediated by the TPP and withdrawal aversions are abolished. Intra-VTA infusions of a cocktail composed of mefloquine and furosemide in naïve rats sustains their naïve state, suggesting a downstream role of Cx36. Moreover, preliminary results suggest that knocking out Cx36 in GABA neurons produces a perpetual drug-naïve state wherein mCPP is always mediated by the TPP. These results demonstrate the necessity of VTA GABA electrical coupling for the switch to a drug dependent motivational state.

Disclosures: G. Maal-Bared: None. **M. Bergamini:** None. **M. Yee:** None. **M. Patel:** None. **D. van der Kooy:** None.

Nanosymposium

644. Translational Studies With Opioids

Location: 143A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***644.06

**Topic: ***G.08. Drugs of Abuse and Addiction

Title: GABRA2 variations affect deficient structural connections of reward driving-control circuit in heroin abusers

Authors: *Y. SUN[1], Y. ZHANG[1], D. ZHANG[2], L. LU[1], Y. FAN[3], J. SHI[1]
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Abstract: Introduction: Drug addiction would arise from imbalance of two opponent processes in the reward circuit: hyperactive reward driving and poor reward control. However, reliable neuroimaging evidence for this hypothesis is still insufficient. Here we want to investigate the structural connectivity characteristics and driving-control subnetwork patterns of the dysfunctional reward circuit in heroin abusers and to screen its genetic risk factors.
Methods: Twelve reward-related brain areas were identified through a systematic literature review, and further grouped into two subnetworks: reward control and reward driving. Diffusion tensor imaging (DTI) and behavioral data were collected from 78 heroin abusers and 79 healthy controls. Structural connecitions between these brain areas were measured using a probabilistic fiber tracking method based on the DTI data. Twenty two candidate genetic loci, which may modulate the reward circuit, were delineated by reviewed the genetic variants of opioid addiction and screened using imaging-genetic analyses. Then the results were validated in a large-sample genetic association (1,035 heroin abusers and 2,887 healthy controls) and expanded-variants analysis.

Results: Significant decreased connectivity strength in 131 connections of the reward circuit was observed the heroin abusers and the connectivity strength was positively correlated with cognition score. Heroin addiction caused deficiency both in the reward driving and control subnetworks. Among all candidate locis, we only found *GABRA2* rs279858 was interacted with heroin addiction to affect the reward circuit. The rs279858 G allele carriers had weaker connectivity strength than the A allele carriers in healthy controls, but the protective effects of A allele on the reward circuit was weaken in heroin abusers. Then we further validated the rs279858 G allele was more distributed in heroin abusers. Besides, the rs693547, rs519270 and rs279871, which in a strong linkage-block with rs279858, also had interactive effects on reward network of heroin abusers.
Conclusion: Heroin abusers had widespread hypoconnections in the structural reward network, which might be synchronously caused by disruption of the reward driving system and reward control system. The *GABRA2* variants may a key factor for modulating the dysfunctional reward circuit in addiction.

Disclosures: Y. Sun: None. **Y. Zhang:** None. **D. Zhang:** None. **L. Lu:** None. **Y. Fan:** None. **J. Shi:** None.

Nanosymposium

644. Translational Studies With Opioids

Location: 143A

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 9:45 AM

**Presentation Number: ***644.07

**Topic: ***G.08. Drugs of Abuse and Addiction

Support: Norwegian Research Council Grant 196621/V50

Title: Phosphorylation of alpha-CaMKII at Thr286 is not required for the acquisition of morphine-induced condition place preference in mice

Authors: *F. BOIX[1], S. H. OPDAL[1], C. P. MUELLER[2], J. M. ANDERSEN[1]
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Abstract: Background: Conditioned Place Preference (CPP) is a procedure where the environment and associated stimuli are coupled with the subjective and behavioral effects of a drug, modeling the association learning mediating the approach to drug conditioned stimuli. This association might be central in triggering new drug intake (1). This association learning is mediated by stimulation of dopaminergic mesolimbic circuits projecting to striatal neurons that undergo long-term synaptic changes. Activation of Calcium/calmodulin-dependent protein

kinase II (CaMKII), by phosphorylation at Thr286, has been shown to be important for synaptic plasticity processes to occur. The aim of the present study was to examine the possible role of the alpha isoform of CaMKII (αCaMKII) and its autophosphorylation at Thr286 (p-αCaMKII) in the establishment of CPP induced by morphine. **Methods:** First, we examined the effects of 10 or 30 μmol/kg morphine on αCaMKII, p-αCaMKII, and β-actin levels in dorsal and ventral striatum, and hippocampus in C57BL/6J mice after morphine-CPP acquisition or after a subchronic treatment regime mimicking the CPP administrations. In a subsequent experiment, the acquisition of CPP using the same morphine doses was tested in autophosphorylation deficient αCaMKIIT286A mice (2). **Results:** In mice exposed to the morphine-CPP procedure, the levels of αCaMKII and β-actin were significantly increased in the three brain areas studied but p-αCaMKII levels were not significantly affected. No significant changes were found in any of these proteins in the animals receiving only the subchronic morphine treatment. No differences were observed in the expression of CPP induced by morphine between αCaMKIIT286A, wild type, and the mice exposed to CPP in the first experiment. **Conclusions:** These results indicate that CPP induced by morphine does not require phosphorylation of αCaMKII at Thr286. This is in contrast with cocaine-induced CPP, which is impaired in αCaMKIIT286A mice (3). However, morphine-induced CPP was accompanied by increases in the levels of β-actin and overall αCaMKII, indicating a possible activation of processes implicated in synaptic plasticity involving other paths than αCaMKII Thr286 phosphorylation. Besides, the changes in β-actin and αCaMKII were observed not only in striatum but also in hippocampus, indicating that this area is also recruited during CPP acquisition. **References** (1) Bardo MT and RA Bevins, 2000 Psychopharmacology (Berl) 153: 31-4; (2) Giese KP et al., 1998 Science 279: 870-73; (3) Easton AC et al., 2014 Transl Psychiatry 4: e457

Disclosures: F. Boix: None. **S.H. Opdal:** None. **C.P. Mueller:** None. **J.M. Andersen:** None.

Nanosymposium

645. Cognitive Development and Numerical Cognition

Location: 156

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***645.01

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH Grant HD047520
NIH Grant HD059205

Title: Failure to neurally differentiate between addition and subtraction problems as a key neurocognitive feature of developmental dyscalculia

Authors: *T. IUCULANO[1], J. NICHOLAS[1], T.-T. CHANG[2], A. METCALFE[3], V. MENON[4]
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Abstract: Neurodevelopmental cognitive deficits, including learning difficulties, are the result of aberrations in multiple brain systems that support successful skill acquisition. Developmental Dyscalculia (DD) is a neurocognitive deficit in acquiring adequate arithmetical skills in the context of otherwise normal intelligence and appropriate education. Although brain systems' aberrancies in DD have been characterized at the structural and functional level, their underlying neural representations are virtually unknown. Here we use multivariate representational similarity (MRS) analyses on functional magnetic resonance imaging (fMRI) data acquired during different types of arithmetic problem solving tasks to assess, for the first time, neural representational deficits in DD. We show that 7-9-year-old children with DD exhibit aberrant neural representations for addition and subtraction problems compared to IQ, age, gender, reading, and working memory-matched typically developing (TD) peers. Specifically, DD children displayed higher MRS values between addition and subtraction problems, suggesting difficulties to appropriately differentiating between these problem-types at a critical stage of mathematical skill development, which is characterized by divergence of strategy-use between arithmetical operations. Critically, multivariate representational similarity effects were evident in regions important for mathematical cognition, including the posterior parietal cortex and the lateral temporal and prefrontal cortices. Together, these results provide novel evidence of neural representational deficits in DD, suggesting that failure to properly differentiate between addition and subtraction problems might be at the core of their arithmetic difficulties.

Disclosures: T. Iuculano: None. **J. Nicholas:** None. **T. Chang:** None. **A. Metcalfe:** None. **V. Menon:** None.

Nanosymposium

645. Cognitive Development and Numerical Cognition

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**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***645.02

**Topic: ***H.02. Human Cognition and Behavior

Support: NSF Grant DUE1534830

Title: Symbolic number comparison in 5- to 9-year-old children: Age-related changes in event-related potentials and their relation to formal math abilities

Authors: *R. LIU, E. BRAHAM, M. LIBERTUS
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Behavioral studies have shown that understanding symbolic numbers is a predictor of children's math abilities. At the neural level, a posterior, positive event-related potential (ERP) peaking around 250-400 ms post-stimulus in children, also called the P2p, has been identified as sensitive to numerical information. However, earlier studies have focused on processing of single-digit numbers. In the present study, the first goal was to examine age-related changes in the neural bases of double-digit number processing in 5- to 9-year-old children who are in the process of learning the meaning of double-digit Arabic numerals. The second goal was to examine the relation between the knowledge of symbolic numbers as measured via ERPs and children's math abilities. To this end, 41 children (mean age = 8.2 years, range: 5.5 - 9.8 years) completed a symbolic number comparison task while their EEGs were recorded. On each trial, children saw 2 Arabic numerals and were asked to indicate the larger number. One third of all trials consisted of 2 single-digit numerals, one third consisted of double-digit numerals in which both the decade and unit numerals consistently indicated the larger number (e.g., 15 vs 28; Congruent condition), and one third consisted of double-digit numerals in which the unit numeral in the overall smaller Arabic numeral was larger than the unit numeral in the overall larger Arabic numeral (e.g., 15 vs 24; Incongruent condition). Orthogonally, the ratios between the 2 numerals varied to create different levels of task difficulty. Children also completed 3 standardized math tests (WJ-III Math Fluency, Calculation, and Applied Problems subtests). During the P2p time window, the easiest ratio elicited significant higher amplitudes compared to the other ratios over right posterior scalp sites. Additionally, several centro-frontal sites showed sensitivity to congruency during multiple time windows (170-300 ms, 600-800 ms). Overall, the Congruent condition had significantly higher amplitudes than the Incongruent condition. We found no link between P2p amplitude differences for easy and hard ratios and age, but significant correlations between the ERP differences for the Congruent and Incongruent conditions between 600-800 ms and children's age (r = .322). Finally, we found a marginal correlation between the P2p amplitude differences for easy and hard ratios and children's scores on the Applied Problems subtest (r = .268). These findings suggest that children's neural responses to symbolic numerical information change as they learn the meaning of double-digit numbers and that these neural responses are linked to their math abilities.

Disclosures: R. Liu: None. **E. Braham:** None. **M. Libertus:** None.

Nanosymposium

645. Cognitive Development and Numerical Cognition

Location: 156

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***645.03

**Topic: ***H.02. Human Cognition and Behavior

Support: NSERC
CIHR

Title: Arithmetic, visuo-spatial working memory, and basic number processing skills undergo common age-related changes within the left IPS

Authors: *A. MATEJKO[1], D. ANSARI[2]
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Abstract: Previous literature has consistently demonstrated that the intraparietal sulcus (IPS) is recruited during the solution of arithmetic problems. The role of the IPS during arithmetic could be multifaceted, because independent neuroimaging studies have shown that the IPS is recruited for visuo-spatial working memory (VSWM) and basic number processing. Therefore, brain activity in the IPS could be a product of domain general or domain specific processes, or a combination of the two. However, our understanding of how arithmetic, VSWM, and number processing are interrelated at the neural level remains limited because no research has examined these abilities within the same sample of participants. Furthermore, it remains unclear as to whether these skills undergo common age-related changes within the cortex. To address these questions, we investigated the neural correlates of arithmetic, VSWM, and basic number processing within a sample of children (n = 35, ages 7-10) and adults (n = 26, ages 19-26). A conjunction analysis was used to identify the statistical overlap in brain activity and revealed that arithmetic, VSWM, and basic number processing elicited brain activity in the bilateral IPS in children and the left IPS in adults. Moreover, adults recruited the left IPS more than children for all three tasks. These findings indicate that IPS is an important brain region for domain general and domain specific skills in arithmetic, and that the role of the IPS during arithmetic is multifaceted. Furthermore, these findings challenge domain-specific accounts of left IPS activation. We discuss how the developmental emergence of left-lateralization for all three tasks could be a product of domain specific changes in the processing of symbolic numbers or could reflect other changes to the organization of the brain that constrain the way information is processed across domains. We also discuss the implications of this research for our understanding of the atypical development of mathematical skills.

Disclosures: **A. Matejko:** None. **D. Ansari:** None.

Nanosymposium

645. Cognitive Development and Numerical Cognition

Location: 156

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**Presentation Number: ***645.04

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH Grant MH101394
NIH Grant MH084164
NIH Grant HD047520

Title: Anterior hippocampal activity increases support math fact learning in children

Authors: *M. J. ROSENBERG-LEE[1], J. B. KANG[2], H. WAKEMAN[3], V. MENON[2]
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Abstract: Growing evidence suggests that the hippocampus is involved when children learn to retrieve math facts. However, whether these changes are directly related to specific educational experiences, or general maturational processes, remains unknown. Previously, we found that anterior hippocampal activity increased over a 1.2 year period from ages 8 to 9 (Qin, 2014), a key period for the acquisition and mastery of math facts. More recently, we examined the effects of an 8-week training program that emphasized conceptual, strategic and speeded practice of single-digit addition facts. Training recapitulated the pattern of anterior hippocampal activity increases, suggesting that behavioral improvements were driven by the memorization components of the program. To test the hypothesis that longitudinal and training related hippocampal changes during arithmetic problem solving are related to educational experiences, we developed a program specifically focused on speeded practice of math facts. Nineteen children, aged 8-11 years, participated in a 5-day training program involving computer games, flashcards and pencil-and-paper practice to repeatedly solve a set of 14 problems, 70 times. Problems were drawn from the set of double- plus single-digit addition problems (e.g., 9 + 47 = 56), which are unlikely to be retrieved prior to training (rather than single-digit problems, where children can differ in initial knowledge levels). Training significantly improved accuracy, reaction times and retrieval rates. During an initial functional imaging session, children were presented with 28 problems, half of which were subsequently trained (sets counterbalanced across participants). Following training, the Trained problems - relative to Untrained problems - elicited greater activity in the left anterior hippocampus. Notably, this region overlapped with the area showing increased activity following eight weeks of more varied training. In contrast to a recent study in adults which found that greater hippocampal activity for Trained, relative to Untrained, problems was driven by deactivation for Untrained problems after training, we found

increases in hippocampal activity only for the Trained problems. Together, these results highlight the specific role of the anterior hippocampus in the acquisition of math facts in childhood.

Disclosures: **M.J. Rosenberg-Lee:** None. **J.B. Kang:** None. **H. Wakeman:** None. **V. Menon:** None.

Nanosymposium

645. Cognitive Development and Numerical Cognition

Location: 156

Time: *Wednesday, November 15, 2017, 8:00 AM - 10:00 AM

Presentation Number: *645.05

Topic: *H.02. Human Cognition and Behavior

Title: The effect of visual parameters on neural activation during nonsymbolic number comparison and its relation to math competency

Authors: ***E. D. WILKEY**[1], J. C. BARONE[1], M. M. M. MAZZOCCO[3], S. E. VOGEL[4], G. PRICE[2]
[1]Dept. of Psychology & Human Develop., [2]Vanderbilt Univ., Nashville, TN; [3]Inst. of Child Develop., Univ. of Minnesota, Minneapolis, MN; [4]Educational Neuroscience, Inst. of Psychology, Univ. of Graz, Graz, Austria

Abstract: Nonsymbolic numerical comparison tasks (whereby a participant judges which of two groups of objects is numerically larger) are thought to index the efficiency of neural systems supporting numerical magnitude perception. Performance on such tasks has been related to individual differences in math competency. However, a growing body of research suggests that task performance is heavily influenced by visual cues of the stimuli (e.g. surface area and dot size of object sets) such that the correlation with math is driven by performance on trials with incongruent visual cues. Almost nothing is currently known about whether the neural correlates of nonsymbolic magnitude comparison are also affected by visual congruency. To investigate this issue, we used functional magnetic resonance imaging (fMRI) to analyze neural activity during a nonsymbolic comparison task as a function of visual congruency in a sample of typically developing high school students (n = 38). Further, we investigated the relation to math competency as measured by the preliminary scholastic aptitude test (PSAT) in 10th grade. Our results indicate that neural activity was modulated by the ratio of the two dot sets being compared in brain regions previously shown to exhibit a ratio effect when calculated from the average of congruent and incongruent trials, as it is in most studies, and that the ratio effect within those regions did not differ as a function of congruency condition. However, there were significant differences in overall task-related activation as well as ratio-dependent activation when congruent and incongruent conditions were contrasted at the whole-brain level. Further,

math competence correlated positively with ratio-dependent neural activation patterns in the right supramarginal gyrus (during congruent trials) and negatively with ratio-dependent neural activation patterns in the left angular gyrus (during incongruent trials), as well as with reaction time. Together, these findings support the idea that performance on the nonsymbolic comparison task relates to math competency, but that congruent and incongruent trials differentially recruit ratio-dependent neural mechanisms and have distinct relations to math competence.

Disclosures: E.D. Wilkey: None. **J.C. Barone:** None. **M.M.M. Mazzocco:** None. **S.E. Vogel:** None. **G. Price:** None.

Nanosymposium

645. Cognitive Development and Numerical Cognition

Location: 156

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***645.06

**Topic: ***H.02. Human Cognition and Behavior

Support: NICHD R01 HD088585

Title: The ratio processing system (RPS) as a foundation for symbolic fractions understanding

Authors: J. V. BINZAK, E. Y. TOOMARIAN, *E. M. HUBBARD
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Abstract: Despite their critical role in the acquisition of higher-order math skills, many students struggle with fractions. Some researchers (e.g., Dehaene, 1997/2011) have argued that fractions are difficult because they do not build on any pre-existing brain system. Other research (e.g., Jacob, Vallentin & Nieder, 2012) has shown that non-human primates have the ability to compare nonsymbolic ratios, and that this ability depends on circuits in the intraparietal sulcus. We have recently argued that this ratio processing system (RPS) is adapted to perceiving nonsymbolic ratios (e.g. the ratio of two line lengths; Lewis, Matthews & Hubbard, 2015), and that it provides an underappreciated neurocognitive startup tool upon which the meaning of symbolic fractions (e.g. ¾) can be built. Although previous studies have demonstrated that the intraparietal sulcus (IPS) and prefrontal cortex (PFC) are involved in processing nonsymbolic ratios and symbolic fractions, no experiment has directly compared activation for these two classes of stimuli in the same participants, or how symbolic fraction and nonsymbolic ratio processing develop with age. We tested the hypothesis that processing symbolic fractions builds on the RPS by having 24 healthy right-handed adults compare the magnitudes of two fractions in three conditions (symbolic fractions, line ratios, or mixed pairs) during an event-related fMRI paradigm. Distance effects were observed in all three notation conditions; participants were

faster and more accurate as the numerical distance between pairs increased. Additionally, adults were faster to compare line ratios than either condition containing symbolic fractions, suggesting that they could not be translating the nonsymbolic ratios to symbolic fractions. Critically, we observed overlapping neural distance effects in bilateral IPS regions for all three conditions, with fMRI activation closely paralleling RT distance effects, using both whole brain analyses and a priori ROIs in the IPS (Arsalidou & Taylor, 2011). These results suggest that, in adults, processing of symbolic fractions and nonsymbolic ratios relies on common neural regions sensitive to ratio magnitudes. We are currently extending the same fMRI task to test the hypothesis that the RPS plays a foundational role in grounding early symbolic fractions knowledge. We compared performance and neural activation between 2nd grade students with little fractions knowledge and 5th grade students who have received formal fractions instruction, and find similar behavioral and neural distance effects, but also note important differences between 2nd and 5th graders, consistent with the RPS account.

Disclosures: J.V. Binzak: None. **E.Y. Toomarian:** None. **E.M. Hubbard:** None.

Nanosymposium

645. Cognitive Development and Numerical Cognition

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**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:00 AM

**Presentation Number: ***645.07

**Topic: ***H.02. Human Cognition and Behavior

Support: NICHD Grant 5R01HD079106

Title: The distinct and shared neural substrates associated with approximate and exact addition

Authors: *S. D. BUGDEN[1], M. G. WOLDORFF[3], E. M. BRANNON[2]
[1]Psychology, [2]Univ. of Pennsylvania, Philadelphia, PA; [3]Ctr. Cognitive Neurosci, Duke Univ., Durham, NC

Abstract: The proposal that the neural underpinning for mathematical thinking relies upon evolutionarily ancient brain regions that support primitive number sense has been much debated within the field of mathematical cognition. The bilateral intraparietal sulcus (IPS) is consistently activated independent of format for basic numerical processing tasks and arithmetic computations. In contrast, language related brain regions within the left temporal and parietal lobes are associated with the visual processing of numerals and the retrieval of single digit arithmetic facts, suggesting a double dissociation between approximate and exact arithmetic (Dehaene et al., 1999). To further examine the relationship between the neural representation of approximate nonsymbolic and exact symbolic arithmetic, we used high resolution fMRI while 25

young adults (age range: 18-34 years) completed well-matched approximate non-symbolic and double-digit symbolic addition verification problems, as well as color-matching control tasks. On addition trials, participants mentally summed two sequentially presented visual-dot arrays (approximate addition) or two double digit numerals (symbolic addition) and indicated whether a third presented value (dot array or numeral, respectively) was the correct sum or not. On the control color tasks, participants indicated whether a third stimulus (dot array or letters) matched either of the first or second stimulus in color. Whole brain contrasts (subtracting activity associated with each respective control task) revealed a network of regions associated with approximate nonsymbolic arithmetic that included the bilateral IPS, bilateral inferior temporal gyri (ITG), as well as the right inferior gyrus (IFG) and right insula. Similar regions were activated for precise symbolic addition, with additional clusters found in frontal and temporal lobes, including the supramarginal gyrus. A conjunction analysis of the approximate and symbolic addition tasks revealed common activation in the bilateral IPS and, notably, the bilateral ITG. Common activity in the bilateral IPS suggests recruitment of abstract numerical representations common to the addition operation, whereas only exact symbolic addition recruited language related brain regions in the temporal lobe. Previous studies have implicated the bilateral ITG for the visual encoding of symbolic numerals and single-digit addition (Daitch et al., 2016. The present study is the first to demonstrate that the ITG plays a role in the operation of both non-symbolic approximate and exact symbolic representations, suggesting a role for the ITG in supporting abstract arithmetic operations.

Disclosures: S.D. Bugden: None. **M.G. Woldorff:** None. **E.M. Brannon:** None.

Nanosymposium

645. Cognitive Development and Numerical Cognition

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**Topic: ***H.02. Human Cognition and Behavior

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Title: Children's neural representations of count words emerge from numerosity representations in parietal cortex

Authors: *A. J. KERSEY, J. F. CANTLON
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Abstract: Learning to map numerical symbols (e.g., number words) onto their quantitative meanings is a key step in the acquisition of formal mathematics. Some behavioral work suggests that evolutionarily-primitive numerosity representations may play a role in the acquisition of numerical symbols, but this work has been inconclusive. Another approach is to test for functional overlap in the neural representations underlying numerosity processing and counting sequences in children who are learning to count. To date there are no neural data examining counting acquisition in human children. If regions that support numerosity processing are important for the acquisition of the counting sequence, then there should be functional overlap of these representations before children have mastered the count list. Specifically, this overlap is expected in the intraparietal sulcus (IPS), which represents numerosities in early childhood and numerical symbols in children who have learned to count. However, previous work in monkeys suggests that inferior frontal cortex might also play an important role in the acquisition of numerical symbols. Alternatively, number words may be acquired in word-processing regions such as middle temporal cortex. Here, we used functional magnetic resonance imaging (fMRI) to first identify primitive numerosity processing regions in 3- to 5-year-old children during a numerosity comparison task. A contrast of difficult versus easy numerosity ratio revealed a numerosity processing network including bilateral intraparietal sulcus (IPS), bilateral inferior frontal cortex, and anterior cingulate cortex (ACC). To identify neural representations of counting, we measured changes in BOLD signal while those same participants listened to the verbal count sequence and the alphabet. We found that the bilateral IPS supported representations of numerosities and counting sequences, but not alphabet sequences. These same regions were also recruited more for number words outside of children's counting range (i.e., unknown count words), suggesting that IPS is important for the acquisition of count words. Taken together, this is the first neural evidence that evolutionarily-primitive numerosity processing regions of the brain are functionally related to the acquisition of counting over child development.

Disclosures: **A.J. Kersey:** None. **J.F. Cantlon:** None.

Nanosymposium

646. Human Studies of Circuits and Systems in Schizophrenia and in First Episode Psychosis

Location: 147A

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Topic: *H.03. Schizophrenia

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Strategic Research Program for Brain Sciences by MEXT

Title: Two network model of aberrant salience in schizophrenia

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Abstract: The precise mechanisms underlying schizophrenia are still unclear. Recently, attribution of aberrantly heightened salience to daily-life stimuli is proposed as the critical process underlying pathogenesis of schizophrenia, and a hyper-activity in the medial temporal lobe-striatal network is indicated to underlie this aberrant salience attribution. Separately, neuroimaging studies have revealed the “salience network”, which comprises the insula and anterior cingulate cortex (ACC), and underlies the processing of stimulus salience. Abnormal functioning in this network has been indicated in schizophrenia. However, no previous studies have investigated the relationship between these two salience-associated mechanisms in the human brain and its abnormality in schizophrenia.
In the current study, we recruited 29 ultra-high-risk for psychosis (UHR) subjects, 53 first-episode psychosis (FEP) patients, and 48 chronic schizophrenia (Chr-SZ) patients as well as matched healthy control (HC) subjects. We performed within- and between-network functional connectivity analysis of resting-state functional magnetic resonance imaging data, using independence component analysis. In this study, we focused on connectivity within/between the insula-ACC salience network (SN), basal ganglia network (BGN) and medial temporal lobe network (MTLN). Statistical threshold was set at $p<0.05$, family-wise error rate correction over space as well as the number of networks and contrasts.
We found significant positive correlation between the SN and BGN and between the SN and MTLN in HCs. Within- and between-network connectivity among these three networks were differently abnormal in UHR, FEP, and Chr-SZ subjects compared with HCs.
Based on these findings, we propose a two-network model of salience in the human brain and its different abnormalities in different stages of schizophrenia. Consideration of disease stages is required for the success of biomarker research and precision medicine of schizophrenia.

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Nanosymposium

646. Human Studies of Circuits and Systems in Schizophrenia and in First Episode Psychosis

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**Presentation Number: ***646.02

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Title: Schizophrenia biomarker using whole brain resting-state functional connectivity MRI: Generalization to independent cohorts from different countries and disorder stages

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Abstract: Although a large number of classifiers have been developed to discriminate schizophrenia from healthy controls using whole brain resting-state functional MRI (rs-fMRI), it is not clear whether the classifiers generalize to different countries, MRI scanners, diagnoses, and stages of schizophrenia in completely independent cohorts. We developed a schizophrenia spectrum disorder (SSD) classifier based on functional connectivity (FC) from Japanese rs-fMRI datasets from two sites in Kyoto. A total of 68 patients with SSD and 102 healthy controls in two sites participated in the present study and scanned by Siemens Trio and TimTrio. The 16 FCs were selected as the SSD classifier by machine-learning technique. The SSD classifier showed high accuracies (74% and 77%) in two sites in Kyoto. We tested the generalizability of the SSD classifier to two independent cohorts: COBRE (Center for Biomedical Research Excellence, University of New Mexico, USA) scanned by Siemens TimTrio and UMCU-TOPFIT (The Outcome of Psychosis and Fitness Therapy, University Medical Centre Utrecht, the Netherlands) scanned by Philips Achieva. The Japanese SSD classifier exhibited high values of area under the curve for COBRE (0.75) and UMCU-TOPFIT (0.66). Kyoto, COBRE, and UMCU-TOPFIT cohorts mainly consisted of patients in chronic stage, and we investigated whether the chronic SSD classifier generalizes to a first episode cohort: JHU-FES (Johns Hopkins University, USA) scanned by Philips Achieva. The classifier did not generalize to JHU-FES with area under the curve of 0.42. Furthermore, we examined whether the SSD classifier is also applicable for other psychiatric disorders (autism spectrum disorder: ASD, attention-deficit hyperactivity disorder: ADHD, and major depression disorder: MDD). The classifier did not distinguish other psychiatric disorders from healthy controls. The SSD classifier developed using Japanese participants could generalize to two completely independent validation cohorts from different countries and MRI scanners. The classifier was specific to chronic patients, and did not generalize either to first episode schizophrenia or to other psychiatric disorders (ASD, ADHD, and MDD).

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Nanosymposium

646. Human Studies of Circuits and Systems in Schizophrenia and in First Episode Psychosis

Location: 147A

Time: * Wednesday, November 15, 2017, 8:00 AM - 10:45 AM

Presentation Number: * 646.03

Topic: * H.03. Schizophrenia

Title: Characterization of first episode psychosis by integrative analysis of multiple MRI contrasts

Authors: *A. V. FARIA[1], N. CASCELLA[5], M. I. MILLER[2], S. MORI[3], A. SAWA[4]
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Abstract: Neuroimaging by MRI has been one of the most active areas of the psychiatric research, producing a large body of descriptive results. However, it has been difficult to identify image discriminating factors that can strongly represent the underlying pathology or phenotypes. To reduce the large amount of information from voxel-level to a much smaller "feature" vector (or matrix) with the minimum loss of disease-relevant features may increase the impact of neuroimaging in clinical scenarios. In this study, we performed dimension reduction and integration of high-resolution T1-weighted images, diffusion tensor imaging - DTI, and resting state functional MRI - rfMRI, through multi-atlas segmentation and structure-based integrative analysis. We tested its value on capturing cross-sectional features of 78 patients in their first episode of psychosis (FEP). The groups (FEP and controls) were compared on features selected by Lasso and covariates (age, gender, race, years of education) by ANOVA, error rate at 0.05 (Bonferroni corrected). The anatomic-connectivity pattern of FEP patients was marked by dilatation of the Sylvian fissure (possibly because of abnormalities in plannun temporally and Insula atrophy), abnormalities in DTI indices in deep white matter structures (i.e., thalamic radiations and corpus callosum), and differences in functional connectivity among thalamus, insula, lingual, precuneus, superior parietal, inferior and middle temporal, medium occipital, inferior frontal, supramarginal, post- and pre- central, anterior cingulate, and fronto-orbital gyri. In addition of confirming previous observations, this pattern provides new insights about the substrates of the disease, the anatomical pattern of FEP, as well as the possibility of binning the entity in more homogeneous phenotypes. The dimensional reduction by the structure-based analysis as well as the integration of multiple MRI features is a promising strategy for the characterization of FEP patients

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Nanosymposium

646. Human Studies of Circuits and Systems in Schizophrenia and in First Episode Psychosis

Location: 147A

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**Presentation Number: ***646.04

**Topic: ***H.03. Schizophrenia

Title: 7T MRS on multiple brain metabolites in the first episode psychosis: Neuronal impairment and neurotransmitter abnormalities

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Abstract: **Purpose** To investigate neurochemical changes using 7 Tesla MRS in patients with first episode psychosis (FEP) and compare to healthy control subjects. **Methods** 78 FEP patients (age: 22.3±4.4 years; 55 males) and 95 healthy controls (age: 23.5±4.0 years; 44 males) were recruit to date. FEP patients were all on antipsychotic medications. Spectra were recorded from five brain regions (anterior cingulate cortex (ACC), left centrum semiovale (CSO), left dorsolateral prefrontal cortex (DLPFC), left orbitofrontal cortex (OFC), and bilateral thalamus (Thal)) on a 7T scanner (Philips 'Achieva', Netherlands) using the STEAM sequence (TE/TM/TR = 14/33/3000 ms) and were analyzed using the LCModel software package. Concentrations of gamma-aminobutyric acid (GABA), glutamate (Glu), glutamine (Gln), glutathione (GSH), lactate (Lac), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), total choline (tCh), total NAA (tNAA), total creatine (tCr), the sum of inositol and glycine (Ins+Gly) and the sum of Gln and Glu (Glx) were calculated and compared between patients and controls using unpaired t-tests. The p-values were corrected by false discovery rate (FDR) and the results with $p<0.05$ were considered significant. **Results** A reduced metabolite levels (except Gln, Lac and tCho) was found in FEP patients. NAA or tNAA has the strongest reduction in multiple brain regions (~5%, $p<0.001$), suggesting significant neuronal loss or dysfunction. Unlike the other metabolites, Gln and Lac show a trend to increase in the FEP group. These may reflect several different possible mechanisms, including abnormal Glu/Gln cycling, increased Gln synthesis secondary to NMDA receptor hypofunction or other reasons, and (for Lac) impaired oxidative glycolysis. **Conclusion** Metabolite levels measured by 7T MRS suggest neuronal damage or dysfunction, disrupted glutamatergic metabolism and oxidative glycolysis in multiple brain regions in FEP patient, which could be helpful to understand the pathophysiology of FEP/schizophrenia.

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**Presentation Number: ***646.05

**Topic: ***H.03. Schizophrenia

Support: NIH

Title: Abnormality of resting-state functional connectivity in right insular cortex in patients with first episode psychosis

Authors: *H. KUGA[1], A. V. FARIA[2], L. SHAFFER[1], J. CRAWFORD[1], T. OGARU[1], D. J. SCHRETLEN[1], S. MORI[2], A. SAWA[1]
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Abstract: The insula is involved in detecting the salience of internal and external stimuli, and it plays a critical role in psychosis. Previous studies have demonstrated the structural and functional alterations of the insula in schizophrenia. To acquire a full picture of the functional alterations of the insula in psychosis, we examined the insula cortical functional connectivity (FC) in patients with first episode psychosis (FEP) and explored the relationship between the connectivity and the neuropsychological function. In this study, 84 patients with FEP and 84 individually age- and sex-matched healthy controls (HC) completed resting-state functional MRI, neuropsychological testing, and social cognition assessments using the Facial Affect Recognition and Memory (FARMS) task. To investigate the functional connectivity values (Z-scores) of the cross-subject analysis, we used Large Deformation Diffeomorphic Metric Mapping (LDDMM) and a deformable brain atlas to parcel each brain into 48 ipsilateral cortical regions. And we computed inter-parcel correlations between insula and another ipsilateral cortical regions in the participants. In the posterior insula, the FEP patients exhibited decreased FC between the right posterior insula and the right middle fronto-orbital gyrus (P<0.001). In the anterior insula, on the other hand, the FEP patients exhibited increased FC between the right anterior insula and the right cerebellum (P=0.001). In addition, the FC between the right posterior insula and the right middle fronto-orbital gyrus were negatively correlated with the social cognition in the measures of Recognition reaction time (r=-0.240, P=0.003), and Memory reaction time (r=-0.221, P=0.006). The results suggested that the right insula might play an important role in the pathological mechanism of psychosis and the dysfunction of insula might disturb the neuropsychological and social cognitive dimensions in a wide range of psychiatric disorders with psychosis.

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Nanosymposium

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Title: Functional brain networks underlying the bias against disconfirmatory evidence and delusions in schizophrenia

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Abstract: Some of the most promising theories regarding delusions in schizophrenia involve cognitive biases, which are tendencies in thinking processes that can contribute to impaired decision-making. The bias against disconfirmatory evidence (BADE) refers to a tendency to disregard information that contradicts a current belief, and is associated with delusions in schizophrenia. We previously identified two sequentially-active functional brain networks associated with evidence integration processes fundamental to BADE in healthy controls: a salience network underlying detection of evidence, and an evaluation network involved in integrating evidence. Comparing a sample of healthy controls (n=40) and schizophrenia patients (n=58), and employing functional connectivity techniques, we investigated how one or both of these networks relates to BADE and delusions in schizophrenia using functional magnetic resonance imaging. Three networks showed increased intensity during integration of disconfirmatory evidence, namely, visual attention (anterior cingulate, insula, nodes of the dorsal attention network), default-mode (ventromedial prefrontal, precuneus), and cognitive evaluation (orbitofrontal, inferior frontal, posterior parietal) networks. The visual attention and cognitive evaluation networks were differentially related to both BADE and delusions. Specifically, activity in the visual attention network during confirmatory evidence was associated with BADE, and was higher in delusional patients. In contrast, cognitive evaluation network activity was associated with BADE during disconfirmatory evidence, and was decreased in delusional patients. These results suggest that the cognitive evaluation network reflects the evaluation and integration of evidence and that hypoactivity in this network during disconfirmatory evidence

underlies BADE in schizophrenia patients with delusions. In addition, hyperactivity during confirmatory evidence integration in the visual attention network in delusional patients may reflect hypervigilance to confirmatory evidence theorized to co-occur with BADE in delusions. These findings highlight distinct functional brain networks underlying two important aspects of delusion maintenance in schizophrenia: the focus on confirmatory evidence and avoidance of disconfirmatory evidence. Future research should examine whether activity in these networks fluctuates with changes in BADE and positive symptoms, and whether they may be normalized through cognitive interventions targeting cognitive biases (e.g., metacognitive training).

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Nanosymposium

646. Human Studies of Circuits and Systems in Schizophrenia and in First Episode Psychosis

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**Presentation Number: ***646.07

**Topic: ***H.03. Schizophrenia

Title: VTA network differences between schizophrenia and major depressive disorder

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Abstract: Dopaminergic neural pathways are linked to multiple psychiatric disorders, including schizophrenia (SCZ) and major depressive disorder (MDD) (Dunlop and Nemeroff 2007; Tost et al. 2010). Most dopamine-producing neurons in the brain are located in the substantia nigra (SN) and ventral tegmental area (VT) in the midbrain. Accumulating evidence from human neuroimaging studies suggests that deficits in SN and VTA neural networks contribute to SCZ and MDD. In a functional magnetic resonance imaging (fMRI) study, MDD patients showed a negative association between anhedonia, which is a core symptom of MDD, and functional neural networks of the mesolimbic reward system, including the VTA/SN (Young et al. 2016). A resting state (rs)-fMRI study reported that unmedicated SCZ patients had reduced VTA/midbrain connectivity with multiple cortical and subcortical regions, including a part of the default mode network and salience network (Hadley et al. 2014). Although deficits in SN and VTA neural networks can contribute to SCZ and MDD, it is still unclear which part of the SN or VTA neural network would differentiate these two psychiatric disorders. To address this question, we used rs-fMRI data to investigate the differences in the SN and VTA neural networks between SCZ and MDD patients. Seventeen SCZ patients (age 33.59 ± 10.54 years; 10 men, 7 women), 29 MDD patients (age 40.03 ± 9.26 years; 14 men, 15 women), and 61 healthy controls (HCs) (age

39.41 ± 8.12 years; 25 men, 36 women) were recruited. All participants provided written informed consent and this study was approved by the Human Investigation Committee at Tokyo University Hospital. Participants underwent a 10-min and 10-s rs-fMRI run with a fixation cross. A seed-based rs-fMRI analysis was performed using the SN and VTA as seeds. In the VTA network, the difference between MDD patients and HCs was greater than the difference between SCZ patients and HCs in the ventromedial prefrontal cortex (vmPFC), even after controlling for age, sex, handedness, and estimated premorbid intelligence quotients (the Japanese Adult Reading Test). Compared with SCZ patients, MDD patients showed a stronger neural connectivity between the VTA and vmPFC. Differences in functions related to the VTA-vmPFC neural connection possibly differentiates SCZ from MDD.

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Nanosymposium

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**Topic: ***H.03. Schizophrenia

Title: Homeostatic plasticity of parvalbumin-expressing inhibitory interneurons for the impaired behavioral flexibility

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Abstract: NMDA receptor (NMDAR) hypofunction in parvalbumin-expressing inhibitory interneurons (PV-IN) may underlie the pathogenesis of psychiatric diseases such as autism and schizophrenia by excitation-inhibition (E/I) imbalance. However, It remains elusive how cellular mechanism of PV-INs are disrupted by chronic NMDAR hypofunction in micro neural circuits, leading to cognitive dysfunction. To rescale E/I balance for rescue of psychiatric diseases, it is important to understand the neural mechanism of homeostatic plasticity in PV-INs and its contribution to behavioral flexibility during chronic NMDAR hypofunction. To figure out this, here, we applied not only *in vitro* system with primary cortical culture pre-treated with the NMDAR antagonist, mk-801 but also *in vivo* mouse model with systemically repeated injection of mk-801 showing several cognitive dysfunctions including hyperlocomotion, impaired working

memory, and disrupted paired-pulse inhibition (PPI). Both *in vitro* primary cortical culture and medial prefrontal cortex (mPFC) *in vivo* mouse model indicated that chronic NMDAR hypofunction in PV-INs induced AMPA receptor (AMPAR) downregulation, while NMDAR and AMPAR in pyramidal neurons (PY) were not affected. In addition to this, in mPFC *in vivo* mouse model , recording evoked inhibitory synaptic currents from PY during optogenetic suppression of PV-IN in mPFC showed that the reduced synaptic strength of PV-INs caused disinhibition onto PYs, leading to less input and less output of PV-IN. This altered network activity by increased E/I ratio and gamma oscillation, associated with impaired working memory. The reduced AMPAR strength in PV-IN was recovered by microinjection of PKA activator, forskolin, into mPFC, giving rise to improved neuronal network oscillation and cognitive function. Moreover, optogenetic excitation of PV-IN in mPFC showed rescue of impaired cognitive function in mk-801 injected mouse. Together, these results demonstrate that chronic NMDAR hypofunction in PV-IN is associated with downregulation of AMPAR through PKA inactivation, which leads to E/I imbalance in mPFC by disinhibition onto PY, conferring psychiatric symptoms.

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Nanosymposium

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Title: Discovering linked dimensions of psychopathology and dysconnectivity in high-dimensional brain networks

Authors: *C. XIA[1], Z. MA[2], R. CIRIC[1], S. GU[1,3], R. BETZEL[3], M. CALKINS[1], P. COOK[4], A. GARCIA DE LA GARZA[1], T. MOORE[1], D. ROALF[1], K. RUPAREL[1], D. WOLF[1], R. GUR[1], R. GUR[1], C. DAVATZIKOS[4], R. SHINOHARA[5], D. BASSETT[3], T. SATTERTHWAITE[1]
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Abstract: It is increasingly recognized that neurobiological abnormalities associated with mental illnesses do not map cleanly to diagnostic categories used in clinical practice. This mismatch suggests common mechanisms of circuit-level abnormalities. Here we sought to identify brain-based dimensions of psychopathology using sparse Canonical Correlation Analysis (sCCA) in a sample of nearly 1000 youths imaged as part of the Philadelphia Neurodevelopmental Cohort. We used sCCA to find relationships between functional network connectivity and psychopathology data, as it aims to simultaneously find linear combinations of variables in each dataset that are maximally correlated with each other, with L1 regularization to achieve sparsity (**Figure 1**). This analysis revealed four dimensions of psychopathology - psychosis, anxious-misery, fear, and externalizing behavior - that were highly associated with specific brain connectivity patterns (**Figure 2**). Furthermore, while each dimension has a distinct pattern of dysconnectivity, there are also notable commonalities across dimensions in systems such as the default mode and the fronto-parietal networks. These results replicated in an independent dataset, and suggest that dimensions of psychopathology may result in part from common and unique patterns of dysconnectivity.

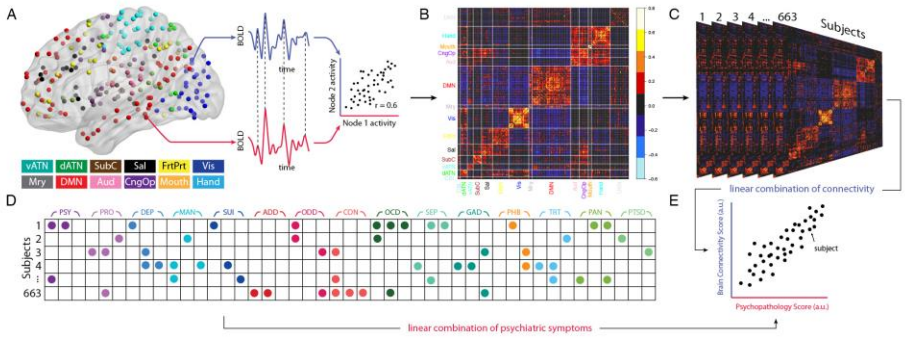

Figure 1 Functional connectivity and psychiatric symptom features into the sparse Canonical Correlation Analysis (sCCA). **A**. resting-state fMRI data analysis schematic and workflow. After preprocessing, BOLD signal time series were extracted from 264 spherical regions of interest (ROIs) distributed across the cortex and subcortical structures. **B**. Whole-brain, 264 × 264 functional-connectivity matrix averaged across all subjects in the discovery sample (n =663 subjects). **C**. Concatenate edge features of each subject as connectivity features into sCCA. **D**. Comprehensive psychiatric evaluations (111 items, based on K-SADS) were assessed for each subject as clinical feature input to sCCA. **E**. sCCA seeks linear combinations of connectivity and clinical symptom that maximize their correlation. *A priori community assignment*: FrtPrt: frontal-parietal cortex; DMN: default mode network; vATN: ventral attention network; dATN: dorsal attention network; Vis: visual cortex; Aud: auditory cortex; Hand: somatosensory/motor hand region; Mouth: somatosensory/motor mouth region; CngOp: cingular opercular cortex; Mry: memory network; Sal: Salience network; SubC: subcortical network; Cbl: cerebellum; Unk: unsorted nodes. *Psychopathology domains*: PSY: psychosis; PRO: predromal psychotic symptoms; DEP: depression; MAN: mania; SUI: suicidality; ADD: attention-deficit hyperactivity disorder; ODD: oppositional defiant disorder; CON: conduct disorder; OCD: obessive-compulsive disorder; SEP: seperation anxiety; GAD: general anxiety disorder; PHB: phobias; TRT: mental health treatment; PAN: panic disorder; PTSD: post-traumatic stress disorder

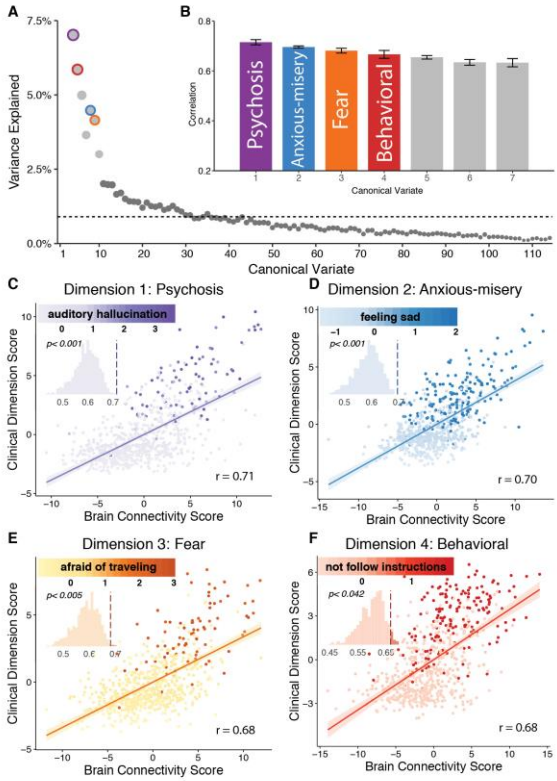

Figure 2 Four symptom-brain connectivity relationships revealed by sparse canonical correlation analysis (sCCA). **A**. The first seven canonical variates were selected based on variance explained. Dashed line marks the average variance explained. **B**. Among them, four with the highest correlation were statistically signficant by permutation testing. **C-F**. Scatter plots of brain and clinical scores as different linear combinations of function connectivity and psychiatric syptoms. Dots in each panel are colored by a representative clinical symptom that contributes the most to this canonical variate dimension. Each insert is the null distribution of sCCA correlation for each canonical variate.

Disclosures: **C. Xia:** None. **Z. Ma:** None. **R. Ciric:** None. **S. Gu:** None. **R. Betzel:** None. **M. Calkins:** None. **P. Cook:** None. **A. Garcia de La Garza:** None. **T. Moore:** None. **D. Roalf:** None. **K. Ruparel:** None. **D. Wolf:** None. **R. Gur:** None. **R. Gur:** None. **C. Davatzikos:** None. **R. Shinohara:** None. **D. Bassett:** None. **T. Satterthwaite:** None.

Nanosymposium

646. Human Studies of Circuits and Systems in Schizophrenia and in First Episode Psychosis

Location: 147A

Time: *Wednesday, November 15, 2017, 8:00 AM - 10:45 AM

Presentation Number: *646.10

Topic: *H.03. Schizophrenia

Support: NIH Grant R01MH101053
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Lieber Institute for Brain Development

Title: Prefrontal working memory function, stress and the childhood environment on neuropsychiatric genetic risk

Authors: *H. TAN[1], H. YAN[2], J. ZHU[1], X. ZHANG[2], G. YANG[1], S. SHAH[1], D. SAHA[1], Q. CHEN[1], M. LA[1], W. YUE[2], D. R. WEINBERGER[3], D. ZHANG[2]
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Abstract: BACKGROUND: Working memory (WM) and prefrontal impairment occurs in several neuropsychiatric disorders, including schizophrenia. Genetic and environmental contributions to risk for psychosis have been implicated. Less, however, is understood about how childhood environmental contexts may influence these brain functions. Indeed urban social stressors and childhoods in urban environments may be associated with increased neuropsychiatric risk. Here, we further examined mechanisms by which WM prefrontal functions associated with genetic risk for psychosis in unaffected siblings of patients, may also be influenced by interpersonal stressors in relation to differing urban and rural childhoods. METHODS: We examined unaffected siblings of schizophrenia patients (N=36) and healthy controls (N=35) to define dorsolateral prefrontal cortical (DLPFC) functions influenced by genetic risk for psychosis in an event-related WM functional MRI paradigm in a 3T scanner. To define the influence of childhood urbanicity on these brain functions, we examined a unique sample of healthy adult individuals currently living in Beijing but with divergent urban or rural childhoods before age 12 (N=200, 204). These subjects engaged a similar WM paradigm in a 3T MRI scanner, but with additional events that induced interpersonal stress during WM. We then examined the effects of interpersonal stress on DLPFC function linked to psychosis risk, and the influence of interpersonal closeness in the diverging childhood environments on these brain functions. RESULTS: DLPFC function during manipulating information in WM was reduced by genetic risk for psychosis in siblings. All results are significant at $p<0.05$ family-wise corrected within regions-of-interest (ROI) in the DLFPC. Within the DLPFC ROI, interpersonal stress also reduced DLPFC function. Interpersonal closeness in urban vs rural childhoods had divergent effects on DLPFC function. Higher interpersonal closeness in rural childhoods was associated with relatively less reduced DLPFC function during stress. Higher interpersonal closeness in urban childhoods, however, was associated with more stress-related reduction in DLPFC function. CONCLUSIONS: We suggest that childhoods in urban environments may influence risk for psychosis in part through brain mechanisms related to interpersonal stress. Interpersonal closeness may be less adaptive in urban than in rural life, potentially negating some of the protective effects of interpersonal relationships, at least on DLPFC function under interpersonal stress.

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Nanosymposium

646. Human Studies of Circuits and Systems in Schizophrenia and in First Episode Psychosis

Location: 147A

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**Presentation Number: ***646.11

**Topic: ***H.03. Schizophrenia

Support: RO1 MH049334

Title: Reduced subcortical activation during paragraph reading in schizophrenia

Authors: *E. C. DIAS, A. MARTINEZ, S. ROHRIG, M. J. HOPTMAN, N. REVHEIM, D. C. JAVITT
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Abstract: Schizophrenia patients (SZP) have cognitive dysfunction that is associated with impairment of their early sensory processing. Reading deficits, in particular, have been associated with reduced activation of the magnocellular visual pathway in SZP (Revheim et al, 2006, 2013; Martinez et al, 2012). This study used a combination of eye tracking, EEG and resting state fMRI (rsfMRI) to further examine neural changes and how they relate to reading parameters in SZP. Simultaneous EEG (ANT Neuro) and eye tracking (Eyelink 1000) data were obtained from 26 healthy controls (HC) and 26 SZP, using standard methods, while subjects were reading paragraphs from the Grey Oral Reading Tests-4. SZP showed impaired reading, as reflected by their increased reading rate (ms/word) ($p<.001$), which was independently correlated with increased number of saccades/word ($p<.001$) and fixation duration ($p<.001$). In addition, patients showed a higher rate of forward saccades/word ($p<.001$) and regressive saccades/word ($p<.001$). Temporal analysis of the fixation-related potentials (FRP), measured over occipito-parietal cortex, showed a significant decrease of the peak of early visual component P1 in SCZ when compared to HC ($p=.033$). P1 amplitude correlated negatively with the number of forward saccades ($p=.007$), number of regressive saccades ($p=.015$) and positively with reading rate ($p=.037$), corroborating and expanding previous reports that impaired early visual information disrupts paragraph reading in SZP. RsfMRI data was obtained for a subgroup of the subjects (15 HC and 12 SZP) (3T Siemens Tim Trio). Analyses showed that functional connectivity between cortical areas known to be active during reading, including middle occipital gyrus (MOG), visual word form area (VWFA) and frontal eye fields (FEF), and subcortical areas superior colliculus (SC) and lateral geniculate nucleus (LGN) correlated with reading rate and specifically with fixation duration. Connectivity between MOG and SC also correlated with the amplitude of the P1 component peak ($p=.015$). To verify if activation of subcortical areas was also reduced in SZP during reading, in addition to reduced functional connectivity between cortical and subcortical areas, data in an fMRI study of similar paragraph reading, from a separate cohort

(Martinez et al, 2012), was re-analyzed to include subcortical areas. There were significant decreases in activity in the SC and the LGN, in addition to previously reported MOG, VWFA and FEF. These data indicate that deficits in neuronal activation that lead to impaired reading in SZP may be traced to the very early processing of visual information in subcortical areas.

Disclosures: E.C. Dias: None. **A. Martinez:** None. **S. Rohrig:** None. **M.J. Hoptman:** None. **N. Revheim:** None. **D.C. Javitt:** None.

Nanosymposium

647. Methods: Non-Invasive Stimulation

Location: 152B

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**Presentation Number: ***647.01

**Topic: ***I.04. Physiological Methods

Support: GRF 15326416
PolyU internal funding 1-YW0Q
Shenzhen Basic Research 2016A016)

Title: Fundamentals and toolkits for precise ultrasonic neuron stimulation

Authors: *Z. QIU[1], J. GUO[2], S. KALA[1], J. WANG[1], J. ZHU[1], H. C. CHAN[2], L. SUN[1]
[1]The Interdisciplinary Div. of Biomed. Engin., The Hong Kong Polytechnic Univ., Hung Hom, Hong Kong; [2]Sch. of Biomed. Sci., The Chinese Univ. of Hong Kong, Sha Tin, Hong Kong

Abstract: Ultrasonic (US) brain stimulation, has been demonstrated to noninvasively alter neuron activity in animals and humans. Capable of non-invasive transmission trough skull with fine focal size (~mm), it is an encouraging means and a good alternative to existing stimulating strategies. However, the bio-effects of US are diverse and thus it is crucial to develop precise neuron control strategies for later translation. Here we focus on the mechanisms of gating mechanosensitive ion channels (MCs) by US and explored as fundamentals for the developing selective US neuron stimulation. The cell membrane tension was approximated by various models and then calculate the interaction with MCs. On gating MCs by ultrasound was verified on Piezo1 expressed HEK293t cells and primary cultured neurons. Calcium imaging and whole cell patch clamp techniques were utilized to characterize the responses. Based on these proof of concept results, sonogenetic toolkits for neuron activity controlling and visualization simultaneously were developed. The first version toolkit contained a rAAV virus which can target MCs to neurons and a ultrasound stimulation and optical calcium imaging readout hardware. This toolkits were verified by using a sleep model in mice. Results shown that ultrasound can mediate membrane tension which can be tuned up to one order magnitude higher

than which required for gating MCs, here Piezo 1 and MscL. The open probability of MCs as a function of acoustic pressure highly depends on frequency. The MCs is more sensitive to lower frequency US. Experimental results clearly demonstrated that ultrasound can activate Piezo1- and MscL-HEK293t cells while no response can be detected for the control cells. The induced inward current and calcium influx are US pressure dependent for Piezo1 overexpressed HEK293T and neurons. The in vivo experiment shown that the ultrasound can wake the mice up with a much lower acoustic pressure for the MCs over-expressed mice. These results show that ultrasound is able to modulate neuronal activity by gating mechanosensitive ion channels by membrane tension. It demonstrates reliable precise control of neuron activity by ultrasound. In conclusion, preliminary in vivo results showed that the concept of sonogenetics is valid and the toolkit are under developing and optimizing.

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Nanosymposium

647. Methods: Non-Invasive Stimulation

Location: 152B

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**Topic: ***I.04. Physiological Methods

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Shenzhen Basic Research 2016A016

Title: Investigate the behavior and functional response of *Caenorhabditis elegans* by ultrasound stimulation

Authors: *S. LEI, Z. QIU, Q. XIAN
Biomed. Engin., The Hong Kong Polytechnic Univ., Hong Kong, Hong Kong

Abstract: The use of tools for stimulating the brain could advance our understanding of how brain functions and provide strategies for treating brain disease. Ultrasound is one of the most promising tools as it can be focused into deep brain region noninvasively with fine spatiotemporal resolution. However, how ultrasound stimulation modulate neural activity is unclear and some of the mechanisms are controversial. In addition, how ultrasound, mechanical stimuli, integrated with different cues to initiate and modulate neuron activity and subsequently modulate the brain function in vivo is unknown. In this study, free moving C elegans with genetically encoded calcium indicator of the entire neurons was used as a model organism to test the ultrasound effects on neuron activity. In addition, chemotaxis and thermotaxis behavior are

utilized to studying the ultrasound stimulation on the advanced behavior. Customized low frequency (0.5MHz and 1 MHz) low intensity pulsed ultrasound stimulation system was incorporated with a customized light-sheet microscopy. The ultrasound propagation path is perpendicular to optical illumination and detection path. Our results show that the calcium spikes in the whole body can be visualized longitudinally with single neuron resolution. The ultrasound stimulation and functional imaging can be performed simultaneously in vivo. The mechanosensitive neurons can be activated by low frequency low intensity ultrasound with calcium influx consequently induce reversal behavior. Furthermore, it is shown by chemotaxis and thermotaxis test that ultrasound can increase the sensitivity of neurons to chemo- and thermos- cues. Compared with high frequency ultrasound and microbubble assisted ultrasound effects on C elegans, the present study with 0.5 MHz and 1 MHz is more clinical relevant because its capability of penetrate through the skull. In addition, all the neurons are visualized during ultrasound stimulation by which we are able to assess the effects of ultrasound stimulation on different neuron types and the interaction with the chemo- and thermo- cues. Collectively, the combination of low intensity pulsed ultrasound stimulation and light-sheet microscopy provides us a powerful way to investigate the mechanisms of ultrasound neuron stimulation. We confirmed that low frequency ultrasound which can modulate mechanosensitive neurons in C elegans and it can also be integrated with natural cues to modulate neuron activity.

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Nanosymposium

647. Methods: Non-Invasive Stimulation

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**Presentation Number: ***647.03

**Topic: ***I.04. Physiological Methods

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SPP 1665, DFG

Title: Effects of anodal tDCS on a cortical auditory learning task

Authors: *G. ARIAS GIL[1], A. OELSCHLEGEL[1,2], J. GOLDSCHMIDT[1,3], K. H. SMALLA[1], M. T. LIPPERT[1,3], F. W. OHL[1,2,3], K. TAKAGAKI[1,2,3]
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Abstract: Transcranial direct-current stimulation (tDCS) is a low cost, non-invasive method that has the potential to actively shape neural activity by sending constant, subthreshold direct current

through the skull via electrodes placed over a region of interest. Positive polarity (anodal stimulation) is thought to depolarize resting membrane potentials and induce excitation of the underlying cortex. However, the mesoscopic extent of such influence is unclear. Furthermore, it is unclear whether such stimulation can influence cortical learning directly. We tested the influence of tDCS on learning and memory behavior in a cortex-dependent learning task, discrimination of modulation direction of frequency-modulated tones in a GO/NO-GO shuttlebox paradigm. This is one of the few rodent sensory discrimination paradigms which has been clearly shown to be cortically dependent (Wetzel et al., 1998, 2008; Ohl et al. 1999), and is thus particularly suited for our purpose. Animals were divided into two experimental groups, an anodal tDCS stimulated group and a control sham stimulation group. Each group underwent 10 minutes of anodal or sham stimulation respectively, right before each training session. Each animal performed a 60 trial session during 10 consecutive days, in which they were expected to attain our learning criteria. Our analyses show that there is better learning in the anodal tDCS group. Of interest, our effect was only seen in animals which took a particular learning strategy, which emphasizes correct discrimination over impulsive detection. In order to investigate the mechanisms of such cortical modulation of learning, we also also mapped spatial patterns of neuronal activity using in vivo SPECT-imaging of regional blood flow and histochemical detection of the uptake of the K+-probe thallium (Tl+). We see clear activation of the relevant cortical areas caused by our tDCS. Electrophysiology also shows significant activation due to tDCS. In order to characterize biochemical changes due to the tDCS, we further collected samples of brain tissue from the animals after behavior and performed mass spectrometry analyses to test for proteomic differences in the expression of critical molecules related to synapse formation and stabilization. In summary, we demonstrate that mesoscopic activation of the cortex by anodal tDCS can lead to improved learning in a cortically-dependent learning task.

Disclosures: **G. Arias Gil:** None. **A. Oelschlegel:** None. **J. Goldschmidt:** None. **K.H. Smalla:** None. **M.T. Lippert:** None. **F.W. Ohl:** None. **K. Takagaki:** None.

Nanosymposium

647. Methods: Non-Invasive Stimulation

Location: 152B

**Time: ***Wednesday, November 15, 2017, 8:00 AM - 10:30 AM

**Presentation Number: ***647.04

**Topic: ***I.04. Physiological Methods

Support: K99NS100986

Title: Transcranial ultrasound impacts monkey choice behavior

Authors: *J. KUBANEK[1], J. BROWN[2], P. P. YE[3], K. BUTTS PAULY[2], W. T. NEWSOME III[4]
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Abstract: Transcranial focused ultrasound (US) has the potential to non-invasively modulate neural activity in specific regions deep in the brain. Successful US neuromodulation has been reported by multiple groups using anesthetized rodents. This body of work opens the possibility that this method could be applied in awake behaving primates including humans. We used the macaque model to test whether 1) we can detect effects of US on behavior 2) long-term stimulation is safe 3) the neuromodulatory effects are excitatory, inhibitory, or a combination thereof. To do so, we engaged a macaque monkey in a stimulus onset asynchrony task in which the animal looked at either a rightward or a leftward target, whichever appeared earlier. US (270 kHz, 0.6 MPa, 300 ms) focused into either left or right frontal eye field (FEF) was applied through the intact skull and skin, 100 ms before the onset of the first target. We interleaved short blocks of trials in which US was applied and in which it was not. We found that US stimulation of left (right) FEF significantly shifted the animal's choices to the rightward (leftward) target. The contralateral nature of the effects suggests neuronal excitation within FEF. The effect was observed specifically when stimulating FEF and not when stimulating motor cortex. The effect was immediate and showed minimal hysteresis. There was no long-term bias in the animals' choices even after 8 days of stimulation of each region, which suggests that the stimulation was safe. The finding that transcranial US can excite neurons to the extent that the effect is observed in monkey's behavior paves the way to noninvasive stimulation of specific brain regions in humans.

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Nanosymposium

647. Methods: Non-Invasive Stimulation

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Title: functional ultrasound imaging (fUSi) for ultra-early assessment of tissue infarction in preclinical stroke research

Authors: *A. URBAN[1], C. BRUNNER[1], N. LAGUMERSINDEZ[2], G. MONTALDO[1], M. ENDRES[2]
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Abstract: While many neuroprotective strategies including reduction of inflammation, oxidative stress, blood brain barrier disruption and/or neuronal apoptosis have been efficiently used to treat stroke in preclinical models, nearly all drugs tested have failed in human trials. Nevertheless, stroke research in rodents is essential. Innovative brain imaging technologies may contribute to reduce failures in preclinical stroke research by evaluating more precisely the efficiency of new therapies. Here we demonstrated that functional ultrasound imaging (fUSi) is an efficient tool for assessing tissue infarction by mapping cerebral blood volume (CBV) and flow (CBF) dynamics in 3D at high spatial resolution (80 µm) and in real time. fUSi was performed continuously for 1 h after stroke onset in rats in which only the distal middle cerebral artery was occluded (MCAo) or with a complementary ligature of the common carotid artery (CCAo) in addition to the MCAo. In these experimental conditions accounting for either mild- (MCAo alone) or a profound ischemia (MCAo-CCAo) respectively, we observed a massive initial drop of the CBV/CBF over 50 % of the baseline level within the first second after occlusion. Moreover, the MCAo model exhibited a rapid reperfusion of the ischemic territory that was not observed in the MCAo-CCAo animals. Finally, the comparison between volumetric-fUSi-images of the ischemic territory taken in vivo 1 hour after stroke and post-mortem infarct volume quantification using cresyl violet staining at 24 h, confirmed the potentiality of fUSi to predict tissue infarction. The use of fUSi may lead to reduce the amount of animals used in pre-clinical studies and to optimize the evaluation of new drug candidates in stroke therapy as well as in other brain pathologies.

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Nanosymposium

647. Methods: Non-Invasive Stimulation

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Topic: *I.04. Physiological Methods

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Title: Wearable transcranial focused ultrasound system for region-specific functional neuromodulation

Authors: *S.-S. YOO, W. LEE, P. CROCE, K. YOON, R. W. MARGOLIN
Radiol, Brigham & Women's Hosp, Harvard Med. Sch., Boston, MA

Abstract: Advancements in focused ultrasound (FUS) techniques, with image-guidance for targeting the sonication focus to a specific region-of-interest, have allowed for the non-invasive transcranial delivery of acoustic energy to cortical as well as deep brain structures with an excellent spatial selectively of only a few millimeters in size (roughly the size of a rice grain). The main objective of our research is to develop a wearable transcranial focused ultrasound (tFUS) environment that reversibly modulates (either elicits or suppresses) region-specific neural activities of the brain using a large animal model (sheep).
We developed light-weight, MRI-compatible, single-element FUS transducers (one made with air-backed, lead zirconate titanate ceramics- 80 gram and the other made with Gas Matrix Piezoelectric, or GMP, material- 95 gram) both operating at 250 kHz. The transducers' housing diameter ranged 4-5 cm, and had focal lengths of 2-3 cm (from the exit plane of the transducer), allowing 'f-number' $\leq$1 for the formation of a sharp focus. The spatial dimension and their major operational characteristics (*i.e.*, acoustic output > 20 W/cm^2) satisfied the intended study requirement. Since the propagation of ultrasound waves is heavily affected by the geometrical shape of a skull, predictive computational tools are of great use for finding a precise localization of the focus. We also developed a computer-based numerical simulation that predicts the location of the acoustic focus as well as the degree of attenuation, and examined the feasibility of deploying multi-resolution approaches for simulating the acoustic propagation through the skull *via* finite difference time domain (FDTD) formulation. The translation of the implemented method to C-family programming language, augmented by utilization of the GPU (Graphic Processing Units), is currently underway to improve the computation speed compatible with real-time simulation (under 10 sec). We integrated the above FUS device with biological signal acquisition/stimulator system that acquire various electrophysiological responses, and assessed the performances of the resulting system among a few anesthetized sheep. As guided by the functional MRI information, sonication given to the M1 area created an EMG response from the hind leg muscle that is contralateral to the sonication. Non-invasive and controllable manipulation of region-specific cortical/subcortical activity in the brain will open new avenues not only for neuroscientific research, but also for clinical applications ranging from functional brain mapping to treatment of numerous neurological and psychiatric disorders.

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Nanosymposium

647. Methods: Non-Invasive Stimulation

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Support: NIH Intramural Research Program

Title: Characterizing neural responses to single pulse direct cortical stimulation in the human cortex

Authors: *C. R. STEINHARDT[1], T. SHEEHAN[2], S. K. INATI[3], K. A. ZAGHLOUL[3]
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Abstract: Direct cortical stimulation has been used in clinical and experimental settings for decades. It is considered a reliable method for identifying areas of eloquent cortex pre-surgery, and it has been shown to be capable of directing or perturbing functionality in brain regions in ways, such as biasing decisions or guiding motor movements. Resultantly, direct cortical stimulation is seen a promising form of neural modulation with clinical applications, such as brain-machine interfaces, and implications for characterizing the network structure of the human brain. However, an important limitation of using such stimulation has been that the specific effects of electrical stimulation on neural activity are poorly understood. Here, we use intracranial EEG (iEEG) recordings captured from subdural and depth electrodes implanted in eight participants with medically refractory epilepsy to characterize the neural responses to electrical stimulation. In each participant, we provide electrical stimulation using a train of 1 Hz square-wave biphasic pulses with amplitudes drawn from a white noise distribution and ranging between -8 and 8 mA. At each electrode site, we quantify the evoked response to the stimulating pulses. The amplitudes provided by the white noise distribution enable us to characterize linear and non-linear modulations of the evoked responses with stimulation amplitude and to identify electrode sites that exhibit a significant response to electrical stimulation. We use the relationships between stimulation amplitude and response at these identified electrode sites to identify network connections between electrode locations, and to predict evoked responses to novel combinations of stimulation pulses.

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Nanosymposium

647. Methods: Non-Invasive Stimulation

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**Topic: ***I.04. Physiological Methods

Support: MCubed, University of Michigan

Title: Probing GABAergic function in the visual cortex with transcranial magnetic stimulation

Authors: *D. KHAMMASH[1], M. SIMMONITE[2], T. A. POLK[2], S. F. TAYLOR[3], S. K. MEEHAN[1]
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Abstract: Transcranial magnetic stimulation (TMS) is a non-invasive tool used to stimulate a localized region of the cortex. When delivered over motor cortex, TMS evokes a motor evoked potential (MEP) in the contralateral muscle that can be recorded using surface electromyography and that scales with increasing stimulation intensity. When the evoking stimulus is conditioned by a preceding magnetic stimulus, the MEP can also act as a benchmark to quantify intracortical facilitation and inhibition. Despite widespread use in motor cortex the application of TMS in sensory areas, like visual cortex, is limited by the use of variable, qualitative metrics and by challenges in translating motor parameters to other cortical areas. The present study assessed the reliability and validity of tracing phosphenes, short-lived artificial percepts, to investigate cortical excitability and short-interval cortical inhibition (SICI) in the visual cortex. Participants completed two identical sessions at least 1 week apart. During each session participants were seated in the dark facing a 46” computer screen positioned to span their visual field. The point of stimulation, or phosphene “hotspot”, was defined as the site of stimulation that elicited the phosphenes of greatest, most consistent intensity. Phosphene threshold (PT) was defined as the stimulator intensity at which phosphenes were induced on 5 out of 10 stimuli. Single pulse recruitment curves were derived by scaling stimulator output at 10% increments between 60-150% of PT and having participants outline the area of the computer screen covered by the resulting phosphene. Paired-pulse recruitment curves were captured by preceding a test stimulus (TS, 120% of PT) by a conditioning stimulus (CS) 2ms earlier. The amplitude of the CS was scaled between 30-150% of PT in increments of 15%. Single pulse phosphene recruitment curves scaled with stimulus intensity in a manner consistent with motor cortex. The absolute and relative reliability of the recruitment was high across session. For both sessions, paired pulse recruitment curves demonstrated inhibition at a CS intensity of 45% of PT. This differs from the motor cortex, where inhibition is greatest at CS intensities approximating 80% of resting motor threshold. Again, relative and absolute reliability was high across session. These results show

that TMS-induced phosphenes are a valid and reliable tool for studying SICI in the visual cortex using appropriate stimulation thresholds and intensities. This opens the door to the use of SICI in neurological disorders linked to GABA dysfunction of visual cortex (e.g. psychosis).

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Nanosymposium

647. Methods: Non-Invasive Stimulation

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Title: Estimating perturbational complexity at the level of EEG sensors in different states of consciousness

Authors: *R. COMOLATTI[1], M. FECCHIO[2], A. PIGORINI[2], S. SARASSO[2], M. ROSANOVA[2], S. CASAROTTO[2], O. GOSSERIES[3], S. LAUREYS[4], M. MASSIMINI[2], A. CASALI[1]
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Abstract: The recent introduction of the Perturbational Complexity Index (PCI) as a measure of the information content of distributed causal interactions in the brain has addressed the challenge of objectively evaluating the level of consciousness of brain-injured, unresponsive patients. By quantifying the complexity of binary patterns of spatiotemporal activation extracted from TMS-evoked EEG signals, PCI was able to reliably discriminate the level of consciousness in a large benchmark population. Despite its success, calculating PCI involves several steps, such as EEG source modeling, nonparametric statistics and algorithm complexity, which are computationally demanding and hinder its clinical use. Here we advance towards the development of a bedside index of consciousness by introducing a measure of perturbational complexity that can be calculated directly at the EEG-sensors level. Instead of relying on source modeling, we take a dimensionality reduction approach and look at the trajectory generated by the TMS-evoked response in the space spanned by its principal components. After preprocessing and

dimensionality reduction, recurrence quantification analysis is performed: i) the Euclidean distance matrix between all timepoints of the trajectory is calculated and thresholded at several scales; ii) the complexity of the trajectory is then estimated by the total number of threshold-crossings (NTC). The method was tested on 173 TMS-EEG sessions recorded from 44 healthy subjects during wakefulness, NREM sleep and anesthesia (propofol, midazolam and xenon). The index was strongly correlated with PCI values (Figure 1A) and reliably discriminated all sessions between consciousness and unconsciousness at the level of single individuals (Figure 1B). Since the measure is calculated directly on the EEG signal, it is potentially suited to the clinical setting as a real-time index of the level of consciousness. Moreover, its application could be easily extended to intracranial EEG and in vivo/in vitro LFP recordings as measure of spatiotemporal complexity in stimulation protocols.

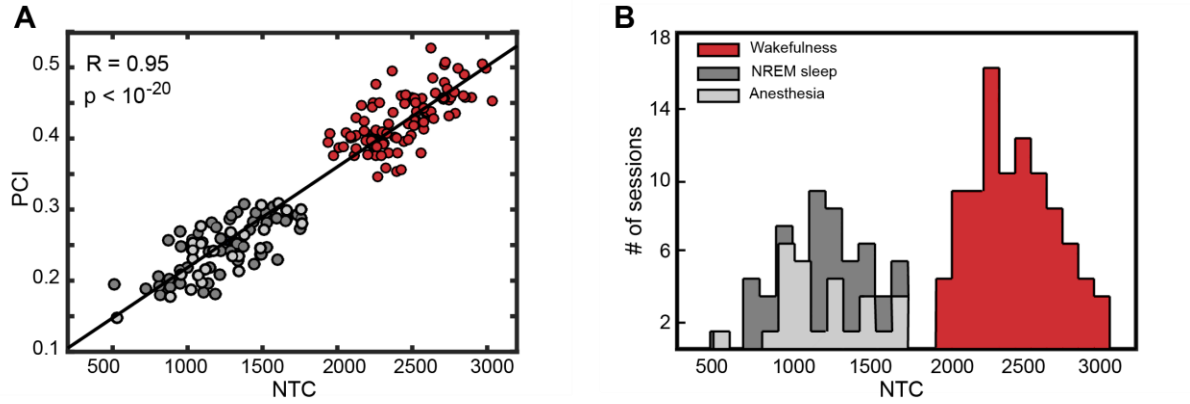

Figure 1: Results of Recurrence Quantification Analysis on TMS-EEG recordings in different states of consciousness. **A)** Correlation between PCI and NTC values. **B)** NTC distributions among subjects.

Disclosures: R. Comolatti: None. **M. Fecchio:** None. **A. Pigorini:** None. **S. Sarasso:** None. **M. Rosanova:** None. **S. Casarotto:** None. **O. Gosseries:** None. **S. Laureys:** None. **M. Massimini:** None. **A. Casali:** None.

Nanosymposium

647. Methods: Non-Invasive Stimulation

Location: 152B

Time: *Wednesday, November 15, 2017, 8:00 AM - 10:30 AM

Presentation Number: *647.10

Topic: *I.04. Physiological Methods

Support: Univ. Tübingen Junior Grant 2287
Univ. Tübingen Clinician Scientist Grant 391-0-0

Title: Brain-state dependent brain-stimulation with real-time EEG-triggered TMS: Phase of alpha oscillations reflects excitability and determines the direction of plasticity induced in human motor cortex

Authors: *C. ZRENNER, P. BELARDINELLI, D. DESIDERI, U. ZIEMANN
Ctr. for Neurol., Univ. Hosp. Tübingen, Tuebingen, Germany

Abstract: The brain is not a static black box but a generator of behavior, exhibiting rapidly fluctuating dynamic states at millisecond scale. This means that we cannot stimulate the same brain twice and limits the scope of open-loop experiments. The dynamics of ongoing neural activity explains the variability of evoked responses in mammalian cortex and the phase of neural oscillations determines the direction of synaptic plasticity induced in hippocampal slice experiments. This insight has, however, not yet been translated to human physiology in the 30 years of transcranial magnetic stimulation (TMS) for probing and modulating human brain networks. One reason for the high variability of outcome and low effect size of TMS is the variability of instantaneous brain state at the time of stimulation.
Here we show, using a custom-built brain-state-dependent millisecond-accurate EEG-triggered method for transcranial magnetic stimulation (TMS) of human motor cortex, that phases of EEG peak negativity vs. positivity of the endogenous sensorimotor μ-alpha rhythm reflect high- vs. low-excitability states of corticospinal neurons (Fig. 1). We also show that otherwise identical repetitive TMS, triggered consistently at these high-excitability vs. low-excitability states, leads to LTP- vs. LTD-like change in corticospinal excitability lasting for more than 30 minutes. This raises the intriguing possibility that real-time information of instantaneous brain state can be utilized to modulate brain networks in awake behaving humans, thus bearing paradigm-shifting potential for therapeutic applications of open-loop TMS.

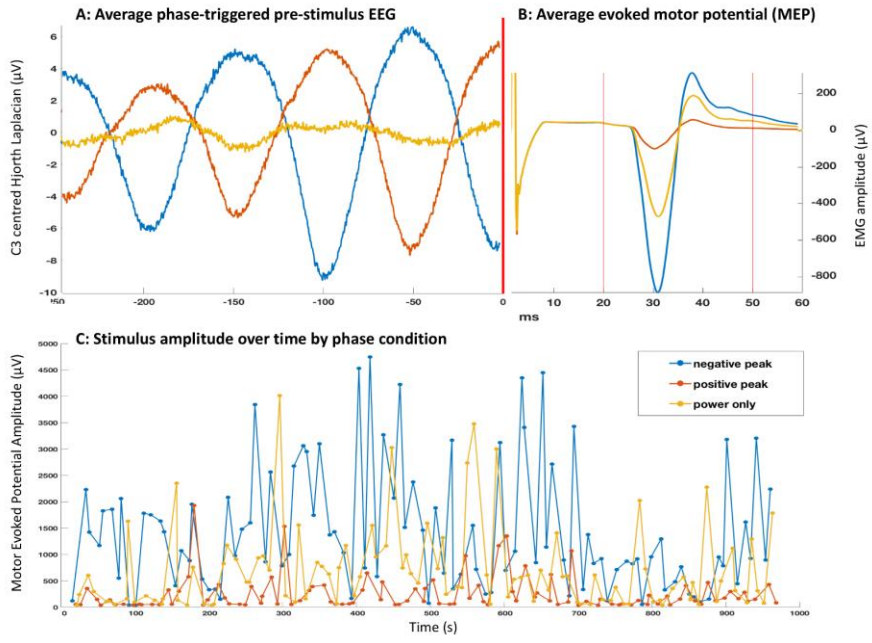

Fig. 1: Exemplary data from one subject receiving 300 TMS stimuli over left motor cortex,

triggered by three different EEG phase conditions, 100 stimuli each, in randomized order either by positive peak, negative peak or random phase of ongoing μ-alpha oscillations over a period of 17 minutes, showing an all-or-none response with large evoked responses during negative peak phase (blue) and almost no responses during the surface positive peak (red).

Disclosures: C. Zrenner: None. **P. Belardinelli:** None. **D. Desideri:** None. **U. Ziemann:** None.

Nanosymposium

728. Autism: Physiology and Behavior

Location: 152A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***728.01

**Topic: ***A.07. Developmental Disorders

Support: Wellcome Trust
European Commission

Title: Brain dynamics in high-functioning autistic adults

Authors: *T. WATANABE[1], G. E. REES[2]
[1]Inst. of Cognitive Neuroscience, Univ. Col. London, London, United Kingdom; [2]Univ. Col. London, London, United Kingdom

Abstract: Conceptually, individuals with autism spectrum disorder (ASD) should have atypical brain dynamics. However, it remains unclear how brain activity changes over time in individuals with the prevalent neurodevelopmental disorder. In this study, we identify large-scale brain dynamics in autism by applying an energy-landscape analysis to resting-state fMRI data collected from high-functioning adult males with ASD and age-/sex-/IQ-matched neurotypical controls. While neurotypical brain activity frequently transited between two major brain states via an intermediate state, the brain dynamics of adults with ASD showed fewer transitions due to an unstable intermediate state. In addition, these atypically infrequent transitions in the ASD group predicted the overall symptomatic severity of autism. Moreover, the transition frequency was positively correlated with IQ scores in the neurotypical controls, whereas the general cognitive ability of individuals with ASD was predicted by the stability of their brain dynamics. Furthermore, such associations between brain dynamics and behaviours could be explained by differences in strength of functional segregation between brain networks. These observations suggest that atypical functional coordination in the brains of adults with ASD underpins atypically stable neural dynamics, which is associated with both their symptoms of autism and cognitive skills.

Disclosures: **T. Watanabe:** None. **G.E. Rees:** None.

Nanosymposium

728. Autism: Physiology and Behavior

Location: 152A

Time: *Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

Presentation Number: *728.02

Topic: *A.07. Developmental Disorders

Support: NIH Grant DA02399
NIH Grant EY002593
Kavli Institute for Neuroscience at Yale

Title: Metabolic disorders impair mitochondrial-ER-Ca^{2+} homeostasis in radial glial cell fibers and disrupt neuronal migration to the neocortex

Authors: ***B. G. RASH**[1], T. L. HORVATH[2], P. RAKIC[3]
[1]Dept. of Neurosci., [2]Section of Comparative Med., [3]Dept. of Neurosci. and Kavli Inst. for Neurosci., Yale Univ., New Haven, CT

Abstract: Studies have indicated that gestational metabolic disorders can lead to adverse cognitive development, including autism, but the cellular basis of this disease link is unexplored. Using a mouse model, we examined intracellular dynamics of primary cortical stem cells, known as radial glial cells (RGCs), focusing on how they are affected by excess glucose or a model of diet-induced obesity. RGCs perform key roles in cortical development, functioning as both stem cells and guides for neuronal migration to the cortical plate. Intracellular Ca^{2+} signaling is emerging as one essential regulatory feature of RGCs, but its interplay with cellular metabolism and full role in cortical development is not understood. Using multiphoton confocal videomicroscopy of GCaMP5 optogenetic sensors in embryonic mice, we identified a core mechanism of RGC scaffold development and maintenance involving a mitochondria-endoplasmic reticulum (ER)-Ca^{2+} homeostatic system. We found that Ca^{2+} signaling regulates mitochondrial motility in RGC fibers, ensuring the proper distribution of metabolic support throughout their length. Conversely, Ca^{2+} activity is abolished by uncoupling aerobic respiration. Hyperglycemia disrupts this feedback mechanism and impairs development of the RGC scaffold, and an *in vivo* model of diet-induced obesity results in mild cortical laminar malformations and neuronal heterotopias. Our findings offer a mechanism by which maternal hyperglycemia, often due to gestational diabetes associated with obesity, could play a role in the pathogenesis of certain developmental disorders of the cerebral cortex.

Disclosures: **B.G. Rash:** None. **T.L. Horvath:** None. **P. Rakic:** None.

Nanosymposium

728. Autism: Physiology and Behavior

Location: 152A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***728.03

**Topic: ***A.07. Developmental Disorders

Support: Simons Foundation
Stanley Center for Psychiatric Illness
Rettsyndrome.org

Title: Mapping microglia heterogeneity in the developing brain using single-cell sequencing

Authors: *T. R. HAMMOND[1], A. WYSOCKER[2], B. SEICOL[1], A. SAUNDERS[3], E. MACOSKO[4], J. NEMESH[2], S. MCCARROLL[5], B. A. STEVENS[6]
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Abstract: Microglia, the brain's resident immune cells rapidly transform from a homeostatic to an "activated" macrophage-like state following injury or disease. Much less is known about microglia's role in the developing brain, a period thought to be disrupted in autism (ASD) and other neurodevelopmental disorders. Emerging evidence suggests microglia perform key functions in the healthy developing brain, including synapse pruning, neurotrophic factor release, and contributions to circuit development and behavior, however microglia signaling during early brain development is still poorly understood. Microglia develop from myeloid progenitors in the yolk sac and infiltrate the brain during the second embryonic week (E8) and have the potential to influence many functions required to build and wire the developing brain. During this time microglia are morphologically and spatially heterogenous, but whether this underlies a diverse functional repertoire is unknown. Several studies have shown that microglia are altered during these critical early periods in neurodevelopmental disorders like ASD, but without a detailed molecular fingerprint it has been impossible to determine how these microglia are altered or might contribute to neural dysfunction.To address microglia diversity in normal developing brain and in environmentally challenged and genetically altered mice, we profiled over 100,000 individual mouse microglia transcriptomes from early embryonic development into early adolescence. We identified several transcriptionally unique subpopulations of microglia that expressed markers of cell division, inflammation/phagocytosis, and cell motility. Some of these subpopulations represented less than 10% of the total microglia in the brain and were spatially restricted to certain brain areas. We created a fingerprint for each subpopulation by identifying genes that were highly enriched specifically in those cells. Interestingly, a single immune challenge during early development shifted the relative number of microglia in each

subpopulation, raising the possibility that specific cellular functions, including signaling and neuron-microglia interactions, could be altered in small subsets of microglia. Our results are the first to create a detailed map of microglia heterogeneity during early development and in a neurodevelopmental disorder model. We have initiated further in depth analysis to determine how different microglia subpopulations might drive normal brain development and whether these different subpopulations could be identified and targeted in individuals with ASD.

Disclosures: T.R. Hammond: None. **A. Wysocker:** None. **B. Seicol:** None. **A. Saunders:** None. **E. Macosko:** None. **J. Nemesh:** None. **S. McCarroll:** None. **B.A. Stevens:** None.

Nanosymposium

728. Autism: Physiology and Behavior

Location: 152A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***728.04

**Topic: ***A.07. Developmental Disorders

Support: European Community's Seventh Framework Programme under the grant agreements No. 115300 (Project EU-AIMS)
European Community's Seventh Framework Programme under the grant agreements No. 602805 (Project EU-AGGRESSOTYPE)
European Community's Seventh Framework Programme under the grant agreements No. 602450 (Project EU-IMAGEMEND)
German Federal Ministry of Education and Research grant No. 01ZX1314GM
German Federal Ministry of Education and Research grant No. 01GQ1102

Title: A functional imaging investigation of typical and atypical development of the social brain

Authors: *C. MOESSNANG[1], A. MOSCICKI[4], U. BRAUN[1], S. BAUMEISTER[2], D. BRANDEIS[2], S. BARON-COHEN[5], S. DURSTON[6], A. M. PERSICO[7], W. SPOOREN[8], D. MURPHY[9], E. LOTH[9], J. BUITELAAR[10], T. BANASCHEWSKI[2], H. TOST[3], A. S. MEYER-LINDENBERG[1]
[2]Dept. of Child and Adolescent Psychiatry and Psychotherapy, [3]Dept. of Psychiatry and Psychotherapy, [1]Central Inst. of Mental Hlth., Mannheim, Germany; [4]Harvard Med. Sch., Boston, MA; [5]Cambridge Univ., Cambridge, United Kingdom; [6]Rudolf Magnus Brain Ctr., Utrecht, Netherlands; [7]Unit of Child and Adolescent Psychiatry, Univ. of Messina, Messina, Italy; [8]Hoffmann-La Roche, Basel CH 4070, Switzerland; [9]Sackler Inst. for Translational Neurodevelopment, King's Col. London, London, United Kingdom; [10]Donders Inst. for Brain, Cognition and Behaviour, Radboud Univ. Nijmegen Med. Ctr., Nijmegen, Netherlands

Abstract: The so-called social brain is a well-defined set of regions that commonly co-activate during the processing of social information. Alterations in the interplay of these regions might contribute to social impairments as encountered in autism spectrum disorder (ASD). We aimed at identifying potential alterations by investigating the typical and atypical development of social brain function. As part of the Longitudinal European Autism Project (Loth et al., 2015), 224 typically developing (TD) individuals and 264 individuals with ASD (6-30 years) performed a spontaneous mentalizing task during functional magnetic resonance imaging (fMRI) at six European sites. Following quality control and the application of standard preprocessing routines (SPM12), fMRI data were analyzed in three complementary ways: 1) Functional activation was assessed as task-specific increase in signal strength; 2) functional connectivity was calculated as task-specific increase in synchrony (i.e. correlation) of time series between regions; and 3) network analysis was used to assess system integration and between-system segregation. Analyses 1) and 2) were based on voxel-wise general linear modeling. For analysis 3), we defined 270 nodes which were assigned to large-scale brain systems (Power et al., 2010), supplemented by an empirically derived social brain network. Within- and between-system segregation was calculated as previously described (Bassett et al., 2015). Effects of diagnosis, age, sex and site were statistically evaluated at $P_{corr}<.05$. Activation analyses revealed robust responses of core structures of the social brain which were not influenced by age or diagnosis. Likewise, functional connectivity was modulated by task demands, but not age and diagnosis. In contrast, network analysis revealed an increasing segregation of the social brain from the rest of the brain with age in both TD and ASD. However, social brain system segregation from the default mode network (DMN) and visuo-sensory areas was delayed in individuals with ASD, the latter of which related to poorer task performance and clinical symptoms. The absence of a clear-cut age and diagnosis effect in conventional fMRI measures (activation, connectivity) suggests that task-triggered responses of the social brain are well developed by the age of 6 in both TD and ASD subjects. Further analyses need to address potential nonlinear effects and additional sources of variance (e.g. IQ, clinical profile). In contrast, network neuroscience approaches were sensitive to age and diagnosis effects, suggesting a delayed disengagement of the social brain from other systems, with behavioral relevance.

Disclosures: C. Moessnang: None. **A. Moscicki:** None. **U. Braun:** None. **S. Baumeister:** None. **D. Brandeis:** None. **S. Baron-Cohen:** None. **S. Durston:** None. **A.M. Persico:** None. **W. Spooren:** None. **D. Murphy:** None. **E. Loth:** None. **J. Buitelaar:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Roche, Vifor. F. Consulting Fees (e.g., advisory boards); Janssen Cilag BV, Eli Lilly, Lundbeck, Shire, Roche, Medice, Novartis, Servier. **T. Banaschewski:** 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.; Shire, Viforpharma. F. Consulting Fees (e.g., advisory boards); Actelion, Hexal Pharma, Lilly, Medice, Novartis, Oxford outcomes, PCM scientific, Shire and Viforpharma, Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. **H. Tost:** None. **A.S. Meyer-Lindenberg:** F. Consulting Fees (e.g., advisory boards); AstraZeneca, Elsevier, F. Hoffmann-La Roche, Gerson Lehrman Group, Lundbeck, Outcome Europe Sárl, Outcome Sciences, Roche Pharma, Servier International, Thieme Verlag, Abbott, Aula Médica Congresos, BASF, Boehringer Ingelheim, Groupo Ferrer

International, Janssen-Cilag, Lilly Deutschland, LVR Klinikum Düsseldorf, Otsuka Pharmaceuticals, Servier Deutschland.

Nanosymposium

728. Autism: Physiology and Behavior

Location: 152A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***728.05

**Topic: ***A.07. Developmental Disorders

Support: Simons SFARI 344904

Title: Disrupted neural circuits in a mouse model of ASD

Authors: *J. GIOVANNIELLO[1], S. AHRENS[2], B. LI[2]
[1]Bo Li Lab., [2]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Autism Spectrum Disorders (ASD) refer to a range of complex neurodevelopmental phenotypes with characteristic symptoms of social interaction difficulties, restricted interests and repetitive behaviors, as well as verbal and non-verbal communication deficits. Though numerous genomic abnormalities have been associated with ASD in patients, very little is known about the circuits disrupted in ASD and how they drive or contribute to aberrant behavioral phenotypes. Using a mouse model, we are examining effects of the most common de novo Copy Number Variation (CNV) found in patients with ASD - the 16p11.2 microdeletion - on learning, sensitivity to feedback, behavioral inhibition, and cognitive flexibility. We believe that disruption of circuits controlling these fundamental cognitive processes may contribute to the repetitive behaviors, deficits in inhibition, self-injurious behavior, and learning differences described in patients with the disorder. Our data suggests mice harboring 16p11.2 microdeletion are more perseverative, less flexible in learning new behavioral contingencies, and generalize learned associations. Furthermore, electrophysiological data suggests that specific neural circuits controlling these behaviors may have elevated activity. Investigating the mechanisms by which 16p11.2 microdeletion disrupts circuits controlling learning, flexibility, and inhibition will illuminate better avenues for treatment of ASD.

Disclosures: J. Giovanniello: None. **S. Ahrens:** None. **B. Li:** None.

Nanosymposium

728. Autism: Physiology and Behavior

Location: 152A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***728.06

**Topic: ***A.07. Developmental Disorders

Support: NIMH grant R01ES019004

Title: Maternal insecticide exposure during pregnancy and risk of autism in offspring from a national birth cohort

Authors: *A. S. BROWN[1,2], K. CHESLACK-POSTAVA[2], P. RANTAKOKKO[3], H.-M. SURCEL[4], S. HINKKA-YLI-SAOMÄKI[4], I. MCKEAGUE[5], H. KIVIRANTA[3], A. SOURANDER[4]
[1]New York State Psychiatric Inst., New York, NY; [2]Columbia Univ., New York, NY; [3]Natl. Inst. for Hlth. and Welfare, Kuopio, Finland; [4]Turku Univ., Turku, Finland; [5]Columbia Univ. Mailman Sch. of Publ. Hlth., New York, NY

Abstract: Dichlorodiphenyl dichloroethene (DDE) is a metabolite of the insecticide DDT and is a persistent organic pollutant. Despite declining levels with time, ongoing prenatal exposure potential exists for nearly all children. DDE is transferred across the placenta, demonstrated by high correlations between levels of this pollutant in maternal serum and placenta and maternal and cord serum. Maternal prenatal serum DDE levels have been correlated with lower scores on standardized early childhood neurocognitive tests and low birthweight.
We sought to examine whether elevated maternal DDE levels during pregnancy were related to an increased risk of autism in a large sample of offspring from a national birth cohort.
The study is based on a nested case-control design. Cases with autism were identified from the national Finnish Hospital Discharge Registry and linked to the Finnish Maternity Cohort, which includes archived maternal serum specimens from virtually all pregnancies in Finland (over 1.5 million). Cases were born from 1987-2005 and followed up until 2007. Cases were matched 1:1 to controls drawn from the birth cohort who were without ASD (N=778 matched pairs) on date of birth, sex, birthplace, and residence in Finland. The samples were assayed for DDE using gas chromatography tandem mass spectrometry (GC-MS/MS). In previous work the detection rate for DDE was >96%. DDE was classified as a dichotomous variable, with the cut-point at the 75th percentile of the control distribution. Data were analyzed using conditional logistic regression for matched pairs.
Maternal exposure to DDE levels in the highest quartile was associated with a 41% increased risk of offspring autism (OR=1.41, 95% CI=1.11-1.80, p=0.005), adjusting for maternal age, parity, and psychiatric history. No associations were observed between maternal levels of polychlorinated biphenyls (PCBs), another persistent organic pollutant, and autism. We found no

evidence that the association between maternal DDE and autism is mediated by perinatal complications.
In conclusion, we found an increased risk of autism among subjects who were exposed during pregnancy to elevated levels of DDE, a metabolite of the insecticide DDT. These data suggest that prenatal exposure to this insecticide is related to the risk of autism in offspring. Strengths of the study include a large, population-based, national sample and prospective measures of exposure. This work may ultimately lead to an improved understanding of the neurodevelopmental mechanisms that underlie autism and suggest preventive strategies.

Disclosures: A.S. Brown: None. **K. Cheslack-Postava:** None. **P. Rantakokko:** None. **H. Surcel:** None. **S. Hinkka-Yli-Saomäki:** None. **I. McKeague:** None. **H. Kiviranta:** None. **A. Sourander:** None.

Nanosymposium

728. Autism: Physiology and Behavior

Location: 152A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***728.07

**Topic: ***A.07. Developmental Disorders

Support: Department of Defense Grant AR140105
Arizona Alzheimer's Disease Core Center Grant NIA P30 AG19610-03
State of Arizona Alzheimer's Consortium

Title: Large-scale brain networks in middle-aged adults with autism spectrum disorder: Functional connectivity differences and relationships with symptoms

Authors: *M. STOECKMANN[1,2], L. BAXTER[3], C. SMITH[4], B. BRADEN[2]
[1]Dept. of Speech and Hearing Sci., Autism Brain Aging Lab., Tempe, AZ; [2]Arizona State Univ., Tempe, AZ; [3]Neuroimaging, Barrow Neurolog. Inst., Phoenix, AZ; [4]Southwest Autism Res. & Resource Ctr., Phoenix, AZ

Abstract: ***Background***: Autism spectrum disorder (ASD) has become known for its prevalence and heterogeneity, but it is less known that the first adults diagnosed with ASD are approaching advanced aging. Yet, there is little research on aging adults with ASD. Abnormalities observed in resting-state functional connectivity (rs-FC) of large-scale brain networks are thought to underlie ASD symptoms. These rs-FC abnormalities parallel the changes observed in normal aging adults that are linked to age-related cognitive decline. Collectively, this raises concern that large-scale networks are vulnerable to exacerbated age-related changes in adults with ASD. Understanding rs-FC profiles in older adults with ASD and relationships with symptoms has the

potential to delineate the unique needs of this population and inform appropriate interventions.
Methods: Using a six-minute, eyes closed MRI scan, we evaluated differences in rs-FC of the default mode network (DMN), executive network (EN), and salience network (SN). Participants were 24 middle-age (40-64 years) adults with high-functioning ASD and 19 neurotypical (NT) controls. Independent component analysis was used to identify rs-FC networks, and group comparisons were made using SPM12. Correlations between network rs-FC in middle-age adults with ASD and core symptom profiles from the Social Responsiveness Scale-2 and Repetitive Behavior Scale-Revised were also investigated using SPM12.
Results*:* Groups were well-matched according to age, IQ (83-131), and education (9-20 years). No significant group differences in network connectivity were observed in key network nodes of the DMN and SN between the middle-aged adults with ASD and NT participants. However, ASD participants demonstrated significant hypoconnectivity in the right dorsolateral prefrontal cortex of the EN (p=.02, FWE-corrected). Furthermore, a significant correlation was observed between connectivity in this region and social symptom severity (r(21)=-.43, p=.04) in ASD participants.
Conclusions*:* In one of the first rs-FC investigations of older adults with high-functioning ASD, we demonstrated hypoconnectivity in the EN, but not the DMN and SN, compared to well-matched NT adults. Furthermore, the relationship between EN rs-FC and social symptom severity sheds light on the brain mechanisms underlying symptoms in older adults with ASD. Future research will examine differential aging trajectories for rs-FC between adults with ASD and NT.

Disclosures: M. Stoeckmann: None. **L. Baxter:** None. **C. Smith:** None. **B. Braden:** None.

Nanosymposium

728. Autism: Physiology and Behavior

Location: 152A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***728.08

**Topic: ***A.07. Developmental Disorders

Support: NIH - K01-MH103594
NIH - R01-NS078223

Title: Imaging brain function in children with autism spectrum disorder with diffuse optical tomography

Authors: *A. T. EGGEBRECHT[1], J. P. CULVER[2]
[1]Dept. of Radiology, Washington Univ. Sch. of Med., St Louis, MO; [2]Radiology, Washington Univ. in St Louis, Saint Louis, MO

Abstract: Autism Spectrum Disorder (ASD), defined by deficits in social functioning, communication, and restricted interests/repetitive behaviors is a serious psychiatric disorder of childhood. Previous neuroimaging studies using task-based functional magnetic resonance imaging (fMRI) have identified specific brain regions that exhibit significantly different responses during processing of language paradigms or socially-relevant stimuli in participants with ASD than in typically developing controls. However, the loud and constraining environment of MRI-based neuroimaging severely limits studies on auditory processing and language generation and especially direct within-room social interactions. MRI is also a challenging setting for sensitive participants, such as school-aged and, in particular, young children or those severely affected with ASD. Diffuse Optical Tomography (DOT) provides a silent and wearable technology (Fig. 1a-c) ideally suited to naturalistic investigations of language and social communication processing in school-aged children with autism (Fig. 1d). Feasibility of DOT-based neuroimaging in school-aged children with (n=20, age range 9-15 yrs) and without ASD (n=10, age range 8-15 yrs) was established by assessing (1) the time in the imaging system, (2) raw data quality metrics, (3) maps of brain function in response to language (Fig. 1e,f) and biological motion tasks (Fig. 1g). In summary, this study establishes initial feasibility to apply DOT in research on school-aged participants with ASD. We are currently collecting data on more subjects, expanding the task paradigms to include within-room dyadic social interactions, and applying the methods to younger participants including toddlers.

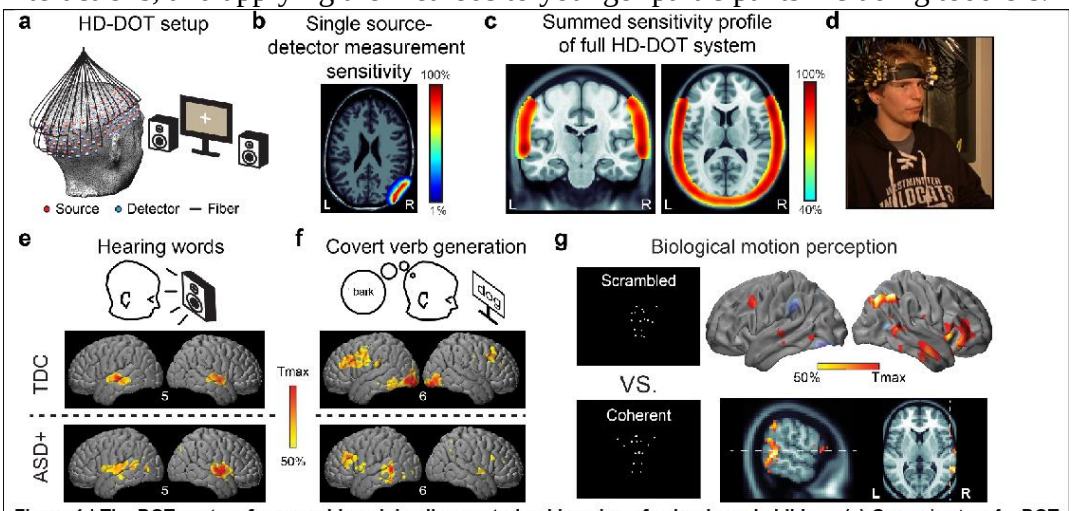

Figure 1 | The DOT system for wearable, minimally constrained imaging of school-aged children. (a) General set-up for DOT (a subset of fiber optics shown for clarity). Participants sit in an adjustable chair opposite a LCD monitor and stereo speakers. **(b)** Sensitivity of a single source-detector measurement. **(c)** The high density grid provides multiple overlapping measurements that when combined create a smooth sensitivity profile throughout the imaging domain. **(d)** Cap fit on example school-aged participant with ASD (image courtesy of www.ivanhoe.com). **(e-f)** Functional brain activations reflecting language processing in response to **(e)** passive hearing of words or **(f)** active covert generation of verbs averaged within the respective groups (TDC, typically developing controls; ASD+, autism spectrum disorder). Color bar reflects random-effects t-tests within each group. **(g)** Coherent and scrambled point-like movies of biological motion were presented in an alternating block design (6 blocks, 24 seconds each). A GLM-based contrast map (coherent vs scrambled) was generated for each participant. A random-effects t-map across all participants is displayed both on an inflated cortical surface (top) and on slices through the volume (bottom), revealing expected strong differential activity in the superior temporal sulcus (on all images, left is on left).

Disclosures: A.T. Eggebrecht: None. **J.P. Culver:** None.

Nanosymposium

728. Autism: Physiology and Behavior

Location: 152A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***728.09

**Topic: ***A.07. Developmental Disorders

Title: Awake mouse functional MRI for the detection of the abnormal neural circuit in autism model mouse

Authors: *T. TSURUGIZAWA[1], K. TAMADA[2], A. KITAMURA[3], N. ONO[3], S. KARAKAWA[3], Y. KODAMA[3], T. TAKUMI[2]
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Abstract: Preclinical MRI using small animal could be useful for translational approach from rodent model to humans. However, given that the current mouse functional MRI (fMRI) requires the anesthetics for suppression of motion and physiological noise, it has been difficult to directly compare the result of fMRI in “unconsciousness” mice of disease model with that in “consciousness” patients. Here, we developed the awake fMRI protocol in the mouse to perform the fMRI study (resting state fMRI (rsfMRI) and odor cognition task in the MRI bore) in *15q dup* mice, a copy number variation model of autism spectrum disorder (ASD), and wild type (WT) mice. Furthermore, we compared the result of fMRI with the brain amino acid profile and social behavior. The abnormal functional connectivity and brain activation to odor cognition task was observed in ASD mice. The profile of amino acid concentration in the forebrain was altered in ASD mice. Our results indicate that awake fMRI is useful to investigate the alteration of brain function in ASD model mice.

Disclosures: T. Tsurugizawa: None. **K. Tamada:** None. **A. Kitamura:** None. **N. Ono:** None. **S. Karakawa:** None. **Y. Kodama:** None. **T. Takumi:** None.

Nanosymposium

729. Protective and Pathogenetic Mechanisms in Alzheimer's Disease

Location: 140A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***729.01

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

Support: Bright Focus A2016397S
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Title: Validation of novel genetically diverse mouse model for understanding complex etiology of Alzheimer's disease

Authors: *S. M. NEUNER[1,2], R. RICHHOLT[3], M. DE BOTH[3], M. J. HUENTELMAN[3], K. M. S. O'CONNELL[2], C. C. KACZOROWSKI[2]
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Abstract: Alzheimer's disease (AD) is a complex and multifactorial neurodegenerative disease that is difficult to study in human populations. Model systems, particularly mouse models of AD, provide an important resource in which to study mechanisms that contribute to disease development. However, current mouse models of AD that are maintained on a single or few genetic backgrounds have failed to translate into effective therapeutics. We hypothesize lack of genetic diversity in existing mouse models may be a leading cause of discrepancy between mouse and human AD. In order to test this hypothesis, we have developed a novel mouse panel that incorporates high-risk human familial AD (FAD) mutations on a background of genetic diversity (BXD panel). The result is a genetically diverse mouse panel whose members harbor identical 'high-risk' human FAD mutations, referred to as the AD-BXDs. We monitored cognitive function in these mice across their lifespan and show that age at first symptom onset varies widely in our panel, paralleling the variation observed in human FAD populations. Comparison of the AD-BXD hippocampal transcriptome to published datasets generated from alternative mouse AD models and human tissue revealed greater similarity between the transcriptional profile of our AD-BXD panel and that of human AD brain. Finally, we identify the APOE locus as a significant modifier of cognitive deficits at 14 months of age. Overall, we demonstrate that the incorporation of genetic diversity into the study of AD genetics better recapitulates the genetic, transcriptomic, and phenotypic hallmarks of human AD, suggesting the new QTLs and candidate genes identified here are highly likely to be informative for human AD. Due to the reproducible nature of our panel, the AD-BXDs represent an outstanding resource that is poised to not only contribute significantly to our understanding of the genetic and molecular mechanisms underlying AD but also enhance the general utility of mouse models of complex disease.

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Nanosymposium

729. Protective and Pathogenetic Mechanisms in Alzheimer's Disease

Location: 140A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***729.02

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

Title: A novel angiotensin converting enzyme 1 mutation is associated with increased risk for Alzheimer’s disease and may reduce cell survival

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Abstract: Introduction; The Cure Alzheimer’s Fund Genome Project identified a novel, highly penetrant mutation in the angiotensin converting enzyme 1 (ACE1) gene that is associated with increased risk for Alzheimer’s disease (AD). ACE1 is best known for converting angiotensin I to the vasoconstrictor angiotensin II (AngII), thus raising blood pressure. This functional variant could cause AD pathogenesis by increasing angII production, since midlife hypertension has been previously associated AD. However, ACE1 is expressed in all tissues, can cleave a broad array of substrates including amyloid-beta (Aβ) and has been implicated in diverse physiological functions. Therefore, it is conceivable that any of the myriad ACE1 functions in the brain or periphery could have a role in AD pathogenesis. The goal of this study is to investigate the mechanism by which this mutation increases the risk of AD.
Methods; CRISPR-Cas9 gene editing was used to introduce the AD-associated ACE1 mutation into the murine genome to make cognate mutant knock-in (KI) mice. The role of mutant ACE1 in AD pathogenesis was investigated *in vitro* in cortical neurons from wild-type (WT) and KI mice and in human neuronal SH-SY5Y cells stably expressing either WT ACE1 or mutant ACE1 and *in vivo* in aged cohorts of WT and KI mice. To determine the effect of ACE1 KI on amyloid pathology, rAAV1- BRI2-Aβ-42, or control rAAV1-BRI2-KR, were stereotaxically injected into the hippocampus and cortex of 3 month old WT or KI mice.
Results; KI mice show significantly higher ACE1 protein levels in both cortical and cerebellar brain regions compared to WT mice. ACE1 levels are also higher in cultured cortical neurons from KI mice than in cortical neurons isolated from WT mice. Unexpectedly, expression of mutant ACE1 reduces cell survival in both mouse cortical neurons and in stably overexpressing human SH-SY5Y cells. The mechanism by which mutant ACE1 affects cell survival remains unclear but preliminary data suggest that the unfolded protein response activates endoplasmic reticulum stress pathways and induces apoptosis.
Conclusions; Our findings show that a novel mutation in ACE1 increases the risk of AD at least in part by increasing neuronal cell death. These studies will provide information about the physiological function of neuronal ACE1, and how altered ACE1 function may cause AD.

Disclosures: **L.K. Cuddy:** None. **R.E. Tanzi:** None. **R.J. Vassar:** None.

Nanosymposium

729. Protective and Pathogenetic Mechanisms in Alzheimer's Disease

Location: 140A

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Presentation Number: *729.03

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

Title: Retromer viral vector technology for Alzheimer's Disease

Authors: ***Y. H. QURESHI**[1], D. E. BERMAN[1], R. L. KLEIN[2], V. M. PATEL[1], G. A. PETSKO[3], S. A. SMALL[1]
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Abstract: Recent genetic and cell biological findings in Alzheimer's disease (AD) have implicated 'endosomal trafficking' as playing central role in disease pathophysiology. Retromer is a protein assembly that has emerged as a "central conductor" of endosomal trafficking, and a range of studies have linked retromer defects to AD. Retromer's core is a trimer of proteins, Vps35, Vps26, and Vps29. While previous studies in cell culture and in invertebrate models are suggestive, it remains unclear whether increasing retromer levels in the living mammalian brain can improve endosomal function and ameliorate indicators of AD.
In this study we address this outstanding question, and its overarching hypothesis-- based on previous and preliminary data-- is that increasing the expression of one key retromer protein in the mouse brain will enhance retromer and endosomal function and ameliorate indicators of AD. In order to test this hypothesis we used a systematic series of studies, beginning with a cell culture systems to address two related and fundamental questions: Overexpression of which retromer core protein best increases retromer and endosomal function? And, which protein tagging system is best suited for mapping its expression without disrupting function? We tested VPS35 tagged with HA and GFP in HeLa cells and then proceeded with development of AAV9 vectors using these constructs. We have identified that tagging retromer with a bulky GFP protein at the c-terminal results in some loss of its function and even toxicity in some cases, whereas a smaller tag like HA does not have these issues. Using a Vps35-HA construct we were able to achieve stable levels of expression of Vps35-HA (~89%), in mouse primary neurons, which led to secondary increases in Vps29 (~83%), Vps26a (21%) and cation independent mannose 6-phosphate receptor (CI-M6PR) (~27%). Conditioned medium from these experiments showed a decrease in production and/or secretion of Aβ fragments. We are now in the process of validating these findings in-vivo mouse models of AD by stereotactically injecting these viruses

in specific brain regions.
Our data supports the hypothesis that we will successfully identify the optimal expression vector for increasing retromer function. We believe that the results of this study will further strengthen the mechanistic and causal link between retromer and AD pathophysiology and will open up a novel therapeutic avenue for AD interventions.

Disclosures: Y.H. Qureshi: None. **D.E. Berman:** None. **R.L. Klein:** None. **V.M. Patel:** None. **G.A. Petsko:** None. **S.A. Small:** Other; Memebr Scientific advisory board of Denali Therapeutics, Memebr Scientific advisory board of Janssen Pharmaceuticals.

Nanosymposium

729. Protective and Pathogenetic Mechanisms in Alzheimer's Disease

Location: 140A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***729.04

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

Support: INNT
Capes
CNPQ

Title: Boosting monoaminergic transmission counteracts cognitive and psychiatric symptoms in Alzheimer’s disease

Authors: *D. BECKMAN[1,2], J. H. LEDO[2], L. E. S. SANTOS[2], M. V. LOURENCO[2], F. C. RIBEIRO[2], S. BOSCHEN[4], J. T. S. FORTUNA[2], C. D. CUNHA[4], P. F. GARDINO[3], F. G. DE FELICE[2,5], S. T. FERREIRA[2,3]
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Abstract: Alzheimer’s disease (AD) is the most common form of dementia in the elderly, and is clinically characterized by progressive cognitive deficits and memory loss. These hallmark symptoms are accompanied by important but frequently overlooked psychiatric disturbances, including depression, a major co-morbidity and risk factor for AD. Physiologically, serotonin and dopamine modulate motivation and several aspects of mood and cognition. However, their potential roles in the pathophysiology of AD and AD-related depression remain largely unexplored. Here, we show that exposure to Aβ oligomers (AβOs), toxins known to trigger synapse failure and cognitive impairment in AD, induce microglial activation and decrease

serotonin levels in the mouse brain. Pharmacologically reducing inflammation restores serotonin levels and prevents depressive-like behavior triggered by intracerebroventricular administration of AβOs. We also report that dopamine signaling is impaired in in vitro and in vivo models of AD, and that selective activation of dopamine D1 receptors rescues AD-linked synaptic and behavioral deficits. Notably, enhancing dopamine signaling with bupropion, a clinically employed dopamine reuptake inhibitor, rescues anhedonia and social interaction deficits induced by AβOs in mice. Our findings suggest that defective monoaminergic signaling underlies mood and cognitive alterations in AD. Results further point to boosting monoaminergic signaling as a promising approach to combat the cognitive deficits and psychiatric disturbances of AD patients.

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Nanosymposium

729. Protective and Pathogenetic Mechanisms in Alzheimer's Disease

Location: 140A

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

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Title: Intersection of TREM2-C1q in Alzheimer disease

Authors: *B. P. LEUNG[1], K. R. DOTY[2], C. J. MILLER[3], T. M. WEITZ[5], A. W. VESLING[3], M. F. UCHOA[1], K. W. IM[1], D. GATE[6], A. M. QUIHUIS[1], M.-V. GUILLOT-SESTIER[7], J. RODRIGUEZ, Jr[7], K. T. CHANG[4], A. J. TENNER[8], M. COLONNA[9], T. TOWN[10]
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Abstract: Alzheimer disease (AD), the most common form of dementia, robs patients of their memories and their identity. In addition to environment, genetic variants are key risk factors for late onset AD (LOAD). Recent gene-wide association studies and gene-network analyses indicate that two distinct innate immune pathways are strongly associated with LOAD: Triggering Receptor Expressed on Myeloid cells 2 (TREM2) and the protein complement system. While classically regarded to regulate different immunological responses, we now show that TREM2, C1q, and Aβ physically interact in a heteromeric complex. We further demonstrate that monomeric Aβ preferentially binds to TREM2, while C1q more avidly associates with Aβ aggregates. These findings have important implications for immunoproteostasis. TREM2 expression is significantly altered in LOAD brains, and studies in the TgF344-AD rat model show that TREM2 is expressed by peripheral mononuclear phagocytes as opposed to brain-resident microglia. Strikingly, compound genetic loss of TREM2 and C1q leads to dramatically altered AD-like pathological features in mouse models. Lack of TREM2 expression promotes a form of innate immune tolerance to Aβ in microglia, which is broken in TREM2-expressing peripheral mononuclear phagocytes. These results indicate an unexpected interaction between TREM2 and C1q in AD pathogenesis.

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Nanosymposium

729. Protective and Pathogenetic Mechanisms in Alzheimer's Disease

Location: 140A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***729.06

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

Support: Alberta Innovates / Alberta Prion Research Institute

Title: Expanding roles for prion protein PrP^C in Alzheimer Disease: An ancient conserved interaction

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Abstract: Aims: The normal biology of PrP^C and APP, especially including the molecular mechanisms behind their diverse roles, remains largely unexplored despite years of intense study of their misfolded/ aggregated forms in prion diseases and Alzheimer’s disease (AD),

respectively. Many normal functions of these proteins are partially lost and/or subverted during the course of disease, and understanding their normal physiology enables alternative therapeutic avenues. We previously expanded upon a role for PrP^C in AD by demonstrating its interaction with the APP holoprotein, via co-IP and concerted knock-down/replacement in zebrafish. Here we improve the latter genetic approach by engineering mutant zebrafish and further stringent tests of reagent specificity. **Methods:** We generated zebrafish *prp1* and *appa* loss-of-function alleles as well as zebrafish compound *prp1*$^{-/-}$*; prp2*$^{-/-}$ mutants and compound *prp1*$^{-/-}$;*appa*$^{-/-}$ mutants. Morpholinos were used to accomplish acute gene knockdown and were used in these mutants to assess reagent specificity. **Results:** Zebrafish *prp1*$^{-/-}$ and compound *prp1*$^{-/-}$;*prp2*$^{-/-}$ mutants resemble mammalian *Prnp* knockouts insofar as they lack overt phenotypes, which surprisingly contrasts reports of severe phenotypes when either *prp1* or *prp2* are acutely knocked down. Unexpectedly, *appa*$^{-/-}$ and compound *prp1*$^{-/-}$;*appa*$^{-/-}$ mutants also lacked overt phenotypes, but were slightly smaller than wild type fish at some developmental stages. In remarkable contrast, *appa*$^{-/-}$ mutants were more sensitive to *prp1* knockdown than wild type fish, demonstrating a genetic interaction during neural development. Similarly, *prp1*$^{-/-}$ mutants were more sensitive to *appa* knockdown than wild type fish. Both *prp1* and mammalian *Prnp* mRNA could rescue these effects. **Conclusion:** Taken together, these results support a fascinating genetic interaction between *prp1* and *appa*, support specificity of the mutant phenotypes, and raise novel questions about differences in acute vs. long-term loss-of-function in these pathways. The results confirm ancient conserved roles for the prion protein and key members of its interactome, and thus an expanded role for PrP^C in AD. Appreciating roles for the loss and subversion of protein function that accompanies misfolding in prion-like diseases is likely to inspire and inform therapeutic options. Zebrafish provide a tractable platform to assess these roles via delivery and comparison of mammalian homologs accompanied by increasingly elegant fluorescent reporters of neuron morphology and function.

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Nanosymposium

729. Protective and Pathogenetic Mechanisms in Alzheimer's Disease

Location: 140A

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

Support: CNPq
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ISN/CAEN 1B Grant

Title: FNDC5/irisin corrects memory deficits in animal models of Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by brain amyloid deposition, synaptic failure and memory loss. Mounting clinical and experimental evidence has indicated that regular physical exercise reduces AD risk in the elderly and attenuates cognitive decline in AD patients. Still, neuroprotective actions of physical exercise have not been fully elucidated. FNDC5/irisin is an exercise-derived myokine also expressed in the brain, where it induces neurotrophic factors. Here we aimed to determine if FNDC5/irisin levels are altered in AD, and whether restoring FNDC5/irisin levels could protect against memory dysfunction in experimental models of AD. We initially found that FNDC5/irisin levels are reduced in the brains and cerebrospinal fluid of AD patients, and in the brains of APP/PS1 mice. AβOs reduced FNDC5/irisin in cultured hippocampal neurons, and in the hippocampus of mice given an intracerebroventricular injection of AβOs. Furthermore, knockdown of brain FNDC5/irisin induces object recognition memory impairment in wild-type mice. Finally, restoring brain FNDC5/irisin levels, either pharmacologically, through adenoviral expression or through regular physical exercise, corrected memory failure in mouse models of AD. Our findings uncover new potential protective actions of FNDC5/irisin against memory impairment in AD models, likely contributing to identify novel therapeutic targets in AD and to help explain neuroprotective actions of physical exercise against dementia.

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Nanosymposium

729. Protective and Pathogenetic Mechanisms in Alzheimer's Disease

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

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Title: Roles of amyloid-beta precursor protein and metabolites in acute traumatic brain injury

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Abstract: Traumatic brain injury (TBI) is widely prevalent in the USA, primarily due to falls, unintentional blunt trauma, and motor vehicle collisions. While certain behavioral diagnoses of TBI, such as post-concussive symptoms and loss of consciousness, have become associated with TBI onset, a biological biomarker profile has remained difficult to ascertain. We examined blood samples for the identification of possible biomarkers. We hypothesized the involvement of amyloid-beta precursor protein (APP) and its metabolites as indicator of neuronal health. Therefore, we examined samples from 12 patients diagnosed with TBI from day 1 (admission) up to 9 of hospital stay and measured levels of total soluble APP (sAPP). Mixed-level GLM vs the Glawsgow Coma Scale (GCS) showed significant effects for sAPP and for the interaction between sAPP and length of stay and between sAPP and disposition at discharge (alive vs. dead). Specifically, as sAPP increased, GCS decreased, and this relationship was more intense for longer stays and for patients who survived. We also measured potentially toxic Aβ40, and this increased over time in both patients, suggesting an upregulation of the amyloidogenic pathway. Our observations suggest that soluble total APP may have diagnostic and/or mechanistic potential in the study of TBI. We have previously demonstrated regulatory roles for microRNA (miRNA) species and expression of APP and its processing enzymes. TBI could disrupts miRNA profiles. Given the inverse relationship between sAPP and GCS, we suggest the enhanced levels of APP may grant net neuroprotection in the short term. The limited patient set suggests that specific metabolites of APP may play important roles.

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Nanosymposium

729. Protective and Pathogenetic Mechanisms in Alzheimer's Disease

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Washington University School of Medicine
Hope Center for Neurological Diseases

Title: The diversity of amyloid-beta proteoforms in alzheimer's disease brain

Authors: *N. C. WILDBURGER[1], T. J. ESPARZA[1], R. D. LEDUC[4], R. T. FELLERS[4], P. M. THOMAS[4], N. J. CAIRNS[1,2], N. L. KELLEHER[4,5,6], R. J. BATEMAN[1,2,3], D. L. BRODY[1,3]
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Abstract: Background: Amyloid-beta (Aβ) plays a key role in the pathogenesis of Alzheimer's disease (AD), but the toxic forms of this protein present in human AD brain are poorly understood. We used high-resolution mass spectrometry to analyze intact, undigested Aβ from purified soluble aggregates and insoluble material in brains of six cases with severe dementia and pathologically confirmed AD.
Methods: Human frontal cortical tissue samples were obtained from the Knight ADRC at Washington University School of Medicine. Extraction and separation of soluble Aβ aggregates and more insoluble material is described in detail in Esparza *et al* 2016. Briefly, 1 g of frozen frontal cortical samples were dounce homogenized at a 10:1 buffer-to-tissue ratio. The resulting homogenate was processed via differential centrifugation. The 100k and 475k x g pellets were immunoprecipitated with 100 uL/mL sepharose beads conjugated to HJ3.4 and HJ5.1 antibodies. 5 ng of Aβ eluant from each sample was analyzed by top-down mass spectrometry (MS).
Results: We found a diversity of Aβ peptides, with 26 unique proteoforms including various N- and C-terminal truncations. N- and C-terminal truncations comprised 73% and 30%, respectively, of all Aβ proteoforms. The truncated Aβ proteoforms segregated between the soluble aggregates and more insoluble material with N-terminal truncations predominating in the more insoluble material and C- terminal truncations segregating into the soluble aggregates. In contrast, canonical Aβ comprised the minority of the identified proteoforms (15%) and failed to distinguish the soluble aggregates from the more insoluble material. Lastly, post-mortem interval (PMI) correlated highly with the oxidation status of Aβ. We observed a decrease in the soluble aggregates as a function of PMI (≥12 hrs), but an increase in oxidized Aβ proteoforms in the more insoluble fraction. However, PMI was not correlated with the relative abundance of truncated Aβ, suggesting they are not the result of post-mortem artifacts.
Conclusions & Future Directions: The heterogeneity of Aβ proteoforms deepens our understanding of AD and offers new avenues for investigation into pathological mechanisms of the disease, with implications for therapeutic development. The truncated, soluble forms of Aβ may be a new target for therapeutic development, as no publicly disclosed antibody therapeutic

specifically recognizes these proteoforms. Future work will examine the abundance of these proteoforms in AD progression, as certain Aβ proteoforms may play a role in the pathogenesis of AD. In addition, we are continuing to improve the sensitivity of our MS method to map additional novel proteoforms.

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Nanosymposium

729. Protective and Pathogenetic Mechanisms in Alzheimer's Disease

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

Support: AG054025
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Title: Tau-induced neurodegeneration in TBI brain

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Abstract: Neurodegeneration following traumatic brain injury (TBI) is well documented, and late-life dementia is directly correlated to the severity of TBI. A clinical study done on TBI-exposed US Navy and Marine veterans demonstrated that moderate TBI, characterized by loss of consciousness (LOC) for 1-24 hours, doubles the risk, and a severe TBI, LOC for more than 24 hours, quadruples the risk for late-life dementia. Unlike a single mild TBI exposure, repetitive mild TBI exposure is also considered to increase the risk for late-life dementia. Recent studies propose that TBI-induced dementia and Alzheimer’s disease might share a tau induced-neurodegeneration mechanism. Mechanisms underlying TBI-induced neurodegeneration, and the potential role of tau oligomeric strains in TBI-induced dementia are still unclear. The lack of treatment/preventive methods that protect against TBI-induced dementia necessitates the investigation of the role of tau oligomers in TBI-induced neurodegeneration. Therefore, in this study, we characterize TBI brain-derived tau aggregates and investigate their toxicity. Tau oligomers were isolated by immunoprecipitation from 4 different groups of mice depending on the TBI paradigm and time point after TBI. The following brains were collected: 1) sacrificed at

24 hours after a 50 psi single blast treatment, 2) sacrificed at 3 weeks after a 50 psi single blast treatment, 3) sacrificed at 3 weeks after repeated blast treatment (6 blasts over two weeks), 4) sacrificed at 3 weeks following anesthesia (sham group). The isolated tau oligomers were seeded with recombinant tau proteins and further analyzed biochemically via dot blot, Elisa, western blotting, and Proteinase K (PK) digestion. Moreover, their toxicity, internalization and spreading were tested in cell culture. Results show that the TBI brain-derived tau samples resemble tau oligomeric strains in terms of PK digestion pattern and reactivity with tau oligomer monoclonal antibodies. In addition, some of the samples were found to be toxic, and expressed different internalization levels into SY5Y cells in culture. Results suggest that different TBI brain-derived tau oligomeric-like strains contribute to the neuronal death observed after TBI. Future experiments will investigate the samples' differential ability to induce cell toxicity and neurodegeneration in vitro and in vivo. Results hold substantial translational implications towards applying tau-immunotherapy techniques to reduce the risk for late-life dementia.

Disclosures: **A. Bittar:** None. **T.F. Hasan:** None. **F. Bassal:** None. **B. Lucke-Wold:** None. **A. Logsdon:** None. **C. Rosen:** None. **R. Turner:** None. **R. Kayed:** None.

Nanosymposium

729. Protective and Pathogenetic Mechanisms in Alzheimer's Disease

Location: 140A

Time: *Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

Presentation Number: *729.11

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

Support: NIH Grant R01AG047116

Title: Assembly of A and A familial mutants: Structures and mechanism

Authors: ***M. T. BOWERS**[1], M. DOWNEY[1], M. GIAMMONA[2], S. K. BURATTO[1]
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Abstract: The current paradigm for initiation of Alzheimer's disease, and other important diseases like Type 2 Diabetes and Parkinson's disease, is the formation of oligomers of strategic peptides or proteins that then proceed to damage of kill neurons or other cells essential for bodily function. While this is now a widely accepted mechanism it has proven extremely difficult to study the oligomer formation and structural evolution process using standard bio-analytical tools. It is also very difficult to determine the mechanism for transitioning between oligomers and fibrils and the potential importance this may have on disease etiology. Here we present recent results using a combination of ion mobility based mass spectrometry (IMS-MS) and atomic force

microscopy (AFM) to provide definitive information on structures of size selected oligomers and their mechanism of transition to higher order assemblies for Aβ40 and Aβ42 for both wild type and several familial mutants. The structures and mechanisms are surprisingly different in all cases even for what appears to be the most minor familial mutant A21G. The results will be discussed.

Disclosures: **M. Downey:** None. **M. Giammona:** None. **S.K. Buratto:** None.

Nanosymposium

729. Protective and Pathogenetic Mechanisms in Alzheimer's Disease

Location: 140A

Time: *Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

Presentation Number: *729.12

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

Support: NIH Grant R21AG046711-01

Title: Prion-like amyloid seeding from Alzheimer's disease and pathological aging brain lysates

Authors: ***B. MOORE**[1], S. FROMHOLT[1], J. M. LEWIS[2], D. R. BORCHELT[3]
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Abstract: Recent studies have shown that amyloid-β (Aβ) deposition can be induced by protein templating or seeding, similar to prion disease. Hippocampal injection of brain extracts derived from either aged β-Amyloid precursor protein (APP) mouse models or human Alzheimer's disease (AD) brains can induce Aβ deposition in APP transgenic mice, similar to prion protein. Targeting the formation of these Aβ seeds is an ideal therapeutic strategy for treating AD during its earliest stages. Pathological aging (PA) patients are thought to represent a prodromal phase of AD. PA patients are reported to be cognitively normal prior to death even though they have abundant and widespread amyloid plaques; described as diffuse in nature. There are fewer cored plaques and there is little or no inflammatory reaction, neuritic pathology or neurofibrillary tangles in the cortex. Our laboratory analyzed sequentially extracted Aβ peptides from the pre-frontal cortex of AD patients, PA patients and non-demented control patients. We found Aβ levels in PA lysates were similar to the levels in AD lysates, overlap between PA and AD Aβ peptide profile and no major differences in SDS-stable Aβ oligomeric assemblies. These results could suggest that PA represents a prodromal phase of AD and these individuals would eventually develop clinical symptoms of AD, if they lived long enough. Alternatively, the amyloid pathology of PA cases could be a distinct strain, conformer, of Aβ that is less prone to progress to full-blown AD with neurofibrillary tangle pathology and neurodegeneration.
In this study, we examined the seeding capacity of AD, PA and control brain homogenates in a

mouse model derived from crosses of Tg-APPswe/ind mice to 4R0Ntau$_{P301L}$ mice. Neonatal mice expressing APP, Tau or APP and Tau were injected intracerebrally at neonatal day 0 and were aged either 6, 9, 12 or 18 months. Amyloid deposition and neurofibrillary pathology were assessed in all 4 genotypes by immunohistochemical and biochemical methods. AD lysates seeded widespread, diffuse amyloid deposition in APP mice, but not Tau or NTg mice; Tau pathology was not induced. We observed variability in seeding efficiency of the PA lysates, one of four robustly induced amyloid deposition by 12 months of age while three modestly seeded amyloid deposition. In all cases of animals injected with PA brain, we observed an accumulation of insoluble Aβ42. This study provides epidemiological evidence that Aβ conformers, from non-demented PA patients, are capable of seeding accelerated Aβ deposition. These models may provide a platform to gain insight towards the question of whether there are polystructural and/or polyfunctional strains of Aβ in AD.

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Nanosymposium

730. Amyloid-Beta and Tau Biochemistry and Toxicity

Location: 150A

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**Presentation Number: ***730.01

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

Support: NIH Grant AG051085
Owens Family Foundation
Cure Alzheimer's Fund
Alzheimer's and Related Diseases Research Award Fund Grant 17-5
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NIH Grant EB020843

Title: A novel lysosome-to-mitochondria signaling pathway disrupted in Alzheimer's disease

Authors: A. NORAMBUENA, H. WALLRABE, Z. SVINDRYCH, D. BIGLER-WANG, R. CAO, S. HU, *G. S. BLOOM
Univ. of Virginia, Charlottesville, VA

Abstract: Healthy mitochondria allow proper delivery of nutrient-derived energy as ATP, and provide timely clearance of reactive oxygen species and buffering of calcium. These functions are fundamental for maintaining neuronal homeostasis. However, current methods to track mitochondrial metabolism in live cells or tissues have limited discovery of the molecular mechanisms controlling activity and how they go awry in disease. We have developed a two-

photon fluorescence life time imaging assay that detects mitochondrial activity in live cultured cells by monitoring autofluorescence of the coenzyme(s), NAD(P)H, specifically in mitochondria. Variations in enzyme-bound NAD(P)H fractions are used as a read-out for changes in mitochondrial activity. In primary mouse cortical neuron cultures and human neural progenitor cells, added nutrients (arginine plus leucine) or insulin induce rapid increases in perikaryal mitochondrial activity. This effect was negatively regulated by: 1)Torin1, an inhibitor of mTOR, the catalytic subunit of two kinase complexes, mTORC1 and mTORC2, which regulate intracellular behavior by sensing extracellular cues; 2) knocking down Raptor, an essential mTORC1 subunit; or 3) forcing mTORC1 to associate with the plasma membrane instead of lysosomes. Moreover, we found that this new pathway does not involve mTORC1-mediated regulation of mRNA translation, protein synthesis, or fatty acid transport into mitochondria, but instead mTORC1-dependent signaling that is disrupted by soluble oligomeric forms of the amyloid-β peptide (Aβ), a main driver of Alzheimer's disease (AD). In contrast, nutrient-induced mitochondrial activity (NiMA) did not involve: 1) mTORC2 activity; 2) eIF4E, which mediates mTORC1-regulated mRNA translation; or 3) tau or α-synuclein. NiMA was found to occur independently of autophagy or fatty acid transport into mitochondria, but was strongly reduced by Aβ oligomers (AβOs), which activate mTORC1 at the plasma membrane, but not at lysosomes (Norambuena et al, 2016. Alzheimers Dement. 13(2017): p.152-167). Furthermore, by using state-of-the-art multi-parametric photoacoustic microscopy (Ning et al, 2015. Scientific Reports. 18775), which allows high-resolution and quantitative imaging of hemodynamics and oxygen metabolism in the live mouse brain, we also found that arginine plus leucine significantly altered cerebral oxygen consumption *in vivo*. Collectively, these results suggest a novel AβO-sensitive, nutrient-dependent and mTORC1-mediated regulation of mitochondrial activity, and a new mechanistic link connecting mitochondrial metabolic dysfunction and AD.

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Nanosymposium

730. Amyloid-Beta and Tau Biochemistry and Toxicity

Location: 150A

Time: *****Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

Presentation Number: *****730.02

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

Support: NIH Grant R01-AG046275

Title: Diffusible Alzheimer's disease brain-derived Aβ disrupts synaptic plasticity

Authors: W. HONG[1], Z. WANG[1], W. LIU[1], T. O'MALLEY[1], M. FROSCH[2], *D. M. WALSH[3]
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Abstract: Alzheimer's disease (AD) is a brain disorder that first manifests in the form of intermittent memory problems and then progresses to dementia and ultimately death. The molecular changes leading to AD are not well understood, but substantial data indicate that the amyloid β-protein (Aβ) plays a central initiating role. Although the toxic forms of Aβ remain unresolved, numerous studies have shown that non-fibrillar, water-soluble forms of Aβ are potent synaptotoxins. Importantly, Aβ extracted from the aqueous phase of post-mortem AD brain, inhibits long-term potentiation (LTP), facilitates long-term depression, reduces synaptic remodeling, and impairs memory consolidation. Nevertheless, there has been controversy about the source of the Aβ that actually confer these AD-like phenotypes. Here, we show that only a fraction of Aβ present in aqueous brain extracts is bioactive, and that the bulk of this material can be extracted from brain tissue without homogenization. Two gram lots of frozen temporal cortex were diced into small chunks using a McIlwain chopper (at 500 μM). The diced tissue was gently mixed and then divided into halves. One portion was added to ice-cold artificial CSF (aCSF) and incubated at 4^{o}C for 30 min. Thereafter, this suspension was centrifuged at low speed and the upper 90% of the supernatant was removed and spun at 200,000 g for 110 min. The resulting supernatant, designated as the diffusible (D) fraction was removed and stored. The other portion of diced cortex was Dounce homogenized in aCSF and then centrifuged at 200,000 g. The upper 90% of supernatant was removed and designated as the extracted (E) fraction. Brains from 9 individuals who died with AD and one individual who died free of AD were processed in this manner and the D and E fractions analyzed for: total protein, APPs, BDNF, and various forms of Aβ. D and E contained comparable levels of total protein, APPs and BDNF, but E contained much lower levels of Aβ (<30% of D). Remarkably, when extracts were tested for their effects on LTP, both D and E blocked LTP. In each case the block was Aβ-dependent as prior immunodepletion of Aβ from D and E prevented impairment. Moreover, when the D fractions were diluted so as to match the Aβ content measured in E, these fractions either no longer blocked LTP or had a greatly diminished effect on LTP. These data demonstrate that these diffusible synaptotoxic forms of Aβ constitute only a small fraction of total brain Aβ.

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Nanosymposium

730. Amyloid-Beta and Tau Biochemistry and Toxicity

Location: 150A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***730.03

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

Title: Characterization of the high molecular weight Abeta oligomers derived from the brains of APP transgenic mice

Authors: *T. HASHIMOTO, Y. NAKA, T. TAJIRI, M. HAKOZAKI-KASHIWAGI, T. IWATSUBO
The Univ. of Tokyo, Tokyo, Japan

Abstract: Alzheimer’s disease (AD) is pathologically characterized by a massive deposition of amyloid beta peptides (Abeta) in the brains. Current wisdom holds that soluble oligomers of Abeta intermediate species formed during the course of Abeta fibrillization, might be the culprit molecules causative to synaptic or neuronal toxicity in AD brains. However, the biochemical and pathological characteristics of the brain-derived soluble Abeta oligomers remain elusive. Here, we biochemically characterized the soluble Abeta oligomers extracted from the brains of APP transgenic (tg) mice, and examined their relationship with Abeta deposition, as well as their activity to propagate Abeta pathology by injection experiments. We separated the Tris-buffered saline (TBS)-soluble fractions from the brains of 18-month-old APP tg mice (A7 line) by size-exclusion chromatography using a Superdex 75 column. TBS-soluble fractions positive for Abeta by ELISA were separated into three peaks, eluting at ~200-250 kDa (peak 1 Abeta), ~50-80 kDa (peak 2 Abeta), and ~10-20 kDa (peak 3 Abeta). We quantified the percentage of Abeta-positive areas (Abeta burden) in the hippocampus of the 18-month-old APP tg mice by morphometry, and found a positive correlation between the levels of peak 1 Abeta and Abeta burden in the hippocampus. Peak 2 Abeta was detected in the TBS-soluble fractions of the brains of 6-month-old APP tg mice that had not formed plaques yet, in which peaks 1 and 3 Abeta were not detectable. These results led us to speculate that the peak 1 Abeta is derived from those associated with Abeta plaques. To examine whether the brain-derived Abeta oligomers of different sizes are capable of propagating the Abeta deposition *in vivo*, we inoculated peak 1 or peak 2 Abeta into the hippocampus of APP tg mice, and found that peak 1 Abeta induced a robust and characteristic pattern of Abeta propagation in the hippocampus, whereas peak 2 Abeta did not. From these data, we conclude that the ~200-250 kDa high molecular weight soluble Abeta oligomers, which might be associated with plaques, are the species that play a critical role in the progression of Abeta deposition.

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Nanosymposium

730. Amyloid-Beta and Tau Biochemistry and Toxicity

Location: 150A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***730.04

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

Support: NIH/NIA 5R01AG044404

Title: Amyloid-β peptide activates NFκB through cytosolic phospholipase A2 in cerebral endothelial cells

Authors: *T. TENG[1], D. M. RIDGLEY[1], A. TSOY[2], G. Y. SUN[3], S. ASKAROVA[2], J. LEE[1]
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Abstract: Alzheimer's disease (AD) is an irreversible progressive neurodegenerative disease among older people. Although the cause of AD remains unknown, Amyloid-β (Aβ) is thought to play a crucial role in the AD pathology. Aβ interferes different cell types through different mechanisms. Cerebral endothelial cells (CECs) are integral components of the blood brain barrier (BBB), which is important for maintaining neuron function. The BBB regulates transportation of materials between peripheral blood and brain parenchyma. Aβ has been reported to disrupt calcium homeostasis, increase oxidative stress and inflammation in CECs resulting in alterations of CEC functions. In this project, we demonstrate that oligomeric Aβ increased calcium influx, and production of superoxide, leading to activation of extracellular signal-regulated kinases (ERK), cytosolic phospholipase A2 ($cPLA_2$) and subsequently NFκB in immortalized mouse CECs (bEnd.3). Aβ-triggered activation of NFκB was suppressed through inhibition of $cPLA_2$ activation using azelnidipine (ALP), a L-type calcium channel blocker to block calcium influx, and methyl arachidonyl fluorophosphonate (MAFP), a $cPLA_2$ inhibitor. Taken together, these results demonstrate that Aβ is capable of triggering both oxidative and inflammatory pathways in CECs and $cPLA_2$ is involved in both pathways.

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Nanosymposium

730. Amyloid-Beta and Tau Biochemistry and Toxicity

Location: 150A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***730.05

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

Support: NIH Grant AG030399
NIH Grant AG042082

Title: IL17A reduces brain amyloid beta load by upregulating ATP-binding cassette efflux transporter

Authors: *J. YANG[1], J. KOU[1], R. LALONDE[2], K.-I. FUKUCHI[1]
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Abstract: Neuroinflammation is a pervasive feature of Alzheimer's disease (AD) and characterized by activated microglia, increased proinflammatory cytokines and/or infiltrating immune cells. T helper 17 (Th17) cells are found in AD brain parenchyma and interleukin-17A (IL-17A) is identified around deposits of aggregated amyloid β. However, the role of IL-17A in AD pathogenesis remains to be elucidated. In the current study, we overexpressed IL-17A in the brains of TgAPP/PS1 mice, an AD mouse model, via recombinant adeno-associated virus serotype 5 (rAAV5)-mediated gene delivery. IL-17A overexpression improved glucose metabolism and reduced Aβ levels in the cerebrospinal fluid, hippocampus and cerebral blood vessels (cerebral amyloid angiopathy) without exacerbating neuroinflammation and modestly but significantly improved anxiety and learning deficits in TgAPP/PS1 mice. Moreover, the ATP-binding cassette subfamily A member 1 (ABCA1), which may be involved in Aβ clearance from the brain, significantly increased in IL-17A-overexpressing mice. In vitro treatment of brain endothelial bEnd.3 cells with IL-17A induced increases in ABC transporters including ABCA1, ABCA7, ABCB1 and ABCG2, all of which have been reported to reduce brain Aβ load in experimental animals. Our study suggests that IL-17A may decrease Aβ levels in the brain by upregulating ABC transporters in blood-brain barrier endothelial cells.

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Nanosymposium

730. Amyloid-Beta and Tau Biochemistry and Toxicity

Location: 150A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***730.06

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

Title: The astacin protease meprin β is involved in formation of pyroglutamate-modified Aβ peptides

Authors: *S. SCHILLING[1], D. SCHLENZIG[1], H. CYNIS[1], M. BUCHHOLZ[1], M. HARTLAGE-RÜBSAMEN[2], S. D. ROSSNER[2], H.-U. DEMUTH[1]
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Abstract: The formation of β-amyloid (Aβ) peptides is causally involved in the development of Alzheimer's disease (AD). A significant proportion of deposited Aβ is N-terminally truncated and modified at the N-terminus by a Pyroglutamate (pGlu) residue (pGlu3-Aβ). These forms show enhanced neurotoxicity compared to full-length Aβ. Although the truncation may occur by aminopeptidases after formation of Aβ, recently discovered processing pathways of APP by proteases such as meprin β may also be involved. Here, we assessed a role of meprin β in forming Aβ3-40/42, which is the precursor of pGlu-Aβ3-40/42 generated by glutaminyl cyclase (QC). Similar to QC, meprin β mRNA is significantly upregulated in *post mortem* brain from AD patients. A histochemical analysis supports the presence of meprin β in neurons and astrocytes in vicinity of pGlu3-Aβ containing deposits. Cleavage of APP-derived peptides by meprin β *in vitro* results in peptides Aβ1-x, Aβ2-x and Aβ3-x. The formation of N-truncated Aβ by meprin β was also corroborated in cell culture. A subset of the generated peptides was converted into pGlu-Aβ3-40 by addition of glutaminyl cyclase, supporting the preceding formation of Aβ3-40. Further analysis of the meprin β cleavage revealed a yet unknown dipeptidyl-peptidase-like activity specific for the N-terminus of Aβ1-x. Thus, our data suggest that meprin β contributes to formation of N-truncated Aβ by endopeptidase and exopeptidase activity to generate the substrate for QC-catalyzed pGlu3-Aβ Formation.

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Nanosymposium

730. Amyloid-Beta and Tau Biochemistry and Toxicity

Location: 150A

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**Presentation Number: ***730.07

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

Support: LuMind RDS Foundation
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Cure Alzheimer Fund

Title: Gamma-secretase modulator reduces A-beta mediated changes in endosomal structure and function

Authors: M. SAWA[1], X.-Q. CHEN[1], R. E. TANZI[2], S. WAGNER[1], *W. C. MOBLEY[1]
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder. Neuropathological, genetic and cell biological studies implicate the Amyloid Precursor Protein (APP), and its proteolytic products including the Amyloid-beta (A-beta) peptide, in the pathogenesis of AD. A leading hypothesis is that A-beta peptides present in one or more species of soluble oligomers (sA-bos) induce synaptic and cellular degeneration. However, the cellular bases for the sA-bos actions is defined only in part. To decipher cellular mechanisms induced by sA-bos we employed the conditioned medium (CM) of a CHO cell line (7PA2) that expresses the human Indiana mutation of APP (APP V717F); CM7 was used to designate this CM, which contains sA-bos with A-beta peptides whose C-termini end at residues 42 (120pM), and 40 (1600 pM). The conditioned medium of wild type CHO cells (CMC) served as a control. We assessed CM7 effects on PC12 cells and rat primary hippocampal and cortical neurons. CM7 treatment for 2hr induced several AD-relevant cellular abnormalities: increased activation of Rab5, enlarged early endosomes, and defects in the axonal trafficking of neurotrophin signals. These phenotypes were prevented by preadsorbing CM7 with a monoclonal antibody to A-beta 42 but not to A-beta 40. Gamma-secretase modulators (GSMs) provide an alternative means for reducing A-beta 42. GSM 15606 treatment of 7PA2 cells markedly reduced the levels of A-beta 42 as well as 40. In so doing, the CM of GSM treated 7PA2 cells (CM7-GSM) failed to induce activation of Rab5, to increase size of early endosomes and to reduce trafficking and signaling of neurotrophins. These data are consistent with GSM 15606-mediated reduction in A-beta 42 levels. Ongoing studies explore GSM 15606 effects on AD-related phenotypes.

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Intellectual property rights to other GSM compounds being examined in clinical trials by Neurogenetic Pharmaceuticals, Inc. **S. Wagner:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holder of patent and patent applications assigned to UCSD and Harvard University, Intellectual property rights to other GSM compounds being examined in clinical trials by Neurogenetic Pharmaceuticals, Inc. **W.C. Mobley:** 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.; LuMind RDS Foundation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holder of patent and patent applications under UCSD and Harvard.

Nanosymposium

730. Amyloid-Beta and Tau Biochemistry and Toxicity

Location: 150A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

**Presentation Number: ***730.08

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

Support: CNPq
INNT
CAPES
FAPERJ

Title: An oxidative mechanism for cholinergic dysfunction in neurons exposed to Alzheimer's-linked Aβ-oligomers

Authors: *L. E. SANTOS[1], C. FIGUEIREDO-FREITAS[1], S. T. FERREIRA[1,2], F. G. DE MELLO[2]
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Abstract: Acetylcholine is a major neurotransmitter in the central nervous system (CNS), synthesized by transfer of an acetyl group from acetyl-coenzyme A to choline. This reaction is carried out by choline acetyltransferase (ChAT), a phenotypic marker of cholinergic neurons. Defective cholinergic transmission may underlie the onset and development of several CNS pathologies, including Alzheimer's disease (AD). Previous work by our group, using the avian retina as a CNS model, showed that ChAT activity in cultured or ex vivo neurons is markedly and specifically down-regulated by excitotoxic stimuli requiring calcium influx and nitric oxide (NO) production, before any changes in cell viability or enzyme levels occur. More recently, we

reported similar results in a more specific pathological context, using amyloid-β peptide oligomers (AβOs). These are diffusible toxins that accumulate in the brains of AD patients and animal models of AD, and are currently regarded as possible culprits of the disease. Exposing cultured cholinergic neurons to AβOs inhibited ChAT activity in the absence of neuronal death or changes in enzyme expression. We further showed that the effect of AβOs on ChAT activity is linked to excitotoxicity and to increased production of reactive oxygen species (ROS) that cause oxidative damage to the enzyme. In the current work, we expand those observations to a mammalian model, using cultured neurons of the rat septal region, and attempt to identify oxidative modifications involved in ChAT inhibition. Using S-nitrosothiol resin-assisted capture and labeling of reduced thiols, we show that cysteine modification is not central to the mechanism of inhibition. Tyrosine nitration, on the other hand, was found to be induced in cultures exposed to glutamate, AβOs and NO donors, and correlated well with loss of ChAT activity. Results suggest a novel mechanism of cholinergic dysfunction that precedes neuronal death, and may be relevant in early-stage AD pathology.

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Nanosymposium

730. Amyloid-Beta and Tau Biochemistry and Toxicity

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

Support: NIA K01 AG050719
McDonnell Center for Systems Neuroscience Small Grant
New Vision Award through Donors Cure Foundation
P01 NS080675

Title: Chronic treatment with the sulfonylurea, glyburide, decreases Alzheimer’s disease pathology by altering neurovascular coupling, neuronal activity, CNS metabolism, and amyloid-β production

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Abstract: Type-2-diabetics (T2D) have an increased risk for developing Alzheimer's disease (AD), although the relationship between these diseases remains poorly understood. Our studies demonstrate that hyperglycemia, a key feature of T2D, increases extracellular amyloid-β (Aβ) levels, a primary pathology in AD, in an activity-dependent manner by modulating ATP sensitive, inward rectifying (K_{ATP}) potassium channels. Since glyburide, a K_{ATP} channel antagonist, is a common anti-diabetic medication, we explored whether chronic glyburide treatment could alter Aβ pathology in a model of cerebral amyloidosis, the APPswe/PSEN1dE9 (APP/PS1) mouse. Four-month-old female APP/PS1 mice were treated with glyburide or placebo for 3 months via the implantation of a subcutaneous, slow release pellet. Analyses for APP metabolism and Aβ pathology demonstrated that glyburide treated mice had decreased 1) Aβ deposition, 2) insoluble hippocampal Aβ40 and Aβ42, and 2) steady state Aβ levels compared to placebo. No changes in Aβ clearance mechanisms were observed; therefore, mechanisms known to increase Aβ production, such as increased neuronal activity, were explored. Neuronal activity and neurovascular coupling following an evoked response were investigated using optical intrinsic signal imaging (OIS), laser speckle contrast imaging (LSCI), and electroencephalography (EEG). In placebo treated mice, neuronal activity, cerebral blood volume (CBV), and cerebral blood flow (CBF) were increased in the somatosensory cortex in response to forepaw stimulation, demonstrating that the hemodynamic response remains tightly coupled to neuronal activity. Although increases in neuronal activity and the hemodynamic response were observed in the glyburide group in response to forepaw stimulation, the changes in neuronal activity, CBV, and CBF were significantly blunted by when compared to placebo. These changes correlated with reduced glucose uptake in the brain and alterations in CNS metabolism. Therefore, our data suggests that glyburide affects neurovascular coupling, leading to decreased neuronal activity, CNS metabolism, and decreased Aβ production. Over time, chronic treatment with glyburide significantly reduces Aβ deposition and plaque formation, offering a novel therapeutic approach for AD.

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Nanosymposium

730. Amyloid-Beta and Tau Biochemistry and Toxicity

Location: 150A

Time: *Wednesday, November 15, 2017, 1:00 PM - 4:00 PM

Presentation Number: *730.10

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

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MPG
Tau Consortium

Title: A-type K^+ channels drive enhanced excitability in CA3 pyramidal neurons in a mouse model of tauopathy

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Abstract: Hippocampal hyperexcitability is a major symptom of many neurodegenerative diseases. While the mechanisms that underpin this phenomenon are investigated with a great intensity, they take place predominantly in the CA1 area. It is important to consider that these alterations may not be generated independently in CA1. In addition to other, mutually not exclusive, mechanisms they may be observed as embedded within interconnected network, in which CA1 neurons integrate the output from CA3. Yet, the physiology of CA3 pyramidal neurons remains unexplored in these conditions. Using whole-cell patch-clamp physiology and pharmacology in a mouse model expressing human full-length Tau with the Tau mutation A152T, our findings indicate that the mutation influences several action potential characteristics, including smaller amplitudes, narrower half-widths with faster repolarization leading to a higher firing frequency (at 10-14 months). Furthermore, using biochemical analyses, we demonstrate that membranes of CA3 neurons contain more Kv4.2/Kv4.3 A-type K^+ channels and that their redistribution closely resembles that one of the Tau protein underscoring possible molecular interactions.

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Nanosymposium

730. Amyloid-Beta and Tau Biochemistry and Toxicity

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

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IIT Gandhinagar

Title: Carbamylation, an age related protein modification as a facilitator of *In vitro* tau oligomerization and fibrillization

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Abstract: Carbamylation is a non-enzymatic post-translational modification (PTM) of proteins involving covalent modification of N-terminus or side chain functionalities of lysine, Arginine and occasionally cysteine residues. Carbamylation is considered to be a consequence of protein aging and has been implicated in several chronic disorders including Chronic Kidney Disease and Coronary Heart Disease. Surprisingly not much attention has been paid to carbamylation when it comes to neurodegenerative diseases even though age is a very strong risk factor and amyloidogenic proteins such as tau and α-synuclein being lysine rich are more susceptible to carbamylation. In the present study, using a highly aggregation prone and fibril forming tau core hexapeptide ^{306}VQIVYK^{311} (PHF6) as a model, we have elucidated the effect of carbamylation on aggregation and three-dimensional architecture of PHF6 fibril. Our experimental results showed that carbamylation can alter aggregation pathway and cause structural changes in PHF6 fibrils. Further, molecular dynamics (MD) simulations have been used to elucidate the effect of carbamylation induced variations in the three-dimensional architecture of PHF6 fibrils. MD simulations corroborated the experimental findings that carbamylation of PHF6 results in more tightly packed but broken fibrils with a predictable helical pitch. We have further extended our studies to the full-length tau protein and have shown that a similar change in aggregation pathway is observed upon carbamylation. Not only carbamylated tau protein aggregates faster than the unmodified tau but also the resulting fibrils and oligomer preparations show significantly higher toxicity in neuronal cell culture. Perhaps, carbamylation, which is notoriously difficult to detect by proteomics, is the missing link that could explain the sporadic occurrence and slow development of neurodegenerative disorders such as Alzheimer's disease.

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Nanosymposium

730. Amyloid-Beta and Tau Biochemistry and Toxicity

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Seedcorn Fund

Title: Age-related alterations to electrical membrane properties of CA1 hippocampal glutamatergic and GABAergic neurons in a mouse model of progressive tauopathy

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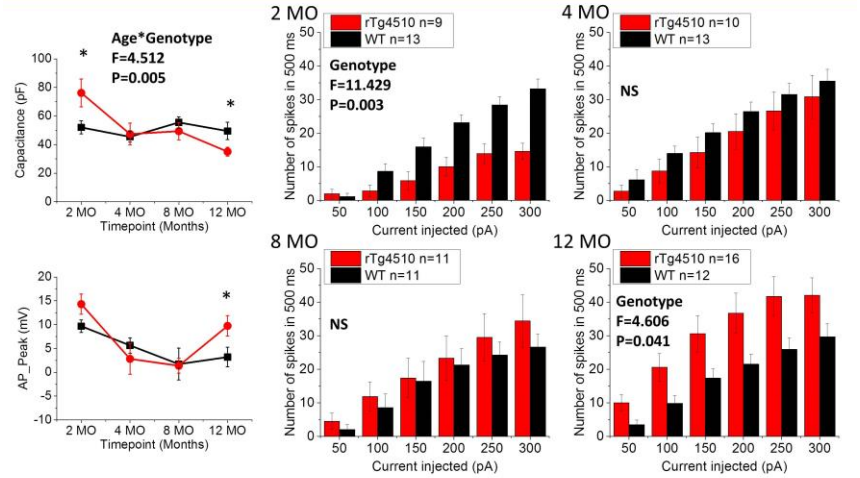
Abstract: Functional imbalances between excitatory and inhibitory synaptic function have been suggested to occur in Alzheimer's disease (AD). Pathogenic species of protein tau, including hyperphosphorylated tau, chronically and progressively accumulate in the brain of people with tauopathies, of which AD and fronto-temporal dementia (FTD) are the most common forms.
In this study, we have investigated the effects of progressive tauopathy on the intrinsic excitability of excitatory CA1 pyramidal cells (CA1-PCs), inhibitory CA1 Oriens-Lacunosum moleculare interneurons (OLMs) and Neurogliaform cells (NGFs). Single-cell patch-clamp recordings were performed in coronal hippocampal slices obtained from 2, 4, 8 or 12 month-old rTg4510 and age-matched WT littermate control mice: this transgenic mouse model of progressive tauopathy overexpresses the P301L mutated gene of human tau, responsible for a familial form of FTD. We measured electrotonic (i.e. input resistance - R_i - , capacitance - CAP - and I_h-dependent SAG) and electrogenic (i.e. firing rates upon depolarization and action potential - AP -) properties.
OLM interneurons showed increased R_i, mirrored by higher firing output and decreased AP peak at 12 months, in rTg4510 compared to WT control mice. NGFs showed increased and decreased CAP at 2 and 12 months, respectively, but no changes at 4 and 8 months. The progressive decrease in CAP in rTg4510 mice was mirrored by the firing output, lower at 2 months but higher at 12 months, and by the action potential peak, larger at 12 months (Figure 1). CA1-PCs showed increased SAG at 2-4 and 12 months and decreased AP duration at 12 months.
These data may provide a mechanistic correlate to the progressively altered oscillatory activity and cognitive performance observed in people with AD and FTD: to test the causal relationship between single-cell and network alterations in hippocampal CA1, we are currently performing *in silico* modelling based upon these experimental data. This approach could potentially lead to novel therapeutic and diagnostic strategies based on the modulation of neuronal activity.

Figure 1. The progressive reduction of capacitance is mirrored by the age-dependent change of firing properties in rTg4510 Stratum lacunosum-moleculare neurogliaform interneurons. NS=non significant. * = P<0.05 with Bonferroni correction for multiple comparisons.



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Nanosymposium

731. Motor Neuron Disease Mechanisms

Location: 150B

Time: *Wednesday, November 15, 2017, 1:00 PM - 3:30 PM

Presentation Number: *731.01

Topic: *C.05. Neuromuscular Diseases

Support: ALSA
Les Turner ALS Foundation

Title: Converging and diverging paths in upper motor neuron vulnerability

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Abstract: Corticospinal motor neurons (CSMN, a.k.a. upper motor neurons and Betz cells in patients) are a critical component of motor neuron circuitry for their ability to collect and propagate cortical input to spinal cord targets. They are vastly modulated at the site of their apical dendrite by numerous different types of excitatory and inhibitory cortical neurons, located

at different locations of the cerebral cortex. Even though they undergo progressive degeneration in motor neuron diseases, we begin to realize that their vulnerability is initiated via different cellular events. We generated reporter lines of CSMN that become diseased due to increased ER-stress, presence of mSOD1, Profilin pathology and absence of Alsin function, and that express eGFP which is stable and long-lasting. FACS purification of CSMN that are healthy and diseased due to different underlying causes coupled with RNASeq analysis at different time points began to reveal the common and unique biology responsible for their early vulnerability. Our studies began to shed light on the converging and diverging paths that are important for upper motor neuron pathology in diseases in which voluntary movement and motor neuron circuitry is affected.

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Nanosymposium

731. Motor Neuron Disease Mechanisms

Location: 150B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***731.02

**Topic: ***C.05. Neuromuscular Diseases

Title: Systems biology approach to understanding factors driving disease progression in ALS motor neurons and muscle

Authors: *I. LEAF
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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by rapid muscle degeneration due to loss of motor neurons. To date, the only approved treatment for ALS is riluzole that has been shown to extend life by about two to three months. With an exception of small percentage of inherited cases with a defined mutation, the cause of ALS is not known. Several hypotheses have been proposed regarding the mechanism implicated in ALS disease initiation and progression leading to motor neuronal death: ‘excitotoxicity’ theory (excessive activation of glutamate receptors), dysregulated protein misfolding and toxic protein aggregation, endoplasmic reticulum stress, loss of trophic factors, oxidative stress, inflammation, disrupted protein trafficking, and mitochondrial dysfunction. However, there is limited data linking these studies to human ALS pathology and the mechanisms driving the disease are not well understood.
Here we applied a systems biology approach and performed a comprehensive analysis of transcriptional changes associated with ALS in human spinal cords, motor neurons, and muscle by comparing ALS tissue to controls from GSE833, GSE18920, GSE76220, GSE41414. While

the overlap between differentially expressed genes (DEGs) is modest, the upstream regulators of the DEGs that were identified using Ingenuity Pathway Analysis (IPA) are conserved between different datasets and even across tissues. After ranking these upstream regulators we identified top three activators for ALS signature in the muscle, motor neurons and spinal cord: 1. TGFB1, 2. Beta-estradiol, 3. TP53; and for motor neurons: 1. Tretinoin (all-trans retinoic acid), 2. TGFB1, 3. TNF. We explored TGFB1, ATRA and TNF ALS- associated signatures in terms of their biological functions using STRING, IPA, and DAVID and transcription factor binding site enrichment. Interestingly, we also found that these upstream regulators drive expression of DEGs in an excitotoxic *in vitro* model (glutamate treatment) and a mouse SOD1 *in vivo* model of ALS. We propose that further understanding of these mechanistic networks and therapies targeted towards inhibiting specific TGFB1, ATRA and TNF ALS- associated signatures might be protective in preventing motor neuronal death and restoring muscle function in ALS.

Disclosures: I. Leaf: None.

Nanosymposium

731. Motor Neuron Disease Mechanisms

Location: 150B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***731.03

**Topic: ***C.05. Neuromuscular Diseases

Title: Histone deacetylase expression is altered in amyotrophic lateral sclerosis

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Abstract: Amytorphic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the progressive loss of motor neurons. Currently there are no therapies that can extend lifespan beyond a few months in ALS, demonstrating a clear and urgent need for the development of novel treatments. Although the exact mechanisms involved in the onset and progression of the disease remain unknown, transcriptionalitoanl dysregulation has been implicated in ALS pathogenesis. One mechanism whereby transcription can be regulated is through the activity of hHistone deacetylases (HDACs). HDACs are epigenetic erasers that play a critical role in regulating gene expression by catalyzing the removal of acetyl groups from lysine residues on histones, thereby promoting condensation of chromatin and incactivation of transcription. HDACs have been implicated in several neurodegenerative diseases, including ALS. In ALS, histone acetylation is reduced and there is an increase in in HDAC2 levels in the

vental horn of the spinal cord in ALS patients. In addition, alterations in HDAC6 were implicated in pathogenesis in mouse models of ALS. More importantly, treatment with HDAC inhibitors improved survival, motor function, increased histone acetylation, and reduced the stress response in the SOD1 G93A mouse model of ALS. Lastly, a phase II human ALS trial demonstrated that sodium phenylbutyrate, an HDAC inhibitor, significantly increased histone acetyaltion in blood and that the drug was safe and well tolerated. Thus HDAC inhibitors are considered as a potential neuroprotective treatment for ALS. However, there are no studies to date that have comprehensively assessed HDAC leveles in ALS. Our study aimed to further characterize alterations in histone acetylation and HDACs in ALS. We used western blots and measured alterations in histone H3 and H4 acetylation as well as HDAC levels in postmortem motor cortex and ventral horn of the spinal cord in 20 ALS patients and 8 controls. The results indicate that while there is no change in HDAC 1, 2, 4, or 8 levels, there is a specific and significant increase in HDAC3 levels in the ventral horn of the lumbar spinal cord in ALS patients compared to control. In addition, there is a significant increase in HDACs 3 and 4 in the motor cortex of ALS patients compared to both ALS prefrontal cortex as well as control cortex. Lastly, our results indicate that HDAC2 levles are signficantly decreased in the prefrontal cortex of ALS patients. Together, these findings demosntrate that HDACs are altered in ALS and may provide a viable target for therapeutics for the treatment of ALS.

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Nanosymposium

731. Motor Neuron Disease Mechanisms

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**Topic: ***C.05. Neuromuscular Diseases

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ALS Association

Title: The nuclear pore complex is compromised in ALS and ALS/FTD

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Abstract: An expanded hexanucleotide repeat in intron 1 of the C9orf72 gene is the most common genetic cause of familial and sporadic Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD). Recent work from our group and others simultaneously showed that dysfunction in nucleocytoplasmic transport may be a fundamental pathway for C9orf72 ALS-FTD pathogenesis. In order for any cell to function properly, it is imperative that macromolecules be efficiently and selectively exchanged between the nucleus and cytoplasm. This critical task is achieved by nuclear pore complexes (NPC), which serve as the main nuclear gateway. Each NPC consists of multiple copies of 30 different proteins called nucleoporins (NUP) and mutations in various NUPs result in tissue-specific diseases. Interestingly, some of the longest-lived proteins in the mammalian brain are specific NUPs and may represent the "weakest link" in the aging proteome. Finally, 1/3 of all NUPs contain multiple repeats of hydrophobic phenylalanine-glycine (FG) and these FG-NUPs are found along the entire transport route of the NPC. FG-NUPs create an entropic barrier to diffusion through the NPC, are highly dynamic, have short residence times, interact directly with transport receptors, control nucleocytoplasmic transport, and determine the pore permeability limit. We now present data that the NPC is not only compromised in models of C9orf72 but also sALS, suggesting that NPC dysfunction may be a common insult and pathogenic mechanism in the majority of ALS. More specifically, we have surveyed the majority of NUPs in transgenic and BAC C9orf72 mice, iPS neurons, and human postmortem brain tissue using IF, IHC, super resolution imaging, western blot, shRNA, and proteomic analysis. We have identified a unique set of NUPs and transport machinery with critical and disease relevant functions that are consistently affected across not only models of C9orf72 but also sALS, with the majority of these being components of nuclear import machinery that have FG-repeats. Knockdown of FG-NUPs disrupts the ran gradient responsible for fueling nucleocytoplasmic transport and also causes cytoplasmic mislocalization of pTDP43 and critical non-FG-NUPs. General inhibition of nuclear import causes cytoplasmic mislocalization of FG-NUPs and pTDP43 as well as stress granule formation. Finally, all these deficits can be rescued when treating with a potent small molecule inhibitor of nuclear export. This data suggests that NPC dysfunction may be a common insult in the majority of ALS and that disruption of FG-containing NUPs/transport receptors involved in nuclear import may be the first "dominoes" to fall in the disease cascade.

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Nanosymposium

731. Motor Neuron Disease Mechanisms

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**Topic: ***C.05. Neuromuscular Diseases

Title: Lipocalin-2 levels are increased in amyotrophic lateral sclerosis and activate microglia

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Abstract: Although the etiology of Amyotrophic lateral sclerosis (ALS) is not yet fully understood, accumulating evidence suggests that neuroinflammatory processes are crucial for the initiation and progression of disease. Neuronal death can be caused by activation of resident innate immune cells such as activated microglia and reactive astrocytes. However, a fundamental question in ALS is exactly how reactive astrocytes or microglia contribute to neuronal death. One possibility is the secretion of soluble neurotoxic factors that stimulate microglial activation, resulting in neuronal death. Indeed previous *in vitro* studies support this hypothesis and have demonstrated that cultured astrocytes expressing mutant superoxide dismutase 1 (SOD1) secrete neurotoxic factors that when transferred to cultured motor neurons cause cell death. One such toxic and secreted candidate is lipocalin-2 (LCN2), a protein already relevant as a biomarker in acute kidney injury, Alzheimer's disease, multiple sclerosis, depression, and cancer. LCN2 is important for the innate immune response and performs an antimicrobial role. Additionally, emerging evidence associates LCN2 with modulation of cell processes that are dysregulated in ALS. Although LCN2 levels in biological fluids are generally low, they are discernably increased in several diseases. Our studies are the first to demonstrate that there is a significant and progressive increase in LCN2 levels in plasma from ALS patients that may correlate with disease progression. In addition, there is a significant increase in LCN2 levels in postmortem motor cortex and lumbar spinal cord from ALS patients. Similarly, LCN2 levels are significantly increased in the lumbar spinal cord of symptomatic transgenic SOD1 mice. Lastly, LCN2 treatment increased TLR4, TNFa, and IL1B expression in microglia isolated from the lumbar spinal cord of wild-type mice. Together these findings demonstrate that LCN2 upregulation may be a key trigger of neuroinflammation leading to microglia activation. In addition, our results highlight the role of LCN2 as a potential new biomarker in ALS.

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Nanosymposium

731. Motor Neuron Disease Mechanisms

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Presentation Number: *731.06

Topic: *C.05. Neuromuscular Diseases

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Knut och Alice Wallenbergs Stiftelse
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Västerbottens Läns Landsting
Hållstens Stiftelse

Title: Mutant SOD1 aggregates from human ventral horn transmit templated aggregation and fatal ALS-like disease

Authors: ***T. BRANNSTROM**[1], E. EKHTIARI BIDHENDI[1], J. BERGH[1], K. FORSBERG[2], B. PAKKENBERG[4], P. ZETTERSTROM[1], P. M. ANDERSEN[3], S. L. MARKLUND[1]
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Abstract: Mutations in *SOD1* are a common known cause of ALS. Both ALS patients and transgenic mice develop aggregates of hSOD1 in motor neurons. In symptomatic mice two different types of aggregates (denoted A and B) can arise (Bergh et al. *Proc Natl Acad Sci U S A,* 2015;112:4489-94). Inoculation of minute amounts of these into spinal cords of asymptomatic hSOD1 transgenic mice initiates spreading, exponentially growing templated hSOD1 aggregation concomitantly with premature fatal motor neuron disease (Bindhendi et al. *J. Clin. Invest.* 2016:126:2249-53). Here we explored whether prion-competent mutant hSOD1 aggregates also exist in human ALS using an binary epitope mapping assay (Bergh et al, as above) enhanced with 7 additional antibodies. Aggregate seeds were prepared from spinal cords from a patient and transgenic mice carrying the p.G127Gfs*7 h*SOD1* truncation mutation (Andersen et al, *Brain*, 1997, 120:1723-37) by centrifugation through density cushions. The core structure of p.G127Gfs*7 aggregates was strain A-like. Inoculation of the seeds into lumbar spinal cord of hSOD1-expressing mice induced spreading strain A aggregation and fulminant

ALS-like disease, demonstrating for the first time the presence of prion-competent hSOD1 aggregates in human ALS. The binary epitope mapping profiles suggest that the fibril cores of $hSOD1^{G85R}$ strain A aggregates and $hSOD1^{G127Gfs*7}$ aggregates are similar. The potency of the seeds was extremely high, and initiated disease under physiological conditions plausible to exist in human motor areas. Our results suggest that specific templated spread of hSOD1 aggregation is the primary pathogenic mechanism in human ALS caused by mutations in *SOD1*.

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Nanosymposium

731. Motor Neuron Disease Mechanisms

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**Topic: ***C.05. Neuromuscular Diseases

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Title: MicroRNAs profile of iPSCs-derived motor neurons as molecular therapy for ALS

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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal disorder characterized by progressive degeneration of motor neurons (MNs). The pathomechanisms underlying the disease and specific proteins involved are almost unknown, even though the role of alterations in RNA metabolism has been increasingly recognized. In particular, dysregulation in miRNA-related pathways in the central nervous system (CNS) is associated with severe neuronal injury and cell death, which can lead to the development of neurodegenerative disorders, such as ALS. Mutations in genes encoding for DNA/RNA-binding proteins, such as TDP-43 and FUS, and the hexanucleotide intronic repeat expansions in C9ORF72 have been associated with familial ALS (fALS) and represent the first genetic cause of sporadic ALS (sALS). In particular, TDP-43 and FUS have been implicated in several steps of RNA metabolism, including microRNA (miRNA) processing. Since ALS-linked genes can affect miRNA expression, we aim to investigate the role of miRNAs dysregulation and their relative proteomic changes in induced pluripotent stem cells

(iPSCs)-derived MNs from fALS/sALS patients and in exosomes secreted by them. We performed Next Generation Sequencing (NGS) analysis in order to identify dysregulated miRNAs in ALS. We will further characterize them to assess their biological targets by bioinformatic tools, molecular and proteomic studies both *in vitro* and *in vivo*. This approach can increase the chances of modifying complex diseases, such as ALS, by targeting the entire gene networks. Moreover, the identification of feasible miRNAs as targets of the disease can lead to the discovery of new disease biomarkers and therapeutic strategies.

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Nanosymposium

731. Motor Neuron Disease Mechanisms

Location: 150B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:30 PM

**Presentation Number: ***731.08

**Topic: ***C.05. Neuromuscular Diseases

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Title: Synaptotagmin 13 protects motor neurons from degeneration in ALS and SMA

Authors: *S. CORTI[1], M. NIZZARDO[1], F. RIZZO[1], M. TAIANA[1], I. FARAVELLI[1], I. ALLODI[2], J. AGUILA BENITEZ[2], J. NIJSSEN[2], V. MELZI[1], R. DEL BO[1], N. BRESOLIN[1], G. P. COMI[1], E. HEDLUND[2]
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Abstract: Mechanisms responsible for motor neuron (MN) subtype-selective degeneration in amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), two fatal neurological diseases, remain largely unknown. However, the molecular signature of degeneration-resistant oculomotor neurons (OMNs) is distinct from that of vulnerable spinal, cortical and lower brainstem MNs, thus offering some clues to differential vulnerability. We here demonstrate that OMNs show preferential expression of synaptotagmin 13 (SYT13) and that expression is

maintained in OMNs and remaining spinal MNs in end-stage ALS patient tissues, suggesting a role in their relative resistance. Overexpression of SYT13 in human *in vitro* models of ALS and SMA improves MN survival and increases motor axon length. Adeno-associated virus-mediated delivery of *Syt13* to transgenic ALS and SMA mouse models improves pathology, delays muscle denervation and prolongs survival. Mechanistically, an increase in SYT13 reduces endoplasmatic reticulum stress and apoptotic signs. These findings sustain a role of SYT13 as a disease modifier and candidate therapeutic target for MN diseases. Our study demonstrates that exploring differential neuronal vulnerability may lead to new therapeutic strategies to prevent the progressive degeneration in MN diseases.

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Nanosymposium

731. Motor Neuron Disease Mechanisms

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**Presentation Number: ***731.09

**Topic: ***C.05. Neuromuscular Diseases

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Title: Molecular pathology of early-onset amyotrophic lateral sclerosis associated with a novel TARDBP S375G variant

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Abstract: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder that most frequently occurs between the fourth and seventh decades of life. A woman presented with symptoms of ALS at age 22. History of ALS in distant relatives was known. A neuropathologic study of the Central Nervous System (CNS) showed upper and lower motor neuron loss, corticospinal tract degeneration, and skeletal muscle atrophy consistent with denervation. Through DNA sequencing, a change was detected that would predict a Glycine (G) for Serine (S)

substitution, at residue 375 in the C-terminal region of TDP-43. The analysis of TDP-43 neuropathology in multiple CNS regions, and that of TDP-43 aberrant phosphorylation, compared to mRNA and protein expression levels, were carried out in parallel. Our results are significant in showing a lack of correlation between expression levels of TDP-43 and its aberrant phosphorylation in disease, as shown by postmortem ALS tissue analysis. Since the S375G change was reported in ALS databases as a variant with unclear significance, we investigated its possible consequences on TDP-43 cellular localization, pre-mRNA splicing activity, and toxicity. To compare our results with published data, neighboring mutations G376D, N378D, and Y374X, known to be pathogenic, were analyzed in parallel. Our results show that none of them seem to affect TDP-43 nuclear localization. However, S375G and N378D display a small gain-of-function in their ability to regulate CFTR exon 9 skipping. Furthermore, S375G is toxic when expressed in cultured cell lines. Taken together, our results highlight the need for more comprehensive research for a better understanding of the potential pathogenicity of TDP-43 variants, that are not infrequently found in sporadic ALS, but are hypothesized to be benign.

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Nanosymposium

731. Motor Neuron Disease Mechanisms

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Title: A novel ALS-associated variant in UBQLN4 regulates motor neuron axon morphogenesis

Authors: *Y. C. MA[1,2], J. YAN[2], N. MILLER[2], H. X. DENG[2], T. SIDDIQUE[2], B. M. EDENS[2]
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Abstract: The etiological underpinnings of amyotrophic lateral sclerosis (ALS) are complex and incompletely understood, although contributions to pathogenesis by regulators of proteolytic pathways have become increasingly apparent. Here, we present a novel variant in *UBQLN4* that is associated with ALS and show that its expression compromises motor axon morphogenesis in

mouse motor neurons and in zebrafish. We further demonstrate that the ALS-associated *UBQLN4* variant impairs proteasomal function, and identify the Wnt signaling pathway effector beta-catenin as a *UBQLN4* substrate. Inhibition of beta-catenin function rescues the *UBQLN4* variant-induced motor axon phenotypes. These findings provide a strong link between the regulation of axonal morphogenesis and a new ALS-associated gene variant mediated by protein degradation pathways.

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Nanosymposium

732. Chronic Pain and Trigeminal Processing

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**Topic: ***D.03. Somatosensation: Pain

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DE025137

Title: Neuronal ERK signaling in the anterior cingulate cortex contribute to the development of dynamic allodynia after nerve injury

Authors: C. BIAN, R. HU, J. YANG, J. ASGAR, W. GUO, S. ZOU, R. DUBNER, K. REN, *F. WEI
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Abstract: Two types of tactile allodynia have been discriminated in patients with neuropathic pain: a static allodynia induced by applying a light static pressure to the skin and a dynamic allodynia evoked by lightly stroking the skin. Dynamic allodynia is one of the most frequently reported persistent pain symptoms negatively impacting on the quality of life and is refractory to treatment. Recent evidence indicates that dynamic allodynia represents a different pathologic entity from static allodynia. Some studies suggest that specific neuronal circuits in the spinal dorsal horn and certain cortical regions such as mPFC are predominately implicated in central mechanisms underlying the development of dynamic allodynia. However, whether the anterior cingulated cortex (ACC) contributes to the cortical mechanisms of dynamic allodynia remains unknown. We have previously established a rodent model of secondary static allodynia with CCI of the infraorbital nerve (ION), and explored a novel central mechanism mediating the

development of secondary hyperalgesia/allodynia in the skin adjacent to area innervated by the injured nerve. In the present study, we further examined whether secondary dynamic allodynia developed and the ACC was involved in this syndrome. For measurement of primary or secondary static allodynia, von Frey filaments were applied to the ipsilateral skin of the whisker pad (V2 skin) innervated by ION or the lower jaw within the V3 area, respectively. For measurement of dynamic allodynia, the V2 or V3 skin was stimulated by using a #4 camel's hair artist's brush. Different from the onset of static allodynia at 3d, dynamic allodynia in the V2 and V3 skin started at 7d and lasted over 28d after CCI. Fos mapping in ACC sections suggests that brushing in the V3 skin induced robust neuronal activation in the ACC from CCI-treated rats at 14d but less at 5d when compared to that in rats with sham surgery. Consistent with our previous observation, using pERK as another functional marker of cortical neuronal activation, we further found that brushing stimulation induced an increased number of pERK-expressing neurons in the layer II-III of the ACC at 14 or 28d compared to that at 5d after CCI, but not in sham animals. Bilateral microinjection of the ERK inhibitor PD98059 into the ACC completely blocked enhanced pERK expression and attenuated both secondary dynamic and static mechanical allodynia. Furthermore, single application of PD98059 resulted in a stronger and longer attenuation of dynamic allodynia than static allodynia, suggesting that ERK signaling-mediated neuronal sensitization in the ACC may play a critical role in the development of dynamic mechanical allodynia.

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Nanosymposium

732. Chronic Pain and Trigeminal Processing

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**Topic: ***D.03. Somatosensation: Pain

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Title: Sex differences in orofacial zoster pain model

Authors: P. KRAMER[1], C. P. STINSON[2], P. R. KINCHINGTON[3], M. B. YEE[3], M. RAO[1], *L. L. BELLINGER[1]
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Abstract: Varicella zoster virus (VZV) infection results in chickenpox followed by viral latency and reactivation later in life causign herpes zoster (HZ) or “shingles”. VZV often infects neurons of the trigeminal ganglia causing ocular problems, orofacial disease and occasionally chronic pain. Importantly, the incidence of zoster associated pain is higher in women, although reasons for this sex difference remain unclear. Previous reports from our lab suggest gamma-aminobutyric acid (GABA) had a role in the different orofacial pain responses between males and females. Thus, we wanted to test the hypothesis that estrogen and GABA have a role in VZV associated pain. In these studies VZV was injected into the whisker pad of rats, the pain pathways altered and the nociceptive responses measured. Our results showed that male rats had a reduced nociceptive response compared to female rats. Administration of estradiol was shown to decrease the response due to VZV injection. Adeno-associated virus (AAV) was infused into the thalamus to alter these pain pathways. Specifically, AAV constructs producing shRNA against vesicular GABA transporter increased the pain response. Moreover, reduced activity of GAD1 positive cells in the posterior/lateral thalamic region increased the affective/motivational nociceptive responses resulting from virus infection of the rat whisker pad. These studies suggest estradiol has a role in the zoster associated pain response and that GABAergic signaling has a role in controlling the affective nociceptive response. These results are consistent with the idea that estradiol contributes to the greater pain response observed in women through the control of GABAergic pathways. Future work will modulate GABAergic mechanisms with treatment of estradiol to test this association.

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Nanosymposium

732. Chronic Pain and Trigeminal Processing

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Brain Pool Program

Title: Role of mechanosensitive ion channel Piezo2 in dental primary afferent neurons

Authors: S. OH[1], *J. WON[1], H. VANG[1], P. LEE[1], Y. KIM[2], H. KIM[1], Y. KANG[3]
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Abstract: The expression of mechanically sensitive ion channels in dental primary afferent (DPA) neurons has been investigated since the proposal of hydrodynamic theory. Piezo2, a mechanosensitive, rapidly inactivating (RI) ion channel, has been recently identified in dorsal root ganglion (DRG) neurons to mediate tactile transduction. In this study, we hypothesized that a subpopulation of DPA neurons are mechanosensitive and investigated DPA neurons for functional Piezo2 expression.
Rat DPA neurons were labeled with fluorescent retrograde tracer, DiI or Fluorogold. The labeled DPA neurons were investigated for mechanical sensitivity by using whole cell patch clamp. Mechanical stimulation was delivered with a fire-polished glass pipette moving in 1μm horizontal steps, and kinetics of mechanically-activated currents were further characterized. Piezo2 current in DPA neurons were confirmed by Piezo2 targeted-siRNA knockdown. The expression of Piezo2 was also verified with RT-PCR, in situ hybridization, single-cell RT-PCR in trigeminal ganglion and DPA neurons. Piezo2 mRNA was preferentially expressed in medium- to large-sized DPA neurons. Single cell RT PCR verified the high coexpression of neurofilament 200 (NF200) and calcitonin gene-related peptide (CGRP) in Piezo2 mRNA-positive DPA neurons. 69% of mechanosensitive DPA neurons exhibited Piezo2-like currents with rapidly decaying kinetics (τ<10ms). The Piezo2-like mechanosensitive currents were reversibly blocked by 30uM ruthenium red, and the proportion of DPA neurons which show Piezo2-like currents was decreased by Piezo2 siRNA transfection. Mechanosensitive DPA neurons with Piezo2-like currents were exclusively IB4-, and based on the capsaicin sensitivity, Piezo2-like currents were smaller in capsaicin sensitive DPA neurons than the insensitive neurons. Our results strongly indicate that DPA neurons are indeed mechanically sensitive, and suggest that Piezo2 may be a possible mediator of mechanical sensitivity from the pulpal system. Piezo2 positive Based on our findings, DPA neurons seem to be functionally distinct from conventional nociceptive neurons.

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Nanosymposium

732. Chronic Pain and Trigeminal Processing

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Title: Cdk5 activity modulates TRPA1 nociceptive responses

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Abstract: TRPA1 is a polymodally activated transient receptor potential channel that is involved in mechano- and chemo-sensation, and the phosphorylation of this channel can lead to both hyperalgesia (increased pain response to noxious stimuli) and allodynia (experience of pain from non-noxious stimuli). TRPA1 activity can be affected by different kinases. Cyclin-dependent kinase 5 (Cdk5) is a proline-directed serine/threonine kinase whose activity plays an important role in regulating peripheral as well as orofacial nociceptive signaling and in mediating inflammatory hyperalgesia. We have previously reported that Cdk5 is able to modulate thermal nociception by phosphorylating and sensitizing TRPV1, a thermosensitive TRP channel. Because Cdk5 activity plays an important role in pain transduction, specifically by modulation of calcium influx through TRPV1, we examined a second thermosensitive TRP channel for prospective Cdk5 phosphorylation sites. We identified six potential Cdk5 sites in the ankyrin repeats of the chemo-nociceptive ion channel TRPA1. Further analysis revealed that 4 of the 6 TRPA1 peptides encompassing the Cdk5 consensus sites could act as substrates for Cdk5. In addition, immunoprecipitated TRPA1 was phosphorylated by Cdk5, and this phosphorylation could be blocked by TFP5, a peptide inhibitor of Cdk5 activation. Using calcium imaging in trigeminal neurons derived from mice with either reduced or increased Cdk5 activity, we determined that Cdk5 activity governs the percentage of neurons responding to the TRPA1 agonist, allylisothiocyanate (AITC). *In vivo* experiments revealed that increased or decreased Cdk5 activity substantially influences TRPA1-mediated avoidance behavior. Overall, our findings demonstrate that TRPA1 is a substrate of Cdk5 and that Cdk5 activity is able to modulate TRPA1 agonist-induced behavioral responses.

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732. Chronic Pain and Trigeminal Processing

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Topic: *D.03. Somatosensation: Pain

Support: 2008-0062282
2012M3A9B6055414

Title: Role of central VEGF pathway in the development of trigeminal neuropathic pain

Authors: *D. K. AHN[1], J. SON[2], J.-S. JU[3], S.-H. KANG[4], K.-Y. YANG[5], M.-K. PARK[6], M.-K. LEE[7]
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Abstract: The present study investigated a role of central VEGF pathway in the development of trigeminal neuropathic pain. Sprague-Dawley male rats were anesthetized with ketamine (40 mg/kg) and xylazine (4 mg/kg). Under anesthesia, the left lower second molar was extracted, followed by the placement of a mini-dental implant to intentionally injure the inferior alveolar nerve. The blood-brain-barrier (BBB) permeability was assessed by detecting the concentrations of sodium fluorescein and Evans' blue in the medullary dorsal horn. Inferior alveolar nerve injury by mal-positioned dental implant produced prolonged mechanical allodynia compare to the sham group. Intracisternal infusion of VEGF antibody (250, 500 ng/ 24 hr/ 7 days) significantly attenuated mechanical allodynia. Representative immunofluorescence images and western blot analysis revealed that inferior alveolar nerve injury produced upregulation of VEGF expression and upregulated VEGF is co-localized with the astrocytes in the medullary dorsal horn. Intracisternal injection of ZM 306416, a VEGF receptor 1 inhibitor, or vandetanib, a VEGF receptor 2 inhibitor, produced inhibition of mechanical allodynia. Double immunofluorescence analysis revealed that VEGF receptor 1 and 2 are co-localized with BBB markers and GFAP, respectively, in the medullary dorsal horn. Inferior alveolar nerve injury significantly increased concentration of Evans' blue dye compare to the sham group. Finally, intracisternal administration of $VEGF_{164}$ siRNA attenuated the upregulated VEGF expression and produced anti-allodynic effects in rats with trigeminal neuropathic pain. These results suggest that central VEGF pathway play a critical role in the development of trigeminal neuropathic pain and blocking of VEGF pathway is a new potential therapeutic target for neuropathic pain control including the orofacial area pain

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**Topic: ***D.03. Somatosensation: Pain

Title: Involvement of neuron-glia interactions in extraterritorial orofacial pain under pathological condition

Authors: *K. IWATA, A. KATAGIRI, M. SHINODA
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Abstract: This presentation will focus on the functional interactions between neurons and satellite glial cells within TG involving extraterritorial orofacial pain spread associated with trigeminal nerve injury or orofacial inflammation. We have currently manifested the increased excitability of TG neurons innervating the trigeminal 2nd branch (V2) region following inferior alveolar nerve (V3) transection or lower lip (V3) inflammation. V3 nerve injury also resulted in significant reduction of potassium current in TG neurons innervating the V2 region, resulting in hyperexcitability of uninjured TG neurons. The alteration of molecular expression in TG was also evident in neurons as well as satellite glial cells following trigeminal nerve injury or orofacial inflammation. The expression of P2Y12 in satellite glial cells and nitric oxide in neurons was significantly increased in the V1/V2 region following lingual nerve injury or inferior alveolar nerve transection, and the NGF released in TG was also involved in spreading excitability of nociceptive neurons following lower lip (V3) inflammation, suggesting that changes in the expression of these molecules may be involved in extraterritorial orofacial pain mechanisms. Also, over-expression of connexin 43 (Cx43) participates spreading satellite glial cell activation, and indeed we recently observed that the expression of the Cx43 protein was strongly enhanced in satellite glial cell activation in association with inferior alveolar nerve transection. These findings suggest that the functional interactions between neurons and satellite glial cells in TG play a pivotal role in spreading of neuronal hyperexcitability following trigeminal nerve injury and orofacial inflammation, resulting in sensitization of TG neurons innervating uninjured or uninflamed orofacial region.

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Title: Role of TRPV1 and TRPM8 in ocular pain-like behavior in a rat model for dry eye

Authors: *D. A. BEREITER, R. THOMPSON, P. THAMMASUPAPONG, H. SAITO, M. RAHMAN
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Abstract: Dry eye disease (DE) often presents with signs of ocular dryness and symptoms of pain. Ocular pain in DE has been difficult to manage due in large part to the uncertainty of underlying mechanisms. Translational studies have been limited by reliable measures of ocular pain-like behavior in animals. This study measured forelimb eye wipe behavior in conscious male rats and orbicularis oculi muscle activity (OOemg) in anesthetized rats to assess the roles of transient receptor potential ion channels, TRPV1 and TRPM8, in mediating ocular nocifensive behavior in a model for tear deficient DE. Two weeks after exorbital gland removal tear volume was reduced ~50% and forelimb eye wipe behavior evoked by ocular application of hypertonic saline (HS) or capsaicin was enhanced compared to sham rats. Under urethane anesthesia, HS-evoked total orbicularis oculi muscle activity (OOemg) and long duration activity (OOemgL) were greatly enhanced in DE versus sham rats and were reduced by TRPV1 antagonists (capsazepine, AM9810) or co-application of capsaicin and the charged lidocaine derivative, QX-314. OOemgL activity was consistent with forceful eyelid closure or squint-like behavior in conscious subjects. By contrast, short duration OOemg activity (OOemgS), consistent with eye blink behavior, was not affected. Ocular application of L-menthol alone did not evoke eye wipe behavior; however, selective blockade of TRPM8 receptors (AMTB) partially reduced HS-evoked OOemg activity. TRPV1 protein levels were significantly increased in anterior eye segment and trigeminal ganglion samples of DE rats, whereas TRPM8 levels were not affected. These results suggested that activation of TRPV1, and to a lesser extent TRPM8, played a major role in mediating adverse ocular sensations induced by ocular dryness and was sufficient to account for the symptoms in persistent DE ranging from dryness sensation to burning pain. Targeting specific transducer molecules on corneal nerves may prove beneficial as adjunct therapy in managing ocular pain in moderate to severe cases of DE. OOemgL activity may serve as a useful measure of ocular nocifensive behavior in anesthetized animals.

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NIH Grant DE025137
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Title: Voluntary biting behavior as a functional measure of orofacial pain in mice

Authors: *K. REN, S. ZOU, J. YANG, Z. MOHAMMAD, F. WEI, R. DUBNER, M.-K. CHUNG, J. RO, W. GUO
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Abstract: Pain-related behavior secondary to masticatory function can be assessed with the rodent bite force model. A reduction of the bite force has been shown to be a functional measure related to pain associated with the masseter muscle and jaw activity, while an increase in bite force suggests improvement of muscle function and less pain. We have evaluated the use of the voluntary biting behavior, mainly at incisors, as a functional measure of orofacial pain in mice. C57Bl/6 mice were habituated to bite on a pair of aluminum plates attached to a force displacement transducer. The transduced voltage signals were amplified and fed into Spike 2 via CED 1401 Plus, and converted to force through calibration with a standard weight set. A customized interactive data capture script program was used to set up for data acquisition and analysis. Voluntary biting behavior was recorded for 100 seconds/session and those with bite forces ≥ 1N were analyzed. After analysis of overall biting behavior and to reduce the interference of random bites of smaller forces, the strongest 15 bite forces (BF15) were chosen as a measure of masticatory function and related to pain behavior. Both male (n=48) and female (n=27) mice exhibited similar BF15 (M: 7.6±0.16N vs. F: 7.4±0.23N, $p>0.05$), although the mean biting incidents of the males was slightly higher than females (Biting incidents/session: 57±3 vs. 47±4, $p<0.05$). Mice maintained their biting strength throughout the 8w observation period (±15% of baseline). At 4d after a unilateral masseter tendon ligation injury (TL), the BF15 reduced to 46±3% and 23±5% of the baseline for male (n=9) and female (n=6) mice, respectively ($p<0.01$). The BF15 gradually returned to the baseline level at 4-6w after TL. The von Frey and conditioned place avoidance tests indicated that mechanical allodynia/hyperalgesia persisted at the time when the biting force had returned to the pre-injury level, consistent with the view that feeding behavior is highly protected in rodents. The window of abnormal biting after injury allowed evaluation of the effect of pain-relieving manipulations. Infusion of bone marrow stromal cells improved biting behavior in males (n=10) and females (n=6) as shown by

significantly increased BF15 and biting incidents, compared to vehicle-treated mice. These results indicate that mice voluntary biting behavior can be used to assess orofacial pain behavior at the earlier phase of injury. However, since the protected biting behavior can successfully compete with painful conditions, lingering pain that lasts for months may not be detectable with this method.

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Topic: *D.03. Somatosensation: Pain

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Title: A role for the purinergic receptor $P2X_3$ in brainstem astrocytes in the mechanism of craniofacial neuropathic pain

Authors: ***Y. BAE**[1], W. MAH[1], S. LEE[1], J. LEE[2], J. BAE[1], J. JU[3], C. LEE[2], D. AHN[3]
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Abstract: The purinergic receptor $P2X_3$, expressed in the central terminals of primary nociceptive neurons in the brainstem, plays an important role in pathological pain. However, little is known about expression of $P2X_3$ in the brainstem astrocytes and its involvement in craniofacial pathologic pain. To address this issue, we investigated the expression of $P2X_3$ in astrocytes in the trigeminal caudal nucleus (Vc) in a rat model of craniofacial neuropathic pain, chronic constriction injury of infraorbital nerve (CCI-ION). We found that 1) $P2X_3$-immunoreactivity is observed in the brainstem astrocytes, preferentially in their fine processes, 2) the number of $P2X_3$-positive fine astrocytic processes and the density of $P2X_3$ in these processes were increased significantly in CCI-ION rats, compared to control rats, and 3) administration of MPEP, a specific mGluR5 antagonist, alleviated the mechanical allodynia and abolished the increase in density of $P2X_3$ in fine astrocytic processes caused by CCI-ION. These findings reveal preferential localization of $P2X_3$ in the fine astrocytic processes in the Vc, propose a novel role of astrocytic $P2X_3$ in the mechanism of craniofacial neuropathic pain.

Disclosures: **Y. Bae:** None. **W. Mah:** None. **S. Lee:** None. **J. Lee:** None. **J. Bae:** None. **J. Ju:** None. **C. Lee:** None. **D. Ahn:** None.

Nanosymposium

732. Chronic Pain and Trigeminal Processing

Location: 143A

Time: *Wednesday, November 15, 2017, 1:00 PM - 4:15 PM

Presentation Number: *732.10

Topic: *D.03. Somatosensation: Pain

Support: R01 (DE26139)
Barker Foundation
Owens Foundation

Title: Regulation of TRPV1 activities by serotonin-mediated sexually dimorphic mechanisms

Authors: ***N. B. RUPAREL**[1], *N. B. RUPAREL[1], M. ESKANDER[2], A. N. AKOPIAN[3], M. A. HENRY[4], K. M. HARGREAVES[5]
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Abstract: Numerous studies indicate that women and men differ in prevalence of pain disorders or pain intensity, possibly due to sexually dimorphic differences in detection, processing or responses to noxious stimuli. Recent studies demonstrate sexually dimorphic effects of serotonin (5-HT) on female versus male capsaicin-sensitive neurons from isolated human dental pulp, suggesting that peripheral sexually dimorphic pain mechanisms are present. **Aim of Investigation:** We hypothesized that 5-HT releases a "soluble factor" from female human biopsies but not male biopsies and this factor sensitizes capsaicin-sensitive peripheral nerve fibers. **Methods:** Dental pulp from females and males participants were treated with 5-HT and a combination of 5HT antagonists was added to the conditioned media (to prevent effects of residual 5HT) and then applied to trigeminal neurons. Patch clamp electrophysiology was used to determine the effects the conditioned media (CM) on rat trigeminal neurons and 2D gel electrophoresis/mass spectrometry and ELISA to identify the soluble factor released. **Results**: 1. CM only from female dental pulp treated with 5-HT sensitized I_{CAP} responses; 2. The soluble factor is a peptide and not a lipid; 3. Proteomics revealed that the soluble factor is complement C3a (C3a); 4. C3a receptor antagonists and anti-C3a antibody block CM-induced sensitization of I_{CAP}. **Conclusions:** Collectively, these novel data suggest that 5-HT triggers a peripheral

sexually dimorphic pain mechanism in women via release of complement peptides that leads to enhanced activity of capsaicin-sensitive trigeminal nociceptors.

Disclosures: N.B. Ruparel: None. **M. Eskander:** None. **A.N. Akopian:** None. **M.A. Henry:** None. **K.M. Hargreaves:** None.

Nanosymposium

732. Chronic Pain and Trigeminal Processing

Location: 143A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***732.11

**Topic: ***D.03. Somatosensation: Pain

Support: CIHR Grant MOP-4918

Title: Neuroplastic changes in face sensorimotor cortex in a rat model of orofacial neuropathic pain

Authors: *B. J. SESSLE[1], D. YAO[2]
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Abstract: Background and aims. Trigeminal nerve injury can induce sensorimotor disturbances as well as orofacial pain but whether neuroplastic changes in the face sensorimotor cortex (face-SMCX) are involved is unclear. This study aimed to determine if infraorbital nerve transection (IONX) in rats induces neuroplasticity in face-SMCX as well as nociceptive behaviour reflected in facial mechanical hypersensitivity. Methods. Adult male Sprague-Dawley rats (n=14) had unilateral IONX under general anaesthesia; sham-operated rats (n=11) served as controls. Mechanical sensitivity of the upper lips was tested with von Frey filaments in awake animals pre-operatively and at 1-28 days post-operatively. Intracortical microstimulation (ICMS; 35-ms train, 12 x 0.2 ms pulses, 333 Hz, 60 µA) was also applied bilaterally at histologically verified sites in a series of systematic microelectrode penetrations at post-operative days 7, 14 and 28 in anaesthetized animals to map the anterior digastric (AD) and genioglossus (GG) motor representations in face-SMCX by analyzing ICMS-evoked AD and GG electromyographic activity and jaw movements. Results. IONX induced a significant (2-way repeated-measures ANOVA, $P<0.001$) decrease in facial mechanical threshold from post-operative days 4-28 (right upper lip) and post-operative days 6-28 (left upper lip). In sham control animals, there was an extensive bilateral representation of AD and GG in face-SMCX. However, IONX animals had a significantly fewer number of AD plus GG sites in face-SMCX compared to sham control animals at post-operative days 14 and 28 (t-test, $P<0.001$) and in the number of AD sites at post-

operative day 28 (P<0.001). Conclusions. These findings indicate that trigeminal nerve injury induces neuroplastic alterations in tongue and jaw motor representations in face-SMCX that are associated with mechanical hypersensitivity and that may contribute to sensorimotor changes following trigeminal nerve injury.

Disclosures: B.J. Sessle: None. **D. Yao:** None.

Nanosymposium

732. Chronic Pain and Trigeminal Processing

Location: 143A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***732.12

**Topic: ***D.03. Somatosensation: Pain

Support: NIH Grant DE023846

Title: Capsaicin receptor in craniofacial muscle pain

Authors: *M.-K. CHUNG, S. WANG, J. LIM, J. JOSEPH, S. WANG, F. WEI, J. Y. RO
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Abstract: Spontaneous pain and function-associated pain are prevalent symptoms of multiple acute and chronic muscle pathologies. We established mouse models for evaluating spontaneous pain and bite-evoked pain from masseter muscle, and determined the roles of TRPV1 and the contribution of TRPV1- or NK1-dependent nociceptive pathways. Masseter muscle inflammation increased mouse grimace scale (MGS) scores and face wiping behavior which were attenuated by pharmacological or genetic inhibition of TRPV1. Masseter inflammation led to a significant reduction in bite force. Inhibition of TRPV1 only marginally relieved the inflammation-induced reduction of bite force. These results suggest differential extent of contribution of TRPV1 to the two types of muscle pain. However, chemical ablation of TRPV1-expressing nociceptors or chemogenetic silencing of TRPV1-lineage nerve terminals in masseter muscle attenuated inflammation-induced changes in both MGS scores and bite force. Furthermore, ablation of neurons expressing neurokinin 1 (NK1) receptor in trigeminal subnucleus caudalis also prevented both types of muscle pain. Our results suggest that TRPV1 differentially contribute to spontaneous pain and bite-evoked muscle pain, but TRPV1-expressing afferents and NK1-expressing second order neurons commonly mediate both types of muscle pain. Therefore, manipulation of the nociceptive circuit may provide a novel approach for management of acute or chronic craniofacial muscle pain.

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Nanosymposium

732. Chronic Pain and Trigeminal Processing

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Time: *Wednesday, November 15, 2017, 1:00 PM - 4:15 PM

Presentation Number: *732.13

Topic: *D.03. Somatosensation: Pain

Support: NIH Grant DE025943

Title: Pain vulnerability is inherent in affective dimension of pain

Authors: C. LI, C.-H. ZHOU, Y. CAI, *Z. Z. PAN
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Abstract: The affective dimension of chronic pain, induced by sustained sensory pain-induced negative emotion including anxiety, depression and stress, exacerbates pain sensitivity and contributes to pain chronification. Individual variability and vulnerability to developing chronic pain has been well demonstrated in clinical reports, but it has not been explored in preclinical pain studies in animals. In this study, we investigated individual variance and vulnerability in response to chronic pain conditions of both sensory and affective dimensions, using two commonly used rodent models of chronic neuropathic pain: a rat model of infraorbital nerve (ION) ligation-induced orofacial pain and a mouse model of spared nerve injury (SNI)-induced pain. We found that, while the animals had relatively small variations in their sensitized behavioral responses of sensory pain measured by the von Frey test for mechanical allodynia and the paw-withdrawal test for thermal hyperalgesia, they displayed, 30 days after the pain surgery, dramatic individual variations in their behavioral responses of affective pain as negative emotion measured by the open filed test and elevated plus maze test for anxiety-like behaviors and by the forced swim test for depression-like behaviors. Interestingly, this individual vulnerability to developing the chronic sensory pain-induced behaviors of affective pain was mostly consistent across different aspects of negative emotion, i.e., the animals that were more vulnerable to anxiety were likely also more vulnerable to depression. Furthermore, our molecular analysis revealed that the vulnerable animal group showed a significantly decreased protein level of DNA methyltransferase 3a (Dnmt3a) in the central nucleus of amygdala (CeA), a critical brain site for integrating and regulating emotion behaviors in response to rewarding or aversive conditions such as pain. These findings indicate that individual pain vulnerability is largely inherent in the emotion disorders of affective pain and CeA Dnmt3a and its regulation of DNA methylation may

play an important role in the adaptive epigenetic responses to chronic pain for the pain vulnerability.

Disclosures: C. Li: None. **C. Zhou:** None. **Y. Cai:** None. **Z.Z. Pan:** None.

Nanosymposium

733. Development of Sensory Systems

Location: 152B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***733.01

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

Title: Elp3 controls early cochlear development

Authors: *L. DELACROIX, S. D. FREEMAN, Jr, S. MATEO-SANCHEZ, R. L. POUYO, A. CZAJKOWSKI, L. NGUYEN, B. MALGRANGE
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Abstract: The polarised alignment of cells across a tissue plane, namely planar cell polarity (PCP), is essential for the integration of cells into tissues. In the inner ear, the organ of Corti exhibits exquisite planar polarity, most obviously observed by the V-shaped stereocilia hair bundles all pointing in the same, lateral, direction. This polarity is functionally important as it ensures the coordinated activation of mechanosensory cells that are essential for hearing.
A key event in the establishment of PCP in the organ of Corti is the migration of the kinocilium towards the lateral side of the hair cell, where it serves as a guidepost that orchestrates the morphogenesis and orientation of the stereocilia hair bundle. Kinocilium migration is controlled by proteins encoded by a set of evolutionarily conserved genes that are more commonly associated with the regulation of centrosome positioning during cell division. The heterotrimeric Gα protein $G\alpha_i$ and its adaptor molecule LGN localize to the lateral edge of the hair cell, sequester cytoplasmic motor proteins, and generate pulling forces on microtubules that shift the nascent kinocilium laterally.
Elp3 is the catalytic subunit of Elongator, a conserved complex that maintains translational fidelity via its regulation of tRNA modifications. Elongator facilitates the addition of 5-methoxycarbonylmethyl and 5-carbamoylmethyl groups to the uridine^{34} wobble position in the anticodons of a subset of tRNAs - a process that is essential to proteostasis. Here we show that conditional deletion of Elp3 in the developing organ of Corti results in the accumulation of misfolded protein aggregates in HCs, slowing vesicular transport along microtubules, and disrupting the localization of the proteins that govern kinocilium migration. The absence of Elp3 thus results in hair cell polarity defects that are associated with severe hearing loss. These findings highlight the importance of protein homeostasis during inner ear development and

suggest that regulators of protein translation and quality control may prove to be new candidate deafness-causing genes.

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Nanosymposium

733. Development of Sensory Systems

Location: 152B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***733.02

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

Support: IUAP P07/7
FNRS
FLF

Title: miRNAs and inner ear

Authors: *B. MALGRANGE, P. VAN DEN ACKERVEKEN, A. MOUNIER, A. HUYGHE, R. SACHELI, L. DELACROIX, L. NGUYEN
Univ. of Liege, LIEGE, Belgium

Abstract: MicroRNAs are important regulators of gene expression and are known to be involved in numerous cellular processes such as cell proliferation or differentiation, particularly during development of numerous organs including the inner ear. However, it is still unknown if miRNAs are required during the earliest stages of otocyst and cochlear duct development. Here, we report that Dicer-cKO mice showed a defect in the early development of inner ear, especially caused by an increase in DNA damage followed by a p53-mediated apoptosis. In addition, progenitors in the prosensory domain of the cochlea do not exit the cell cycle. Among the potential miRNAs/target gene responsible for this phenotype, we identified ItgA3 as a target of miR-183, an otic vesicle enriched miRNA, and observed that the repression of ItgA3 could be a key mechanism in the regulation of cell proliferation in the developing cochlea. Collectively, our results reveal, for the first time, that Dicer and miRNAs play essential roles in the regulation of early inner ear development.

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Nanosymposium

733. Development of Sensory Systems

Location: 152B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***733.03

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

Support: NIH DC015333
NASA NNX10AK63H

Title: Transplantation of ears reveals molecular guidance mechanisms for finding targets within the central nervous system

Authors: *K. ELLIOTT THOMPSON, C. GORDY, B. FRITZSCH
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Abstract: Sensory neurons make stereotyped connections to nuclei within the hindbrain. Trigeminal ganglia project to the trigeminal nucleus, epibranchial placode derived taste neurons project to the solitary tract and vestibular and cochlear neurons project to the vestibular and cochlear nuclei. Careful analysis of central projection formation of the various cranial nerves show a spatiotemporal progression into the hindbrain based on the timing of entry in a simple order: trigeminal>ear>lateral line>electroreceptors. Auditory and vestibular sensory neurons project to the correct nuclei before the second order neurons differentiate, even without target nuclei differentiation. Ideas that inner ear afferent neuronal processes navigate along neural crest-derived Schwann cells to target their nuclei have been refuted: afferents target their nuclei in Sox10 null mice lacking Schwann cells. Altering the entry point of inner ear sensory neurons in mutants still results in nearly correct navigation within the brain, implying diffusible cues to guide inner ear afferents. We hypothesize that inner ear sensory neurons use molecular gradients associated with the dorso-ventral patterning of the hindbrain to navigate to their proper target column. We test this hypothesis by excluding other possibilities through heterotopic, heterochronic and xenoplastic ear transplantations in frogs, chicken and mice. With this approach we can eliminate timing cues and afferent-substrate interactions, allowing only diffusible factors from the hindbrain to molecularly guide inner ear afferents. Transplantation of otocysts from the same age or younger donor chicken or frogs rostral to the native ear result in proper afferent hindbrain targeting/navigation from the transplanted ear. In addition, transplantation of a mouse otocyst rostral to the native chicken ear also results in proper hindbrain targeting, indicating conservation of molecular guidance between mice and chicken. Transplantation of otocysts adjacent to the spinal cord in chickens or frogs results in navigation to a dorsal entry point comparable to the hindbrain. Wnt, BMP, and Sonic hedgehog are defining dorso-ventral patterning in the hindbrain and spinal cord in vertebrates and could provide the apparently conserved molecular gradients for mouse ear afferents to navigate to the chicken hindbrain. In

contrast, transplantation of otocysts to the frog or chicken orbit, replacing the eye, results in random projections to the midbrain, likely correlated with molecularly distinct midbrain dorso-ventral patterning cues. We are currently investigating the role of likely morphogens in inner ear afferent guidance.

Disclosures: K. Elliott Thompson: None. **C. Gordy:** None. **B. Fritzsch:** None.

Nanosymposium

733. Development of Sensory Systems

Location: 152B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***733.04

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

Support: NIH R01DA035025

Title: Rewiring the Taste System

Authors: *H. LEE[1], L. J. MACPHERSON[1], *C. A. PARADA[1], C. ZUKER[1], *N. J. P. RYBA[2]
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Abstract: The sense of taste informs an organism of the nutritive value and potential toxicity of foods. In mammals, taste buds typically contain 50-100 tightly packed taste receptor cells (TRCs), each tuned to a taste quality: sweet, sour, bitter, salty and umami. Notably, mature TRCs have life spans of about two weeks and are constantly replenished by differentiation of taste stem cells. Given the importance of establishing appropriate connectivity between TRCs and their partner ganglion neurons (i.e. ensuring that a labeled line from sweet TRCs connect to sweet neurons, bitter TRCs to bitter neurons, sour to sour, etc.), we examined how new connections are specified and maintained to retain fidelity of signal transmission. Our results show that bitter and sweet TRCs provide instructive signals to bitter and sweet target neurons via different guidance molecules**.** Together, we uncover the basic logic of the wiring of the taste system at the periphery, and explain how a labeled-line sensory circuit preserves signaling integrity despite rapid and stochastic turnover of TRCs.

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Nanosymposium

733. Development of Sensory Systems

Location: 152B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 2:45 PM

**Presentation Number: ***733.05

**Topic: ***D.05. Olfaction and Taste

Title: Functional and structural plasticity of adult-born versus preexisting granule cells of the olfactory bulb during simple and complex perceptual learning in mice

Authors: *J. FOREST[1], J. SACQUET[1], I. CAILLE[2], M. RICHARD[1], A. DIDIER[1], N. MANDAIRON[1]
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Abstract: Olfaction is important in many behaviors such as food search, predator avoidance, conspecific recognition or reproduction. To reliably perform these behaviors, animals must have an olfactory system able to discriminate between odorants. Discrimination performances can be improved by perceptual learning which is an increase in discrimination capabilities between two perceptually close odorants after passive exposure to them. We know that a key supporting structure of this learning is the olfactory bulb (OB). Interestingly, the olfactory bulb is the target of an adult neurogenesis. Indeed, new interneurons (mostly granule cells) are formed throughout life from neural stem cells located in the subventricular zone of the lateral ventricle, which migrate and functionally integrate into the neuronal network. Previous work modulating neurogenesis has shown that adult-born interneurons were required for a perceptual learning task (Moreno et al. 2009). In order to understand the specificity of adult-born neurons, it is important to compare them to preexisting ones. In addition, we asked the question of the respective role of these two populations in conditions of more complex learning. We thus trained mice in perceptual learning tasks with an increasing number of odorant pairs (1, 2, 3 or 6 odor pairs). We showed that i) mice were able to learn to discriminate between two similar odorants of up to 6 odor pairs simultaneously ; ii) adult-born cell density increased with learning independently of its complexity (using Brdu labeling) : iii) adult-born neurons' functional recruitment in the processing of the learned odorant linearly increased with complexity ; iv) during simple perceptual learning, only adult-born neurons (labeled with GFP lentivirus injected in adult mice, P60) activated in response to the learned odorants (Zif268-positive neurons) showed structural plasticity evidenced by an increased spine density both at the apical and basal dendritic domains. During complex perceptual learning these same changes occurred but independently of neuronal activity ; v) in preexisting neurons (labeled with DsRed lentivirus injection at P0-P1), only complex learning elicited an increased spine density and only at the apical dendritic domain. To summarize, these data suggest that improvement in discrimination is underlain by structural

plasticity of adult-born neurons and in a second step preexisting neurons depending on the complexity of learning.

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Nanosymposium

733. Development of Sensory Systems

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Time: *Wednesday, November 15, 2017, 1:00 PM - 2:45 PM

Presentation Number: *733.06

Topic: *D.05. Olfaction and Taste

Support: a pre-doctoral fellow of the Japan Society for the Promotion of Science
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Title: Nrp2 is sufficient to instruct circuit formation of mitral-cells to mediate odor-induced attractive social responses

Authors: ***K. INOKUCHI**[1,3], F. IMAMURA[6], H. TAKEUCHI[2], R. KIM[7], H. OKUNO[8], H. NISHIZUMI[4], H. BITO[9], T. KIKUSUI[10], H. SAKANO[5]
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Abstract: Odor information induces various innate responses that are critical to the survival of the individual and for the species. An axon guidance molecule, Neuropilin 2 (Nrp2), is known to mediate targeting of olfactory sensory neurons to the posteroventral main olfactory bulb (PV MOB) in mice. Here, we report that Nrp2-positive (Nrp2+) mitral cells (MCs) play crucial roles in transmitting attractive social signals from the PV MOB to the anterior part of medial amygdala (MeA). Semaphorin 3F, a repulsive ligand to Nrp2, regulates both migration of Nrp2+ MCs to the PV MOB and their axonal projection to the anterior MeA. In the MC-specific Nrp2 knockout mice, circuit formation of Nrp2+ MCs and odor-induced attractive social responses are

impaired. In utero electroporation demonstrates that activation of the Nrp2 gene is sufficient to determine the functional lineage of MCs and instruct their circuit formation from the PV MOB to the anterior MeA.

Disclosures: **K. Inokuchi:** None. **F. Imamura:** None. **H. Takeuchi:** None. **R. Kim:** None. **H. Okuno:** None. **H. Nishizumi:** None. **H. Bito:** None. **T. Kikusui:** None. **H. Sakano:** None.

Nanosymposium

733. Development of Sensory Systems

Location: 152B

Time: *Wednesday, November 15, 2017, 1:00 PM - 2:45 PM

Presentation Number: *733.07

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

Support: FCT, POPH/FSE, Portugal
Lowy Medical Research Institute
HHMI

Title: Retinoic acid is a conserved pathway regulating patterning of a high acuity visual area

Authors: ***S. I. SILVA**, C. L. CEPKO
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Abstract: Most vertebrate species that use vision as their major sensory modality have evolved local retinal specializations optimized for high acuity. Among mammals, only some Primates possess a high acuity area (HAA), the fovea. In humans, this area is particularly prone to degeneration, such as in age-related macular degeneration (AMD). In diurnal species, HAAs are characterized by a high density of specialized cone photoreceptors (PRs), which enable vision in daylight intensities and initiate color vision. HAAs often have no rod PRs, which are active in dim light. In addition HAAs are characterized by a higher density of cells in the ganglion cell layer (GCL), a decreased ratio of cones to retinal ganglion cells (RGCs) concomitant with a specific low convergence connectivity, defined in primates as the midget foveal system. Despite its critical role for human vision the molecular mechanisms underlying fovea formation during development remain unknown. Birds, like humans, depend highly on their visual sensory input. We have previously described a retinal region in the chick that functionally resembles the primate fovea, comprising only cones, i.e. devoid of rods, the rod-free zone (RFZ). This region coincides with the peak density of RGCs, designated the area centralis and with a specialized morphological structure in the inner nuclear layer, the aster. Here we show that retinoic acid (RA) signaling pathway is a major regulator of HAA formation in the chick. RA-synthesizing and -degrading enzymes exhibit specific and dynamic expression patterns during retinogenesis,

whereas manipulation of RA signaling in vivo affects all hallmark features of the HAA, that is, induces appearance of rods in an otherwise rod-free area without affecting the overall distribution of rods in the retina, disrupts aster radial symmetry and induces loss of the high density of cells in GCL. Mechanistically, RA acts through Fgf8 in a negative manner and Fgf8 knocked down recapitulates the effects induced by RA injection. Notably, patterned expression of RA signaling components are conserved in human fetal retina at equivalent developmental stages to the chick. These findings provide a framework for the molecular mechanisms underlying the patterning of HAAs, and point to a conserved molecular mechanism between chick and human. In addition, our studies provide the first mechanistic insight regarding fovea development in humans, which can impact the development of stem cell based therapies in human diseases, such as AMD.

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Nanosymposium

734. Interrogating Neurovascular-Coupling in Functional Imaging

Location: 147B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***734.01

**Topic: ***F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH NS R01 NS095933

Title: Diverse character of negative hemodynamic response is inconsistent with linearity

Authors: *E. HALFEN, A. TAYLOR, J. KIM, D. RESS
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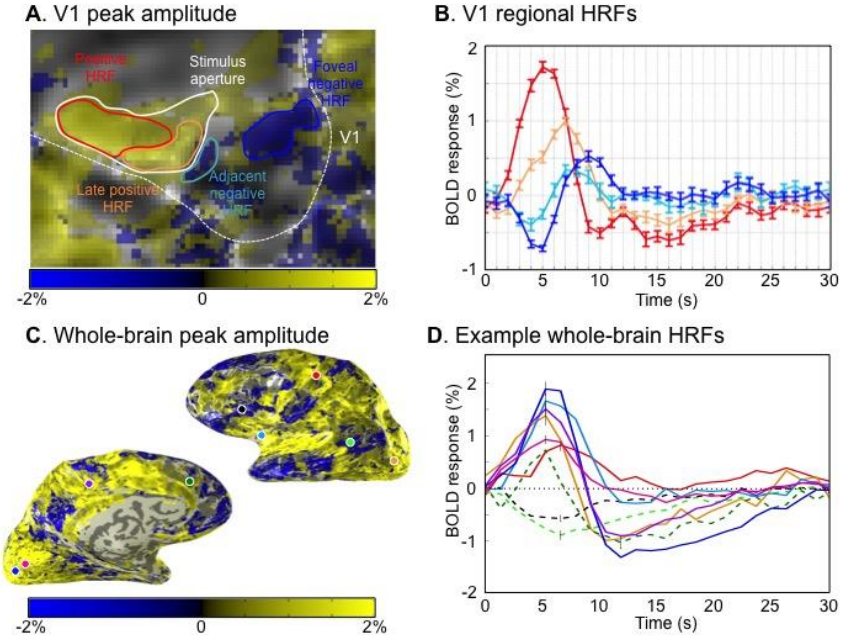
Abstract: The negative BOLD response (NBR) is usually evoked by blocked or travelling-wave experimental designs that obscure details of their temporal dynamics. To better understand the NBR, we designed two slow, event-related paradigms to elicit strong negative hemodynamic response functions (HRFs) that allow us to study the physiology and physics behind the negative HRF. Methods: In both paradigms, the HRF is elicited by having the subject perform a challenging task upon a brief (2-3 s) sensory stimulus ("impulse"), while maintaining fixation. The subject then performs a non-challenging and infrequent fixation dot task for 26-28 s. This cycle is repeated 14-16 times each run, with 4-6 runs/session. In our 1st paradigm, the subject views an annulus (6-8°) of moving dots (4°/s) and performs a motion-discrimination task. In the 2nd paradigm, the impulse is audiovisual with a finger-movement task designed to elicit HRFs across the majority of cortex. Results: The 1st stimulus elicits a positive HRF within the V1 representation of the stimulus aperture, and there are strong negative HRFs (Fig **A**, **B**) near the

fovea. Remarkably, the HRFs from the foveal edge of the stimulated region exhibit a strong initial dip and a late positive peak. The 2nd stimulus evokes strong negative (blue) and positive (yellow) HRFs over the majority (>75%) of cortex (Fig **C**). A fraction (~18%) of these HRFs are negative. Negative HRFs (Fig **D**) show substantial variability in the early negative and late positive peaks. Discussion: Our 1st paradigm reveals a transition across the V1 representation of the stimulus aperture from positive HRFs to partially negative HRFs, suggesting hemodynamic edge effects such as "blood steal." Our 2nd paradigm reliably elicits a variety of negative HRFs across a pattern of cortical regions that resemble the default mode network (DMN), suggesting that they are evoked by suppression of activity in this rest-related network. Overall, results indicate variable contributions of blood flow and oxygen metabolism to the negative HRF that are inconsistent with linear scaling of the positive HRF.



A. Color overlay of peak HRF amplitude on flat view of V1. Four ROIs shown: positive HRF (red), late-peaking positive HRF (orange), adjacent negative HRF (light blue), and foveal negative HRF (dark blue). **B.** Timeseries from each ROI, plotted in respective colors. **C.** Whole-brain peak HRF amplitude map. **D.** Example positive and negative HRFs from whole-brain results. Colors correspond to dots in Fig. C.

Disclosures: E. Halfen: None. **A. Taylor:** None. **J. Kim:** None. **D. Ress:** None.

Nanosymposium

734. Interrogating Neurovascular-Coupling in Functional Imaging

Location: 147B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***734.02

Topic: *F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Max Planck Institute internal support

Title: Decipher the concurrent bidirectional regulation of the fMRI signal by astrocytes

Authors: ***M. WANG**[1], Y. HE[1], T. J. SEJNOWSKI[2], X. YU[1]
[1]High-Field Magnetic Resonance, Max Planck Inst. For Biol. Cybernetics, Tübingen, Germany; [2]Salk Inst., La Jolla, CA

Abstract: Astrocytic Ca^{2+}-mediated gliovascular interactions regulate the neurovascular network in situ and in vivo. However, it is difficult to measure directly both the astrocytic activity and fMRI to relate the various forms of BOLD signaling to brain states under normal and pathological conditions. In this study, fMRI and GCaMP-mediated Ca^{2+} optical fiber recordings revealed distinct evoked astrocytic Ca^{2+} signals that were coupled with positive BOLD signals and intrinsic astrocytic Ca^{2+} signals that were coupled with negative BOLD signals (Fig 1). Furthermore, the evoked and intrinsic astrocytic Ca^{2+} signal could occur concurrently to mediate positive or negative BOLD signal changes respectively. Unlike propagating Ca^{2+} waves in spreading depolarization/depression, the intrinsic Ca^{2+} spikes occurred simultaneously in both hemispheres and were initiated upon the activation of the central thalamus and midbrain reticular formation (Fig 2). These results reveal a crucial role for astrocytes in mediating bidirectional fMRI signals based on the thalamic regulation of cortical states, providing a better understanding of how the BOLD signal is linked to brain activity at the cellular, circuit, and systems levels.

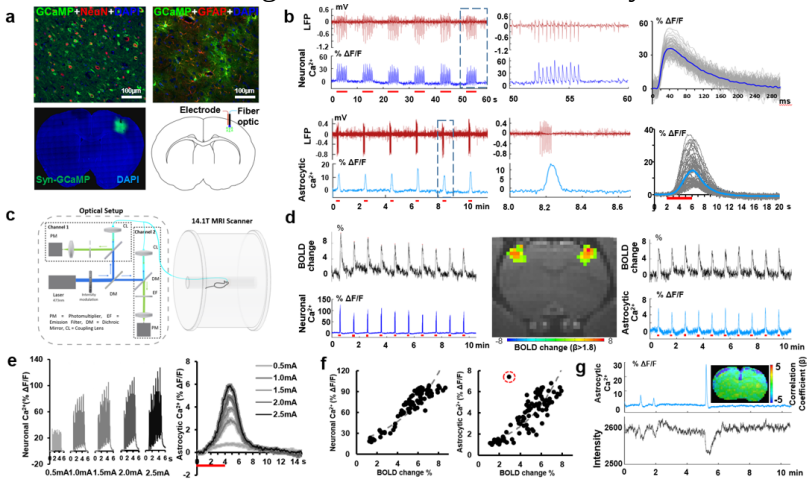


Fig. 1 Sensory-evoked neuronal /astrocytic Ca^{2+} recordings with simultaneous LFP or BOLD fMRI. (**a**) The co-localized GCaMP (green) with neurons (NeuN, red), or with astrocytes (GFAP, red). Lower panel: immunostaining image (left) and a schematic drawing (right) for simultaneous LFP and fiber-optic Ca^{2+} recording. (**b**) Simultaneous LFP (red) and Ca^{2+} signal traces (blue) from neurons or astrocytes in FP-S1 with forepaw electrical stimulation (3 Hz, 4 s, 1 mA). Middle panel: enlarged figures of the dashed box in left panel. Right panel: the averaged trace of evoked Ca^{2+} signal (gray lines are individual traces from 6 rats). (**c**) The schematic drawing of the two channel fiber-optic recording system with fMRI. (**d**) The time courses of evoked fMRI signal from bilateral FP-S1 and simultaneous neuronal (left) / astrocytic (right) Ca^{2+} signal (inset, a representative color-coded BOLD-fMRI map at 2.0 mA). (**e**) The stimulation intensity dependent Ca^{2+} signal from neurons or astrocytes. (**f**) The scatter plot of the evoked Ca^{2+} signal amplitude vs. simultaneous fMRI peak amplitude at different stimulation intensities (red dashed circle, outlier). (**g**) The representative traces of the intrinsic astrocytic Ca^{2+}spikes and simultaneous fMRI signal acquired from the entire cortex (inset, color-coded negative correlation map).

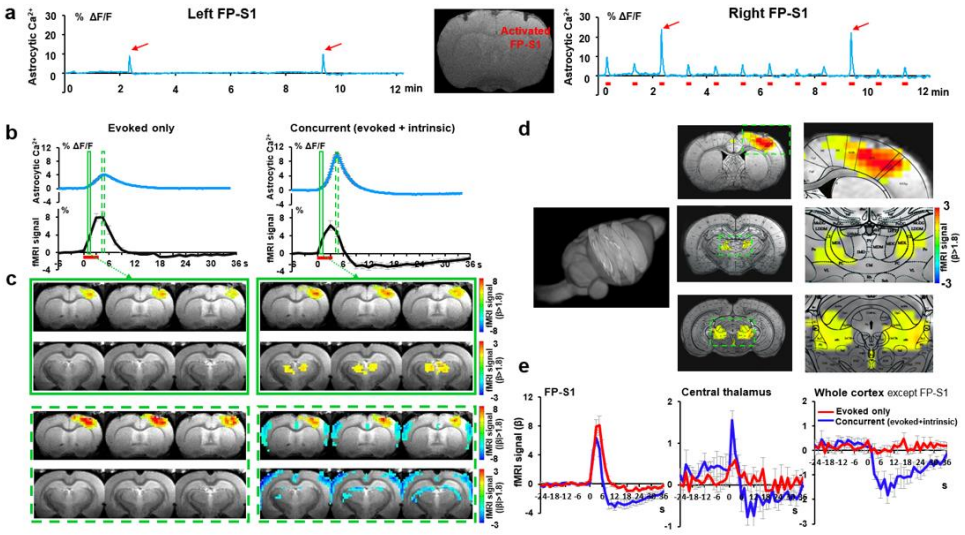


Fig. 2 Subcortical fMRI activation patterns underlying the intrinsic astrocytic Ca2+ spikes. (**a**) The representative traces of the FP-S1 astrocytic Ca2+ signals in both hemispheres (Right FP-S1 activation, 12 epochs, 3 Hz, 4 s, 1.5 mA; inset, fiber traces in the anatomical MRI image; concurrent events, epoch 3 and 10, red arrows). (**b**) The averaged astrocytic Ca2+ and simultaneous fMRI signal of the evoked only and concurrent events. (**c**) The time-lapsed function maps at 1.5 s (solid green box) and 4.5 s (dashed green box) after onset of stimulation (left, evoked only FP-S1 activation; right, concurrent events, thalamic activation at 1.5 s, followed by the negative fMRI signal in the cortex and ventricle areas at 4.5 s). (**d**) The concurrent event functional maps at 1.5 s were overlapped on three anatomic slices characterized from a 3D whole brain and the corresponding brain atlas (right panel, the enlarged images with activity patterns on the FP-S1, central thalamus, and the midbrain reticular formation region). (**e**) The time course of the BOLD fMRI signal from FP-S1, central thalamic region and the whole cortex except FP-S1 (trial #= 72; rats, n=6, mean ± SEM).

Disclosures: **M. Wang:** None. **Y. He:** None. **T.J. Sejnowski:** None. **X. Yu:** None.

Nanosymposium

734. Interrogating Neurovascular-Coupling in Functional Imaging

Location: 147B

Time: *Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

Presentation Number: *734.03

Topic: *F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NSF Award 1641133
NSF Award 1541612
New York Medical College Recruitent Funds

Title: Classifying acute brain injury based on noninvasive measurements of neurovascular sensory reactivity

Authors: H. JANG[1,2], L. WANG[1], S. HUANG[2], M. YE[2], D. X. HAMMER[2], C. G. WELLE[3], *J. A. FISHER[1]
[1]Dept. of Physiol., New York Med. Col., Valhalla, NY; [2]US Food and Drug Admin., Silver Spring, MD; [3]Dept. of Neurosurg., Univ. of Colorado, Aurora, CO

Abstract: A challenge for developing technology capable of classifying the severity of mild traumatic brain injury (mTBI) outside of a clinical setting is the lack of quantitative biomarkers for which the underlying neurological bases are understood. In the absence of the ability to detect anatomical changes, ongoing brain activity, most commonly electrophysiological, has been utilized for monitoring abnormalities associated with injury. This approach is sensitive to injury, yet on its own does not necessarily provide a complete mechanistic portrait, given that vascular damage also impacts electrical activity. We explored potential biomarkers for TBI by noninvasively monitoring sensory neurovascular reactivity—the combined effects of sensory-evoked electrical and hemodynamic activity—using a novel hybrid optical and electrophysiological measurement approach. By combining diffuse correlation spectroscopy (DCS) with co-localized electrophysiological measurements in a mouse model of TBI, we observed concomitant alterations in sensory-evoked cerebral blood flow (CBF) and somatosensory evoked potentials (SSEPs) following controlled cortical impact (CCI). In general, CCI acutely reduced the amplitude of the prominent features of the hemodynamic response function (HRF) as well as SSEP peaks. These signals mostly, if not completely, recovered to baseline amplitude within 30 minutes following mechanical insult. Beyond global amplitude reductions, injury yielded a spectrum of more subtle yet highly significant alterations in the sensory-evoked responses and correlations between electrophysiological and hemodynamic components. For example, although short-latency peaks in the SSEP were perturbed by injury, they demonstrated relatively poor correlation with aspects of the hemodynamic response function; in contrast, mid-latency peaks were highly correlated with alterations in the peak of the HRF. Injury additionally introduced new spectrotemporal features into the HRF waveform and altered the inter-trial coherence of functional responses. Overall, our results reveal a novel set of potential biomarkers for brain injury based on noninvasive assessment of neurovascular "uncoupling." Additionally, based on our findings of electrical and hemodynamic correlations, we explored methods for extracting this information from noisy measurements.

Disclosures: H. Jang: None. **L. Wang:** None. **S. Huang:** None. **M. Ye:** None. **D.X. Hammer:** None. **C.G. Welle:** None. **J.A. Fisher:** None.

Nanosymposium

734. Interrogating Neurovascular-Coupling in Functional Imaging

Location: 147B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***734.04

**Topic: ***F.06. Brain Blood Flow, Metabolism, and Homeostasis

Title: Two channel fiber optic mediated glutamate and calcium recording with simultaneous fMRI

Authors: *Y. JIANG, X. YU
High field magnetic resonance, Max Planck Inst. For Biol. Cybernetics, Tübingen, Germany

Abstract: Glutamate, a primary excitatory neurotransmitter, provides us key understanding of the signaling of neuron-glia-vessel network due to its roles in trans- and extrasynaptic transmission in synaptic release and propagation. Using virally expressed genetically encoded fluorescent reporter iGluSnFR for extracellular glutamate sensing and genetically encoded calcium indicator GCaMP6f for calcium sensing, we demonstrate iGluSnFR with a more rapid temporal features of sensory response than the evoked calcium signal detected by GCaMP6f (**Fig. 1 A**). iGluSnFR showed earlier onset time (~11 ms vs ~20ms) and time to peak response (~20 ms vs ~40 ms) when it is compared to GCaMP6f. Extracellular clearance following synaptic glutamate release evoked by multiply electrical forepaw stimuli (2mA, 1Hz,10s and 2 mA, 3Hz,10s) showed comparable signal-to-noise ratio with GCaMP6f (**Fig. 1 B & C**). The temporal profile of extracellular glutamate might help deciphering the cellular mechanism underlying blood-oxygen-level-depended (BOLD) signal in the brain of rodents. Implemented together with functional magnetic resonance imaging (fMRI) and simultaneously two channel fiber-optic fluorescent recording, robust BOLD signal in response to electrical forepaw stimulation were observed in both iGluSnFR and GCaMP6f expressed somatosensory region (**Fig.1 D**). This combined method may lead to a better understanding of neurovascular coupling through the neuron-glia-vessel network in the animal brain.

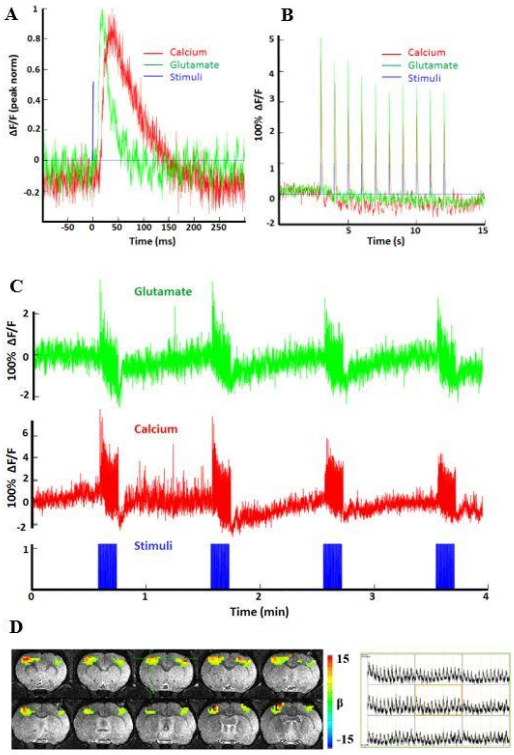


Figure 1. Characterizations of iGluSnFR and GCaMP responses and BOLD signal in rat somatosensory cortex by evoked forepaw electrical stimulation. **(A)** Temporal features of sensory response of the evoked iGluSnFR and GCaMP signal. Two channel fiber optic recording of glutamate and calcium response features induced by multiply electrical forepaw stimuli with one trial (2mA, 1Hz,10s) **(B)** and several trials stimuli (2 mA, 3Hz,10s) **(C)**. **(D)** BOLD fMRI signal and representative time course of iGluSnFR and GCaMP expressed in rat somatosensory cortex by evoked forepaw electrical stimulations.

Disclosures: Y. Jiang: None. **X. Yu:** None.

Nanosymposium

734. Interrogating Neurovascular-Coupling in Functional Imaging

Location: 147B

Time: *Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

Presentation Number: *734.05

Topic: *F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH NS07391
NIH MH18273
NIH EB018903
NIH EB003324
IBS-R015-D1

Title: What layer-specific fMRI responses in the rat olfactory bulb tell us about vascular regulation, hemodynamic spread, and the role of GABAergic cells in neurovascular coupling

Authors: *A. J. POPLAWSKY[1], H. FUKUDA[1], B. IORDANOVA[1], A. VAZQUEZ[1], B.-M. KANG[2,3], J. KIM[2], M. SUH[2,3], S.-G. KIM[2,3]
[1]Radiology, Univ. of Pittsburgh, Pittsburgh, PA; [2]Ctr. for Neurosci. Imaging Research, Inst. for Basic Sci., Suwon, Korea, Republic of; [3]Biomed. Engin., Sungkyunkwan Univ., Suwon, Korea, Republic of

Abstract: High-resolution fMRI detects localized neuronal activity via the hemodynamic response, but it is unclear if it can identify neuronal activity specific to individual layers or whether activation of GABAergic inhibitory neurons will increase fMRI signals. For the past several years, we have been addressing these issues in the rat olfactory bulb by targeting synaptic activity in single bulb layers and by preferentially evoking inhibitory neurons with electrical stimulation of different white matter tracts (lateral olfactory tract, LOT; anterior commissure, AC). Electrophysiology, laser-doppler flowmetry of cerebral blood flow (CBF), and blood oxygenation level-dependent (BOLD) and contrast-enhanced cerebral blood volume-weighted (CBVw) fMRI at 9.4 T were independently performed. We found that the greatest CBVw fMRI responses were discretely separated to the same layers as the evoked synaptic activities for each stimulus, while BOLD signals were poorly localized. Furthermore, we measured the laminar spread of the CBVw fMRI evoked responses in the external plexiform layer (EPL) during electrical stimulation of LOT at a 55 × 55 μm^2 in-plane resolution. The mean full-width at half-maximum of these fMRI peaks was 347 ± 102 μm (± SD, n = 30 peaks from 5 rats), while the mean anatomical thickness of EPL was 265 ± 65 μm. The functional spread was 106 ± 65 μm (linear regression intercept ± SE) beyond EPL, corresponding to a 53-μm spread from one edge of the layer. We then compared the vascular architecture of EPL using a Clear Lipid-exchanged Anatomically Rigid Imaging/immunostaining-compatible Tissue hYdrogel (CLARITY)-based method. Vessels with an outer diameter of <11 μm accounted for 64.3% of the total vascular volume and had a mean segment length of 55.3 ± 40.4 μm (n = 472), similar to the CBVw fMRI signal spread. Finally, excitation of inhibitory granule cells during LOT or AC stimulations decreased the spontaneous multiple-unit activities of excitatory mitral cells, and subsequently increased CBF, CBVw, and BOLD signals. Further, these layer-specific hemodynamic increases were blocked by topical application of NMDA receptor antagonists and reversed with drug washout during simultaneous fMRI measurements. These results indicate that the vasculature is regulated within individual layers and CBVw fMRI has a higher fidelity to the evoked synaptic activity compared to BOLD; and that increased postsynaptic activity of inhibitory neurons is necessary for vasodilation in EPL. Our findings are significant for understanding the neuronal origin and spatial specificity of hemodynamic responses, especially for the interpretation of laminar-resolution fMRI.

Disclosures: **A.J. Poplawsky:** None. **H. Fukuda:** None. **B. Iordanova:** None. **A. Vazquez:** None. **B. Kang:** None. **J. Kim:** None. **M. Suh:** None. **S. Kim:** None.

Nanosymposium

734. Interrogating Neurovascular-Coupling in Functional Imaging

Location: 147B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***734.06

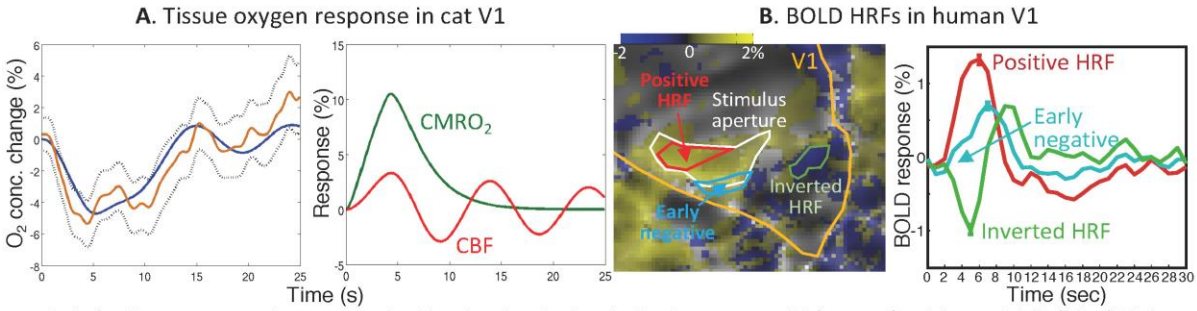
**Topic: ***F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH NS R01 NS095933
NSF BCS 1063774

Title: Modeling the negative blood oxygen-level dependent hemodynamic response function

Authors: *D. RESS, E. HALFEN, J. KIM
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: The negative BOLD response has been widely observed experimentally in a variety of contexts, but its physiology and physical coupling to the MRI signal are not yet well understood. Previous measurements of tissue oxygen levels, reported in our earlier work, indicated showed strong and long-lasting drops in oxygen concentration in cat primary visual cortex induced by 4-s duration visual stimulation (Fig **A**, upper, orange). We could describe these measurements using our Arterial Impulse Model (blue), which predicted that such early negative responses were the consequence of strong oxygen metabolic demands ($CMRO_2$; Fig A, lower, green) coupled with a weak inflow of arterial blood (CBF; red). To better understand these results, we are developing methods to evoke the negative BOLD HRF in human early visual cortex to provide experimental results amenable to analysis with our model for BOLD contrast. **Methods**: Stimulus was a pair of annular sectors of moving dots (4 °/s) presented bilaterally at eccentricity 6—9° for 2-s duration every 30-s. Between presentations, the subject attended a dot at fixation, which changed color rapidly, and subject was requested to report a specific target color that appeared infrequently (~8 s). **Results**: BOLD responses with distinct characteristics were observed in three regions (Fig **B**). First, in gray-matter representation of the stimulus region, a typical positive HRF is observed (Fig **C**, red). Second at the foveal edge of the stimulus region, we see an early negative response (cyan). Third, near the foveal representation, we observe a negative HRF (green), with an early negative peak followed by an "overshoot." **Discussion**: Modeling indicates that the early negative response observed at edge of the stimulus aperture could be caused by strong metabolic demands that are not fully compensated by oxygenated blood flow. However, the para-foveal negative HRF is most consistent with an underdamped flow reduction response, suggesting that neuronal suppression is accompanied by reductions in blood flow.



A. Left: tissue oxygen changes evoked by 4-s visual stimulation in cat area 17 (orange), with model fit (blue) Right: corresponding model predictions of $CMRO_2$ (green) and CBF (red). **B**. Left: HRF amplitudes evoked by human visual stimulation on flattened image of V1. Right: distinct HRFs occur in three regions: positive HRF near center of stimulus aperture (red); early-negative near foveal aperture edge (cyan), and inverted HRF in para-foveal areas (green).

Disclosures: D. Ress: None. **E. Halfen:** None. **J. Kim:** None.

Nanosymposium

734. Interrogating Neurovascular-Coupling in Functional Imaging

Location: 147B

Time: *Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

Presentation Number: *734.07

Topic: *F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NS37853

Title: Tau alters neurovascular coupling by impairing NMDA receptor-dependent nitric oxide production

Authors: *L. PARK, K. UEKAWA, Y. HATTORI, G. WANG, P. ZHOU, J. ANRATHER, C. IADECOLA
Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: The microtubule associated protein tau is a major pathogenic factor in Alzheimer's disease (AD) but it remains unclear how tau impairs brain function. Hyperphosphorylated tau may alter NMDA receptor signaling by destabilizing the link between the receptor and accessory proteins necessary for its downstream signaling, such as nitric oxide synthase (NOS). Since NO mediates the increase in cerebral blood flow (CBF) evoked by glutamatergic synaptic activity, a critical mechanism matching brain function with the delivery of energy substrates through blood flow (functional hyperemia), we tested the hypothesis that tau suppresses the CBF response to neural activity. CBF was assessed using laser-Doppler flowmetry in the somatosensory cortex of urethane-chloralose anesthetized male mice equipped with a cranial window (n=5/group). In wild-type (WT) mice, neocortical superfusion with tau (0.4 µM) attenuated the increase in CBF

evoked by neural activity (whisker stimulation, WS) (vehicle, +22±1%; tau, +15±1; $p<0.05$). However, the increase in CBF produced by neocortical application of acetylcholine, a response mediated by endothelial NO, was not attenuated (vehicle, +24±2%; tau, +24±1%; $p>0.05$). Similarly, the increase in CBF produced by WS was suppressed in transgenic mice expressing mutated tau (WT: +23±2%; rTg4510: +11±2%; PS19: +14±1-%; $p<0.05$), an effect independent of reductions in the field potential evoked by somatosensory activation (WT: -5.1±1.8; PS19: -4.4±2.1 mV; $p>0.05$). Next, we examined the CBF increase induced by glutamate receptor activation. The CBF response to neocortical application of NMDA (40 µM) was attenuated (WT: +26±3%; rTg4510: +13±2%; $p<0.05$), whereas the response to AMPA (10µM) was not (WT: +31±4%; rTg4510: +36±3%; $p>0.05$). Neocortical superfusion with the NOS inhibitor L-NNA (1 mM) attenuated the CBF increase evoked by WS in WT mice (-52±2%; $p<0.05$), but not in rTg4510 mice ($p>0.05$), suggesting that the NO-dependent component of the response was already maximally suppressed. In neuronal cultures from rTg4510 mice, NMDA (40 µm) failed to increase NO production assessed by DAF (WT, +31±2%; rTg4510, +0.04±0.01%; $p<0.05$ from WT NMDA; $p>0.05$ from vehicle; n=8/group). We conclude that tau suppresses the NMDA-dependent component of functional hyperemia by reducing the production of neuronal NO evoked by NMDA receptor activation. The findings unveil a previously unrecognized aspect of tau pathobiology with potential implications for the neurovascular and cognitive dysfunction of AD and other tauopathies.

Disclosures: L. Park: None. **K. Uekawa:** None. **Y. Hattori:** None. **G. Wang:** None. **P. Zhou:** None. **J. Anrather:** None. **C. Iadecola:** None.

Nanosymposium

734. Interrogating Neurovascular-Coupling in Functional Imaging

Location: 147B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***734.08

**Topic: ***F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant AG044467

Title: Attention modulates the negative BOLD response in DMN without disrupting its functional connectivity

Authors: *Q. R. RAZLIGHI, D. B. PARKER
Neurol., Columbia Univ., New York, NY

Abstract: *Introduction*
The topography of the default mode network (DMN) can be obtained by two different fMRI

methods; 1) functional connectivity in resting-state or task-based fMRI, and 2) the deactivations in task-based fMRI, here referred to as negative BOLD response (NBR). In this work, we hypothesize that these two networks are representative of two separate but overlapping neurophysiological processes.

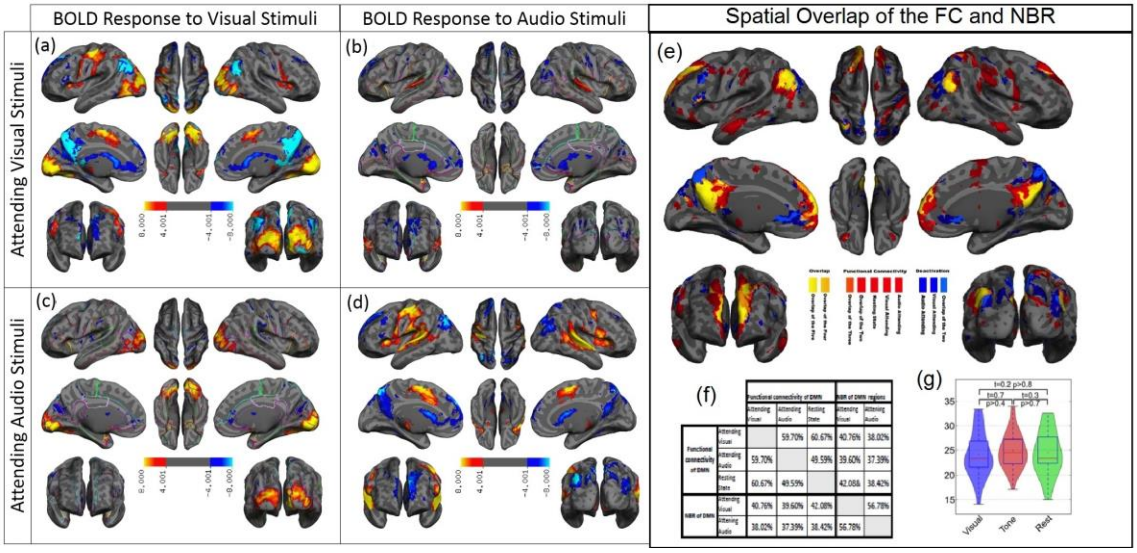
Results

Figures 1a~1d show the group-level activation map using z statistics for two robust sensory stimuli (visual and audio) when the subject are attending (1a and 1d) and not attending (1b and 1c). It is clear from this figure that attending stimuli (either visual or audio) generate significant NBR (illustrated by cold colors) in the DMN regions whereas the unattended stimuli produce only scattered NBR mostly outside the DMN regions. The solid blizzard-blue color mask overlaid on figures 1a and 1d shows the regions where the magnitude of NBR for attended stimuli is significantly higher than unattended stimuli.

Figure 1e shows the extent of the three FC networks obtained from two task-based and one resting-state scans overlaid on top of each other. The quantitative overlap between the spatial extents of these masks are also given in figure 1f using Dice overlap measure. The similarity between the topography of these three FC maps shows that the DMN are up and running whether the participants are attending to a task, not attending to a task, or at resting-state. Figure 1g shows the subject-wise expression of the DMN in the three scans using violin plot, highlighting that there are no significant differences between the levels of FC in the DMN region during the three fMRI scans.

Discussion

Using attention specificity of the NBR, we showed a disassociation between FC of the DMN and its task-based NBR as evidence indicating that they are representative of separate neurophysiological processes. This finding may suggest that FC of the DMN provides an infrastructure for task-related network of neuronal activation, thus it could be considered as a lower level process in functional hierarchy of the brain.



Disclosures: **Q.R. Razlighi:** None. **D.B. Parker:** None.

Nanosymposium

734. Interrogating Neurovascular-Coupling in Functional Imaging

Location: 147B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***734.09

**Topic: ***F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant AG044467

Title: The negative BOLD response varies according to cognitive task domain

Authors: *S. M. NELSON[1,2,3], Q. R. RAZLIGHI[4]
[1]Ctr. of Excellence for Res. on War Veterans, Waco, TX; [2]Ctr. for Vital Longevity, Univ. of Texas - Dallas, Dallas, TX; [3]Psychology & Neurosci., Baylor Univ., Waco, TX; [4]Neurol., Columbia Univ., New York, NY

Abstract: Although much of the functional MRI (fMRI) literature focuses on the task-based positive blood oxygen level-dependent (BOLD) response (PBR), the accompanying negative BOLD response (NBR) is less well-understood and is often left uninterpreted or obscured. This is surprising since studies investigating NBR started as early as the introduction of BOLD-fMRI, motivated by early findings from positron emission tomography (PET; Shulman et al., 1997). While there are some limited studies that utilize NBR in the investigation of Alzheimer's disease (AD), this topic has been largely neglected. In particular, the task-specificity of the NBR has received very little attention.

Here, we aim to show that there is heterogeneity in the NBR for tasks across different cognitive domains. Heterogeneity in the DMN has been demonstrated for task-related activation (PBR; Laird et. al., 2009), but whether such heterogeneity exists for deactivation (NBR) remains unclear. Second, we show that the NBR in DMN regions is highly task-specific.

To assess our hypotheses, we analyzed data from 12 well-known cognitive tasks from 4 different cognitive domains (episodic memory, fluid reasoning, perceptual speed, and vocabulary) in 150 young and healthy participants. Within-domain convergence and across-domain divergence of the PBR as well as NBR were calculated using the similarity and dis-similarity of the activated and deactivated regions. A task-specificity measure was formulated simply by subtracting the inter-domain similarity of the BOLD response from the intra-domain similarity. Permutation testing was used to demonstrate the significance of the difference observed between PBR and NBR task-specificity.

Group-level activation maps for all 12 tasks were calculated and grouped separately for each cognitive domain. The data qualitatively illustrate the heterogeneity of the NBR in different cognitive domains. For instance, a core region of the default mode network (DMN), the posterior cingulate, does not demonstrate significant deactivation for episodic memory in comparison to the other three cognitive domains. In addition, inferior parietal lobule (IPL), another well-

recognized DMN region, does not significantly deactivate for fluid reasoning tasks in comparison to the tasks in the other three domains. The results indicate that deactivated regions show significant domain specificity and selectivity. All in all, we hope that these findings can help elucidate the mechanisms underlying cognitive processes represented in distinct locations of the brain by attending more closely to the full dynamic repertoire that the BOLD signal exhibits.

Disclosures: S.M. Nelson: None. **Q.R. Razlighi:** None.

Nanosymposium

735. Motivation: Subcortical Neurocircuitry

Location: 146C

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***735.01

**Topic: ***G.02. Motivation

Support: Helen Lyng White Fellowship to VMKN
NIDA F32-DA041184 to JMO
NIMH F32-MH113327 to JRR
NIDA R01-DA032750 to GDS
NIDA R01-DA038168 to GDS

Title: Medial orbitofrontal cortex ensemble dynamics during cue-reward associative learning

Authors: *V. K. NAMBOODIRI[1], J. M. OTIS[3], K. VAN HEESWIJK[4], E. VOETS[4], J. RODRIGUEZ-ROMAGUERA[4], L. E. H. ECKMAN[4], G. D. STUBER[2]
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Abstract: Learning the associations between environmental cues and rewards is essential for survival. However, such cue-reward associations can also contribute to maladaptive actions such as cue induced drug seeking or food craving. Orbitofrontal cortex (OFC) is thought to play a fundamental role in the learning and maintenance of cue-reward associations and is hypothesized to relay reward expectation signals to other regions essential for learning such as the ventral tegmental area (VTA). However, how neural ensemble encoding of reward expectation emerges in OFC is unknown. Thus, uncovering how ensembles of OFC neurons acquire and maintain cue-reward associations may instruct our ability to understand and modify adaptive and maladaptive motivated behaviors. Using in vivo 2-photon calcium imaging through implanted GRIN lenses, here we monitored and tracked the activity of the same ensemble of medial OFC neurons during learning and subsequent variations of a Pavlovian cue-reward trace conditioning task. By recording thousands of cells, we show that evolution of mOFC neural responses over

learning tracked the behavioral emergence of cue-induced reward seeking, with inter-animal difference in behavioral learning correlated with the evolution of neural population response. By studying behavioral and neural adaptation to the modification of task parameters after initial acquisition, we also found that there is weak ensemble correlation between such adaptation and initial acquisition. By then extinguishing the cue-reward pairing by omitting reward following cue and subsequently reinstating the cue-reward pairing, we found that ensemble responses during reinstatement are correlated with responses after initial learning, suggesting stable encoding of cue-reward associations. Lastly, by investigating mOFC neurons projecting to VTA, we found that these cells also respond strongly to cue-induced reward expectation. Interestingly, while we found no behavioral effect on cue-induced reward seeking post learning by inhibiting CaMKii expressing cells in mOFC, we found that inhibiting VTA projecting mOFC cells caused a persistent reduction in cue-induced reward seeking and suppressed trial-by-trial updating of reward expectation based on reward history.

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Nanosymposium

735. Motivation: Subcortical Neurocircuitry

Location: 146C

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**Presentation Number: ***735.02

**Topic: ***G.02. Motivation

Support: F32MH107206
U01 NS094342

Title: Function of basal ganglia circuitry in motivation

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Abstract: Motivation is commonly separated into two distinct processes: directional and activational. The directional aspect of motivation can direct animals towards or away from stimuli, while the activational aspect can act towards speeding up or invigorating behavior. While recent work has begun to tease apart circuits devoted to directional processes, little is known about circuits that are involved in activational processes. To study the activational aspects of motivation, we designed a set of behavioral tasks for mice where effort and reward magnitude could be independently manipulated. As expected, we found that trials requiring a greater level

of effort (or trials with smaller rewards) led to consistently slower responses. We used these tasks to investigate the role of dopamine neurons in the substantia nigra pars compacta (SNc) and medium spiny neurons in the dorsomedial striatum. We performed bulk calcium imaging using fiber photometry to show that tonic dopamine responses were much greater in blocks of trials where the reward rate was high, as predicted by theory. Next, we examined single-cell activity of direct and indirect pathway medium spiny neurons (dMSNs and iMSNs) with a head-mounted microscope, where we find cell-type specific signaling that strongly correlates with movement vigor, indicating a key role for basal ganglia circuitry in activational processes.

Disclosures: C.H. Donahue: None. **A.C. Kreitzer:** None.

Nanosymposium

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Title: Dopaminergic modulation of projection-defined prefrontal circuits

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Abstract: Two of the primary downstream projections of DA neurons in the ventral tegmental area (VTA), include the nucleus accumbens (NAc) and the medial prefrontal cortex (mPFC). Projections from the VTA to the NAc support reward-related processes and positive reinforcement. In contrast, the role of dopaminergic innervation of the mPFC from the VTA is still debated. We demonstrate that presentation of an aversive stimulus induces rapid DA release in the mPFC. To investigate how this signal may be influencing activity to encode aversive

stimuli, we used in vivo deep brain calcium imaging in freely-moving animals to record projection-defined subpopulations within in the mPFC. We found that mPFC neurons projecting to the dorsal periaqueductal gray (mPFC-dPAG) predominantly encode aversive stimuli, while mPFC neurons projecting to the NAc (mPFC-NAc) respond to both aversive and rewarding stimuli. To determine if these encoding patterns were casually related to behavior, we photostimulated mPFC-dPAG neurons and found that activity within this pathway elicits avoidance. Further, we show that DA selectively inhibits activity in mPFC-NAc neurons using optogenetic activation of VTA DA terminals during whole-cell patch-clamp recording of retrogradely-labeled mPFC projection neurons. Finally, by combining single-cell calcium-imaging of mPFC neurons during optogenetic manipulation of VTA DA terminals in freely-moving mice, we find that activation of VTA DA terminals enhances the signal-to-noise in mPFC-dPAG neurons, reflected as decreasing the frequency and enhancing the amplitude of calcium events. Our data suggest that DA input differentially influences projection-defined mPFC subpopulations.

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Title: Activity transients in dopaminergic neurons modulate action initiation but not action execution

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Abstract: Substantia nigra compacta (SNc) dopamine neurons have been implicated in a variety of key brain functions such as plasticity, reward based learning, movement and motivation. When these neurons are lost in Parkinson's disease, there is a very striking motor phenotype. Nevertheless it remains unclear how movement is regulated by the activity of SNc dopamine

neurons. In our work we explore the role of SNc dopamine neurons in spontaneous behaviours and self-paced action sequences. Using microendoscopic calcium imaging, we imaged SNc neurons while mice freely explored an open field and also while performing a learned action sequence (pressing a lever 8 times to obtain a reward, FR8). We aligned the activity of recorded neurons to different events in the action sequence, including the consumption of reward.
We found that some SNc dopamine neurons were transiently active before the initiation of spontaneous movements in an open field. Also, when imaging during the FR8 task, we found a higher proportion of neurons positively modulated by the first press than by other presses in the sequence. In fact the number of first press related neurons was similar to the number of reward related neurons, with little overlap between the populations.
Finally, to test whether this activity related to spontaneous movement and sequence initiation had a causal role, we inhibited SNc dopamine neurons during these two different contexts. Interestingly, inhibition before spontaneous movement initiation or action sequence initiation perturbed the initiation of movement while inhibition during spontaneous movement or after the sequence was initiated had no effect on ongoing movement or action execution.
These results argue for a specific role of SNc dopamine neurons in movement initiation.

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Title: The spatiotemporal organization of striatal direct- and indirect-pathway projection neurons encodes action space

Authors: *A. KLAUS[1], G. J. MARTINS[2], V. B. PAIXAO[1], P. ZHOU[3], L. PANINSKI[4], R. M. COSTA[5]
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Lisboa, Portugal; [3]Carnegie Mellon Univ., Pittsburgh, PA; [4]Dept. of Statistics, Columbia Univ., New York, NY; [5]Neurosci., Columbia Univ., New York, NY

Abstract: The striatum contributes to natural and learned behaviors via the striatonigral (direct) and the striatopallidal (indirect) neuronal pathways. Although the average activity of both pathways increases during movement, little is known about the precise ensemble organization of these neurons. Using one-photon microendoscopy in mice, we imaged the spatiotemporal organization of direct- and indirect-pathway striatal spiny projection neurons (SPNs) selectively expressing the calcium indicator GCaMP6-fast. Intracellular calcium dynamics were recorded simultaneously with body movements measured using video and a 3-axis accelerometer. We found that SPNs of both pathways formed ensembles with predominantly local but also some long-range correlations. In line with previous reports, the average SPN activity in both pathways increased during movement. To investigate the precise ensemble organization during more specific actions, we clustered the behaviors and calculated the similarity between them. Action-related neurons showed increased overall correlations and were spatially closer. In addition, we found in both pathways a direct correlation between the behavior similarity and the SPN ensemble similarity irrespective of movement speed. Accordingly, the accuracy of decoding behavior from the SPN ensemble activity was directly related to the dissimilarity between behavior clusters. These results identify a predominantly local, but not spatially compact, organization of direct- and indirect-pathway SPNs that encodes action space independently of movement speed. This organization, in which striatal ensembles continuously map action identity, might support further aspects of striatal function during the learning of new actions.

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EMBO ALTF 352-2015

Title: Heterogeneous coding of sensory, motor, and cognitive variables in midbrain dopamine neurons

Authors: *B. ENGELHARD[1], J. FINKELSTEIN[1,2], D. W. TANK[1,3], I. B. WITTEN[1,2]
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Abstract: There is increased appreciation that dopamine (DA) neurons in the midbrain respond not only to reward and reward-predicting cues, but also other variables such as distance to reward, movements and behavioral choices. However, the relative contribution of these variables to DA responses has not been examined quantitatively, either within individual neurons or across the population. This is because DA recordings have not been performed in a behavioral task with sufficient complexity to examine these diverse variables simultaneously. To address this challenge, we used 2-photon calcium imaging through a GRIN lens to record the activity of > 170 midbrain DA neurons in the VTA and SNc during a decision making task. As mice navigated the central stem of a virtual T-maze, they observed transient reward-predicting cues on the left and right of the maze stem which signaled which maze arm was most likely to be rewarded. In this central stem, responses of most DA neurons were modulated by more than one of the following variables: choice accuracy (whether or not the mouse made the correct choice on that trial), reward history, reward-predicting cues, kinematics (speed, acceleration, view angle), and distance to reward. On average, choice accuracy was the best predictor of neural responses, followed in descending order by reward-predicting cues, reward history, kinematic variables, and finally distance to reward. Across the population, there were significant correlations between the partial contributions of many pairs of these variables for predicting neural responses, including strong negative correlations between the contributions of kinematics and the other variables. These correlations suggest specialization in coding properties within individual DA neurons, which may aid downstream circuits in correctly interpreting the range of signals transmitted by these cells.

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Title: Role of hippocampal VIP interneurons in reward-oriented spatial learning

Authors: *G. F. TURI, W.-K. LI, Z. LIAO, J. D. ZAREMBA, A. GROSMARK, M. LADOW, A. LOSONCZY
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Abstract: Disinhibition mediated by GABAergic interneurons selectively inhibiting other interneurons is a canonical motif of neocortical microcircuits, but much less is known how disinhibitory microcircuits support network operations conducive to navigation and learning in the behaving hippocampus. VIP INs have been shown to provide disinhibitory control over principal neurons' activity via inhibiting other IN subclasses. While many functional consequences of this peculiar circuit motif have been revealed in neocortical circuits, there is no data available from the hippocampus on in vivo functional dynamics of these INs during hippocampus-dependent behaviors. To determine the activity of VIP INs in hippocampal area CA1, we carried out a series of two-photon calcium imaging experiments in our head fixed mouse model during random foraging or goal-oriented learning (GOL). We found that the strongest drive of VIP neurons' activity was the locomotion. Interestingly, VIP cells in stratum pyramidale did not form a uniform cell population based on their responses to running start or stop events but rather broke up to several functional clusters. By tracking the same set of cells during trial days, we found that the clusters were largely stable. A subset of VIP INs was strongly modulated by the appetitive water rewards. Thus we hypothesized that these cells were involved in goal-directed spatial learning. To test this we used optogenetic methods to manipulate VIP cells' activity in the reward zone during the GOL task. We found that silencing or activation of VIP INs significantly repressed or improved the learning performance of the mice respectively. To examine where the locomotion and reward related information comes from to VIP INs we performed retrograde rabies mapping which reveled large retrogradely labeled cell populations in CA1 and CA3, the septal area in the median raphe nucleus. There is a high degree of similarity in the functional and physiological responses of cortical and hippocampal VIP INs: the activity of these cells is coupled to the locomotor behavior and strongly modulated by reinforcement signals. Because of their reciprocal connections with other INs these cells are in a key position to regulate the integrative properties of the entire somatodendritic domain of pyramidal cells regulating thereby neuronal plasticity in sensory cortices. Our study provides new information on the functional characterization of hippocampal VIP neurons in the behaving rodent and suggests a specific permissive role of these cells in reward related spatial learning.

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Title: Nociceptin neurons in the bed nucleus of the stria terminalis regulate anxiety

Authors: *J. RODRIGUEZ-ROMAGUERA[1], R. UNG[1], H. NOMURA[1], V. K. NAMBOODIRI[1], J. M. OTIS[1], J. ROBINSON[1], S. RESENDEZ[1], J. A. MCHENRY[1], L. E. H. ECKMAN[1], O. KOSYK[1], H. E. VAN DEN MUNKHOF[1], P. ZHOU[3], L. PANINSKI[3], T. KASH[2], M. R. BRUCHAS[4], G. D. STUBER[1]
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Abstract: The neuropeptide Nociceptin/Orphanin FQ (N/OFQ) has been traditionally implicated in pain sensitivity; however, recent findings point to a role in both positive and negative motivational states. Prepronociceptin (*PNOC*) is the genetic precursor of N/OFQ and is highly expressed in a subset of neurons within the bed nucleus of the stria terminalis (BNST). This region is essential for regulating a variety of motivational states, such as reward seeking, aversion and anxiety, but the genetic heterogeneity of its neurons has hindered efforts to disentangle the precise neural circuitry of BNST. Using a transgenic mouse line that expresses Cre in $PNOC^{+}$ neurons, we are able to selectively target and study $BNST^{PNOC}$ neurons. Using histological techniques, we find that $BNST^{PNOC}$ neurons in the anterodorsal BNST (adBNST) co-express Vgat and CaMKII. We also find that $BNST^{PNOC}$ neurons are distinct from the more widely studied interneuron subtypes within this region (e.g., somatostatin and protein kinase C δ). Further anatomical analyses show that these neurons project heavily both within BNST and to distal regions, with predominant projections to the medial amygdala and the medial preoptic area. Patch-clamp electrophysiological experiments reveal that local projections from $BNST^{PNOC}$ neurons inhibit both $PNOC^{-}$ and $PNOC^{+}$ neurons within adBNST. Therefore, $BNST^{PNOC}$ neurons play a major inhibitory role within adBNST and are candidates to regulate motivational states.

Next, we monitored the activity dynamics of these cells by applying *in vivo* calcium imaging in freely moving mice using miniature epifluorescence microscopes. We find that $BNST^{PNOC}$ neurons are more active when animals are avoiding threatening environments (open arms in an elevated plus maze or predator odor in home cage). Using *in vivo* optogenetics, we find that photoactivating or photosilencing $BNST^{PNOC}$ neurons enhances or suppresses anxiety in the EPM, respectively. Interestingly, photoactivation of $BNST^{PNOC}$ neurons in a non-threatening environment does not cause avoidance behavior, as seen in a real-time place preference assay. Together, these findings suggest that $BNST^{PNOC}$ neurons are important to modulate anxious behavior when threats are present, suggesting that targeting $BNST^{PNOC}$ neurons may be a novel and potentially effective target for patients suffering from anxiety disorders.

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Title: Modulation of contextual fear discrimination by the locus coeruleus noradrenergic system in the dentate gyrus

Authors: ***D.-O. SEO**, L. E. MOTARD, L. XIA, M. R. BRUCHAS
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Abstract: The locus coeruleus (LC) in the brainstem is the primary source of norepinephrine (NE) in the mammalian brain. The noradrenergic neurons in the LC provide diverse projections to other brain regions including the dentate gyrus (DG), a subregion of the hippocampus. The DG is thought to be an important structure for encoding and separating similar contextual information of a new experiences from prior experiences. Pharmacological and physiological studies support a role for NE in modulating synaptic activity in the DG, however it is unclear if NE in the DG impacts behavioral outcomes in aversive experience. Here, we seek to whether the LC-NE system plays a critical role in modulating contextual fear discrimination (CFD) using

optogenetic approaches to control the NE release and adrenergic receptor signaling in the DG cells *in vivo*. First, we suppressed NE release in the DG, expressing the genetically modified light-sensitive proton pumps (AAV5-CAG-Flex-ArchT) in the LC-NE system (TH-Cre^{LC-DG}) while mice were trained in a CFD task. Photo-inhibition of NE release in the DG (TH-Cre^{LC-DG}::ArchT) resulted in enhanced discrimination performance compared to control animals. Next, to test the possibility that the local interneurons suppress the granule cells activity that are involved in the CFD, we expressed the light sensitive G_s-coupled receptor that mimics beta-adrenergic receptor signaling (AAV5-EF1α-DIO-Opto-β_2AR). We expressed Opto-β_2AR in the interneurons of the DG (VGat-Cre^{DG}) during the CFD. Photo-stimulation of beta-adrenergic signaling of DG-interneurons (VGat-Cre^{DG}::Opto-β_2AR) caused enhanced fear generalization. These results suggest that local interneurons in the DG are phasically activated by NE, and that the local network affected by NE provides inhibition of the granule cells that distinguish similar information from prior experiences, and this results in fear generalization. In addition, to dissect the role of the LC-NE system in modulating e DG function, we applied optical calcium imaging techniques (freely moving GCaMP6f imaging) to monitor neuronal ensemble changes in the DG during the CFD while controlling input activity from the LC chemogenetically. These findings provide new molecular, and circuit level insights into the neural mechanisms underlying fear generalization. Additionally, we these efforts will further guide development of therapeutic strategies using currently available noradrenergic antagonists now being more commonly used for targeting psychiatric disorders characterized with fear generalization, such as post-traumatic stress disorders.

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Title: Ensemble coding of amygdala circuits in anxiety and fear behaviours

Authors: *J. GRUNDEMANN[1], Y. BITTERMAN[1], T. LU[1], S. KRABBE[1], K. HAGIHARA[1], B. F. GREWE[2], M. J. SCHNITZER[3], A. LÜTHI[1]

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Abstract: Learning and memory shape our daily life, social interactions and mental well-being. Mapping large-scale network activity on identified neuronal circuits during memory formation and retrieval will be essential to understand the neurophysiological and pathophysiological basis of behaviour. Here we follow the activity patterns of large populations of amygdala neurons across paradigms of anxiety and learned fear behaviours with the help of intersectional viral tools and a deep brain imaging miniature microscope approach in freely moving animals. We use computational neuroscience tools to reveal general, cross-paradigm coding principles and to elucidate how defined neuronal populations in the amygdala encode anxiety states and acquired fear behaviours in a projection pathway-specific manner.

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Title: Hypothalamic ensemble representations during social interactions, mating and fighting

Authors: *R. REMEDIOS
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Abstract: Distinct neural ensemble representations of conspecific sex, in the hypothalamus require social experience for their formation. We used microendoscopy to image a region of the hypothalamus (VMHv) that controls innate social behaviours, in male mice that were freely socially interacting with conspecific males and females. In sexually and socially experienced adults, divergent, reproducible neural ensembles represented the sex of a conspecific intruder. Surprisingly, in socially inexperienced adults, overlapping populations of neurons were activated by male and female conspecifics, and little mounting or attack behaviors were observed. This suggests that sex-specific ensembles gradually diverged as the mice acquired social experience.

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Nanosymposium

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Title: Using *In vivo* microscopy to assess the role of striatal medium spiny neurons in compulsive behavior and response to pharmacological treatment

Authors: *S. C. PIANTADOSI[1], J. R. HYDE[2], S. E. AHMARI[1]
[1]Psychiatry, [2]Translational Neurosci. Program, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Study: Perseverative thoughts and actions are hallmark symptoms of Obsessive Compulsive Disorder (OCD), and are often present in other severe neuropsychiatric illnesses, including autism and schizophrenia. Aberrant activity in cortico-striatal circuitry has been linked to compulsive behavior in both correlative studies in humans and causal studies in rodents. Using head-mounted mini-microscopes for *in vivo* calcium imaging (Inscopix), we sought to determine the role of medium spiny neurons (the principal striatal cell type) in mediating compulsive behavior in mice with a highly penetrant compulsive grooming phenotype (*Sapap3*-KO mice). We have also investigated how the first-line OCD pharmacotherapy, the selective serotonin reuptake inhibitor fluoxetine, alters striatal activity patterns.
Methods: *Sapap3* knockout (KO) mice, which have both a hyperactive striatum and compulsive OCD-like grooming phenotype, were injected with AAV-GCaMP6m and implanted with a GRIN lens in the centromedial striatum (CMS) to visualize striatal calcium activity during spontaneous grooming behavior. All mice received 7 days of treatment with the SRI fluoxetine (5 mg/kg), and underwent imaging and grooming assessments on days 3, 5, and 7 of treatment.
Results: At baseline, *Sapap3*-KO mice displayed elevated grooming behavior and increased calcium activity during grooming relative to WT mice. This increase in calcium activity may stem from a strong increase in striatal activity at the onset of grooming events, a phenomenon that was not observed in WT mice. Further, activity of D1-MSNs is elevated at a trend level in *Sapap3*-KO mice, suggesting an increase in direct pathway drive. Treatment with the SRI fluoxetine reduced observed calcium activity in all striatal cells with a rapid (3 day) time-course. *Ex vivo* data suggest that fluoxetine may be modulating the activity of striatal fast spiking interneurons (FSIs) in order to normalize striatal activity. Ongoing work is further dissecting striatal patterns that may contribute to compulsive behavior and its treatment.

Conclusion: Hyperactivity of the striatum and compulsive grooming behavior can be reversed with successful SRI treatment in a valid mouse model of OCD-like behaviors.
Significance: Understanding cell-type specific effects of successful and unsuccessful SRI treatment may help us develop treatments for patients with improved efficacy and fewer side effects.

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Title: The central amygdala controls learning in the lateral amygdala

Authors: *K. YU[1], S. AHRENS[1], X. ZHANG[1], H. C. SCHIFF[1], C. RAMAKRISHNAN[3], L. FENNO[3], K. DEISSEROTH[3], P. ZHOU[4], L. PANINSKI[4], B. LI[2]
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Abstract: Both the lateral and the central nuclei of the amygdala are required for adaptive behavioral responses to environmental cues predicting threats. While experience-driven synaptic plasticity in the lateral amygdala is thought to underlie the formation of association between a sensory stimulus and an ensuing threat, how the central amygdala participates in such learning process remains unclear. Here we show that a specific class of central amygdala neurons, the protein kinase C-δ-expressing neurons, is essential for the synaptic plasticity underlying learning in the lateral amygdala, as it is required for lateral amygdala neurons to respond to unconditioned stimulus, and furthermore carries information about the unconditioned stimulus to instruct learning. Our results uncover an amygdala functional organization that may play a key role in diverse learning processes.

Disclosures: **K. Yu:** None. **S. Ahrens:** None. **X. Zhang:** None. **H.C. Schiff:** None. **C. Ramakrishnan:** None. **L. Fenno:** None. **K. Deisseroth:** None. **P. Zhou:** None. **L. Paninski:** None. **B. Li:** None.

Nanosymposium

735. Motivation: Subcortical Neurocircuitry

Location: 146C

Time: *Wednesday, November 15, 2017, 1:00 PM - 4:30 PM

Presentation Number: *735.14

Topic: *G.02. Motivation

Support: National nature and science fundation 31671100

Title: Midbrain GABAergic pathways for feeding behavior

Authors: ***S. HAO**, H. YANG, X. WANG, X. WU, L. PAN, Y. LIU, H. LOU, S. DUAN, H. WANG
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Abstract: Overeating is a serious problem in the modern society and could cause many health problems including obesity. Although hypothalamus has been previously identified as the key brain structure that regulates body weight homeostasis, non-canonical neural signaling pathways involved in feeding behavior remain largely uncharacterized yet. Here, we discovered that GABAergic cells in the vlPAG plays an essential role in regulating feeding behavior. Optogenetic silencing GABAgeric cells in the vlPAG induces dramatically food consumption immediately, whereas activation of these cells reduces the food intake in starving mice. Long-term inhibition or excitation of these GABAergic cells' activity *via* chemogenetics could either increase or decrease body weights, respectively. Further studies suggest that GABAergic cells in the vlPAG receive long projection GABAergic inputs from both of BNST and lateral hypothalamus. We also found that BNST send projections to vlPAG and LH in one-to-one configuration through rabies retrograded tracing technique. Activation either $BNST^{GABA}$-vlPAG or LH^{GABA}-vlPAG pathway was sufficient to induce feeding behavior. Overall, our studies revealed novel midbrain GABAergic pathways and highlighted an important role of GABAergic cells in the vlPAG in regulating feeding behavior.

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Nanosymposium

736. Self-Control and Decision Making

Location: 145B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***736.01

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH Grant F32MH110135-01A1
NIH Grant R01DA038063

Title: Stress and incentive effects on the subjective cost of self-control

Authors: *C. M. RAIO, P. GLIMCHER
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Abstract: Characterizing the decision processes underlying why individuals choose tempting rewards that do not align with their broader goals has been of great interest to researchers for decades. Recent work suggests that rather than a 'failure' of self-control or an irrational decision, deviations from goal-directed behavior may arise from a rational decision-making process that weighs the costs and benefits of exerting cognitively demanding control. These 'control costs' are thought to stem from the limited cognitive resources available to support the demands of exercising control. Given these costs, an important strategy to promote optimal decision-making might be to prospectively eliminate or restrict temptation from one's environment—known in behavioral economics as 'pre-commitment'. Here, we used a novel economic decision-making task aimed at precisely quantifying the cognitive costs individuals were willing to incur in order to adopt pre-commitment strategies that allowed them to avoid temptation, allowing us to directly measure the subjective cost of self-control. Healthy dieters first provided subjective ratings for food items, allowing us to identify a highly tempting food for each individual. Both before food exposure and at regular intervals after exposure, participants reported their willingness-to-pay to have us remove the tempting food for the remainder of the experimental period. Bids were realized using a standard economic auction procedure (Becker-DeGroot-Marschak method) at a fixed low hazard rate such that all costs and risks were held constant during the experiment. Further, we measured how bids differed in participants who first underwent an acute stressor, which is widely thought to compromise the use of self-control. Across two studies, we found novel evidence that individuals were willing to pay to restrict their exposure to temptation. Further, we found a striking dissociation between stress exposure and bidding behavior depending on whether or not participants were offered monetary incentives during the task to refrain from eating the tempting food. Specifically, when offered a $15 bonus for not eating the food, stressed participants paid less on average to restrict temptation (Study 1). However when this added incentive to exercise control was absent, stressed participants paid significantly more to restrict temptation (Study 2). Consistent with an emerging framework

viewing goal-directed control as a cost-benefit decision-making process, these data suggests that the subjective cost of self-control can be quantified in humans and that these costs are highly sensitive to changes in affective and motivational states.

Disclosures: C.M. Raio: None. **P. Glimcher:** None.

Nanosymposium

736. Self-Control and Decision Making

Location: 145B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***736.02

**Topic: ***H.02. Human Cognition and Behavior

Title: Indulgent food options can paradoxically increase dietary self-control

Authors: *N. SULLIVAN[1], G. FITZSIMONS[2], M. L. PLATT[3], S. A. HUETTEL[1]
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Abstract: Despite extensive research on the mechanisms of dietary self-control, it is not well understood how these mechanisms are altered by contextual cues. Food preferences could be altered by other options in the choice set, especially when choices involve tradeoffs between health and taste goals. Such context effects have been demonstrated in tasks ranging from simple perceptual decisions to complex financial choices, and can lead to suboptimal outcomes (Trueblood et al. 2013; Huber, et al. 1982). Research suggests that the presence of a healthy option can counterintuitively result in more indulgent choices (Wilcox, et al. 2009), and the current study examines how the health and taste of irrelevant decision options can bias dietary decisions, potentially through mediating processes of attention.
In this experiment, participants (N = 79) chose between two gambles, each containing two foods with equal chances of delivery. On the key trials, the two gambles each contained one food that was matched to the other gamble (i.e., a common consequence, CC) and one unique food. We varied whether the matched CC food was healthy but not tasty (Healthy CC Condition; HC) or tasty but not healthy (Tasty CC Condition; TC). Both gambles featured a common item, so participants would have a 50% chance of receiving it regardless of their choice. Rationally, this common food should then be ignored, so the choice would be reduced to a simple binary choice between the two unique foods present in the choice. Therefore, the identity of this CC should be irrelevant to the choice between the other food items – and thus there should be no differential effects of HC and TC trials upon choice (e.g, whether they choose the gamble with the healthier unique food).
However, the healthier gamble was selected less often in HC trials (24% vs. 50%; T = -8.04, p =

$3x10^{-13}$). There is a bias toward weighting taste more, and health less, in HC trials (paired t-tests: for taste, T = 5.20, p = $2x10^{-6}$; for health, T = -4.76, p = $9x10^{-6}$). Gaze to the common food consisted of 49.5% (SD 3%) of food fixation time, despite being irrelevant. Between conditions, dwell time to the CC was not different (z = .86, p = .39), and was correlated (R^2 = .81, p = $5x10^{-29}$) suggesting a generalized tendency to attend to it. However, increased gaze to the CC in the HC condition significantly predicts fewer healthy choices, when controlling for average gaze to the CC in the TC condition as well (R^2 = .24, β = .0009, p = $5x10^{-5}$). Attention to the CC does not similarly predict percentage of healthier choices in the TC condition (p > .30). In summary, we find that the health and taste of an irrelevant option in dietary choice can bias decisions, and that is partially driven by attention.

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Nanosymposium

736. Self-Control and Decision Making

Location: 145B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***736.03

**Topic: ***H.02. Human Cognition and Behavior

Title: The utility of affective stimuli: A value-based computational approach to continuous self-control

Authors: *P. SOKOL-HESSNER, K. A. SHAFFER
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Abstract: The study of self-control has seen a recent shift toward models emphasizing rationality. This shift reconceptualizes issues of willpower as optimization problems in which the individual maximizes utility, subject to constraints of the environment (e.g. task structure) and of themselves (e.g. cognitive capacity). Studying self-control within this framework of value-based decisions becomes a challenge of identifying and quantifying constraints and sources of utility. Previously, we created a novel task to quantify the dynamics of classic self-control problems in a value-based framework. For 60 uninterrupted minutes, participants performed a boring, but monetarily rewarding task. They monitored a white circle on the screen with a "clock hand" that ticked in small ($1/100^{th}$) increments every second. Rarely (p = 0.01), the hand moved double the normal distance ($2/100^{th}$). Participants received (lost) a dollar if they correctly (incorrectly) indicated the occurrence of a double movement. The other half of the screen displayed images that changed on a similar timescale. Using eye-tracking, we leveraged the temporal and monetary structure of the task to assess how participants traded off between looking at the "clock" (for money) and the images. By computationally modeling this tradeoff, we inferred the

consumption utility of the images in units of dollars per second, separate from the initial salience of the images on both short (1s) and long (60min) timescales. However, recent studies focused on male participants with a restricted and repeating set of images (379 images from the IAPS rated positively by males), limiting our ability to identify differences between individuals and between categories of stimuli as well as quantify changes over time in either.
The current study extends previous research in several important ways. First, we recruited participants across genders and sexual orientations, widening the scope of individual differences identified by the model. Second, we used 3,600 unique images of both positive and negative valence, extending our computational model to estimate the utility derived from negative images (e.g. of medical procedures), and eliminating repetition confounds. Critically, we find quantitative evidence that people consume utility from negative images, as well as significant individual differences in this effect, challenging the notion that the utility of affective stimuli reduces to pleasure. This novel extension of a computational model connecting affect to utility promises to provide new insights into the characteristics of self-control in both healthy and clinical populations in the moment and over time.

Disclosures: P. Sokol-Hessner: None. **K.A. Shaffer:** None.

Nanosymposium

736. Self-Control and Decision Making

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**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***736.04

**Topic: ***H.02. Human Cognition and Behavior

Support: Templeton Foundation Grant 10008405

Title: Constraints associated with cognitive control and the stability-flexibility dilemma

Authors: *S. MUSSLICK[1], S. J. JANG[1], M. PANICHELLO[1], L. BUSTAMANTE[1], A. SHENHAV[2], J. D. COHEN[1]
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Abstract: One of the most compelling characteristics of controlled processing is our limitation to exercise it. Recent decision making theories of control allocation account for such limitations by assuming a cost of control that functionally constrains how much control is allocated to a given task. However, this leaves open the question of why constraints on control allocation exist in the first place? The stability-flexibility dilemma provides a computational argument for the necessity of such constraints: allocating more cognitive control to a task results in greater activation of its neural representation but also in greater persistence of this activity upon

switching to a new task, resulting in task switch costs.
Here, we test the hypothesis that constraints on cognitive control provide an optimal solution to the stability-flexibility dilemma in neural systems. We first introduce a set of simulations in which a recurrent neural network switches between multiple task attractor states in environments with different task switch probabilities (demands for flexibility). For each environment we optimize control bias parameters that determine the amount of activity allocated to each task processing unit. We then compare performance predictions for optimized networks with human subject performance in a cued task switching experiment that we designed to match the task switch probabilities in the simulation. Participants switched between mini-blocks of two perceptual decision-making tasks with different task switch probabilities across subject groups. Our neural network modeling results confirm that higher inhibitory biases on task processing units improve task switching performance, by constraining the maximum activation allocated to a task within a mini-block (thereby limiting the increase in stability of a task with repeated performance, yet increasing its flexibility). These constraints become stronger as the environment demands more task switches. Human subject performance matches our model predictions, such that task switch costs are lower and overall reaction time within a mini-block is higher for environments with higher switch rates. Finally, using a novel method of fitting the parameters of individual's task attractor landscape (e.g., the depth of the task attractors), we show that participants in higher switch rate environments have shallower task attractors, reflecting stronger constraints on the degree of control allocated to a task. Overall these results suggest that functional constraints on how much control is allocated to a task may reflect the optimization of a tradeoff between stability and flexibility demands in task environments.

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Nanosymposium

736. Self-Control and Decision Making

Location: 145B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***736.05

**Topic: ***H.02. Human Cognition and Behavior

Title: Self-control in decision making involves prefrontal theta band oscillatory dynamics

Authors: *H. LIN, B. SAUNDERS, C. A. HUTCHERSON, M. INZLICHT
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Abstract: Decisions and choices that require self-control or cognitive control are often associated with increased activity in prefrontal regions, in particular the medial prefrontal cortex

(mPFC) and lateral PFC (lPFC). Functional magnetic neuroimaging studies of dietary choice have found that the mPFC carries subjective value signals, and these signals were modulated by activity in the lPFC when dieters made healthier choices. In addition, electroencephalography (EEG) studies have shown that mPFC and lPFC activity—specifically theta band oscillatory dynamics—was associated with self-control processes such as monitoring for conflict and signaling the need for increased cognitive control, but mostly during perceptual and sensory-motor decisions. Whether prefrontal theta band oscillations support self-control during value-guided choice remains less clear. Here we investigate whether prefrontal theta band oscillations measured using EEG are associated with self-control during a dietary choice task. Healthy, hungry, and non-dieting participants indicated how much they wanted to eat different foods that varied in tastiness and healthiness, and were occasionally asked to focus their attention on how healthy or tasty each food was. Behaviorally, we found that participants responded more slowly when they did not have strong preferences for a given food. In parallel, this decision conflict was reflected in enhanced midfrontal theta power. Participants made more or less healthy choices when focusing on healthiness or tastiness respectively, and this effect was supported by mPFC and lPFC theta dynamics. These findings suggest that prefrontal theta band oscillatory dynamics, which have usually been associated with action monitoring and cognitive control during inhibitory tasks such as the flanker task, might also underlie successful self-control during value-guided choice.

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Nanosymposium

736. Self-Control and Decision Making

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Title: Binding oneself to the mast: Stimulating frontopolar cortex enhances precommitment

Authors: *A. SOUTSCHEK[1], G. UGAZIO[1], C. RUFF[1], M. J. CROCKETT[2], T. KALENSCHER[3], P. N. TOBLER[1]
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Abstract: Humans often give in to temptations that are in conflict with valuable long-term goals like health or saving for the future. Such willpower failures represent a prevalent problem in everyday life as well as in many psychiatric disorders. One important strategy to overcome such willpower failures is to voluntarily precommit, i.e. to restrict one's future action space by removing the tempting short-term option from the choice set, thereby leaving only the long-term option for implementation. The neural mechanisms necessary to implement precommitment have remained unknown. Here we test whether anodal transcranial direct current stimulation (tDCS) over the frontopolar cortex (FPC) can improve precommitment. Participants performed a self-control task in which they could precommit to obtain a delayed larger reward by removing an immediately available smaller reward from the future choice options. We found that anodal stimulation over FPC selectively increased the propensity to precommit. By contrast, tDCS had no effects on non-binding decisions, impulse control, or reward preference. Our data establish a causal role for the FPC in the implementation of precommitment, revealing a novel route to improving resistance against temptations.

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Nanosymposium

736. Self-Control and Decision Making

Location: 145B

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**Presentation Number: ***736.07

**Topic: ***H.02. Human Cognition and Behavior

Title: Behavioral evidence for PID-like feedback control

Authors: *H. RITZ[1], M. R. NASSAR[1], M. J. FRANK[2,1], A. SHENHAV[1,2]
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Abstract: When an environment is noisy and non-stationary, adaptive control requires an individual to flexibly incorporate feedback into ongoing expectations. While it may often be useful to rely on explicit structural models of the environment, for many real-world problems such models are insufficiently constrained to be useful. Engineers frequently address just this sort of practical challenge by using control models that are robust, computationall frugal, and do not require explicit environmental knowledge. The proportional-integral-derivative (PID) controller is the most popular model in industrial process control for exactly this reason. The PID controller combines simple estimates of errors in the past (error integral), present (error), and expected future (error derivative), allowing for robust regulation with neurologically-plausible

computations. Here, across three experiments, we tested whether aspects of human decision-making and cognitive control can be usefully described by the PID algorithm. We found that the PID controller was an accurate model of participants' decisions in noisy, changing environments. First, in a re-analysis of a change-point detection experiment by McGuire and colleagues (2014), we found that the PID model predicted participants' choices better than the standard delta-rule model. Based on this finding, we explicitly designed a decision task that could differentiate PID control from delta-rule control, using outcomes that drift over time in a manner that could be predicted based on their past trajectories. This modified task again provided strong evidence that participants integrate and derivate over past prediction errors, leading to better performance than could be achieved by the delta-rule alone.
Finally, we examined whether PID control generalizes to how individuals flexibly allocate attention in a cognitive control task. We designed a modified version of a Simon task, involving parametrically varying response conflict, where the degree of conflict drifted over trials. We found that participants' reaction times depended on both the history of conflict intensities and the history of trial-by-trial changes in conflict, consistent with the integrative terms in our model. These experiments provide preliminary evidence that decision-making and cognitive control in dynamic environments can be well-described by PID control. While further research is needed to differentiate PID control from other models of control, this work demonstrates that the PID control model has the potential to characterize some core algorithmic properties of cognitive control.

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Title: Metacontrol in reinforcement learning

Authors: *W. KOOL, F. A. CUSHMAN, S. GERSHMAN
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Abstract: Theoretical accounts of decision making posit that choice is sometimes controlled by a fast, automatic system that relies on habit, and sometimes by a controlled system that plans

towards goals. Reinforcement learning (RL) theory formalizes this distinction as a competition between a computationally cheap but inaccurate "model-free" system and an expensive but accurate "model-based" system. However, it remains unclear how the brain chooses to allocate control between the model-free and model-based systems. Here, we describe a new RL model which adaptively arbitrates between the two systems using a 'policy gradient' algorithm. The model selects between controllers as a function of their 'controller values', which integrate their costs and benefits. These values are learned by updating them with controller prediction errors (PEs), the difference between observed reward and the expected reward of the maintained controller. In short, if the current controller performs worse than expected, the arbitration model reduces the probability it being selected. We test our model on a class of decision-making tasks, known as two-step tasks, which dissociate model-free from model-based control. First, our new adaptive arbitration model learns to prefer the model-based strategy in a new two-step task where model-based control leads to increased reward, but not in the original variant where there is no such tradeoff. Second, Bayesian model comparison shows that the new model provides a superior fit to data from participants (n = 120) performing these two tasks. Finally, we used fMRI to test for neural correlates of the PEs in the arbitration model (n = 19). We show that neural signal in the ventral striatum, the canonical area for PEs, is explained better by the PEs from the new adaptive arbitration model compared to those from the default modeling approach. Second, we found that activity in ventromedial prefrontal cortex, an area implicated in value representation, correlated positively with the controller PEs, whereas activity in anterior cingulate cortex, bilateral anterior insula, and right inferior frontal gyrus, commonly associated with the monitoring of cognitive demands and choice difficulty, showed negative correlations with the controller PEs. This suggests that when a controller performs better than expected, valuation regions encode this positively, whereas demand-monitoring areas decrease activity, possibly due to the reduced demands for strategy switching. Together, our results suggest that the brain flexibly and adaptively integrates the costs and benefits of model-free and model-based control in order to guide arbitration between them.

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Nanosymposium

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Title: Variability in the timing of value-based decisions is associated with hippocampal BOLD activity

Authors: *A. BAKKOUR[1], H. R. KANG[2], M. N. SHADLEN[3], D. SHOHAMY[4]
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Abstract: The speed and accuracy of many decisions conform to regularities of bounded evidence accumulation. Such models have proven successful for understanding perceptual decisions made from dynamic sensory input, where integration of independent samples of evidence is normative. However, the same framework applies to value-based decisions, such as choices between snacks, where the stimuli are static (Krajbich et al., 2010; Milosavljevic et al., 2010). This begs the question: what is the source of independent samples of evidence in value-based decisions? Here, we test the hypothesis that they are derived and constructed through a process that involves memory retrieval. Thirty healthy young adults were scanned with fMRI while performing a value-based decision task that involved a series of choices between pairs of foods. The subjective values of the food items were assessed prior to scanning. The difference in value between the two foods (ΔV) varied from trial to trial. The same participants performed two additional tasks: (1) a perceptual decision task in which they reported the predominant color in a dynamic random dot display comprised of yellow and blue dots; (2) a memory retrieval unrelated to the food items or value. Consistent with prior findings, participants chose the higher-value food more often and their reaction time (RT) decreased as a function of $|\Delta V|$. Similarly, participants accurately indicated the predominant color in the color dots display more often and their RT decreased as a function of the color difficulty. The fMRI data showed that RT in the value-based task correlated with magnitude of BOLD activity in the hippocampus. This effect was absent in the perceptual task. Furthermore, a psychophysiological interaction (PPI) analysis revealed stronger functional connectivity between the hippocampus and striatum for value-based choices that took longer. These findings are consistent with the hypothesis that the time it takes to decide about value may be related to memory retrieval. One possibility is that the striatum and hippocampus cooperate to inform decisions by constructing value or by conveying evidence about relative value bearing on choice behavior.

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736. Self-Control and Decision Making

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**Presentation Number: ***736.10

**Topic: ***H.02. Human Cognition and Behavior

Title: The opportunity cost of time modulates cognitive effort expenditure

Authors: *R. OTTO[1,2], N. D. DAW[3]
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Abstract: A spate of recent work demonstrates that humans seek to avoid the expenditure of cognitive effort, much like physical effort or economic resources. Less is clear, however, about the circumstances dictating how and when people decide to expend cognitive effort. Here we adopt a popular theory of opportunity costs and response vigor and to elucidate this question. This account, grounded in Reinforcement Learning, formalizes a trade-off between two costs: the harder work assumed necessary to emit faster actions and the opportunity cost inherent in acting more slowly (i.e., the delay that results to the next reward and subsequent rewards). Recent work reveals that the opportunity cost of time—operationalized as the average reward rate per unit time, theorized to be signaled by tonic dopamine levels, modulates the speed with which a person responds in a simple discrimination tasks. We extend this framework to cognitive effort in a diverse range of cognitive tasks, for which 1) the amount of cognitive effort demanded from the task varies from trial to trial and 2) the expenditure of cognitive effort holds measureable consequences in terms of accuracy and response time. In the domains of cognitive control, perceptual decision-making, and task-switching, we found that subjects tuned their response speeds in accordance with the experienced average reward rate: when the opportunity cost of time was high, subjects responded more quickly. That is, expenditure of cognitive effort appeared to be modulated by the opportunity cost of time. Further, and consistent with our account, the strength of this modulation covaried with individual differences in efficacy of cognitive control, operationalized as response slowing on incongruent trials. Taken together, our results provide a cost-benefit informed examination of the circumstances dictating how and when people expend cognitive effort.

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Title: Subjective value encoding during cognitive effort-based decision-making

Authors: *J. A. WESTBROOK
Brown Univ., Providence, RI

Abstract: Growing interest in the clinical and theoretical implications of motivation for cognitive effort prompts new questions about mechanisms of effort-based decision-making. One question concerns where dimensions of subjective value are encoded as decision-makers weigh the costs and benefits of expending effort. To investigate this, fMRI was used in combination with a powerful behavioral economic paradigm which operationalizes cognitive effort in terms of reward discounting. The operational measure integrates information about objective reward magnitude, working memory load, and both trait and state subjective sensitivity to effort costs, and is used as a parametric regressor of brain activity while participants evaluate offers to expend effort in pursuit of reward. Results support the encoding of subjective value dimensions in a canonical network of regions otherwise implicated in encoding diverse rewards varying by delay, risk, or demands for physical effort, particularly within the ventromedial prefrontal cortex and ventral striatum. Notably, these regions are distinct from those engaged for difficult relative to easy decisions, which include the anterior cingulate and dorsolateral prefrontal cortex and intraparietal sulcus. In addition, greater reward sensitivity in the ventral striatum, during offer valuation, corresponds with greater willingness to expend cognitive effort for reward. Finally, dynamics in prefrontal regions, during first offer evaluation, predict subsequent choice, implicating them causally in decision-making.

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736. Self-Control and Decision Making

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**Topic: ***H.02. Human Cognition and Behavior

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Title: Learning to (mis)allocate control: Maltransfer can lead to self-control failure

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Abstract: Our ability to bias our processing away from default responses in the service of task-relevant goals is referred to as cognitive control and represents one of the most striking features of human cognition. Despite its high utility in daily life situations (e.g. the ability to solve a math problem in the face of distractions such as incoming text messages), there are situations in which control allocation can be detrimental. For example a driver who focuses so much of their attention on solving a complex math problem that they fail to notice the traffic ahead of them. Here we investigate the mechanisms that underlie overexertion of cognitive control, the phenomenon that people engage in effortful controlled processing even when it harms performance relative to automatic alternatives. We build on the Expected Value of Control theory (Shenhav, 2013), according to which control allocation follows a cost benefit analysis by weighing reward outcomes associated with exerting control against intrinsic control costs to select the control signal with maximal expected value. We extend this framework using a computational model that allows the value of control to be efficiently approximated based on the features present in a task. This model suggests that failures of self-control may result from maltransfer of the value of control they have learned in a particular situation to other situations with similar features. To test this hypothesis, we designed a novel color-word Stroop paradigm where reward for a task performed on an incongruent stimulus is jointly determined by the color and meaning of the word. In an initial "association phase" words and colors were reinforced for performing either color-naming (CN) or word-reading (WR). In a "transfer phase" CN was rewarded when either the word or the color were previously associated with it (SINGLE trials) but when both the word and the color were associated with CN the correct response was WR (X trials). We varied SINGLE trial frequency from 0% to 50% in a between-subjects design. We hypothesized participants would incorrectly transfer the control demand they experienced on SINGLE trials to X trials and consequently reduce their reward rate. Empirical data from 30

participants confirmed this hypothesis and supports the conclusion that maltransfer in learning about the value of control can mislead people to overexert cognitive control even when it hurts their performance. The finding of control-overexertion is particularly striking because people generally avoid the cost and effort associated with cognitive control.

Disclosures: L.A. Bustamante: None. **F. Lieder:** None. **S. Musslick:** None. **A. Shenhav:** None. **J.D. Cohen:** None.

Nanosymposium

736. Self-Control and Decision Making

Location: 145B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***736.13

**Topic: ***H.02. Human Cognition and Behavior

Support: Wellcome Trust 091593/Z/10/Z

Title: Disentangling neural representations of confidence and certainty in the human brain

Authors: *D. BANG, S. M. FLEMING
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Abstract: Despite widespread agreement that decision confidence is a useful quantity for guiding behaviour, there is currently little consensus on its neural basis. Candidate correlates of decision confidence in the brain include lateral intraparietal sulcus, ventral striatum, dorsal anterior cingulate cortex and lateral prefrontal cortex. We suspect that this anatomical heterogeneity reflects conflation of different contributors to confidence. In particular, using current tasks, it is difficult to disentangle decision confidence from other task-relevant representations of certainty. For example, in a typical perceptual decision task, there is a monotonic relationship between the certainty associated with the sensory representation upon which a decision is based and the probability that the decision is correct: the more clearly we perceive the stimulus, the more confident we feel about our decision. However, from a normative perspective, decision confidence is computationally and behaviourally separable from other task-relevant representations of certainty. Here we hypothesise that decision confidence and sensory certainty depend on distinct neural substrates, and, further, that neural substrates previously implicated in representing decision confidence may actually track sensory certainty. We used a novel version of the random-dot motion task where the same degree of sensory certainty (percentage of coherently moving dots) could be associated with different degrees of decision difficulty (angular distance between the net motion direction and a decision reference that appeared after the termination of the motion display). By means of this design, we could

decouple neural signatures of sensory certainty and decision confidence. We confirm that human participant's overt estimates of decision confidence are constructed by combining trial-by-trial estimates of sensory certainty with decision difficulty. We show that, while parietal areas, the middle temporal area (MT+) and the ventral striatum track sensory certainty, decision confidence is represented in the perigenual anterior cingulate cortex – an area which previously has been implicated in tracking of self-performance on the basis of the recent feedback. Our results are consistent with a separation between neural representations of sensory certainty and decision confidence, and point to a noticeably focal and hitherto undiscovered neural substrate supporting the sense of confidence in our choices.

Disclosures: D. Bang: None. **S.M. Fleming:** None.

Nanosymposium

736. Self-Control and Decision Making

Location: 145B

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:30 PM

**Presentation Number: ***736.14

**Topic: ***H.02. Human Cognition and Behavior

Title: Association with decision uncertainty, not value comparison in ventromedial prefrontal cortex

Authors: *N. YINMEI[1,2], S. JIE[2], S. WANG[2], X. WAN[2]
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Abstract: The neural mechanism of economic decisions remains obscure. A decade of neuroimaging studies in neuroeconomics have reached to a broad consensus that ventromedial prefrontal cortex (vmPFC) plays critical roles in value comparison, as the vmPFC activity is proportional to the absolute value difference (AVD). On the contrary, dorsal anterior cingulate cortex (dACC) is inversely correlated with AVD. Decision-making is usually accompanied by uncertainty. As we have previously revealed, an extensive frontoparietal control network, including dACC, is positively correlated with decision uncertainty. As vmPFC is negatively regulated by the frontoparietal control network during the tasks or the resting state, vmPFC is then negatively correlated with the decision uncertainty. As AVD and decision uncertainty is usually anti-correlated, we here hypothesize that the correlation of the vmPFC activity with AVD is negatively regulated by the metacognition network, involved in decision uncertainty monitoring, but not involved in value comparison. To test this hypothesis, we first devised a value-based decision-making task in which there was no uncertainty in decisions (it was confirmed by the subjects' confidence report). The dACC and vmPFC activations were

disappeared in the control task, though the AVD was identical in each pair of options. Thus, this finding confirms that the dACC and vmPFC activities were merely correlated with decision uncertainty, but not AVD. To further illustrate that the vmPFC activity is negatively regulated by the cognitive control network, e.g., dACC. We employed offline rTMS protocols (1-Hz and 10-Hz) to interference the dACC region, respectively, and compared the activities associated with the decision uncertainty and AVD. The correlation of the vmPFC activity with AVD was altered by rTMS on the target at the dACC between the two conditions, while the correlation of the dACC activity with the decision uncertainty was altered between the two conditions. Thus, this finding causally illustrate that the vmPFC activity in value-based decisions was regulated by the dACC activity. Taken these two findings together, it was proved that vmPFC was not involved in value comparison. In the third experiment, we sequentially presented the two options, and found that intra-parietal sulcus (IPS) was associated with the value difference between the two options, while the TMS interference at the IPS region affect the choice behaviors by shifting the choice bias. Therefore, our findings suggest that it is IPS, but not vmPFC, that is involved in value comparison.

Disclosures: **N. Yinmei:** None. **S. Jie:** None. **S. Wang:** None. **X. Wan:** None.

Nanosymposium

737. Individual Differences in Cognition and Behavior

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**Presentation Number: ***737.01

**Topic: ***H.02. Human Cognition and Behavior

Support: FWF(Austrian Science Fund), W 1233-G17

Title: Are brain and body oscillations frequency-ratio related?

Authors: *E. EL RASSI[1], G. DORFFNER[3], W. KLIMESCH[2]
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Abstract: For the investigation of brain oscillations, frequency bands play an important role. It is an interesting fact that the center frequencies of these bands exhibit a doubling-halving relationship. Alpha, as the dominant frequency of about 10 Hz has two neighboring frequencies, theta with about 5 Hz and beta with about 20 Hz. Theta and beta have neighboring frequencies, delta with about 2.5 Hz and gamma with about 40 Hz (e.g., Klimesch, 2012). Based on this observation, Klimesch (2013) has suggested that the center frequencies of brain and body

oscillations form a singly binary hierarchy system in which all frequencies are aligned to each other. In this system, any higher frequency (n) always is a binary multiple of a lower frequency (m): $n = m*(2^x)$; x = 1, 2, etc.; e.g., n = 2m, 4m, etc.). In the present study, we investigate the hypothesis, whether brain and body oscillations are frequency related according to this binary hierarchy principle. We hypothesize that alpha (α) and heart rate (HR) exhibit an 8:1 ratio and HR to breathing frequency (BF) a 4:1 relationship. If all frequencies are hierarchically aligned to each other, it follows that α and BF will exhibit a 32:1 relationship.

Disclosures: E. El Rassi: None. **G. Dorffner:** None. **W. Klimesch:** None.

Nanosymposium

737. Individual Differences in Cognition and Behavior

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**Presentation Number: ***737.02

**Topic: ***H.02. Human Cognition and Behavior

Support: Penn State Social Science Research Institute
Penn State Department of Psychology

Title: Microstructural properties of fiber tracts in the left hemisphere are related to individual differences in face recognition behavior

Authors: *D. B. ELBICH[1], S. SCHERF[2]
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Abstract: There are vast individual differences in face recognition abilities, which have recently been linked to the size and magnitude of neural activation within multiple regions in the face processing network (Elbich & Scherf, 2017). Superior behavior is also associated with more distributed activation within the face processing network and with different patterns of directed functional connections throughout this network (Elbich et al., under review). The goal of this project was to examine individual differences in the micro- and macrostructural properties of the anatomic connections within the face processing network among adults who vary in face recognition abilities. The participants were screened for neurological and psychological conditions in themselves or their first-degree relatives. They completed the Cambridge Face Memory Task long form (CMFT+) to measure unfamiliar face recognition abilities and the Faces Before Fame Task (FBF; Elbich & Scherf, 2017), which measures the ability to recognize faces of famous individuals from photographs of them before they were famous. Participants included 40 individuals who varied in face recognition behavior on a continuum that spanned ± 1 SD around the mean of a sample of more than 200 individuals tested in these tasks. Participants were

scanned using diffusion tensor imaging (64 directions, 2.5 mm^3 voxels, b=1000). We used deterministic tractography with established protocols for defining the bilateral inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF) and uncinate fasciculus (UF). From each tract, we extracted both macrostructural (volume, number of tracts) and microstructural indices, including axial, radial, and mean diffusivity (AD, RD, MD). We computed regressions evaluating brain indices as predictors of behavior for the FBF and CFMT+. We found that the RD and MD in the left ILF and RD in the left UF were negatively related to FBF, but not CFMT+, scores. In these tracts, as diffusivity decreases face-recognition ability for familiar faces increases. Since RD is related to myelination, these findings could reflect age- and/or experience-dependent influences on myelination processes in these networks. Since the ILF connects posterior core face processing regions, like those in the fusiform gyrus, with more anterior regions like the anterior temporal lobe and the amygdala, and the UF connects the amygdala with prefrontal regions, like the ventromedial PFC, these findings suggest that individual differences in the recognition of familiar faces are potentially related to ongoing increased structural connectivity within the distributed face processing network.

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Nanosymposium

737. Individual Differences in Cognition and Behavior

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Title: Preliminary evidence for an association of MAOA genotype with functional and structural connectivity estimates in extended brain networks

Authors: *A. HARNEIT[1], U. BRAUN[1], H. WALTER[2], S. ERK[2], S. MOHNKE[2], A. HEINZ[2], N. ROMANCZUK-SEIFERTH[2], S. WITT[1], S. CICHON[3], M. M. NÖTHEN[3], M. RIETSCHEL[1], A. S. MEYER-LINDENBERG[1], H. TOST[1]
[1]Central Inst. of Mental Hlth., Mannheim, Germany; [2]Charité Universitätsmedizin Berlin, Berlin, Germany; [3]Dept. of Genomics, Univ. of Bonn, Bonn, Germany

Abstract: The X-linked monoamine oxidase A gene (*MAOA*) encodes for a key enzyme in monoamine metabolism. A common genetic polymorphism in this gene has been found to impact transcriptional efficiency. The low expression variant of this polymorphism has been linked to impulsive aggression and deficits in emotion regulation. Earlier neuroimaging genetics studies focusing on corticolimbic circuits suggested an effect of *MAOA* on amygdala-prefrontal coupling during emotional face processing. Here we aimed to extend to this approach by 1) testing the entire functional connectome for network-based phenotypes linked to *MAOA* genotype 2) searching for corresponding alterations in white matter structural connectivity using the same whole-brain network approach.

Functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) data was collected from 284 healthy participants. During the fMRI scan, participants completed a well-established emotional face-matching task. The brain was parcellated into 90 anatomical nodes defined by the AAL atlas. Whole brain functional connectivity matrices were calculated by correlating fMRI time series of each pair of nodes. Structural connectivity matrices were generated by whole-brain deterministic fiber tracking with number of connecting streamlines between each pair of nodes as measure of connectivity strength. Network-based statistic (NBS) was used for link-wise comparisons of the functional and structural connectivity matrices between *MAOA* genotype groups.

NBS identified a significant cluster showing increased functional connectivity in the low expression genotype group during emotional face processing ($p_{FWE} = 0.037$) within a large, distributed subnetwork. Analysis of DTI data revealed a similarly extended cluster showing increased structural connectivity in the low expression genotype group ($p_{FWE} = 0.045$). Consistent with prior work, corticolimbic regions were included in the functional subnetwork identified by NBS. However, this functional subnetwork encompassed several additional nodes outside of corticolimbic circuits. Corresponding structural connectivity alterations in a similarly extended network were detected, thereby providing further evidence for a of rather general effect *MAOA* genotype on brain connectivity. Taken together, our findings suggest a global effect of *MAOA* genotype on both functional and structural connectivity within distributed brain networks extending beyond emotion processing circuits.

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Nanosymposium

737. Individual Differences in Cognition and Behavior

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**Topic: ***H.02. Human Cognition and Behavior

Support: ESRC Grant ES/J50001X/1

Title: Exploring predisposition to anomalous visual experiences using transcranial direct current brain stimulation

Authors: *R. MARCHANT[1], J. J. BRAITHWAITE[2]
[1]Psychology, Univ. of Birmingham, Birmingham, United Kingdom; [2]Psychology, Lancaster Univ., Lancaster, United Kingdom

Abstract: Introduction/Rationale: "Anomalous" experiences (AEs) are common in several psychological and neurological disorders, but are also experienced with surprising frequency by many people in the absence of such disorders. The phenomenology and cognitive mechanisms of AEs do not appear to differ significantly between clinical and non-clinical groups. One mechanism by which AEs can arise is known as "cortical hyperexcitability" (CHE); heightened activation of cortical neurons. It is vital to explore how CHE influences conscious perception in non-clinical groups in order to compare data with clinical groups, and also produce findings relevant for the majority of the population.
Methods: A within-participants design was used. 72 participants (70% F, $\bar{x}$ age=20.1yrs) completed two questionnaire measures exploring predisposition to AEs; *Cardiff Anomalous Perceptions Scale* (CAPS; Bell et al., 2006) and *Cortical Hyperexcitability index* (CHi; Braithwaite et al., 2015). CHi comprises three factors; "heightened sensitivity", "negative aberrations" (losses of visual experience, e.g. blind spots), and "positive aberrations" (additions to visual experience, e.g. phosphenes). Participants underwent single-blind anodal (20 mins, 1.5mA) and sham (30s, 1.5mA) tDCS (anode at Pz, cathode at Cz), and completed a Pattern Glare (PG) task 20 mins after stimulation onset. PG task involves rating intensity of anomalous visual distortions (AVDs) experienced when viewing striped gratings (medium/ high frequency). Positive medium-high differences (M-HΔ) in intensity ratings index CHE.
Results: Mean CHi and CAPS scores significantly correlated with one another ($r= 0.60$, $p<0.001$). Only CHi "positive aberrations" factor scores correlated significantly with AVD M-HΔ intensity ratings, under anodal stimulation only ($r=0.31$, $p<0.001$).
Conclusions: Correlation between CHi and CAPS scores suggest that predisposition to anomalous experience is not modality-specific; heightened hyperexcitability may confer predisposition to anomalous experiences across sensory modalities. Correlation of scores from one CHi factor with PG experiences suggests that CHi scores can be used to predict online, state-

based experiences of PG during tDCS. tDCS may simulate a hyperexcitable state. Hyperexcitability may therefore be acute or cyclic in non-clinical groups, and future research should explore the mechanisms that could contribute to these hyperexcitable states (such as circadian rhythm abnormalities).

Disclosures: R. Marchant: None. **J.J. Braithwaite:** None.

Nanosymposium

737. Individual Differences in Cognition and Behavior

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**Topic: ***H.02. Human Cognition and Behavior

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Title: Ventral striatal dopamine transporter availability uniquely predicts lower trait impulsivity in healthy young adults

Authors: *C. T. SMITH[1], D. T. SAN JUAN[1], D. T. KATZ[1], L. C. DANG[1], S. F. PERKINS[1], L. L. BURGESS[1], R. L. COWAN[2], G. R. SAMANEZ-LARKIN[3], D. H. ZALD[1,2]
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Abstract: The dopamine transporter (DAT) is the key molecular target for psychostimulants used to treat attention-deficit hyperactivity disorder (ADHD). Despite dopamine being linked to impulsivity and novelty seeking traits, key features of many with ADHD, little work has investigated the role of DAT availability on these traits. Here, we used the radiotracer ^{18}F-FE-PE2I to assess DAT availability (binding potential, BP_{ND}) along with ^{18}F-Fallypride to assess dopamine D2/3 receptor BP_{ND} with Positron Emission Tomography (PET) in healthy young adults (PE2I: n=20, m=25.9±2.6; 12 male; both PET measures: n=18, m=26.1±2.6; 10 male). We estimated BP_{ND} using PMOD software via the Simplified Reference Tissue Model (SRTM), with the cerebellum serving as the reference region. BP_{ND} maps were warped to MNI space and mean BP_{ND} values were extracted for each participant from the caudate, putamen, and ventral striatum (VS). We observed a modest relationship between VS PE2I and VS Fallypride BP_{ND} (r=0.53, p=0.025) but no significant relationships between PE2I and Fallypride in the other striatal regions. Critically, we found that PE2I BP_{ND} negatively correlated with total Barratt Impulsivity

Scale (BIS) scores in each striatal subregion (VS: r=-0.52, p=0.018; Caudate: r=-0.56, p=0.01; Putamen: r=-0.45, p=0.046), driven by the BIS Motor subscale in VS and caudate (VS: r=-0.58, p=0.008; Caudate: r=-0.59, p=0.006). While we did not find significant relationships between PE2I BP_{ND} and total Tridimensional Personality Questionnaire Novelty Seeking scores (max r=-0.41, p=0.072 in putamen), we investigated the NS2 subscale (impulsivity) specifically as another impulsivity measure in these subjects. We found that VS (but no other subregions) PE2I BP_{ND} was significantly related to NS2 (r=-0.59, p=0.006). In follow-up analyses we tested the relative contributions of DAT and D2/3 BP_{ND} to predict impulsivity via a stepwise regression with PE2I BP_{ND} and Fallypride BP_{ND} from each striatal subregion as predictors. We found that VS PE2I BP_{ND} alone explained (β=-0.54) significant variance in BIS total score (*F* Change= 6.58, p=0.021; Adjusted R^2=0.25) with it only significantly predicting BIS Motor (not Nonplanning or Attentional) subscale scores (Adjusted R^2=0.32). VS PE2I BP_{ND} also explained (β=-0.55) significant variance (*F* Change= 6.87, p=0.019; Adjusted R^2=0.26) in NS2 scores. Striatal Fallypride BP_{ND} did not explain additional variance in impulsivity. These data suggest a unique role of ventral striatal DAT availability on impulsivity and offer new insight into the role of dopamine signaling on this trait.

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Nanosymposium

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Title: The lateral hypothalamic area sends inhibitory projections to the medial septum/diagonal band of broca that drive feeding behavior

Authors: *R. M. CASSIDY[1], Y. LU[2], L. MANGIERI[2], Q. TONG[2]
[1]Dept. of Neurobio. and Anat., The Univ. of Texas Hlth. Sci. Ctr. At H, Houston, TX; [2]The Univ. of Texas Hlth. Sci. Ctr. At Houston, Houston, TX

Abstract: The medial septum/diagonal band of broca (MS/DBB) is a source of forebrain acetylcholine traditionally understood for its role in attention, with recent evidence revealing a role in feeding behavior. The upstream regulators of MS/DBB-mediated feeding behavior are not known. The lateral hypothalamic area (LH) sends projections to this region, but their function is unknown. The inhibitory neurons found within the lateral hypothalamic area (LH) are primary drivers of motivated feeding behavior and are integral to a cue-based feeding response. Our research demonstrates that the LH sends inhibitory projections to the medial septum and diagonal band of broca (MS/DBB) that produce feeding behavior, have positive valence, produce conditioned place preference, increase locomotor activity,and reduce latency to interaction with a novel object. We intend to also demonstrate the neuronal targets of the LH-MS/DBB inhibitory projections and how this alters release of acetylcholine.

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Nanosymposium

737. Individual Differences in Cognition and Behavior

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**Presentation Number: ***737.07

**Topic: ***H.02. Human Cognition and Behavior

Title: Neurotransmitters' diversity and their roles in temperament traits: Functional ecology approach

Authors: *I. TROFIMOVA
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Abstract: Temperament traits, i.e. biologically based individual differences, are observable not only in humans, but also in animals and very young children, i.e. in pre-cultural individuals. Temperament therefore cannot be called "personality", contrary to common beliefs, since "personality" refers to culturally based phenomena. This presentation reviews findings in neurochemistry that link temperament traits to complex relationships between neurotransmitter systems. Specialization between neurotransmitter systems underlying temperament traits is analyzed here from a functional ecology perspective that considers the structure of adult temperament corresponding to the structure of human activities. The roles of monoamine neurotransmitters (serotonin, dopamine, noradrenalin), as well as the roles of acetylcholine,

neuropeptides and opioid receptor systems in the regulation of specific dynamical properties of behavior will be discussed. The functional differentiation within neurochemical systems is compared to models in kinesiology and neurophysiology that investigated key stages of human actions. Parallels to main models of temperament are summarized within the neurochemical Functional Ensemble of Temperament (FET) model. The FET framework allows having both, a common taxonomy for biologically based traits in healthy individuals and for taxonomies of mental illnesses. Temperament and mental illness are considered to be variations along the same continuum of imbalance in the neurophysiological regulation of behavior. The presentation will give examples of how the FET framework can be used in psychiatry and clinical psychology. If time permits, the presentation will report on studies that compared temperament profiles in patients with Major Depression, Generalized Anxiety Disorder and comorbid depression and anxiety, as well as the links between temperament and personality disorders.

Disclosures: I. Trofimova: None.

Nanosymposium

737. Individual Differences in Cognition and Behavior

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**Presentation Number: ***737.08

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH F31 DA041703-02

Title: Paraventricular hypothalamic projections to the ventral tegmental area drive aversion

Authors: *L. R. MANGIERI[1], Y. LU[2], Y. XU[2], R. M. CASSIDY[2], B. R. ARENKIEL[3], Q. TONG[4]
[1]Univ. Of Texas Hlth. Sci. Center-Houston, Houston, TX; [2]Univ. of Texas Hlth. Sci. Center-Houston, Houston, TX; [3]Mol. & Human Genet. and Neurosci., Baylor Col. of Med., Houston, TX; [4]Inst. of Mol. Med., Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX

Abstract: The paraventricular nucleus of the hypothalamus (PVH) contains heterogeneous neural populations that regulate a variety of behaviors, including feeding and stress. We previously demonstrated that bulk activation of PVH neurons, via *Single-minded homolog 1* (*Sim1)-Cre* mediated expression of channelrhodopsin-2 (ChR2) in the PVH coupled with light illumination, acutely increased repetitive self-grooming in mice. The evoked self-grooming via PVH photostimulation was shown to interfere with feeding after a fast, and this suppression of feeding in place of grooming required glutamate release. Here, we show that in addition to self-grooming, optical activation of PVH induces frantic escape behavior (jumping), which also

depends upon release of glutamate. Our results suggest grooming and jumping via PVH activation occur in a scalable manner, where more intense photostimulation increases the transition from grooming to jumping. Interestingly, using a Real Time Place Preference assay, we show PVH photostimulation associated with escape behavior is highly aversive, as mice vehemently avoid the light-paired side even during the fasted state, when the light-paired side contains food. By employing anterograde tracing with AAV vectors encoding synaptophysin, we observed that *Sim1*-PVH neurons densely project to the ventral tegmental area (VTA). Given the well-investigated role of the VTA in reward and aversive-related behaviors, we optically targeted PVH→VTA projections. We found that photostimulation of these projections recapitulated the escape behavior induced by PVH activation. Furthermore, we found that PVH→VTA photostimulation produced profound negative valence and conditioned place aversion to the light-paired side of the testing chamber. PVH→VTA and PVH photostimulation also produced comparable increases in locomotor behavior in the open field. Taken together, our data demonstrate a novel pathway from PVH to VTA that promotes aversion, locomotion, and escape behavior. This circuit may represent a critical manner in which hypothalamic outputs involved in metabolic regulation interact with brain areas implicated in goal-directed behaviors.

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737. Individual Differences in Cognition and Behavior

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**Presentation Number: ***737.09

**Topic: ***H.02. Human Cognition and Behavior

Title: Nash equilibrium in the personality game

Authors: *K. MOGI
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Abstract: The big five model (openness, conscientiousness, extraversion, agreeableness, and neuroticism) of personality provides a standard description of people's traits (Digman 1990, Shrout and Fiske 1995). The variability in personality has been linked to academic performance (Poropat 2009), work success (Mount and Barrick 1998), and the tendency to innovate (Fairweather 2012), thus providing an important predictor of human behavior.
Brain circuits correlating the personality traits have been reported (Kennis et al. 2013, Wei-Yin et al. 2013), suggesting that personality lies at the foundations of the brain’s cognitive strategies to adapt to the environment.

Personality is essentially a social construct. While some variations of personality correlate with genetics (Bleidorn et al. 2014, Turkheimer et al. 2014), social factors play important roles in the development of personality (Harris 1995, Reitz et al. 2014). It is interesting to consider how personality is perceived, develop, and shared by subjects in the social context.
Here I describe a game theoretic approach to personality perception and development. Subjects were asked to provide assessment for the big five traits of personality of the self, while simultaneously requested to estimate how they thought others evaluated their own personality. In general, there are dissociations between the evaluation of personality by the self and others. Analysis of data indicates that there are significant correlations between the perceived and actual dissociations of personality traits, suggesting that subjects are in general aware of other people's expectations for their own personality, while maintaining their self-evaluation.
Game theoretic analysis can be formulated where the subjects have a choice of expressing alternative traits of personality, based on the self-evaluation as well as expectations from others. The reward structure of such interactions would constrain the development and expression of personality traits within the social context. I provide evidence that there is a Nash equilibrium (Nash 1950) in such a personality game, indicating how personality traits could become socially stable entities.

Disclosures: K. Mogi: None.

Nanosymposium

737. Individual Differences in Cognition and Behavior

Location: 144A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***737.10

**Topic: ***H.02. Human Cognition and Behavior

Support: NWO VIDI Grant to Heleen Slagter
Spinoza Centre Amsterdam

Title: 'Trait' or 'state' frontal and occipital GABA and Glx concentrations - How to best predict behaviour?

Authors: *L. J. TALSMA[1], A. M. VAN LOON[3], S. H. SCHOLTE[1], H. A. SLAGTER[2]
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Abstract: Magnetic Resonance Spectroscopy (MRS) can be used to quantify concentrations of neurotransmitters GABA, Glx (a compound measure of glutamate and glutamine) within a specified brain region. On the one hand, MRS is assumed to reliably index stable baseline

metabolite levels and is increasingly used as a trait measure to examine the neurochemical basis of behavioural individual differences. On the other hand, MRS has proven sensitive to differences in activation 'states' of a network, and has therefore also been used as method to assess on-line (and 'in vivo') neuronal activity. Thus, MRS acquired metabolite concentrations may likely reflect both tonic (i.e. 'trait' behavioural measures) and phasic aspects (i.e. 'states' of the system). However, to what extent the MRS signal reflects one or the other is currently unclear. Also, little is known about whether MRS measured at rest ('trait') or during task performance ('state') is a better predictor of behavioural performance. To address these questions, we acquired GABA and Glx concentrations in different activity states and in two brain regions: the left dorsolateral prefrontal cortex (lDLPFC) and the primary visual cortex (V1) of 30 young healthy male subjects. In the lDLPFC, we compared three activity states: resting state (eyes closed), an easy working memory (WM) task and a difficult WM task. In V1, we compared two states, namely a resting state (eyes closed) and an active situation (watching a relaxing movie). Furthermore, in a separate behavioural session, we measured subjects' performance on two working memory tasks - the letter N-back task and the Sternberg task - as well as on a visual discrimination task. We compared GABA and Glx concentrations between the different activity states to examine to what extent the MRS signal reflects a 'trait' or a 'state'. In addition, we examined which MRS measure may best predict behaviour by comparing cross-subject correlations between metabolites and our behavioural measures. Results of this study may thereby have important methodological implications and may enhance both our understanding and interpretation of metabolite concentrations derived from the MRS signal, as well as aid in the design of future MRS studies that aim to link these measures to behaviour**.**

Disclosures: L.J. Talsma: None. **A.M. Van Loon:** None. **S.H. Scholte:** None. **H.A. Slagter:** None.

Nanosymposium

737. Individual Differences in Cognition and Behavior

Location: 144A

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***737.11

**Topic: ***H.02. Human Cognition and Behavior

Support: National Institute of Mental Health Intramural Research Program

Title: Functional connectivity-based neuromarker outperforms gaze, pupillary, and fMRI activation-based markers in predicting reading comprehension

Authors: *D. C. JANGRAW[1], J. GONZALEZ CASTILLO[2], D. A. HANDWERKER[3], M. GHANE[4], M. D. ROSENBERG[5], P. PANWAR[1], P. BANDETTINI[6]

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Abstract: Reading comprehension (RC) is a crucial skill. A reliable link between a person's neural or ocular signals and their RC ability could lead to a better understanding of reading difficulties and better inform the design and selection of future interventions. Previous studies have identified neural regions with activity or functional connectivity (FC) that correlate weakly with RC. However, methods are typically limited to use of a single region or isolated connection and often rely on simplified reading and comprehension tasks. In this study, we compare whole-brain biomarkers, identified from the literature or derived using data-driven methods, that predict performance on a naturalistic RC task.

25 subjects performed a free-viewing reading task with auditory distractions. As they read a transcript of a lecture on ancient Greek history, either white noise or distracting speech was played. Subjects were instructed to ignore the speech and focus on reading during some blocks, and to split their attention between the speech and reading on others. After each pair of blocks, subjects completed multiple-choice comprehension questions on what they read and heard. fMRI, eye tracking, and physiological data were collected during the task. 6 subjects were excluded due to insufficient data, excessive motion, or prior experience with the reading subject material.

Predictions of subjects' relative performance on RC questions were calculated for multiple imaging and behavioral measures during reading. Each was evaluated using the Pearson correlation (r) between the metric and the RC score across subjects (using leave-one-subject-out cross-validation when appropriate), and a p value based on 10,000 scrambled-behavior permutation tests. Using connectome-based predictive modeling, we identified a whole-brain network whose FC strength correlates strongly with subjects' RC scores ($r=0.826$, $p = 0.0008$). The network's spatial distribution indicated that RC is highest when temporal pole regions have higher FC with left occipital regions and lower FC with bilateral supramarginal gyrus. RC was also predicted by FC in the default-mode network ($r=-0.647$, $p<0.0014$) but not other task-related networks. Using a similar data-driven method with fMRI activation features from a task-vs-rest GLM contrast, we identified an activation pattern that predicts performance ($r=0.644$, $p<0.0029$), including visual and language areas. While most ocular metrics previously found to indicate mindless reading (such as blink rate and saccade rate) did not predict RC, pupil dilation during reading did ($r=0.574$, $p<0.0045$), underscoring the role arousal plays in RC.

Disclosures: D.C. Jangraw: None. **J. Gonzalez Castillo:** None. **D.A. Handwerker:** None. **M. Ghane:** None. **M.D. Rosenberg:** None. **P. Panwar:** None. **P. Bandettini:** None.

Nanosymposium

737. Individual Differences in Cognition and Behavior

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**Presentation Number: ***737.12

**Topic: ***H.02. Human Cognition and Behavior

Support: NIH/NIMH Intramural Research Program

Title: Inter-subject correlations in brain activity during an ambiguous narrative predict similarity of subjects' ultimate interpretation of the narrative

Authors: *E. S. FINN[1], P. R. CORLETT[3], G. CHEN[2], P. BANDETTINI[4], R. T. CONSTABLE[5]
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Abstract: While paranoid delusions are a hallmark symptom of schizophrenia and other psychotic illness, paranoia follows a spectrum from normality to pathology in the general population. However, the neural correlates of trait-level paranoia are not well understood. In this work, we developed a long-form narrative describing a complex social scenario that is deliberately ambiguous with respect to characters' trustworthiness and intentions. Behavioral pilot studies confirmed that this narrative evoked a range of interpretations across subjects, from less suspicious to more so. Healthy subjects on a range of trait-level paranoia listened to the narrative during fMRI scanning, and their subsequent feelings and beliefs about the narrative were characterized with an extensive debriefing questionnaire, including open-ended prompts to elicit free speech that was recorded and subsequently transcribed. In a first-level analysis using inter-subject correlation (ISC), we identified a large set of brain regions in both primary sensory and higher-order association cortices that showed stereotyped responses to the stimulus; that is, regions whose activation timecourses during the narrative were similar across all subjects. In a second-level analysis, we aimed to identify regions whose activity timecourses were similar in some subject pairs but not others, and determine whether activation similarity predicted similarity of behavioral response to the narrative. To this end, we submitted the free-recall transcripts to semantic/syntactic analysis, correlated the resulting speech features across all subject pairs, and mapped the resulting correlations to voxelwise ISC values. We identified several brain regions where activation similarity predicted ultimate similarity of narrative recall and interpretation; these were located in higher-order association cortices including medial frontal gyrus, parietal lobule, anterior temporal lobe and precuneus, as well as the cerebellum. One goal of this line of work is to develop a neuroimaging-based "stress test" to draw out

individual differences in brain networks and behaviors of interest, in both clinical and subclinical populations.

Disclosures: E.S. Finn: None. **P.R. Corlett:** None. **G. Chen:** None. **P. Bandettini:** None. **R.T. Constable:** None.

Nanosymposium

737. Individual Differences in Cognition and Behavior

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**Time: ***Wednesday, November 15, 2017, 1:00 PM - 4:15 PM

**Presentation Number: ***737.13

**Topic: ***H.02. Human Cognition and Behavior

Support: CONICYT, FONDECYT/Postdoctorado 3140306 to CD
Iniciativa Cientifica Milenio ICM P10-001-F
P09-015-F
Fundacion Guillermo Puelma

Title: Network complexity of coherence patterns in the delta-theta frequency range correlates with mean subjects' reaction time

Authors: *C. DEVIA[1,2], P. E. MALDONADO[2,3], E. RODRIGUEZ[1]
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Abstract: During the performance of a cognitive task, brain areas interact forming a transient network of brain activity. The relation between activity network characteristics and cognition is poorly understood. Here, we use a reaction time (RT) task to show that the time course of the clustering coefficient, measured on a delta-theta frequency oscillating network, correlates with subject's mean RT. We proceeded by, recording electroencephalography, computing the coherence index, and defining a network from the multigraph of coherence. Results show that the time of maximum clustering coefficient, computed from low frequency coherence networks (below 7 Hz), significantly correlates with subjects' RT (rho = 0.83, p = 0.0002, n=14). We found no significant correlation between RT and the peak of the event related potential, or the mean coherence in slow frequencies. Neither we found significant correlation between behavioral data and the degree of the network nodes, or the path length. Moreover, using a linear approximation, we successfully estimated subjects' mean RT based on the time evolution of the clustering coefficient (median estimation error 42 ms). At the network level, the increment in clustering coefficient occurred on left centro-parietal electrodes (for 13 of 14 subjects), and

started 270 ms after cue onset. These results show that clustering coefficient correlates with changes in brain's state, and can be used to estimate subject‘s performance, something that is not possible from direct measures of brain activity that neglect the complexity of neural interactions during cognitive tasks.

Disclosures: C. Devia: None. **P.E. Maldonado:** None. **E. Rodriguez:** None.

Nanosymposium

738. Schizophrenia: The Immune System

Location: 156

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***738.01

**Topic: ***G.07. Other Psychiatric Disorders

Support: MRC project grant
Stanley Foundation project grant

Title: Are neuronal cell surface antibodies causing a proportion of schizophrenia?

Authors: *B. LENNOX
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Abstract: There are many lines of evidence to suggest that a proportion of psychosis has an autoimmune basis however there have not been any biomarkers to identify individuals that might benefit from immune modifying treatments. This has potentially changed with the discovery of neuronal cell surface antibodies over the last decade. These antibodies have been described in patients with limbic encephalitis, often with prominent psychiatric symptoms and they are recognized as pathogenic - removal of the antibody results in clinical improvement and usually remission. However the relevance of the same antibodies in patients with purely psychiatric presentations has been seen as controversial and screening for antibodies, and treatment when they are detected, is not readily available. I will present our data on the increased prevalence of antibodies against NMDAR, LGI1 and GABAA receptor antibodies in first episode psychosis, and our open label data on the response to treatment with immunotherapy, such as plasma exchange, steroids and intravenous immunoglobulins, in people with psychosis. These data indicate that immunotherapy is acceptable and feasible in people with psychosis, and that most people improve in their psychosis. I will discuss the current controversies around the diagnosis and management of autoimmune psychosis and the challenges that these discoveries pose to psychiatric practice.

Disclosures: B. Lennox: None.

Nanosymposium

738. Schizophrenia: The Immune System

Location: 156

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***738.02

**Topic: ***G.07. Other Psychiatric Disorders

Title: [^{3}H]PK11195 binding to the translocator protein (TSPO) in the DLPFC in schizophrenia

Authors: *K. A. NEWELL[1], H. CAI[2], T. M. DU BOIS[1], X.-F. HUANG[1], C. S. WEICKERT[3]
[1]Sch. Of Med., Univ. of Wollongong, Wollongong, Australia; [2]Schizophrenia Res. Lab/School of Psychiatry, Neurosci. Res. Australia/Unsw, Sydney, Australia; [3]Neurosci. Res. Australia, Sydney, Australia

Abstract: Background: Several lines of evidence indicate an element of neuro-inflammation in some patients with schizophrenia. Radioligands that bind to the translocator protein (TSPO) have been used as in vivo markers of glia-induced inflammation. However, it is unclear which cell types may be most related to TSPO binding, with recent evidence questioning the ability of TSPO radioligands to detect low-grade inflammation in schizophrenia.
Methods: In this study, we used quantitative in situ radioligand binding to measure [^{3}H]PK11195 binding to TSPO in the human dorsolateral prefrontal cortex (DLPFC) in 37 schizophrenia subjects and 37 matched controls. Multiple regression was used to assess correlation between [^{3}H]PK11195 binding and the relative levels of microglia (iba1, MHC-II), astrocyte (GFAP) and monocyte/macrophage (CD14, CD16, CD163) markers.
Results: [^{3}H]PK11195 was not altered in the DLPFC of schizophrenia subjects compared to controls either overall or when subdivided into high and low inflammatory groups. [^{3}H]PK11195 binding was however positively correlated with estimated lifetime chlorpromazine equivalents in schizophrenia subjects ($r=0.365$, $p=0.026$). Regression analyses revealed that CD163 (prominently expressed on perivascular macrophages) was the strongest predictor of [^{3}H]PK11195 variance in control subjects accounting for 13% of [^{3}H]PK11195 binding variability ($r=0.357$, $p=0.033$). In schizophrenia subjects however, CD16 (expressed on monocytes/natural killer cells) was the strongest predictor accounting for 23% of [^{3}H]PK11195 binding variability ($r=0.482$, $p=0.003$).
Conclusion: Our findings indicate that TSPO labeling may not be a sensitive marker of neuro-inflammation in the schizophrenia brain, but may increase in response to antipsychotic drug exposure. Our regression analyses suggest that TSPO may increase with more perivascular macrophages in the control brain, but may increase with a higher proportion of a different population of blood-derived cells (monocytes/natural killer cells markers) in the schizophrenia brain.

Disclosures: **K.A. Newell:** None. **H. Cai:** None. **T.M. du Bois:** None. **X. Huang:** None. **C.S. Weickert:** F. Consulting Fees (e.g., advisory boards); Lundbeck Australia Pty Ltd. Other; Astellas Pharma Inc. Japan.

Nanosymposium

738. Schizophrenia: The Immune System

Location: 156

Time: *Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

Presentation Number: *738.03

Topic: *G.07. Other Psychiatric Disorders

Support: Stanley Medical Research Institute

Title: Evidence for blood-barrier disruption, antibody presence and complement activation in brains of people with schizophrenia

Authors: ***C. S. WEICKERT**[1], H. Q. CAI[1], L. J. GLASS[2], M. J. WEBSTER[3]
[1]Neurosci. Res. Australia, Sydney, Australia; [2]NeuRA, Randwick, Australia; [3]Stanley Med. Res. Inst., Rockville, MD

Abstract: Background Inflammatory cytokines are elevated in the brain of 38% of people with schizophrenia. The cytokine levels in this schizophrenia subgroup are correlated with increased interneuron pathology and astrogliosis. Increased cytokines may change the blood-brain barrier (BBB) by regulating transporters, tight junctions or white blood cell (WBC) adhesion and migration. Other immune factors such as complement cascade molecules, antibodies and immune cells may also be affected in schizophrenia. There are also neuronal proteins that protect from the damaging effects of complement activation such as CD55 and CD59. We hypothesized that molecular markers of BBB disruption, complement activation and IgG antibodies, may be elevated in those with schizophrenia compared to controls. **Methods** The mRNAs relating to BBB function and complement were measured by qRT-PCR in RNA from the prefrontal cortex (dlPFC) of 37 subjects with schizophrenia/schizoaffective disorder (30 male; 7 female) and 37 controls (24 male; 13 female). The cohort was grouped into “high inflammation” schizophrenia (n=14), “low inflammation” schizophrenia (n=23) and “low inflammation” controls (n=33) based on previous cytokine mRNA measurements. Immunohistochemistry for intercellular adhesion molecule (ICAM) and IgG and western blotting for IgG were performed in the same cohort. **Results** *ICAM1* mRNA was increased by 68% in schizophrenia $F(1,67) = 5.80$, $p = 0.019$) as compared to controls. The “high inflammation” schizophrenia subgroup had increased expression of *ICAM1* ($F(2,64) = 12.955$, $p < 0.001$) and decreased expression of an endothelial transporter, breast cancer resistance protein (*ABCG2)* ($F(2,63) = 11.389$, $p < 0.001$) as compared to both the “low inflammation” schizophrenia subgroup and the “low inflammation” control

group. ICAM-1 protein was localized to blood vessel luminal walls and astrocytes, and human IgGs were around cortical blood vessels in both schizophrenia and controls with no diagnostic differences. CD55 and CD59 mRNAs were increased in the dlPFC of people with schizophrenia as compared to controls (both, $F = >4.9$, $p<0.02$), and also in the "high inflammation schizophrenia" group compared to controls ($p<0.0001$) and to the "low inflammation schizophrenia" group ($p=0.0009$). **Conclusion** The endothelial cells of the BBB may be more adhesive and the complement cascade may be overactive in the brains of people with schizophrenia. Brain inflammation may alter BBB function to attract more WBC via increased endothelial ICAM-1. The WBC may then interact with existing endogenous brain IgGs to activate the classical complement cascade in the brain of those with schizophrenia.

Disclosures: **C.S. Weickert:** F. Consulting Fees (e.g., advisory boards); Lundbeck, Astellas. **H.Q. Cai:** None. **L.J. Glass:** None. **M.J. Webster:** None.

Nanosymposium

738. Schizophrenia: The Immune System

Location: 156

Time: *Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

Presentation Number: *738.04

Topic: *G.07. Other Psychiatric Disorders

Support: Stanley Medical Research Institute Grant
NIH Grant MH-94268

Title: Peripheral inflammation, the microbiome and the gut-brain axis in schizophrenia

Authors: ***E. G. SEVERANCE**[1], F. DICKERSON[2], R. YOLKEN[1]
[1]Johns Hopkins Univ., Baltimore, MD; [2]Sheppard Pratt Hlth. Syst., Baltimore, MD

Abstract: Introduction.
A low-level peripheral inflammation is increasingly demonstrated in individuals with schizophrenia. We have developed a research model to explore the idea that behavior and brain biochemistry is altered as a result of a disrupted gastrointestinal (GI) equilibrium, endothelial barrier defects, translocation of toxic products and dysregulation of synapse-related immune factors peripherally and in the central nervous system (CNS). Here, we will review evidence in support of our model and present promising new data that indicate microbiome modulatory treatments are beneficial in schizophrenia.
Methods.
In a large, ongoing study of schizophrenia and non-psychiatric controls, we compared serum levels of biomarkers of microbial translocation and gastrointestinal inflammation (sCD14, LPS-

binding protein, *Candida albicans*, *Saccharomyces cerevisiae*, dietary antigens) and complement activation. In a longitudinal pilot study of this schizophrenia cohort, we focused on the mycobiome and evaluated the effects of probiotics on gut-translocation of *C. albicans*, bowel discomfort and psychiatric symptoms.

Results.

All gut-based biomarkers were significantly elevated in case-control and sex-specific patterns, indicating that GI inflammation is prevalent in schizophrenia. Treatment with probiotics helped to decrease *C. albicans* marker seropositivity, but improvement of both bowel function and psychiatric symptoms were most evident in those who were not *C. albicans*-seropositive. Microbial translocation and particularly *C. albicans* seropositivity was associated with worse positive psychiatric symptoms and decreased cognition in a sex-specific manner. Parallel dysregulation of complement components suggest peripheral activation of this pathway may translate to biochemical CNS effects.

Conclusions.

Certain individuals with schizophrenia have an intestinal pathology that impacts central nervous system function. The identification of susceptible individuals who have GI-based risk factors will enable the design and testing of individualized treatments with the potential to ameliorate both gut and brain-related symptoms. Characterizing the diversity of taxa that contribute to microbial dysbioses and associated gastrointestinal inflammation in psychiatric disorders will further inform appropriate treatment, including the therapeutic application of probiotic agents.

Disclosures: E.G. Severance: None. **F. Dickerson:** None. **R. Yolken:** None.

Nanosymposium

738. Schizophrenia: The Immune System

Location: 156

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***738.05

**Topic: ***G.07. Other Psychiatric Disorders

Support: NIMH U01MH082004

Title: Neuroimmunology and microRNAs

Authors: C. JEFFRIES[1], D. O. PERKINS[2]
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Abstract: Patterns in blood plasma analytes and leukocytic microRNAs differentiate patients presenting mental distress who convert to a diagnosis of schizophrenia within two years from

other patients who do not convert. Several of the distinguishing analytes are prominent in the immune system. The dynamics of microRNAs are often given in terms of their effects in vitro with exogenous enhancement or inhibition. Translation in vitro of a targeted mRNA is assumed to be downregulated and is so in many reports. However, the situation in vivo is different, as predicted by a dynamical system model and verified in our data with immune system proteins. This seems to clarify how microRNAs must actually work in vivo.

Disclosures: C. Jeffries: None. **D.O. Perkins:** None.

Nanosymposium

738. Schizophrenia: The Immune System

Location: 156

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***738.06

**Topic: ***G.07. Other Psychiatric Disorders

Support: NHMRC (AUS) Grant 568807

Title: The interleukin-1 beta single nucleotide polymorphism rs16944 influences verbal memory and prefrontal cortex volume in women with schizophrenia

Authors: *T. W. WEICKERT[1], S.-W. KIM[2], D. LLOYD[3], M. O'DONNELL[4], J. BRUGGEMANN[3], R. LENROOT[1], C. S. WEICKERT[3]
[1]Univ. of New South Wales, Randwick, Australia; [2]Sch. of Med. Sci., Univ. of New South Wales, Kensington, Australia; [3]Sch. of Psychiatry, Univ. of New South Wales, Randwick, Australia; [4]Prince of Wales Hosp., Randwick, Australia

Abstract: Background: Several studies have reported an influence of the IL-1β gene single nucleotide polymorphism (SNP) in schizophrenia. Recent evidence has shown that subgroups of patients with schizophrenia express elevated cytokines (especially IL-1β) in the brain (in post-mortem samples) and in peripheral blood with associated impairment in verbal fluency and reduced Broca's Area volume (in an independent living cohort). Objective: We aimed to determine the extent to which two IL-1β SNPs (rs16944 and rs1143633) influence verbal fluency and Broca's Area volume in schizophrenia. Methods: Ninety-seven outpatients diagnosed with schizophrenia or schizoaffective disorder and 87 healthy controls were assessed for verbal fluency, current and premorbid IQ, and brain volumes for Broca's area and the dorsolateral prefrontal cortex (DLPFC). DNA samples from whole blood were genotyped with Applied Biosystems TaqMan SNP assays for rs16944 and rs1143633. Sex was used as a grouping factor in analyses. Results: Females with schizophrenia displaying the TT genotype for the rs16944 SNP performed significantly worse on verbal fluency, $F(2,36) = 5.133$, $p = 0.012$. Female T

allele carriers for the rs16944 SNP also had significantly lower volumes in the DLPFC (with a 12.3% reduction), $F(1,50) = 16.022$, $p < 0.001$, and in Broca's Area (with a 12.7% reduction), $F(1,50) = 18.301$, $p < 0.001$. No influence was found for the rs1143633 polymorphism and any of the variables assessed. Conclusions: These findings suggest that the rs16944 IL-1β SNP may be a predisposing factor for poor verbal fluency and decreased Broca's Area and DLPFC volumes in females with schizophrenia. This work is also the first to report differential sex influences of an IL-1β SNP in schizophrenia.

Disclosures: T.W. Weickert: None. **S. Kim:** None. **D. Lloyd:** None. **M. O'Donnell:** None. **J. Bruggemann:** None. **R. Lenroot:** None. **C.S. Weickert:** F. Consulting Fees (e.g., advisory boards); Lundbeck.

Nanosymposium

738. Schizophrenia: The Immune System

Location: 156

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***738.07

**Topic: ***G.07. Other Psychiatric Disorders

Support: NIH Grant R25 MH101079
Emory Medical Care Foundation Award

Title: Association between inflammatory markers and negative symptoms in individuals with persistent symptoms of schizophrenia treated with clozapine

Authors: *D. GOLDSMITH[1], S. L. KOPELOVICH[3], D. M. NOVACEK[2], J. R. WIDENER[1], E. C. WOMMACK[1], J. C. FELGER[1], A. H. MILLER[1], R. O. COTES[1]
[1]Psychiatry and Behavioral Sci., [2]Psychology, Emory Univ., Atlanta, GA; [3]Psychiatry and Behavioral Sci., Univ. of Washington, Seattle, WA

Abstract: Background: Negative symptoms of schizophrenia have consistently been identified as those features of the disorder that are most predictive of functional impairment and poor outcome. Moreover, whereas antipsychotic medications are effective in treating positive symptoms, they are less effective in treating negative symptoms. One pathophysiologic pathway that may contribute to negative symptoms in schizophrenia is inflammation. There is a growing literature that inflammatory cytokines may be linked to negative symptoms in individuals with schizophrenia. **Methods:** 10 patients, treated with clozapine, were included in this analysis. Blood was sampling for the following plasma inflammatory markers: high sensitivity c-reactive protein (hsCRP), interleukin (IL) 1beta, IL-6, IL-10, and tumor necrosis factor (TNF). Clinical rating scales to assess negative symptoms included the PANSS as well as the SANS. Pearson

correlation coefficients were calculated for the relationship among inflammatory markers and negative symptoms. **Results:** IL-1beta was significantly correlated with the passive/apathetic social withdrawal ($r = 0.657$, $p = 0.039$) and the disturbance of volition ($r = 0.686$, $p = 0.029$) items of the PANSS, as well as the avolition – impersistence at work or school ($r = 0.644$, $p = 0.045$), global rating of avolition-apathy ($r = 0.751$, $p = 0.012$), and the attention – social inattentiveness ($r = 0.665$, $p = 0.036$) items of the SANS. IL-10 was negatively correlated with the emotional withdrawal ($r = -0.638$, $p = 0.047$) and the passive/apathetic social withdrawal ($r = -0.655$, $p = 0.04$) items of the PANSS as well as the negative symptom total score of the PANSS ($r = -0.792$, $p = 0.006$). **Conclusions:** IL-1beta, a pro-inflammatory cytokine, was significantly correlated with items assessing negative symptom domains of avolition and social deficits. IL-10, an anti-inflammatory cytokine, was negatively correlated with similar negative symptom items, including the negative symptom total score on the PANSS. Though the sample size is small, these data suggest that inflammation may be relevant for negative symptom. Indeed, administration of inflammatory stimuli has been reliably linked to deficits in reward processing and motivation via effects of inflammatory cytokines on regions of the basal ganglia, including the ventral striatum. Individuals with depression and increased inflammation also exhibit decreased functional connectivity in reward circuits in association with anhedonia. Future work should further explore the relationship between negative symptoms and inflammation in individuals with schizophrenia.

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Nanosymposium

738. Schizophrenia: The Immune System

Location: 156

**Time: ***Wednesday, November 15, 2017, 1:00 PM - 3:15 PM

**Presentation Number: ***738.08

**Topic: ***G.07. Other Psychiatric Disorders

Title: Blood-brain barrier genes altered in schizophrenia and bipolar disorder associated with inflammation and stress

Authors: *H. Q. CAI[1,2,3], V. S. CATTS[1,2,3], M. J. WEBSTER[4], C. SHANNON WEICKERT[1,2,3]
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Abstract: Introduction: Abnormal regulation of immune and stress pathways are apparent in neuropsychiatric disorders such as schizophrenia and bipolar disorder (BPD). The blood-brain

barrier (BBB) may be vulnerable during elevated inflammation and stress. BBB integrity is important in maintaining cortical homeostasis by regulating movement of molecules and cells in and out of the brain. We hypothesised that expression of BBB genes would be altered in psychiatric disorders with more severe changes found in patients in an elevated inflammation/stress state.
Methods: Total RNA extracted from the postmortem prefrontal cortex was obtained from the SMRI (35 schizophrenia/31 BPD/34 controls). mRNA levels of the following BBB genes were quantified by qPCR: breast cancer resistance protein (ABCG2), interferon-induced transmembrane protein (IFITM), intercellular adhesion molecule (ICAM1), VE-cadherin (CDH5) and occludin (OCLN). High and low inflammation/stress biotypes based on cortical pro-inflammatory markers and glucocorticoid mRNA expression were previously assigned for this cohort (15 schizophrenia/11 BPD/6 controls with high inflammation/stress biotype and 20 schizophrenia/20 BPD/28 controls with low inflammation/stress biotype) (Fillman, 2014). BBB transcripts were analysed based on these biotypes in addition to diagnostic comparisons.
Results: IFITM mRNA was increased in schizophrenia (53.9%, $p=0.005$) and in BPD (43%, $p=0.024$) compared to controls. ABCG2 mRNA was decreased in schizophrenia (15.4%, $p=0.008$) and in BPD (19.7%, $p=0.010$) compared to controls. Using the inflammation/stress biotypes, high inflammation/stress schizophrenia had elevated IFITM, ICAM1 and lower ABCG2 compared to high inflammation/stress schizophrenia and controls (all $p<0.05$). High inflammation/stress BPD had elevated ICAM1 and IFITM compared to low inflammation/stress BPD (83.1% and 131.2%, respectively) and controls (188.2% and 89.7% respectively, all $p<0.05$).
Conclusions: We replicated the increase in the cytokine-induced mRNA, IFITM, in schizophrenia and also find for the first time that this occurs in BPD. A decrease in efflux transporter expression may result in more toxin build up within the brain. Changes in expression of blood endothelial mRNAs were much greater in the subgroup of patients with elevated cortical inflammation/stress levels. An increase in ICAM1 expression may lead to increased attachment of white blood cells to the brain vessels. Overall, these findings indicate that the BBB may be compromised as a result of increased inflammation and stress in schizophrenia and BPD.

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Nanosymposium

738. Schizophrenia: The Immune System

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Title: Inflammation-associated disruptions in reward circuitry in depression and reversal with levodopa: Preliminary findings

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Abstract: Neuroimaging studies indicate that administration of inflammatory cytokines or cytokine inducing stimuli decrease activation of the ventral striatum in association with increased symptoms of anhedonia and reduced motivation. Our in vivo microdialysis studies in non-human primates suggest that these effects may be driven by decreased striatal dopamine availability and release, which can be reversed by administration of the dopamine precursor, levodopa (L-DOPA). Herein, we examined inflammation-related alterations in functional connectivity with the ventral striatum in relation to symptoms of anhedonia in medically healthy, medication free patients with major depressive disorder (MDD). Preliminary data was also collected from a subset of patients with high inflammation (as defined by plasma C-reactive protein [CRP]) who were administered L-DOPA before and after resting state fMRI. Increased inflammation (higher plasma CRP) was associated with decreased functional connectivity between the ventral striatum and ventromedial prefrontal cortex (vmPFC) in patients with MDD. These changes in functional connectivity were also associated with increased anhedonia. Furthermore, preliminary data indicate that L-DOPA can reverse inflammation-associated decreases in corticostriatal connectivity. These data support the hypothesis that inflammation effects on dopamine availability may play a role in dysfunction of corticostriatal reward circuits that underlies symptoms of anhedonia and reduced motivation in depression. Ongoing work with L-DOPA will provide a foundation for future studies investigating therapeutic strategies that facilitate availability of dopamine precursors or increase dopamine receptor signaling to improve symptoms of anhedonia in patients with depression and increased inflammation.

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Nanosymposium

739. Transcranial Magnetic Stimulation

Location: 147A

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**Presentation Number: ***739.01

**Topic: ***I.04. Physiological Methods

Support: BBSRC BB/N016793/1

Title: Anisotropy of non-invasive brain stimulation in human motor cortex implicates specific interneuron circuits in motor learning

Authors: *R. HANNAH, A. IACOVOU, V. RAWJI, J. C. ROTHWELL
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Abstract: The output from human primary motor cortex (M1) following transcranial magnetic stimulation (TMS) displays clear anisotropy: a posterior-anterior (PA) induced current recruits a different set of excitatory inputs to corticospinal neurones than the opposite anterior-posterior (AP) current. We recently showed that putatively conditioning the excitability of PA- or AP-sensitive inputs produced distinct effects on model-free and model-based learning, indicating that the physiological asymmetry has behavioural relevance. Transcranial direct current stimulation (TDCS) over M1 has been shown to influence M1 excitability and motor learning in a polarity-dependent manner. However, current direction with respect to M1 neurones is poorly defined with traditional electrode montages. We hypothesised that a TDCS electrode montage with a more uniform current direction would reveal polarity-dependent effects on the excitability of PA- and AP-sensitive inputs in M1, and in turn on model-based learning. Human volunteers received TDCS via two electrodes placed 3cm in front and 3cm behind the motor hotspot for the hand with either an anterior anode (A_{An}), posterior anode (P_{An}) or sham (S) TDCS. The electrodes were aligned with the preferred orientation of PA TMS. Expt.1: 15 volunteers received TDCS-P_{An} for 10min at 1mA. MEPs evoked by PA and AP TMS pulses were measured before and at 10min intervals afterwards. Expt. 2: 36 volunteers received TDCS-P_{An}, TDCS-A_{An} or TDCS-S during practice of a ballistic thumb acceleration task, which was used to assess motor learning and retention (48h). PA- and AP-evoked MEPs were recorded before and after practice on day 1. Results of experiment 1 showed that TDCS with a posterior anode supressed PA-evoked MEPs by ~25%, but had no significant effect on AP-evoked MEPs. A control latero-medial electrode montage had no effect on MEPs. In experiment 2, PA-evoked MEPs were suppressed after motor practice with TDCS-P_{An} compared to with TDCS-A_{An} and TDCS-S, with no difference between the latter conditions. Changes in AP-evoked MEPs were variable. Retention of motor learning at 48h and overall learning at the end of the second session tended to be impaired with TDCS-A_{An} compared to TDCS-P_{An} and TDCS-S, which were not different to each other. In conclusion, TDCS effects on M1 are highly sensitive to the direction of current flow. This is relevant

physiologically in terms of effects on distinct inputs to corticospinal neurones and behaviourally in terms effects on the early consolidation of motor learning.

Disclosures: **R. Hannah:** None. **A. Iacovou:** None. **V. Rawji:** None. **J.C. Rothwell:** None.

Nanosymposium

739. Transcranial Magnetic Stimulation

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Presentation Number: *739.02

Topic: *I.04. Physiological Methods

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Title: Corticospinal axonal responses to TMS with different coil orientations

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Abstract: Background: Transcranial magnetic stimulation (TMS) over the motor cortex evokes spinal responses at latencies corresponding to direct (D-wave) and trans-synaptic (I-wave) activation of pyramidal tract neurons. The latency and magnitude of these responses are dependent upon the orientation of the TMS coil as this defines the direction of flow of induced current, which has been proposed to activate different neural elements preferentially. The current study aimed to characterise response profiles to posterior-anterior (PA) and anterio-posterior (AP) TMS at different intensities by recording from individual corticospinal axons. **Methods:** In four anaesthetised macaques, a figure of eight TMS coil was fixed over the left M1 at a 45 degree angle. A custom cable permitted the direction of current flow to be inverted by 180 degrees, enabling both PA and AP stimulation without requiring physical movement of the coil. Sharp glass micropipettes were inserted into the dorsolateral funiculus of the spinal cord at C5 to record from corticospinal axons, which were identified by pyramidal tract stimulation. Following successful impalement of a corticospinal axon, spikes were recorded after TMS stimulation at 120, 150 and 200% of the threshold to evoke an epidural volley. **Results:** Corticospinal axonal responses to PA and AP orientations of TMS were successfully recorded at latencies reflecting D, I1, I2 and I3 waves. **Discussion:** In this study we have characterised the impact of TMS over M1 on corticospinal axons and identified differences in response profile for two orientations of stimulation.

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Nanosymposium

739. Transcranial Magnetic Stimulation

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Topic: *I.04. Physiological Methods

Support: Canadian Institute of Health Research (CIHR) Post-doctoral Fellowship awarded to Dr. Matt Brown.
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Title: Primary somatosensory cortex-motor cortex interactions measured using dual-site transcranial magnetic stimulation

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Abstract: Objective: The somatosensory system, including the primary (S1) and secondary somatosensory cortices, interacts with the primary motor cortex (M1) for motor control. Short-latency afferent inhibition, a measure of fast inhibition of the somatosensory system on M1, is represented by reduced motor-evoked potentials (MEPs) when peripheral electrical stimulation of the median nerve precedes a transcranial magnetic stimulation (TMS) pulse to M1 by ~20-25 ms. It is unclear if this inhibition occurs through cortico-cortical interactions. We hypothesized that S1 cortical stimulation will inhibit M1.
Methods: Intrahemipheric interactions between left S1 and M1 were measured using dual-coil TMS in 16 right-handed participants (mean age 28.2, range 20-38 years). S1-M1 interactions were measured using a paired-pulse protocol with the conditioning stimulus (CS) applied over S1 followed by the test stimulus (TS) over M1. S1 was localized via neuronavigation using individualized MRIs. MEPs were measured from the right first dorsal interosseous (FDI) and abductor pollicis brevis (ABP) muscles using EMG. TS was set to produce MEP amplitudes of ~1 mV. CS intensities were determined using active motor threshold (AMT) measured over left M1. In Experiment 1, S1-M1 interactions were measured with a fixed intensity of 160% of AMT for the CS while inter-stimulus intervals (ISIs) varied from 1, 2, 2.5, 3, 4, 5 or 6 ms prior to TS over M1. In Experiment 2, the effects of different CS intensities, including 50-120, 140, 160%

AMT, were measured on S1-M1 interactions using ISIs of 1 and 2.5 ms. In Experiments 3 and 4, short-interval cortical inhibition (SICI) using paired-pulse TMS over left M1 was measured using similar parameters as Experiment 1 and 2. In Experiment 3, CS intensity was set to 90% AMT rather than 160% AMT while CS intensities between 50-120% were used for Experiment 4. A control experiment was performed to examine current spread from S1 to M1, by measuring AMT while stimulating over S1.
Results: Experiment 1 revealed that right FDI MEPs were inhibited when the CS to S1 preceded the TS by 1 and 2.5 ms. Experiment 2 confirmed that S1 inhibits M1 at 1 and 2.5 ms when CS intensity is at least 120% AMT. Experiments 3 and 4 confirmed previous studies that SICI was largest when CS intensities were set to 0.8 and 0.9 AMT and ISIs at 1, 2 and 2.5 ms. Even at 100% stimulator output, S1 AMT was obtained only in 4 participants.
Conclusion: Our results revealed a fast intracortical inhibitory influence of S1 on M1 at 1 and 2.5 ms. Our control experiment suggest that these inhibitory effects were not driven by current spread to M1, but rather reflect a direct cortico-cortical inhibitory mechanism from S1 to M1.

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Nanosymposium

739. Transcranial Magnetic Stimulation

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**Topic: ***I.04. Physiological Methods

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Title: Mapping effective connectivity between the premotor cortex and contralateral primary motor cortex using dual-coil transcranial magnetic stimulation

Authors: *K. L. BUNDAY[1], S. BETTI[2], J. J. BONAIUTO[1], G. A. ORBAN[3], M. DAVARE[4]
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Abstract: Anatomical studies in monkeys have shown that different regions of the ventral premotor cortex (PMv), which project to the primary motor cortex (M1), have specific contributions to the control of hand movement. Specifically, neurons involved in grasping execution and observation are found in area F5p and F5a/F5c, respectively. In humans, these PMv subdivisions are less well defined. Here we used dual-coil transcranial magnetic stimulation (TMS) to map with high spatial resolution the effective connectivity between different premotor regions of the right hemisphere and contralateral M1. TMS was applied over the left M1 alone (test pulse) or after a conditioning pulse over the right precentral cortex (rectangular grid approx. 5x7 grid points, 1 cm apart) at an inter-stimulus-interval (ISI) of 8 ms. The test stimulus intensity was set to evoke a motor evoked potential (MEP) of approximately 1 mV amplitude in the right first dorsal interosseous muscle. The conditioning stimulus was applied at a suprathreshold (120% of rest motor threshold) intensity. The effective connectivity was investigated while subjects sat at rest (n=9, experiment 1) or performed a simple index finger abduction or precision grip of an object in response to an auditory cue (n=8, experiment 2). In experiment 2, TMS was applied during the preparation phase of each movement. Mean amplitudes of conditioned MEPs were expressed as a ratio of the unconditioned test MEPs and used to compute interpolated connectivity maps over each individual's precentral regions. For each condition, these connectivity maps were then averaged across subjects and t-values from each voxel were used to plot statistical maps. At rest, we found that applying TMS over 2 distinct foci in BA6v facilitated contralateral M1 MEPs. Interestingly, during index finger abduction, the most dorsal BA6v subregion switched to inhibitory interactions with M1 while the ventral BA6v subregion the facilitatory interactions found at rest were abolished. During precision grip, we found a more anterior subregion over BA44-45 showing facilitatory interactions, which switched to inhibition when subjects performed index finger abduction. Thus, our results suggest that it is possible to use dual-coil TMS to define further subregions in the human premotor cortex functionally involved in hand movements. We show that two regions in BA6v are differentially modulated by task and that a more anterior subregion in BA44-45 is further modulated by different hand movements. This complex connectivity pattern between PMv and M1 sheds new light on the multiple roles of PMv in hand motor control.

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Nanosymposium

739. Transcranial Magnetic Stimulation

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**Topic: ***I.04. Physiological Methods

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Title: Selective effects of late I-wave stimulation during human power grip

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Abstract: We recently showed that late I-wave circuits in humans can be preferentially engaged during a power grip (Federico & Perez, 2016). In this study, we examined if the aftereffects of repeated pairs of transcranial magnetic stimulation (TMS) at an interstimulus interval that mimics the rhythmicity of late I-waves on corticospinal neurons can be enhanced by applying the stimulation during a power grip in control subjects. One-hundred and eighty pairs of TMS pulses were applied over the hand representation of the primary motor cortex with the coil oriented in the anterior-posterior (AP) direction at an interstimulus interval of 1.3 ms at a frequency of 0.1 Hz for 30 min during a power grip and index finger abduction (control task) in randomized sessions separated by 2-3 days. We measured motor evoked potentials (MEPs) in the first dorsal interosseous muscle, elicited with the coil in the AP orientation during power grip and the control task before and after stimulation. We found that after repeated stimulation AP MEPs measured during power grip increased in amplitude when paired stimulation was applied during power grip. In the control task, the amplitude of AP MEPs elicited during power grip increased after the repeated stimulation but to a lesser extent than when stimulation was applied during power grip. Notably, AP MEP amplitude measured during index finger abduction increased to a lesser extent than during power grip. Our findings suggest that the aftereffects of repeated paired TMS stimulation targeting late I-wave circuits can be maximized by stimulating humans in a task-dependent manner.

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Nanosymposium

739. Transcranial Magnetic Stimulation

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Title: Linking electric field simulations and physiological measurements to reveal how TMS stimulates the human motor hand area

Authors: *A. THIELSCHER[1], A. ANTUNES[2], A. BUNGERT[3], S. ESPENHAHN[4], M. HAMADA[5], P. J. SØRENSEN[6], E. RAFFIN[7], J. C. ROTHWELL[8], H. R. SIEBNER[9]
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Abstract: Knowledge of the type and position of the neural population stimulated by transcranial magnetic stimulation (TMS) is pivotal for a better understanding of the underlying physiological mechanisms and for advancing a systematic targeting and dosage approach. We will provide evidence that realistic field modeling informed by individual structural MRI, combined with measurements of the elicited motor evoked potentials (MEPs) can help to pinpoint the stimulated brain region and reveal the stimulation depth. We will further show that field modeling can contribute to the understanding of the neural origin of inter-individual differences in MEP latencies.
In 9 healthy participants, we systematically varied the orientation of a standard figure-8 coil and compared the MEP threshold changes for monophasic TMS with the electric field changes in the motor cortex that were calculated using the Finite-Element Method (FEM). In addition, in another 9 participants, we used three figure-8 coils having different field decays to correlate the differences in the electrophysiological thresholds for current direction posterior-to-anterior (PA) with the differences in the calculated field distributions. These two experiments consistently

showed that TMS stimulates the region of the crown and posterior lip of the precentral gyrus and that the maximal electric field strength in this region is significantly related to the MEP threshold. Finally, in 13 participants, we tested the correlation between the field in the motor cortex and the MEP onset delays for anterior-to-posterior (AP) current orientation. We demonstrated that the part of the motor cortex found in the two prior experiments also exhibited a significant negative correlation between the onset delays and the field strength.
The results of our experiments validate the FEM-based field calculations by demonstrating a significant correlation between the electric field estimates and the physiological response to TMS. They further help to resolve uncertainties on the stimulation depth of TMS. They suggest that TMS at the optimal current orientation might mainly stimulate subarea BA 4a of the motor cortex at the transition from the posterior wall to the crown of the precentral gyrus. In addition, in those subjects in which lower field strengths are sufficient to induce a motor response for current orientation AP, later I-waves are recruited. This suggests that local inter-individual differences in cortical organization in the upper part of M1 might underlie the observed latency differences.

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Nanosymposium

739. Transcranial Magnetic Stimulation

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Title: Targeting space and time in the human hand knob with focal transcranial magnetic stimulation

Authors: ***H. R. SIEBNER**[1,2], E. RAFFIN[1,3], A. KARABANOV[1], L. TOMASEVIC[1], M. SAFELDT[1], A. THIELSCHER[1,4], K. H. MADSEN[1,5], R. DUBBIOSO[1,6]
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Abstract: Background: Transcranial magnetic stimulation (TMS) is widely used to study corticomotor physiology in humans by targeting the primary motor hand area (M1-HAND). However, our knowledge about how TMS stimulates the M1-HAND is still rudimentary and targeting the M1-HAND lacks spatial and temporal precision. Aim: Here we exploited structural MRI for spatial neuronavigation and EEG for temporal neuronavigation of TMS to optimize spatial and temporal targeting of the human M1-HAND. Methods: In different groups of healthy individuals ($n \geq 14$), we applied a novel method for spatial neuronavigation, referred to as linear sulcus-shape based TMS mapping. During linear sulcus-shape based mapping, the target site and the orientation of a small figure-of-eight stimulation coil were adjusted to the individual shape of the central sulcus forming the "hand knob". Using the EEG to read out ongoing cortical activity, EEG-informed TMS targeted a specific phase of alpha oscillatory activity of the pericentral cortex (mu rhythm). Results: Linear sulcus-shape based TMS mapping disclosed a centre-surround organisation of short-latency sensory integration in the M1-HAND (study 1) and uncovered spatial and physiological properties of use-dependent intra-area reorganisation in human M1-HAND (study 2). Shifting the sulcus-adjusted mapping line gradually more anterior, we found that approximately half of the subjects showed a maximum motor response at a more premotor location (study 3). These subjects also displayed a more premotor activation peak when performing a motor task during functional MRI and we found MRI-based evidence for increased regional myelinisation of the precentral cortex in the "premotor group". EEG-informed TMS of M1-HAND did not reveal consistent phase-dependent variations in the size of TMS-evoked motor responses at rest (study 4). Conclusion: Targeting the spatial and temporal features of cortical physiology with neuronavigated TMS provides novel insights into how TMS excites the fast-conducting corticomotor pathways and opens up novel possibilities for informed open-loop or closed-loop TMS applications.

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Nanosymposium

739. Transcranial Magnetic Stimulation

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**Presentation Number: ***739.08

**Topic: ***I.04. Physiological Methods

Title: Neural effects of theta-burst Transcranial Magnetic Stimulation on single neurons in macaque parietal cortex

Authors: *M. C. ROMERO, P. JANSSEN, M. DAVARE
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Abstract: Theta-burst transcranial magnetic stimulation (TBS) has recently received much interest because it can be used to up- or downregulate brain activity non-invasively for up to an hour, by a mechanism thought to rely on synaptic plasticity. However, a major issue with TBS is that its behavioral effects are highly variable. A better understanding of TBS effects on different populations of neurons is currently needed to improve its reproducibility. Recently we have recorded single-unit activity in parietal cortex during and after single-pulse transcranial magnetic stimulation (TMS, Romero et al. Soc Neurosci abstract 2016) and found that single-pulse TMS (120% of resting motor threshold) induces a short-latency burst of action potentials in parietal neurons lasting on average 80 ms. Here, we measured the after-effects of continuous TBS (cTBS, 300 pulses) on the TMS-induced burst and spontaneous neuronal activity. Guided by anatomical MRI, we recorded single-cell activity in parietal area PFG in one macaque monkey during passive fixation of real-world objects. We compared trials with and without cTBS (60% of resting motor threshold). In each recording session, we first searched for well isolated single neurons, then ensured we could record stable TMS-evoked bursts before cTBS. If a TMS-evoked response was found we proceeded with applying cTBS, after which we immediately resumed the single-pulse TMS protocol to assess changes in excitability up to 50 minutes after the start of cTBS. On average, cTBS caused a robust reduction (29%, $p<0.001$) in the TMS-evoked population response, which peaked in the 20 to 30 min post-cTBS time interval. This decrease in excitability following cTBS recovered to nearly normal values in the 40 to 50 min post-cTBS interval (5% reduction, ns). Overall, 97% of all cells recorded showed significant reduction in the TMS-evoked response. Interestingly the temporal dynamics of this effect differed strongly between neurons. 48% of the neurons showed early cTBS effects (0-5 min), whereas 44% were not affected in the first 5 min but were inhibited in the 5 to 30 min post-cTBS interval. The remaining 8% showed very late inhibitory effects (>30 min). In addition, we found a significant reduction in the average spontaneous activity (31 %, $p<0.001$), which persisted throughout our recording session (up to 50 min). Our results confirm that cTBS causes long lasting inhibition in PFG neuronal activity which peaks 20 to 30 minutes after stimulation. Further investigating how different neuronal populations respond with a specific time course might reveal the mechanisms

of early stage synaptic plasticity mediated by cTBS. Supported by FWO, Odysseus, and PFV/10/008

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Nanosymposium

739. Transcranial Magnetic Stimulation

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Presentation Number: *739.09

Topic: *I.04. Physiological Methods

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Title: Temporal and spatial patterns of inter-laminar connectivity in the macaque motor cortex leading to I wave generation

Authors: ***S. N. BAKER**[1], W. XU[2]
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Abstract: Previous studies have consistently observed the presence of high frequency (around 600 Hz) volleys recorded in the spinal cord in response single stimuli of the motor cortex via transcranial magnetic and electrical stimulation. The first wave (D wave) has been attributed to direct activation of corticospinal neurons by the stimulus and subsequent waves (I waves) have variously been attributed to activation of intra-cortical synaptic chains and subcortical mechanisms (Kernell & Chien-Ping, 1967; Hicks et al., 1992; Burke et al ., 1993; Cirillo & Perez, 2015). In this study we use sharp electrodes to make intracellular recordings of putative pyramidal neurons from slices of macaque primary motor cortex. Using focal extracellular stimuli at defined cortical depths we show that stimuli at different cortical depths evoke different patterns of spiking and EPSP responses. Neurons in superficial cortical layers are preferentially activated by stimulation of the superficial cortical laminae whereas neurons in layer V are activated to the same degree by stimuli from all cortical laminae. Additionally we find that a single stimulus can evoke repetitive high frequency patterns of spiking in the pooled population output of layer V neurons, which after high-pass filtering reveals 3 peaks at high frequency. The first, second and third peak are due to stimulation of layer I/II, layer V and layer I/II respectively. We propose that this high frequency component in the population response forms the basis of I waves previously recorded in-vivo in downstream volleys after single pulse M1 stimulation. Our data suggest that putative I waves are formed predominantly via the different timings of synaptic inputs onto layer V neurons with negligible contribution from intrinsic spike bursting properties of these neurons.

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Topic: *I.04. Physiological Methods

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Title: Accurate modeling of axonal activation by initial polarization from transverse field in magnetic stimulation

Authors: ***B. WANG**[1], A. S. ABERRA[2], W. M. GRILL[2], A. V. PETERCHEV[1]
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Abstract: The activation of peripheral nerve fibers by the transverse component of the induced electric field from magnetic stimulation has been previously reported (median nerve, *in vivo*, Ruohonen *et al.*, 1996, and phrenic nerve, *in vitro*, Struijk and Durand, 1999), and was attributed to initial polarization of the axons in response to the transverse field. However, modeling studies on transverse stimulation used linear membrane models, and therefore did not accurately account for the effects on thresholds of the nonlinear neural membrane. We derived a modified cable equation to capture both longitudinal and transverse electric field components and applied it to a model of magnetic stimulation of peripheral nerve fibers by a single circular coil and figure-8 coil for a range of lateral and vertical coil placements and both monophasic and biphasic stimulation pulses. The induced electric field was calculated using a simplified volume-conductor, and the Hodgkin-Huxley and Richardson-McIntyre-Grill membrane models were used to represent unmyelinated and myelinated axons, respectively. Thresholds were compared between the modified cable equation and conventional cable equation to quantify the effects of initial polarization on activation thresholds, and the differences were mapped for the various coil placements. Except when axons were closely aligned to the center of the figure-8 coil, the inclusion of initial polarization significantly reduced thresholds for activation of unmyelinated axons, with percentage difference ranging from 60% up to 100% for coil placement yielding almost zero activation function. Thresholds calculated with the modified cable equation were

lower for coil placements where the activating function was weaker compared to those where it was stronger, due to the low spatial gradient of the induced electric field compared to the transverse field strength. For myelinated axons, the effect of initial polarization was insignificant except for coil placements with almost zero activating function. Thresholds were unaffected for most coil placements, and threshold distribution was consistent with predictions using the conventional activating function. Initial polarization by the transverse field only affected unmyelinated axons, and therefore is unlikely to account for the reported transverse stimulation. The contribution of other factors, such as tissue geometry and inhomogeneity, should be investigated.

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Title: On the causal role of cortical beta oscillation for voluntary force control using rhythmic TMS

Authors: *K. UEHARA, J. FINE, M. SANTELLO
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Abstract: Cortical oscillatory activity of the sensorimotor area plays a key role in motor control and related information processing. It has been proposed that movement-related beta oscillatory activity in the sensorimotor area might be a putative neurophysiological mechanism underlying motor control (Mackay 1997, Pfurtscheller et al. 1999). This activity occurs during isometric muscle contractions as well as when movement has to be voluntarily suppressed (Baker 2007, Androulidakis et al. 2007, Brinkman et al. 2016). Although a correlation between cortical oscillation and motor behavior has been demonstrated, their causal relation is not well understood. This study was designed to test whether beta oscillatory activity causally contributes to motor performance. Fourteen heathy right-handed participants were instructed to press a force-sensitive device with their right index finger at three different force levels (5, 10, and 25% of maximal voluntary contraction) for 3 s as quickly and accurately as possible after receiving a visual “Go” cue. Cortical beta oscillatory activity was manipulated using rhythmic transcranial

magnetic stimulation (rhythmic TMS) to entrain cortical oscillatory activity to the stimulated frequency (Thut et al. 2011, Romei et al. 2016). Rhythmic TMS was applied at 20 Hz through short bursts of 5 pulses each over the motor hand area of left primary motor cortex 300 ms before the "Go" cue. Intensity of stimulation was set to 90% of active motor threshold (Romei et al.2016). We also used a sham and catch condition (no TMS sound and no stimulation, respectively) interspersed with TMS trials to control for entrainment to rhythmic acoustic stimulation. Our analysis focused on two performance variables: reaction time and peak force rate. Rhythmic TMS significantly reduced peak force rate (~10%) across all force levels relative to sham and catch conditions ($p < 0.01$), whereas reaction time was not affected. These results are consistent with, and extend previous work showing that transcranial alternating current stimulation at beta-band frequencies reduces movement speed (Pogosyan et al. 2009). Although preliminary, the present findings are consistent with the notion that cortical beta oscillations are causally related to motor execution.

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Title: Cortico-cortical contributions to the silent period in humans with spinal cord injury

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Abstract: A motor evoked potential (MEP) elicited by transcranial stimulation of the contralateral motor cortex is followed by a silent period (SP) in electromyographic activity. It is well known that the duration of the SP is increased in humans with incomplete spinal cord injury (SCI) compared with control subjects (Freund et al., 2011, Barry et al., 2013); however, the mechanisms contributing to this effect remain unknown. Here, we used suprathreshold

transcranial magnetic stimulation (TMS) over the hand representation of the motor cortex to elicit MEPs in an intrinsic finger muscle during 20% and 50% of maximal voluntary contraction (MVC) into index finger abduction with the TMS coil oriented in the posterior-anterior (PA) and anterior-posterior (AP) direction to preferentially activate early and late cortical synaptic inputs onto corticospinal neurons, respectively. PA and AP MEP size was matched across conditions. We found in control subjects that the duration of the SP was prolonged in AP compared with PA MEPs during 20% (by 42.6±27.5 ms) and 50% (by 42.5±25.4 ms) of MVC. In contrast, SCI subjects showed similar duration of the SP in AP and PA MEPs during 20% (by 1.9±23.5 ms) and 50% (by 3.0±14.4 ms) of MVC. Our findings are consistent with previous results (Cirillo et al., 2016) and suggest that cortical structures activated by AP stimuli are altered in humans with incomplete cervical SCI. Late synaptic inputs to corticospinal neurons may represent a target for future strategies aiming to enhance corticospinal output following SCI.

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Title: Transcranial magnetic stimulation of morphologically-accurate, layer-specific neuron models in realistic head geometry

Authors: *A. ABERRA[1], B. WANG[2], A. V. PETERCHEV[1,2,3,4], W. M. GRILL[1,3,4,5]
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Abstract: Transcranial magnetic stimulation (TMS) is a non-invasive technique for modulating brain activity with both clinical and research applications, including the treatment of drug-resistant depression and functional brain mapping. TMS works by discharging a current pulse through a coil placed above the head, which generates a time-varying magnetic field that induces an electric field (E-field) in the brain. Rational design of TMS therapies and neuromodulation strategies is currently limited by our lack of a mechanistic understanding of the neural response to TMS at the level of individual neurons. We developed a model of TMS-induced neuronal

activation by coupling modified versions of realistic, compartmental models of cortical neurons from the Blue Brain network to a detailed finite element method (FEM) model of the human head derived from magnetic resonance images (SimNIBS). Using this multi-scale model, we quantified the effects of varying the spatial and temporal parameters of stimulation on neural activation in the primary motor cortex (M1) across cortical layers and cell types. Large-diameter, myelinated axons had the lowest thresholds for TMS activation and were activated at their intracortical terminations. Pyramidal cells were preferentially activated by E-fields oriented perpendicular to the cortical surface and parallel to the somato-dendritic axis, but the existence of collaterals extending horizontally also allowed for activation by transversely-oriented fields. Cortical interneurons were less sensitive to E-field orientation due to their dense, more spherically symmetric axonal arbors. In the combined FEM and neuronal model, TMS of the hand-knob region of M1 revealed waveform and coil orientation dependent shifts in the spatial distribution of thresholds. Monophasic stimulation oriented in the posterior-anterior (PA) direction activated L2/3 and L5 pyramidal cells on the posterior lip of the gyral crown, while anterior-posterior (AP) stimulation produced an anterior shift in pyramidal cell activation. Biphasic and half-sine waveforms produced deeper activation that was more symmetric with reversal of coil orientation. Threshold ratios between waveforms matched experimental measurements of motor threshold in humans. These results suggest PA and AP stimulation activate different neuronal populations, which may explain differences in motor thresholds, as well as in latencies of motor-evoked potentials recorded in hand muscles.

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Title: Motor cortical changes in reaction time paradigms involving different levels of information about the response time

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Kingdom; [2]UCL Inst. of Neurol., London, United Kingdom; [3]Inst. Neurol, London, United Kingdom

Abstract: In simple reaction-time (RT) tasks, it is possible to prepare the movement fully in advance. In situations where subjects have to respond to an expected imperative stimulus, then the prepared response has to be released only when the stimulus has appeared. In such conditions, there is a short period in which motor-evoked potentials (MEP) are suppressed prior to movement which has been considered as a reflection of "proactive inhibition" that prevents premature release of the movement command. However, there have been no studies of whether the same effect is ever reflected in concurrent EEG signals. The first aim of this study is to test this by analysing decreases in the power of the of the sensorimotor rhythms recorded from the EEG, usually interpreted as states of increased excitability.
The second aim of the study is to compare a standard RT task with a countdown task in which people know exactly when the movement has to be made in advance. It might be expected to see no need for a strong proactive inhibition in this second condition as compared to the first one, which would, in turn, be reflected in the MEP and, maybe also, in the EEG.
Experiments were conducted on 11 subjects using EEG, EMG of the first dorsal interosseous (FDI) muscle and transcranial magnetic stimulation (TMS). Subjects performed trials of the two RT paradigms with and without TMS. In the TMS trials, pulses were delivered at specific times during the movement preparation. Changes in MEPs and in the event-related desynchronization (ERD) patterns were assessed.
On average, a clear motor cortical beta ERD was observed in the EEG signal starting about 400ms prior to movement onset which was similar for both tasks. Despite the fact that beta ERD is generally thought to reflect increased excitability, MEPs in contrast were suppressed by an average of 37% prior to movement (maximum at 200ms), in both paradigms, again with no difference between the tasks.
The lack of correlation between EEG and MEP data suggest that they probe different aspects of cortical processing prior to the onset of simple limb movements. Surprisingly, neither of them reflects the difference in temporal uncertainty between processes involved in reactive and predictive tasks.

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