When citing an abstract from the 2018 annual meeting, please use the format below.

[Authors]. [Abstract Title]. Program No. XXX.XX. 2018 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2018. Online.

Nanosymposium

010. Brain Size, Structure, and Evolution

Location: SDCC 33

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 010.01

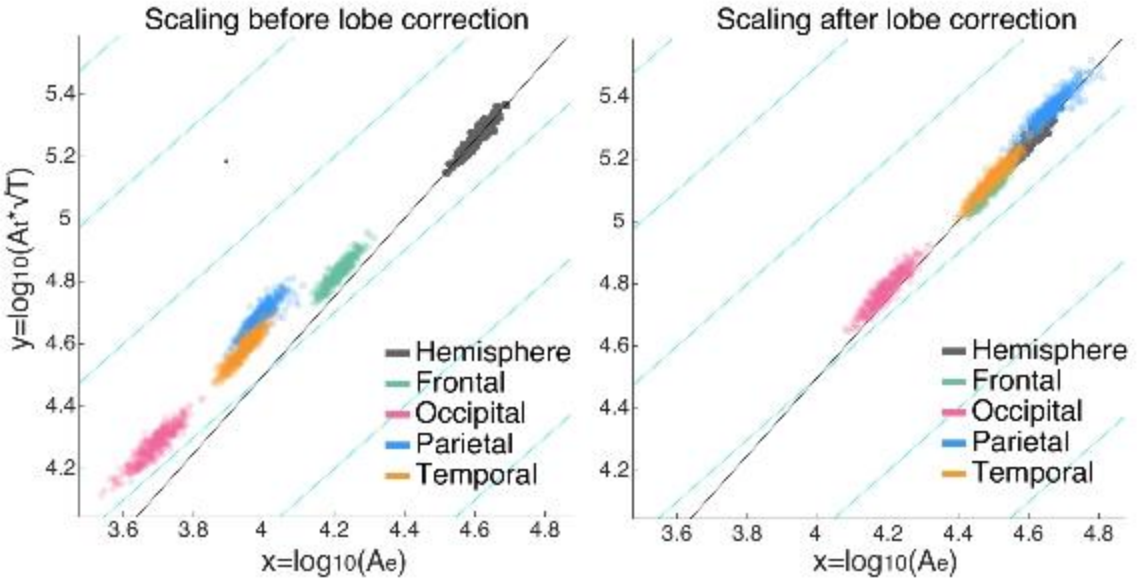
Topic: A.10. Development and Evolution

Support: CNPq N º 12/2017 312837/2017-8

Title: Scaling laws in the gyrification of the cerebral cortex across different regions: Universality and heterogeneity in aging, health and disease

Authors: *B. MOTA[1], J. NECUS[2], 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 that folding in mammalian cerebral cortices follows a universal scaling law that can be derived from a simple physics model[1]. The same scaling law also applies across healthy humans, irrespective of gender, but with a systematic decrease with age in the value of an offset parameter unconstrained by theory[2].
This scaling law, however, in principle only relates measures of complete cortical hemispheres. There are known systematic variations in morphology between different brain regions, and region-specific changes with age. It is therefore of interest to extend our analyses to different cortical regions. Do regions separately still follow the universal rule followed by the whole cortices? How does the gyrification in different regions compare, within and across cortices? How are they affected by age and disease?
Here we present a scaling method for directly comparing the morphology of sub-divisions of the cortical surface in a self-consistent and size-independent way, based on a topological invariant. We chose to segment each cortical hemisphere into lobes, as the definition of each is tolerably consistent across both individuals and species. We then compute the properties of a synthetic complete hemisphere derived from each lobe, with the same gyrification index, average thickness and Gaussian curvature density.
We show that different lobes are morphologically diverse but obey the same scaling law that was observed across human subjects and across mammalian species. This is also the case for subjects with Alzheimer's disease. The age-dependent offset changes at similar rates for all lobes in healthy subjects, but differ most dramatically in the temporal lobe in Alzheimer's disease. This suggests that, while morphological parameters can vary locally across the cortical surface, the processes that drive cortical gyrification, likely involving long-range white matter connectivity, are global.



[1] Mota B, Herculano-Houzel, S (2015) Science, 349 (6243) 74
[2] Wang Y, Necus J, Kaiser M, Mota B (2016) PNAS 113 (45)

Disclosures: J. Necus: None. **Y. Wang:** None.

Nanosymposium

010. Brain Size, Structure, and Evolution

Location: SDCC 33

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 010.02

Topic: A.10. Development and Evolution

Support: NIH Grant 1R21MH115327-01

Title: The co-evolution of brain and cognition within the hominin clade is orchestrated by Transposable Elements

Authors: *F. MACCIARDI[1], O. RICKARDS[2], E. GUICHARD[3], A. BOATTINI[3], F. MARTINI[4], G. GUFFANTI[5]
[1]Pyschiatry and Human Behavior, Univ. of California, Irvine, Irvine, CA; [2]Univ. of Rome "Tor Vergata", Rome, Italy; [3]Univ. of Bologna, Bologna, Italy; [4]Univ. of Florence, Florence, Italy; [5]Harvard Med. Sch., Belmont, MA

Abstract: Recent findings and the progressive re-evaluation of Neanderthals' (HN) behavior are suggesting that they may have had a rather sophisticated cognition, despite probably different from that of Anatomically Modern Humans (AMH). The development of high cognitive functions - like art, broadly defined here as the symbolic representation of the world, or language - requires that a neural machinery be in place that can support these functions. Evidences from archeological investigations showing that Neanderthals had a complex behavior indirectly support the hypothesis of their cognitive abilities, but we are also growing our knowledge of their possible neural structure. Past paleoneurological investigations have shown that Neanderthal's brains were different from AMHs' in their shape and regional architecture, despite a similar global size and volume. AMHs present with a globular rather than an elongated brain, probably due to a marked bulging of the frontal lobes and expanded cerebellar interconnections with prefrontal, premotor, and superior-posterior parietal cortices, which also project densely to the putamen of the basal ganglia. These local adaptations suggest a marked reorganization of the neural architecture in regions that are relevant for cognitive abilities. Integrating evidence from paleoanthropology, comparative genomics, epigenetics and neuroimaging we set out to identify genes associated with such a specific brain evolution and we found that non-coding, regulatory RNA genes rather than protein-coding gene variants are the most important genomic elements that are implicated in these anatomical and possibly functional differences between Neanderthals and AMHs. Our results, however, suggest a more complex pattern, where Neanderthals and AMHs share a very high proportion of cognitively-related genomic elements while only a small set of them appear AMH specific, supporting the hypothesis that Neanderthals already had a cognitively ready brain. These shared genomic elements may then be a common feature of hominins, setting the origin of a symbolic thought deeper in time.

Disclosures: F. Macciardi: A. Employment/Salary (full or part-time):; university of californita. **O. Rickards:** None. **E. Guichard:** None. **A. Boattini:** None. **F. Martini:** None. **G. Guffanti:** None.

Nanosymposium

010. Brain Size, Structure, and Evolution

Location: SDCC 33

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 010.03

Topic: A.10. Development and Evolution

Support: Shriners Hospital for Children- North California

Title: Cortical interlaminar astrocytes in mammalian evolution

Authors: *C. FALCONE[1], M. WOLF-OCHOA[2], S. AMINA[3], P. MANGER[4], V. MARTÍNEZ CERDEÑO[5]
[1]UC Davis, Dept. of Pathology and Lab. Med., Sacramento, CA; [2]Univ. of California-Davis,

Davis, CA; [3]Dept. of Psychiatry and Behavioral Sci., Univ. of California, Davis, Sacramento, CA; [4]3University of the Witwatersrand, Johannesburg, South Africa; [5]1Department of Pathology and Lab. Med., UC Davis, Sacramento, CA

Abstract: Astrocytes increasing complexity during evolution has been suggested to play a key role in the development of human cognitive abilities. Among mammalian astroglial subtypes, Interlaminar Astrocytes (IA) are a novel trait of the primate brain. IA extend long interlaminar processes from layer I to layers II-IV, following the neuronal columnar organization of the cerebral cortex. These astrocytes are known to express GFAP. We assessed the molecular characteristics of IA in the macaque cortex using markers for different neural cell types. We found that they express astrocytic markers S100β and Aqp4, but they do not express neuronal, oligodendroglial, nor microglial markers (NeuN, Sox10, Iba1), verifying their astrocytic nature. Furthermore, they do not seem to be actively proliferating, as they do not express Ki67. IA are known to be present postnatally, but when exactly they appear during development is not known. We assayed IA appearance and differentiation during development, by inspecting specific prenatal and postnatal developmental stages of macaque (*Macaca mulatta*) and human. We found an increasing morphological complexity throughout development, in both species. IA have also been observed in ventral basal cortex of some non-primate species, belonging to bats (*Chiroptera*) and treeshrews (*Scandentia*). We examined if IA are present in related species of bat, treeshrew, insectivore, prosimian, and old and new world primates, never investigated before. We found that IA are present in the ventral cortex of several species of bat, treeshrews and insectivores, and in both dorsal and ventral cortex of all the primate species analyzed. To assess whether IA are unique to primates and their closely related orders, or rather the product of a convergent evolution, we assessed IA presence in species evolutionarily far from primates, such as carnivores (Carnivora), ungulates (Artiodactyla), whales and dolphins (Cetacea), and elephants (Proboscidea), and found that IA are present in the ventral areas of whale and elephant cerebral cortex. Data obtained from this project will shed light on the IA role in the evolution and development of the human cerebral cortex. We will next unravel the molecular mechanisms responsible for the appearance of IA in primate and specifically in the human cerebral cortex.

Disclosures: C. Falcone: None. **M. Wolf-Ochoa:** None. **S. Amina:** None. **P. Manger:** None. **V. Martínez Cerdeño:** None.

Nanosymposium

010. Brain Size, Structure, and Evolution

Location: SDCC 33

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 010.04

Topic: A.10. Development and Evolution

Support: Kavli Foundation for the ENIGMA-Kavli Organizational Support Program

NIH BD2K grant U54 EB020403

Title: ENIGMA-ODS: Managing international neuroscience collaborations in the ENIGMA consortium using organic data science

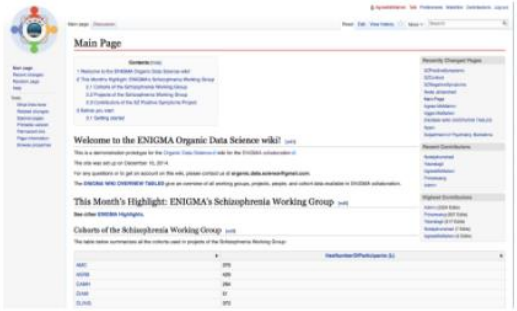
Authors: *A. MCMAHON[1], D. GARIJO[2], R. ESPIRITU[2], F. RASHID[3], M. JANG[2], T. PATTED[2], V. RATNAKAR[2], Y. GIL[2], P. THOMPSON[3], N. JANHANSHAD[3]
[2]Information Sci. Inst., [3]Imaging Genet. Ctr., [1]USC, Marina del Rey, CA

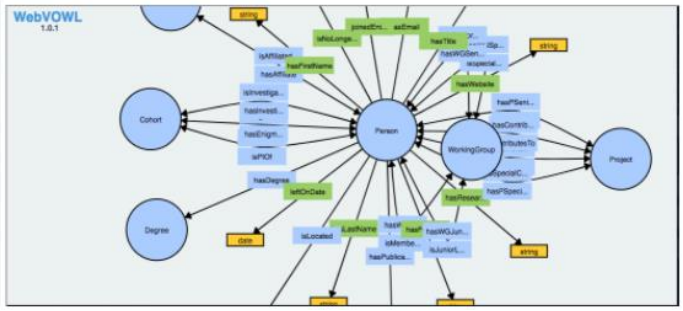
Abstract: Introduction: The Enhancing Neuro-Imaging Genetics through Meta-Analysis (ENIGMA) Consortium is a multifaceted network aiming to leverage legacy neuroimaging data in a collaborative environment. As this multi-center program expands, a customized information system is needed to track collaborations, cohorts, and other pertinent metadata. With over 100 concurrent projects, 37 working groups, and nearly 900 contributors, the programmatic support helps to maintain efficient collaboration and productivity. This unique informatics challenge motivated the creation of the ENIGMA Organic Data Science (ENIGMA-ODS) platform to support dynamic consortium activity.
Methods: ENIGMA-ODS is an extension of the USC Information Sciences Institute's ODS framework. ODS is based on Semantic MediaWiki (http://semantic-mediawiki.org/), which combines the collaborative environment of a wiki with ontological representations using semantic web standards. The ENIGMA-ODS ontology is structured into six modules for describing key consortium entities and their relationships in a machine-readable manner.
Results: ENIGMA's rapid growth demanded a comprehensive information system to expedite research projects and group management. ENIGMA-ODS includes features to query registered cohorts, generate tables and text for publications, and manage ENIGMA's working group organization.
Conclusions: ENIGMA consists of over a hundred concurrent projects, necessitating systematic information management that is specific to collaborative neuroscience efforts. ENIGMA-ODS supports efficient research, aiming to empower analyses of large-scale distributed brain data worldwide.

Growth of the ENIGMA Consortium 2009-2018

	2009	2012	2016	2017	2018	Increase in 1 Year (2016-2017)
Working Groups	3	9	20	37	42	85%
Members*		25	500	900	980	80%
Sites*		20	200	230	234	15%
Countries		12	33	39	40	18%
Projects	1	18	50	166	160	232%
Datasets*		8,000	30,000	53,000	75,549	77%
Publications		2	15	36	44	140%
Twitter Followers			90	310	402	244%
Newsletter Audience			52	705	773	1255%

*estimation





Disclosures: D. Garijo: None. **R. Espiritu:** None. **F. Rashid:** None. **M. Jang:** None. **T. Patted:** None. **V. Ratnakar:** None. **Y. Gil:** None. **P. Thompson:** None. **N. Janhanshad:** None.

Nanosymposium

010. Brain Size, Structure, and Evolution

Location: SDCC 33

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 010.05

Topic: A.10. Development and Evolution

Support: NIH Grant 5U54EB020403

Title: Common genetic influences on human cerebral cortical thickness and surface area support the radial unit hypothesis and implicate Wnt signaling influencing areal expansion

Authors: *J. L. STEIN[1], K. GRASBY[2], N. JAHANSHAD[3], J. PAINTER[2], D. P. HIBAR[4], L. COLODRO CONDE[2], J. BRALTEN[5], P. M. THOMPSON[6], S. MEDLAND[2], T. ENIGMA CONSORTIUM[7]
[1]Dept of Genet. & Neurosci. Ctr., UNC-Chapel Hill, Chapel Hill, NC; [2]QIMR Berghofer, Brisbane, Australia; [3]Neurol., IGC-INI @ USC, Marina Del Rey, CA; [4]Janssen R&D, LLC, San Diego, CA; [5]Radboud Univ., Nijmegen, Netherlands; [6]Stevens Inst. for Neuroimaging & Informatics, Univ. of Southern California (USC), Marina del Rey, CA; [7]USC, Marina del Rey, CA

Abstract: The expansion of the cerebral cortex in humans relative to other non-human primates is thought to underlie our uniquely human cognitive capabilities. Although studies in model organisms have identified many genes influencing cortical thickness and surface area, there are relatively few human loci known to influence brain morphology. Here, we performed a GWAS (genome-wide association study) meta-analysis of the thickness and surface area of cortical

regions derived from structural magnetic resonance imaging (MRI) scans using a meta-analysis of 50 cohorts comprising 32,967 individuals.
Results from the meta-analyses demonstrate that common variation substantially influences the architecture of the human cortex (h^2_{snp}>0.2 for global thickness and surface area) and supports the findings from twin studies that genetic influences on thickness and surface area are largely independent. We identified 11 loci influencing global surface area and 6 loci influencing global cortical thickness (P<5e-8). There is a significant enrichment for loci influencing surface area within regulatory regions of the developing fetal brain, specifically in the neural progenitor associated germinal zone. Genetic loci influencing global cortical surface area cluster near genes involved in chromatin modification and neural progenitor proliferation. This provides support for the radial unit hypothesis in humans and suggests that common genetic variation impacts progenitor associated gene regulation during fetal development to influence post-natal surface area. In addition, significant positive genetic correlations were observed between global surface area and intelligence, Parkinson's disease, and educational attainment. Significant negative genetic correlations were found between cortical measures and major depression, neuroticism, ADHD, and insomnia.
We identified 187 additional loci influencing gyral-defined regional surface area, controlling for global surface area, and 18 loci influencing regional thickness, controlling for global thickness. Loci impacting regional surface area cluster near genes involved in the Wnt pathway, a known pathway influencing areal identity. In all, these findings identify genomic loci and suggest genes involved in human cortical development, indicate biological pathways and cell types involved in human cortical areal expansion, and suggest genetic links between cognitive traits and neuropsychiatric diseases with specific brain regions.

Disclosures: J.L. Stein: None. **K. Grasby:** None. **N. Jahanshad:** None. **J. Painter:** None. **D.P. Hibar:** A. Employment/Salary (full or part-time):; Janssen R&D, LLC. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Janssen R&D, LLC. **L. Colodro Conde:** None. **J. Bralten:** None. **P.M. Thompson:** None. **S. Medland:** None. **T. ENIGMA Consortium:** None.

Nanosymposium

010. Brain Size, Structure, and Evolution

Location: SDCC 33

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 010.06

Topic: A.10. Development and Evolution

Support: U54EB020403 (NIH)
Max Planck Society

Title: Unearthing the evolutionary history of genetic variants influencing human cortical surface area

Authors: *A. K. TILOT[1], S. LIU[2], S. BROTMAN[2], T. ENIGMA-EVOLUTION WORKING GROUP[3], J. BRALTEN[5], K. GRASBY[7], J. PAINTER[7], L. COLODRO CONDE[7], P. LIND[7], N. JAHANSHAD[8], D. P. HIBAR[9], S. MEDLAND[7], P. M. THOMPSON[4], T. ENIGMA CONSORTIUM[3], S. E. FISHER[1,6], J. L. STEIN[2]
[1]Language and Genet. Dept., Max Planck Inst. for Psycholinguistics, Nijmegen, Netherlands; [2]Dept of Genet. & Neurosci. Ctr., UNC-Chapel Hill, Chapel Hill, NC; [4]Stevens Inst. for Neuroimaging & Informatics, [3]Univ. of Southern California (USC), Marina del Rey, CA; [5]Human Genet., [6]Donders Inst. for Brain, Cognition and Behaviour, Radboud Univ., Nijmegen, Netherlands; [7]QIMR Berghofer Med. Res. Inst., Brisbane, Australia; [8]Neurol., IGC-INI @ USC, Marina del Rey, CA; [9]Janssen R&D, LLC, San Diego, CA

Abstract: The size, shape, and cognitive abilities of the modern human brain reflect the cumulative effects of selective pressures over our evolutionary history. Endocranial volume increased dramatically since our last common ancestor with Old World monkeys, with further human-specific refinements to brain shape occurring during the last 300,000 years. These structural changes were accompanied by increasingly sophisticated tool use, spoken language, world-wide migrations, and agriculture. Using data from the ENIGMA Consortium, we investigated the modern impact of this journey on cortical surface area and thickness for 34 regions in over ~33,000 individuals.
We identified polymorphisms within five sets of genomic regions that experienced selective pressure at varying time points (range: 30 Mya to 50 kya), and assessed their contributions to the heritability of cortical surface area and thickness. Using stratified linkage-disequilibrium (LD) score regression, we studied single-nucleotide polymorphisms (SNPs) within human fetal brain enhancer elements that emerged since our last common ancestor with macaques, and found that they make unusually large contributions to the heritability of cortical surface area. These findings were significant even after controlling for the general category of fetal brain enhancers. Effects were found not only for global surface area but also for many gyrally-defined regions after controlling for global surface area, likely due to enhancer impact on progenitor proliferation and neurogenesis genes.
To capture the effects of allele frequency changes over more recent timescales, we applied two measures reflecting selective pressure either 30 (Qx) or 2 (singleton density scores, SDS) kya. The Qx analysis revealed evidence of selection for greater global surface area, and a regional effect on the superior temporal area. Using SDS, we found that positively selected alleles were associated with increased superior temporal and inferior frontal surface area. In sum, selective pressures over the last 30 million years of human evolution may have shaped different aspects of modern human brain structure, from ancient effects on broad growth patterns to very recent influences on regions critical for our capacity for language.

Disclosures: A.K. Tilot: None. **S. Liu:** None. **S. Brotman:** None. **T. ENIGMA-Evolution Working Group:** None. **J. Bralten:** None. **K. Grasby:** None. **J. Painter:** None. **L. Colodro Conde:** None. **P. Lind:** None. **N. Jahanshad:** None. **D.P. Hibar:** A. Employment/Salary (full

or part-time):; Janssen R&D, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Janssen R&D, LLC. **S. Medland:** None. **P.M. Thompson:** None. **T. ENIGMA Consortium:** None. **S.E. Fisher:** None. **J.L. Stein:** None.

Nanosymposium

010. Brain Size, Structure, and Evolution

Location: SDCC 33

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 010.07

Topic: A.10. Development and Evolution

Support: NIH Grant U54 EB020403

Title: Tensor distribution function fractional anisotropy reveals microstructural disruption across all white matter in 22q11.2 deletion syndrome

Authors: *J. VILLALON REINA[1], P. M. THOMPSON[1], C. E. BEARDEN[2], K. MARTÍNEZ[3], E. ENIGMA-22Q11 WORKING GROUP[4]
[1]Neurol., USC Imaging Genet. Ctr., Marina Del Rey, CA; [2]UCLA, Los Angeles, CA; [3]2Department of Child and Adolescent Psychiatry, Hosp. Gen. Universitario Gregorio Marañón, Madrid, Spain; [4]USC, Los Angeles, CA

Abstract: The Tensor Distribution Function (TDF) is a multi-tensor diffusion MRI (dMRI) reconstruction method that models the microstructure by fitting the distribution of all possible tensors within a voxel, making it more robust to complex fiber configurations (crossing, kissing, diverging fibers). Diffusion Tensor Imaging (DTI) on the other hand is limited when fiber orientations are not unique, which occurs in 90% of the brain. 22q11.2 Deletion Syndrome (22q11DS) is caused by a ~3Mb microdeletion in chromosome 22, is the most common copy number variant associated with schizophrenia and its high penetrance might help unveil mechanisms underlying the development of schizophrenia.
We performed the largest dMRI study of 22q11DS to date by comparing fractional anisotropy (FA) derived from TDF and from DTI. Previous DTI studies based on small samples have found differences in DTI-FA between 22q11DS probands and healthy controls (HC). Still, conflicting findings have been reported across studies. To tackle these uncertainties, we pooled data from the ENIGMA-22q Working Group (WG), a global multi-site collaborative network. We analyzed harmonized DTI-FA and TDF-FA across the brain's white matter (WM) between 22q11DS probands and age-matched HC by using the ENIGMA-DTI protocol (http://enigma.ini.usc.edu/protocols/dti-protocols/). The ENIGMA-22q WG contributed dMRI datasets from the USA (four sites), Australia (one site), the Netherlands (two sites), and the UK (two sites). We analyzed 594 participants from 9 sites: 334 individuals with 22q11DS (mean age: 16.8 ± 6.4, 153 females) and 260 HC (mean age: 16.5 ± 8, 123 females).

Differences between 22q11DS probands and HC were estimated for each site and for DTI-FA and TDF-FA by calculating the Cohen's d effect sizes in 18 standardized WM ROIs. Sex, age and age^2 were used as covariates in all linear regressions. We conducted a meta-analysis of the effect sizes across sites for each DTI measure, by ROI. Contrary to DTI, for TDF all WM ROIs showed lower FA in 22q11DS, with highest effect sizes in the corpus callosum, corona radiata, and internal capsules.

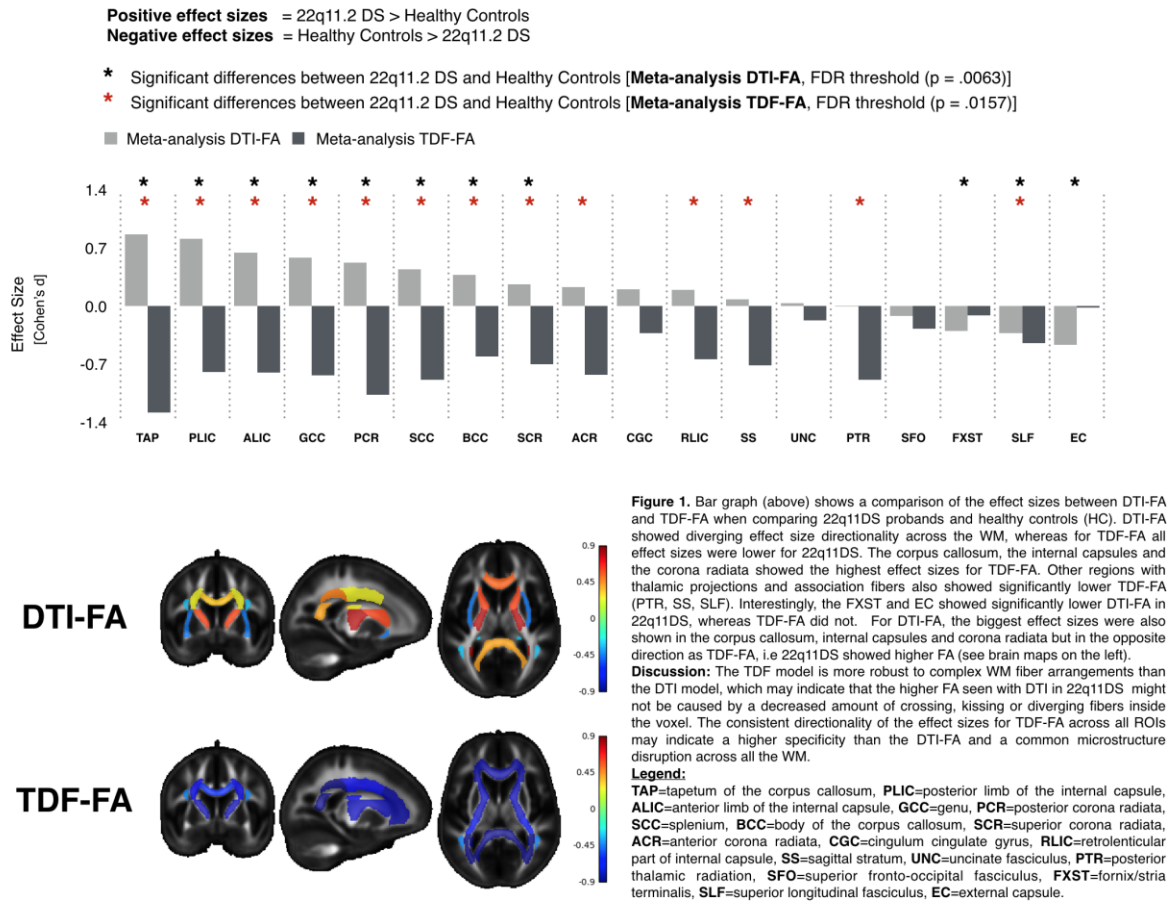


Figure 1. Bar graph (above) shows a comparison of the effect sizes between DTI-FA and TDF-FA when comparing 22q11DS probands and healthy controls (HC). DTI-FA showed diverging effect size directionality across the WM, whereas for TDF-FA all effect sizes were lower for 22q11DS. The corpus callosum, the internal capsules and the corona radiata showed the highest effect sizes for TDF-FA. Other regions with thalamic projections and association fibers also showed significantly lower TDF-FA (PTR, SS, SLF). Interestingly, the FXST and EC showed significantly lower DTI-FA in 22q11DS, whereas TDF-FA did not. For DTI-FA, the biggest effect sizes were also shown in the corpus callosum, internal capsules and corona radiata but in the opposite direction as TDF-FA, i.e 22q11DS showed higher FA (see brain maps on the left).
Discussion: The TDF model is more robust to complex WM fiber arrangements than the DTI model, which may indicate that the higher FA seen with DTI in 22q11DS might not be caused by a decreased amount of crossing, kissing or diverging fibers inside the voxel. The consistent directionality of the effect sizes for TDF-FA across all ROIs may indicate a higher specificity than the DTI-FA and a common microstructure disruption across all the WM.
Legend:
TAP=tapetum of the corpus callosum, **PLIC**=posterior limb of the internal capsule, **ALIC**=anterior limb of the internal capsule, **GCC**=genu, **PCR**=posterior corona radiata, **SCC**=splenium, **BCC**=body of the corpus callosum, **SCR**=superior corona radiata, **ACR**=anterior corona radiata, **CGC**=cingulum cingulate gyrus, **RLIC**=retrolenticular part of internal capsule, **SS**=sagittal stratum, **UNC**=uncinate fasciculus, **PTR**=posterior thalamic radiation, **SFO**=superior fronto-occipital fasciculus, **FXST**=fornix/stria terminalis, **SLF**=superior longitudinal fasciculus, **EC**=external capsule.

Disclosures: J. Villalon Reina: None. **P.M. Thompson:** None. **C.E. Bearden:** None. **K. Martínez:** None. **E. ENIGMA-22q11 Working Group:** None.

Nanosymposium

011. Network Interactions: Oscillations and Synchrony: EEG Studies

Location: SDCC 24

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 011.01

Topic: B.09. Network Interactions

Support: NIH Grant R01 NS025529
CHDI Foundation A-5552
ONR N00014-07-1-0903
ARO W911NF-16-1-0474
Simons Center for the Social Brain
Naito Foundation
KAKEN: Grant-in-Aid for Research Activity start-up

Title: Beta oscillations in the primate striatum predict repetitive negative decision-making states induced by microstimulation

Authors: *K.-I. AMEMORI[1,2], S. AMEMORI[2], D. J. GIBSON[2], A. M. GRAYBIEL[2]
[1]Primate Res. Inst., Kyoto Univ., Inuyama, Japan; [2]McGovern Inst. for Brain Res. and Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: Persistent thoughts inducing abnormally repetitive and pessimistic decisions are often signs and symptoms of obsessive-compulsive disorder (OCD). Although OCD has been associated with regional hyperactivity in the corticostriatal network, it remains unclear if there is oscillatory neural activity involved in OCD-like symptoms. To search for neural oscillations involved in abnormally repetitive decisions, we developed a multi-site neural recording technique using chronically implanted electrodes, which can be used either for microstimulation or for recording of local field potentials (LFPs). With this method, we recorded LFPs from the caudate nucleus (CN) while we delivered microstimulation in the CN or the cingulate cortex of macaques performing an approach-avoidance (Ap-Av) conflict task that had been used to test the anxiety-like behavior. We defined the LFP as exhibiting beta oscillations if the power spectrum of the LFP was significantly greater than the analytic pink noise spectrum (Bonferroni corrected) within the beta band (13-28 Hz). Among 958 CN LFP activities, most of them (81%) exhibited beta oscillations. The majority of the beta oscillations (86%) were deemed to be task-related, as they exhibited significant changes in magnitude during the decision period. We focused on these task-related beta oscillations and artificially induced repetitive choice patterns by microstimulating the CN or cingulate cortex. In 23 of 112 CN stimulation sessions, the microstimulation induced pessimistic decisions with abnormally repetitive choice patterns. By contrast, microstimulation of the cingulate cortex did not induce such abnormal repetition, suggesting that, in this cingulate-striatal circuitry, the CN is involved specifically in the generation of repetitive decisions. We recorded 113 CN LFPs simultaneously during the 23 effective CN stimulation sessions in which we could induce abnormally repetitive choices. Among them, 16 LFPs exhibited significant differences in the magnitude of beta oscillations before the decision period depending on the preceding choices, potentially representing a pessimistic state that affects repetitive choice pattern. Importantly, the group mean of the differential spectra of the 16 LFPs showed a significant increase in the beta band during trials in which the CN microstimulation induced abnormal repetition. We thus found that modulation of CN beta oscillation was correlated with the behavioral effect, suggesting that CN beta oscillation could be part of an underlying mechanism to induce stereotyped and repetitive decision-making patterns, resembling OCD.

Disclosures: K. Amemori: None. **S. Amemori:** None. **D.J. Gibson:** None. **A.M. Graybiel:** None.

Nanosymposium

011. Network Interactions: Oscillations and Synchrony: EEG Studies

Location: SDCC 24

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 011.02

Topic: B.09. Network Interactions

Support: National Science Foundation Graduate Research Fellowship Program
University of California, San Diego Chancellor's Research Excellence Scholarship
Sloan Research Fellowship
Whitehall Foundation (2017-12-73)
National Science Foundation (1736028)

Title: Characterization of neural oscillations using a cycle-by-cycle approach

Authors: *S. R. COLE[1], B. VOYTEK[2]
[1]UCSD, La Jolla, CA; [2]Cognitive Sci., Univ. of California San Diego Dept. of Cognitive Sci., La Jolla, CA

Abstract: As a prominent feature of brain recordings, neural oscillations are frequently correlated to both pathologies and healthy behaviors such as movement, sleep, perception, and cognitive performance. Standard approaches for studying these oscillations are based on the Fourier transform, which decomposes a signal into component sinusoids. However, brain rhythms are not strictly sinusoidal nor stationary, as they come and go with varying amplitudes, frequencies, and waveforms. Therefore, decomposition using the Fourier transform does not parsimoniously capture all of the interesting structure present in neural signals. This is suboptimal because nonsinusoidal and nonstationary features of low-frequency cortical oscillations may contain information about physiological processes.
Few analytic approaches have been designed specifically for characterizing the waveform shape of brain oscillations. We present a time-domain approach, complementary to traditional frequency-domain analysis, designed to characterize nonsinusoidal and transient brain rhythms in order to help quantify information missed in conventional, Fourier-based neural signal processing. This novel framework analyzes oscillatory features on a cycle-by-cycle basis, and the necessary code is made open-source as a user-friendly Python toolbox (https://github.com/voytekresearch/neurodsp). For each cycle, the amplitude, period (frequency), and waveform symmetries are quantified. In contrast to conventional "instantaneous" analysis, cycle-by-cycle measures are computed from straightforward features rather than relying on transforms that assume a sinusoidal structure. Importantly, the output also specifies whether the oscillation of interest is present or absent in the signal during each "cycle" period, as it is

unlikely that the oscillator is present throughout the whole duration of the signal. This is important, as estimates of oscillatory features are meaningless if no oscillation is evident.
We apply our method to several data sets. First, we validate our approach on simulated signals containing both oscillatory bursts and noise to show that it outperforms conventional metrics in uncovering the ground-truth oscillatory properties. Second, we differentiated behavioral conditions in several experiments by characterizing experimental recordings of hippocampal theta, motor cortical beta, and visual cortical alpha. Finally, we studied simultaneous recordings of unit activity and hippocampal theta in the CA1 pyramidal layer and uncovered correlations between the theta waveform shape and neuronal network firing.

Disclosures: S.R. Cole: None. **B. Voytek:** None.

Nanosymposium

011. Network Interactions: Oscillations and Synchrony: EEG Studies

Location: SDCC 24

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 011.03

Topic: B.09. Network Interactions

Support: ERC-YStG-676943
ERC-YStG-263584
ANR-16- CE37-0004-04
ANR-14-NEUC-0002-01

Title: Non-linear machine learning and signal models reveal new insights on neural oscillations

Authors: *A. GRAMFORT[1], T. DUPRÉ LA TOUR[2], M. JAS[2], L. TALLOT[3], L. GRABOT[4], T. MOREAU[1], V. DOYERE[3], Y. GRENIER[2], V. VAN WASSENHOVE[5]
[1]Inria, CEA Neurospin, Palaiseau, France; [2]Telecom ParisTech, Paris, France; [3]CNRS-UMR 9197 Neuro-Psi, ORSAY, France; [4]CEA/DSV/I2BM/NeuroSpin/Unicog, Gif-sur-Yvette, France; [5]CEA.DSV.I2BM.Neurospin, Gif Sur Yvette, France

Abstract: Neural oscillations synchronize information across brain areas at various anatomical and temporal scales. While these oscillations are commonly described through power and phase effects in certain frequency bands (alpha, beta, etc.), such descriptions hide the rich nature of signal statistics and morphologies which are modulated by experimental conditions and pathologies. There is a need to embrace non-linear and non-stationary models to better characterize neural oscillations.
Of particular relevance for neuroscience, slow fluctuations of brain activity have been shown to affect high frequency neural activity, by regulating the excitability level of neural populations. Such cross-frequency-coupling can take several forms. In the most frequently observed type, the power of high frequency activity is time-locked to a specific phase of slow frequency

oscillations, yielding phase-amplitude-coupling (PAC). Even when readily observed in neural recordings, such non-linear coupling is particularly challenging to formally characterize. Typically, neuroscientists use band-pass filtering and Hilbert transforms with ad-hoc correlations. To explicitly address current limitations one can use a probabilistic signal modeling approach, for which statistical inference is fast and well-posed. To statistically model PAC, it consists of non-linear auto-regressive models which estimate the spectral modulation of a signal conditionally to a driving signal. This conditional spectral analysis enables easy model selection and clear hypothesis-testing by using the likelihood of a given model. Thanks to our non-linear signal model, we provide novel neuroscientific insights on previously reported PAC phenomena, capturing two mechanisms in PAC: influence of amplitude and directionality estimation. References: [1] Dupré la Tour T, Tallot L, Grabot L, Doyère V, van Wassenhove V, Gramfort A (2017) Non-linear auto-regressive models for cross-frequency coupling in neural time series. PLOS Computational Biology 13(12) Code: https://pactools.github.io/ with some recent work on morphology learning: [2] Jas M, Dupré La Tour T, Şimşekli U, Gramfort A (2017) Learning the Morphology of Brain Signals Using Alpha-Stable Convolutional Sparse Coding. NIPS Conf. Code: https://alphacsc.github.io/

Disclosures: A. Gramfort: None. **T. Dupré La Tour:** None. **M. Jas:** None. **L. Tallot:** None. **L. Grabot:** None. **T. Moreau:** None. **V. Doyere:** None. **Y. Grenier:** None. **V. van Wassenhove:** None.

Nanosymposium

011. Network Interactions: Oscillations and Synchrony: EEG Studies

Location: SDCC 24

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 011.04

Topic: B.09. Network Interactions

Support: Academy of Finland

Title: Characterizing networks of human cortical phase synchronization with MEG/EEG: Technical challenges and exciting results

Authors: *J. M. PALVA[1], S. PALVA[2]
[1]Univ. Helsinki, Helsinki, Finland; [2]HiLife, Neurosci. Ctr., Univ. of Helsinki, Helsinki, Finland

Abstract: Inter-areal functional connectivity (FC), and neuronal phase synchronization in particular, is thought to constitute a key systems-level mechanism for coordination of neuronal processing and communication between brain regions. Evidence to support this hypothesis has been gained largely using invasive electrophysiological approaches. In humans, neuronal activity can be non-invasively recorded only with magneto- and electroencephalography (MEG/EEG), which have been used to assess FC networks with high temporal resolution and whole-scalp

coverage. MEG and EEG sensor space connectivity estimates, however, yield little anatomical information and synchronization analyses are affected by field spread and signal mixing, which necessitates the usage of source reconstruction methods in MEG/EEG data analysis. Nevertheless, residual mixing after source reconstruction, "source leakage", is a fundamental confounder also for FC analyses in the MEG/EEG source space. We will present how signal mixing leads to two distinct kinds of false-positive observations: artificial interactions (AI) caused directly by mixing and spurious interactions (SI) arising indirectly from the spread of signals from true interacting sources to nearby false loci. To date, several interaction metrics have been developed to solve the AI problem, but the SI problem has remained largely intractable in MEG/EEG all-to-all source connectivity studies. We show how the detection of true-positive connections can be improved and the problem of SIs alleviated by using optimized cortical parcellations that maximize reconstruction accuracy and minimize leakage, and by excluding the least reconstructable connections from the analyses. We also show how the remaining SIs can be compensated for by bundling observed FC connections into hyperedges by their adjacency in signal mixing. Finally, we will present data using these approaches indicating that long-range narrow-band phase synchronization within and between multiple frequency bands characterizes visual attention and visual working memory performance. These findings consolidate the putative mechanistic role of long-range synchronization in coordinating systems-level neuronal processing for achieving integrated cognitive functions. References: Palva JM et al. (2018) Neuroimage; Wang SH et al. (2018) Neuroimage; Lobier M et al. (2018) Neuroimage; Korhonen et al. (2014) J Neurosci Meth; Palva JM et al. (2010) PNAS.

Disclosures: J.M. Palva: None. **S. Palva:** None.

Nanosymposium

011. Network Interactions: Oscillations and Synchrony: EEG Studies

Location: SDCC 24

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 011.05

Topic: B.09. Network Interactions

Support: NIH R01MH106174
NIH RO1EB022889)
NSF CRCNS-1131850
U.S. Department of Veterans Affairs N9228-C
NIH R01NS045130
Fulbright Graduate Study Award
Carney Institute for Brain Science Graduate Research Award

Title: Human, modeling and animal studies uncover novel mechanisms and meaning of transient neocortical beta (15-29 Hz) events

Authors: *H. SHIN[1], R. LAW[2], M. A. SHERMAN[2], S. HAEGENS[4], S. TSUTSUI[2], S. LEE[2], M. HAMALAINEN[5], C. I. MOORE[2], S. R. JONES[3]
[1]Brown University, Neurosci., Providence, RI; [2]Neurosci., [3]Dept. of Neurosci., Brown Univ., Providence, RI; [4]Ctr. for Cognitive Neuroimaging, Donders Inst. for Brain, Cognition & Behaviour, Nijmegen, Netherlands; [5]Massachusetts Gen. Hosp., Harvard Med. Sch., Charlestown, MA

Abstract: Beta oscillations (15-29Hz) are among the most prominent signatures of brain activity. Beta power is predictive of healthy and abnormal behaviors, including perception, attention and motor action. In non-averaged signals, beta can emerge as transient high-power 'events' lasting <150ms. Combining human magnetoencephalography, computational modeling, and local field potential recordings in animal models, we've found that spontaneous neocortical beta events had a stereotypical waveform that emerged from the integration of nearly synchronous bursts of excitatory synaptic drive targeting proximal and distal dendrites of pyramidal neurons (Sherman et al., 2016). The defining mechanism of a beta event was a strong distal drive that lasted one beta period (~50 ms). More recently, we've shown that functionally relevant differences in averaged beta power in primary somatosensory neocortex reflect a difference in the number of high-power beta events per trial, i.e. event rate, more so than event power, duration and frequency span (Shin et al., 2017). Specifically, the greater the number of prestimulus beta events, the less likely a threshold-level tactile stimulus would be perceived. Further, beta events occurring close to the stimulus were more likely to impair perception. These results were remarkably homologous between human and mice recordings, implying a generalizable principle: An increased propensity of beta events predicted the failure to effectively transmit information through specific neocortical representations. Ongoing modeling work suggests this failed transmission is mediated by the recruitment of long-lasting supragranular inhibition occurring during beta events (Law et al., *in prep*). In total, our results provide new insights into the circuit mechanisms and functional meaning of this prominent neocortical dynamic.

Disclosures: H. Shin: None. **R. Law:** None. **M.A. Sherman:** None. **S. Haegens:** None. **S. Tsutsui:** None. **S. Lee:** None. **M. Hamalainen:** None. **C.I. Moore:** None. **S.R. Jones:** None.

Nanosymposium

011. Network Interactions: Oscillations and Synchrony: EEG Studies

Location: SDCC 24

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 011.06

Topic: B.09. Network Interactions

Support: MH095984

Title: Quantifying oscillatory frequency and its role in visual perception and top-down control

Authors: *J. SAMAHA[1,2], A. WUTZ[3], D. MELCHER[4], B. R. POSTLE[5]
[1]UW Madison, Madison, WI; [2]Psychology, Univ. of California, Santa Cruz, Santa Cruz, CA; [3]Picower Inst. for Learning and Memory, MIT, Cambridge, MA; [4]Univ. of Trento, Rovereto, Italy; [5]Univ. of Wisconsin–Madison, Madison, WI

Abstract: Neural oscillations are a pervasive feature of mesoscopic brain recordings and are thought to play an important role in perception and cognition. Oscillatory activity in the brain is most frequently characterized in terms of its amplitude and phase. Although this has led to many important findings regarding the role of these parameters in perception and top-down control, the dominant frequency of narrow-band oscillations may also index important physiological and computational processes. We describe recently introduced techniques for quantifying peak oscillatory frequency in a time-varying manner and apply these methods to better understand the role of alpha-band (8-13 Hz) frequency in shaping temporal integration windows in visual perception. Occipital alpha frequency shows substantial variation across individuals and relative stability within an individual. These individual differences are predictive of the temporal resolution of visual perception, as assessed via two-flash fusion thresholds, revealing that higher alpha frequencies correspond to greater temporal resolution. Time-resolved measurement of alpha frequencies across trials revealed substantial variability, which was also predictive of perceptual performance, indicating that spontaneous, trial-to-trial variability in alpha frequency impacts perception. To understand if variation in alpha frequency is stochastic or if it can be guided by top-down factors such as task demands, we developed two tasks: one that encouraged temporal integration across stimuli, and another that encouraged temporal segregation. Using MEG recordings, we found that occipital alpha frequency decreased when visual task demands required temporal integration compared with segregation. Together, these results provide evidence for a link between the alpha rhythm and temporal windows of perceptual processing, and, for the first time, suggest that alpha frequencies can be modulated by task demands so as to strategically regulate the temporal resolution of visual perception.

Disclosures: J. Samaha: None. **A. Wutz:** None. **D. Melcher:** None. **B.R. Postle:** None.

Nanosymposium

011. Network Interactions: Oscillations and Synchrony: EEG Studies

Location: SDCC 24

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 011.07

Topic: B.09. Network Interactions

Support: Royal Society International Exchanges

Title: The importance of capturing the speed of Alpha activity

Authors: *A. MAZAHERI
Psychology, Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Alpha oscillations (~10 Hz) are the most predominant activity present in electrophysiological signals measured at the scalp. A vast number of published studies over the last decade have now reported the amplitude modulation of alpha activity to play a pivotal role in many cognitive processes such as attention, language and memory. The majority of these studies, barring a few exceptions, treat alpha activity as the mean power between 8-12 Hz. Here, I will provide evidence that the dynamics and nuances of alpha activity might not be fully captured by looking at the average power within a bandwidth. I will also provide empirical evidence that alpha has a peak frequency which fluctuates from moment to moment and individual to individual, with this variability being functionally meaningful. I will then demonstrate the utility of estimating peak alpha frequency and its variability in both basic research (source separation) as well as a potential clinical tool. Finally, I will argue that capturing the peak alpha frequency within a band is not a trivial endeavour, with many caveats to take into consideration. As such, I will propose a simple method for estimating peak alpha frequency which can possibly circumvent some of the pitfalls of other approaches and demonstrate its robustness using both simulated and real data.

Disclosures:

Nanosymposium

011. Network Interactions: Oscillations and Synchrony: EEG Studies

Location: SDCC 24

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 011.08

Topic: B.09. Network Interactions

Title: The multiple oscillation detection algorithm (MODAL) characterizes non-stationary neural signals across species

Authors: *A. WATROUS[1], J. JACOBS[2]
[2]Dept. of Biomed. Engin., [1]Columbia Univ., New York, NY

Abstract: Neural oscillations are typically analyzed using methods that assume the continuous presence of an oscillatory signal with variable amplitude and a fixed frequency. While these methods have illuminated how neural oscillations coordinate cognitive processes, more recent evidence indicates that these assumptions are violated in many neural systems. For instance, there is a shift in the frequency of phase coupling during human spatial and temporal memory retrieval (Watrous et al., 2013a), the dominant human hippocampal “theta” rhythm occurs in discontinuous bouts compared to rodent theta (Watrous et al., 2013b), and there is considerable variability in the dominant frequency of human alpha oscillations (Haegens et al., 2014), which

itself may shift to support perceptual operations (Wutz et al., 2018). These findings motivate the development of new approaches which are able to track non-stationary neural oscillations. Here, we describe a new oscillation detection algorithm ("MODAL"), which tracks the presence and characteristics of neural oscillations in adaptively identified band(s). Going beyond existing methods, MODAL provides the instantaneous power, phase, and frequency of signals in each band that exceed the background spectrum. Analyzing rodent CA1 recordings, we demonstrate that MODAL blindly identifies the canonical ~8Hz theta rhythm and its variation. Further, we describe a study that utilized MODAL to provide the first evidence for phase-coding of human single neuronal firing to slow theta oscillations during virtual navigation. These studies highlight possible avenues for future research using MODAL to characterize how non-stationary neural oscillations vary across behaviors, brain regions, individuals, and species. Given that non-stationary oscillations appear to be particularly prominent in humans, MODAL and other algorithms that carefully track oscillatory dynamics are likely to reveal novel insights into how oscillations support human cognition.

Disclosures: A. Watrous: None. **J. Jacobs:** None.

Nanosymposium

011. Network Interactions: Oscillations and Synchrony: EEG Studies

Location: SDCC 24

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 011.09

Topic: B.09. Network Interactions

Support: Sloan Research Fellowship
Whitehall Foundation [2017-12-73]
NSF [1736028]

Title: Parameterizing neural power spectra

Authors: *T. DONOGHUE[1], M. HALLER[2], E. PETERSON[3], P. VARMA[4], P. SEBASTIAN[5], R. GAO[6], T. J. NOTO[8], R. T. KNIGHT[9], A. SHESTYUK[10], B. VOYTEK[7]
[1]Cognitive Sci., UC San Diego, La Jolla, CA; [2]Helen Wills Neurosci. Inst., Helen Wills Neurosci. Inst., Berkeley, CA; [3]Cognitive Sci., U.C. San Diego, San Diego, CA; [4]Electrical Engin., Univ. of California, Berkeley, Berkeley, CA; [5]UCSD, San Diego, CA; [6]Cognitive Sci., Univ. of California San Diego Dept. of Cognitive Sci., San Diego, CA; [7]Cognitive Sci., Univ. of California San Diego Dept. of Cognitive Sci., La Jolla, CA; [8]Ward Building 13-270, Northwestern Univ., Chicago, IL; [9]Univ. of California Berkeley, Berkeley, CA; [10]Res. and Develop., Nielsen, Berkeley, CA

Abstract: Electrophysiological signals across species and recording scales exhibit both periodic and aperiodic features. Periodic oscillations have been widely studied and linked to numerous

physiological, cognitive, behavioral, and disease states, while the aperiodic "background" 1/f component of neural power spectra has received far less attention. Most analyses of oscillations are conducted on *a priori*, canonically-defined frequency bands without consideration of the underlying aperiodic structure, or verification that a periodic signal even exists in addition to the aperiodic signal. This is problematic, as recent evidence shows that the aperiodic signal is dynamic, changing with age, task demands, and cognitive state. This means that standard analytic approaches easily conflate changes in the periodic and aperiodic signals with one another because the aperiodic parameters—along with oscillation center frequency, power, and bandwidth—are all dynamic in physiologically meaningful, but likely different, ways. In order to overcome the limitations of traditional narrowband analyses and to reduce the potentially deleterious effects of conflating these features, we have recently introduced a novel algorithm for automatic parameterization of neural power spectral densities (PSDs) as a combination of the aperiodic signal and putative periodic oscillations. Notably, this algorithm requires no *a priori* specification of band limits and accounts for potentially-overlapping oscillations while minimizing the degree to which they are confounded with one another. This algorithm has been validated on both synthetic data, and human labelled examples, and is amenable to large-scale data exploration and analysis. Here we demonstrate a series of use cases and applications of this approach. Applying it to resting state magnetoencephalography (MEG) data captures patterns of individual variation of both oscillatory and aperiodic features, including replications of age related slowing of alpha peak frequency and "flattening" of aperiodic, 1/f slope. We also show novel findings regarding patterns of oscillatory activity across the cortical surface, including systematic shifts in oscillatory characteristics, and characteristic inter-relations between bands. This method can be used in task designs, as demonstrated by applying it to trial by trial data from cognitive tasks with concurrent electroencephalography (EEG) recordings, showing how it can be used to capture task related changes in both oscillatory dynamics, and aperiodic activity, notably being able to separate out these two effects while also capturing individual variation.

Disclosures: T. Donoghue: None. **M. Haller:** None. **E. Peterson:** None. **P. Varma:** None. **P. Sebastian:** None. **R. Gao:** None. **T.J. Noto:** None. **R.T. Knight:** None. **A. Shestyuk:** None. **B. Voytek:** None.

Nanosymposium

011. Network Interactions: Oscillations and Synchrony: EEG Studies

Location: SDCC 24

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 011.10

Topic: B.09. Network Interactions

Support: Data collection was supported by the DARPA Restoring Active Memory (RAM) program (cooperative agreement N66001-14-2-4032)
NIH grant R01-MH104606

Title: Spatial analysis of brain oscillations reveals theta, alpha, and beta traveling waves across the human cortex

Authors: J. JACOBS[1], *H. ZHANG[2], A. WATROUS[3]
[1]Dept. of Biomed. Engin., [2]Biomed. engineering, [3]Columbia Univ., New York, NY

Abstract: Direct recordings from the surface of the human brain has shown that neuronal oscillations at multiple frequencies correlate with detailed aspects of various aspects of behavior including memory, navigation, and sensorimotor processing. Much research in this area separately examined signals from individual electrodes, which ignores the possibility that these oscillations reflect coordinated networks across the cortex. We implemented a new methodology for identifying oscillatory patterns that were simultaneously present across contiguous regions of cortex and then testing whether these independently recorded signals were spatially coordinated using circular statistics. Using this approach, we found that the human cortex contains groups of electrodes that oscillate together at frequencies in the theta and alpha bands. These electrode clusters displayed traveling waves, in which the instantaneous phases of oscillations systematically shifted across the cortical surface, like a wave propagating across the ocean. Traveling waves are widespread in the human brain, as they are present at various frequencies including the theta, alpha, and beta ranges and in all lobes of the neocortex. Theta and alpha traveling waves generally propagated in a posterior-to-anterior direction whereas traveling beta oscillations showed a range of directions. The precision of traveling wave propagation correlated with performance in a memory task, which suggests that this phenomenon is relevant for understanding how different brain regions interact to support memory and cognition. More broadly, our findings suggest that the spatial analysis of the instantaneous phase of oscillations is a useful method because it can identify new types of patterns that cannot be measured with conventional single-electrode methods.

Disclosures: J. Jacobs: None. **H. Zhang:** None. **A. Watrous:** None.

Nanosymposium

011. Network Interactions: Oscillations and Synchrony: EEG Studies

Location: SDCC 24

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 011.11

Topic: B.09. Network Interactions

Support: NIH Grant 5T32MH020002-17
ONR Grant N000141210299

Title: Multichannel recordings in neuroscience: New computational methods for spatiotemporal dynamics

Authors: *L. E. MULLER, T. J. SEJNOWSKI
Computat. Neurobio. Lab. (CNL), Salk Inst., La Jolla, CA

Abstract: With new multichannel recording technologies, neuroscientists can now record from neocortex of awake animals with both high spatial and temporal resolution. Early recordings during anesthesia revealed spontaneous and stimulus-evoked waves traveling across the cortex. While for some time these waves were thought to disappear in awake animals and during normal sleep, our recent work has revealed traveling waves in these complex activity states. Their overall role in neural computation, however, remains poorly understood. In recent work, we have introduced a non-parametric, wideband, phase-based method for detecting traveling waves in noisy multichannel data. The wideband nature of this algorithm minimizes the waveform distortion inherent in narrowband treatments of neural signals. Further, it requires no spatial smoothing, which can create artifactual waves and also confounds the measurement of propagation speeds, a critical observable in establishing the underlying network-level mechanisms for these waves. Finally, through appropriate random shuffling permutation controls, the algorithm quantifies evidence for traveling waves compared to the spatiotemporal patterns expected by chance, allowing a quantitative, moment-by-moment test for traveling waves in high-noise multichannel data. At the scale of a single cortical region, this method has revealed that small visual stimuli consistently evoke waves traveling outward from the point of input to primary visual cortex in the awake monkey (Muller et al., *Nature Communications* 5, 2014). At the whole-brain scale, this method revealed that the 11-15 Hz sleep "spindle", a brain oscillation causally implicated in consolidation of long-term memory, is consistently organized as a global rotating wave traveling in a preferred direction (Muller et al., *eLife* 5, 2016). These results demonstrate that traveling waves can play a role in organizing neural activity during multiple behavioral states. In upcoming work, we aim to address the network-level mechanisms generating traveling waves and complex spatiotemporal patterns, under the general aim of understanding their role in neural computation.

Disclosures: T.J. Sejnowski: None.

Nanosymposium

011. Network Interactions: Oscillations and Synchrony: EEG Studies

Location: SDCC 24

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 011.12

Topic: B.09. Network Interactions

Support: NWO VENI grant 451-14-027

Title: Oscillatory mechanisms—taking into account inter-individual, temporal and spectral variability

Authors: *S. HAEGENS
Ctr. for Cognitive Neuroimaging, Donders Inst. for Brain, Cognition & Behaviour, Nijmegen, Netherlands

Abstract: Here I propose a framework in which oscillations provide the scaffolding for information processing in the brain: allowing for the filtering of incoming information, and successfully routing this information—encoded in spike activity patterns—through the brain. These low-level mechanisms then subserve all sorts of higher-level (cognitive) brain functions. Critical in studying these oscillatory mechanisms, is taking into account the non-stationary nature of these dynamics, as well as inter-individual differences between subjects. Specifically, and in light of the proposed framework, I will here focus on the following issues: (1) Taking into account individual variability in alpha peak frequency (~8-14 Hz), which can differ substantially between subjects, and which additionally fluctuates over time and space, as well as under influence of task demands. This variability has implications for doing group-level power and (especially) phase analyses. (2) Differentiating between oscillatory and non-oscillatory dynamics. Here I will consider the case of high-frequency, broadband dynamics which can be observed in intracranial recordings, and argue that these do not constitute oscillatory processes (as opposed to band-limited dynamics). (3) Stringent tests whether low-frequency dynamics (1-7 Hz) in response to rhythmic inputs constitute entrainment in a strict sense or a more general synchronization, less precisely locked to the input rhythm.These points will all be substantiated using original empirical data, mainly MEG recordings from human subjects performing a temporal and spatial attention task (alpha and low-frequency dynamics) in which they had to detect brief visual and auditory stimuli, as well as intracranial recordings in patients performing a challenging visual decision-making task (alpha and broadband dynamics). Overall, taking into account the inter-individual, temporal and spectral fluctuations of brain rhythms is critical in gaining a further understanding of these mechanisms.

Disclosures: S. Haegens: None.

Nanosymposium

012. Animal Models of Epilepsy

Location: SDCC 1

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 012.01

Topic: B.10. Epilepsy

Support: NREF Research Grant

Title: Modulation of neuronal network remodeling in a translational mouse model of temporal lobe epilepsy by the novel Wnt antagonist XAV939

Authors: *K. GUPTA[1], E. SCHNELL[2]
[1]Oregon Hlth. & Sci. Univ., Portland, OR; [2]Portland VA Med. Ctr., Portland, OR

Abstract: Introduction: Mouse models of mesial temporal lobe epilepsy recapitulate aspects of human epilepsy, which is characterized by neuronal network remodeling in the hippocampal dentate gyrus. We hypothesize that ictal zone hyperactivity triggers transcriptional changes in peri-ictal regions, contributing to network remodeling and epileptogenesis. Understanding the molecular mechanisms underlying functional brain remodeling during the development of epilepsy permits development of therapies to prevent epilepsy in high risk patients. Methods: Seizures were induced by intrahippocampal kainate injection in 3-4-month-old POMC-GFP transgenic mice, in which adult-born dentate granule cells express GFP for approximately 2-weeks after mitosis. Animals also received BRDU 48h-72h after seizure induction. Tissue was analyzed using immunohistochemistry and confocal microscopy, and transcriptome analysis was performed using RNA extracted from anatomically microdissected dentate gyri. Results: Our data demonstrate increased hippocampal neurogenesis and dendritic arborization in the peri-ictal regions and decreased neurogenesis in the ictal zone 2-weeks after injection, when compared to saline-injected (control) hippocampi. To investigate the Wnt pathway's role in neuronal network remodeling, we administered XAV939, a canonical Wnt antagonist, daily for 2-weeks after kainate injection. Preliminary data show a further marked increase in neurogenesis and dendritic length in the peri-ictal regions of mice treated with XAV939. Transcriptome analysis demonstrates that canonical Wnt pathway dysregulation occurs in the dentate gyrus shortly after seizure induction, with differential effects in ictal and peri-ictal regions. These changes may underpin the development of delayed epilepsy in this model. Conclusion: Neuronal network remodeling is critical in the development of epilepsy. We hypothesize that the Wnt pathway is critical to changes induced by ictal activity and are utilizing small molecule modulation of Wnt activity to investigate this pathway as a putative target to prevent the development of epileptic circuits in the hippocampus.

Disclosures: K. Gupta: None. **E. Schnell:** None.

Nanosymposium

012. Animal Models of Epilepsy

Location: SDCC 1

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 012.02

Topic: B.10. Epilepsy

Support: NINDS, NIH

Title: Acute and subacute eeg recordings in a rat model of perinatal ischemic stroke

Authors: *I. M. ELI[1], A. ZAYACHKIVSKY[2], M. COULDWELL[3], F. DUDEK[4]
[1]Univ. of Utah Dept. of Neurosurg., Salt Lake City, UT; [2]Univ. of Utah, Salt Lake City, UT; [3]Dept. of Neurosurg., Univ. of Utah, Salt Lake CIty, UT; [4]Neurosurg., Univ. of Utah, Salt Lake City, UT

Abstract: Ischemic stroke is an important cause of neonatal seizures, which can occur during the first month between of life. Neonatal ischemic stroke can lead to cerebral palsy, cognitive impairment and epilepsy. The development of seizures during the stroke and within weeks afterward poses a significant medical challenge due to their obscure presentation, thus resulting in failure of early identification and treatment. The failure to detect seizures early is postulated to lead to worsening brain injury, thus resulting in poor long-term outcome (e.g., possible epilepsy). Here, we sought to evaluate changes of the EEG in a neonatal rat model of ischemic stroke. We hypothesize that ischemic injury will result in early EEG findings of background suppression and then result over time in acquired epilepsy. We used a rat model of permanent middle cerebral artery occlusion (pMCAo) in postnatal day 8 pups. We obtained EEG recordings using a novel miniature telemetry device to analyze EEG activity patterns, and to compare them with sham procedures entailing a unilateral common carotid artery (CCA) occlusion. We analyzed EEG patterns during acute and sub-acute periods via daily 2-hr recordings for the first 2 weeks, followed by continuous recording for up to 3 months. The preliminary results show that the pMCAO injury result in >50% mortality in the rat cohort due to lack of feeding and severe weight loss in the pups. A sub-cohort develops acute seizures and die <72 hr after pMCAO without loss of weight. The surviving pups develop background suppression, but no acute seizures. We are in the process of analyzing the acute and subacute EEG findings (n=4 pMCAO; n=4 CCA occlusion) and are in the process of obtaining more animals with pMCAO and HI injury.
Supported by grants from NINDS, NIH

Disclosures: I.M. Eli: None. **A. Zayachkivsky:** None. **M. Couldwell:** None. **F. Dudek:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. F. E. Dudek has received consulting fees and equipment discounts from and has equity interest in Epitel, Inc., the company that produced the miniature telemetry transmitters used in this study..

Nanosymposium

012. Animal Models of Epilepsy

Location: SDCC 1

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 012.03

Topic: B.10. Epilepsy

Title: A novel mouse model for ALDH7A1-mediated pyridoxine-dependent epilepsy displays interictal epileptiform discharges and increased delta power

Authors: *T. E. FAUST[1], W. XIN[2], B. J. LEE[4], S. SAHA[3], T. CASH-PADGETT[5], S. DESHPANDE[3], A. BONCI[8], M. W. JONES[9], J. GELINAS[10], C. DAVIS[11], H. JAARO-PELED[6], A. SAWA[7]
[1]Psychiatry, Johns Hopkins Univ. Dept. of Psychiatry and Behavioral Sci., Baltimore, MD; [2]Neurosci., [3]Johns Hopkins Univ. SOM, Baltimore, MD; [4]Psychiatry, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [6]Psychiatry and Behavioral Sci., [7]Dept. of Psychiatry, [5]Johns Hopkins Univ., Baltimore, MD; [8]Office of the Scientific Director, Natl. Inst. On Drug Abuse, Baltimore, MD; [9]Univ. of Bristol, Bristol, United Kingdom; [10]Columbia Univ., New York, NY; [11]Washington State Univ., Spokane, WA

Abstract: Epilepsy is a common neurological problem with a lifetime incidence of 4%. Genetic factors are known to contribute to pathogenesis, but many cases remain described as "idiopathic". Rare single-gene genetic disorders allow for study of the contribution of isolated causal factors to pathophysiology. These studies can also shed light on the close association between epilepsy and other neuropsychiatric disorders such as austism spectrum disorders and schizophrenia. One such rare-genetic form of epilepsy known as pyridoxine-dependent epilepsy is characterized by seizures, as well as cognitive and emotional deficits. This disease has been linked to genetic mutation of aldehyde dehydrogenase 7a1 (*ALDH7A1*). Recently, several models with depletion of ALDH7A1 in zebrafish have been generated to examine molecular profile in the brain. However, the physiological mechanisms linking this gene to seizure risk and brain function remains unknown. We therefore generated ALDH7A1 knockout mice to perform a comprehensive physiological assessment of the effects of ALDH7A1 depletion by combining behavioral, electroencephalographic, and electrophyiological analyses in a mammalian system. We validated the efficacy of ALDH7A1 depletion at both the gene and protein expression levels, and functionally through unbiased RNA-Seq and metabolomics analyses. Consistent with patient phenotypes, ALDH7A1 knockout mice exhibit a variety of behavioral abnormalities affecting multiple functional domains including working memory, sensorimotor gating, and affective behavior. Electroencephalogram studies revealed the presence of interictal epileptiform discharges and increased delta wave amplitude during sleep. Intriguingly, these mice did not display any differences in sleep duration or phases transitions. At the cellular level, we observed changes in the frequency and strength of inhibitory inputs within the cortex. However, ALDH7A1 is not expressed at high levels in neurons, suggesting that other cell types and tissues may be causative to this observed effect. Ongoing experiments will attempt to identify the cellular source of ALDH7A1 dysfunction. This model will serve continued use for investigation of patient pathophysiology.

Disclosures: T.E. Faust: None. **W. Xin:** None. **B.J. Lee:** None. **S. Saha:** None. **T. Cash-Padgett:** None. **S. Deshpande:** None. **A. Bonci:** None. **M.W. Jones:** None. **J. Gelinas:** None. **C. Davis:** None. **H. Jaaro-Peled:** None. **A. Sawa:** None.

Nanosymposium

012. Animal Models of Epilepsy

Location: SDCC 1

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 012.04

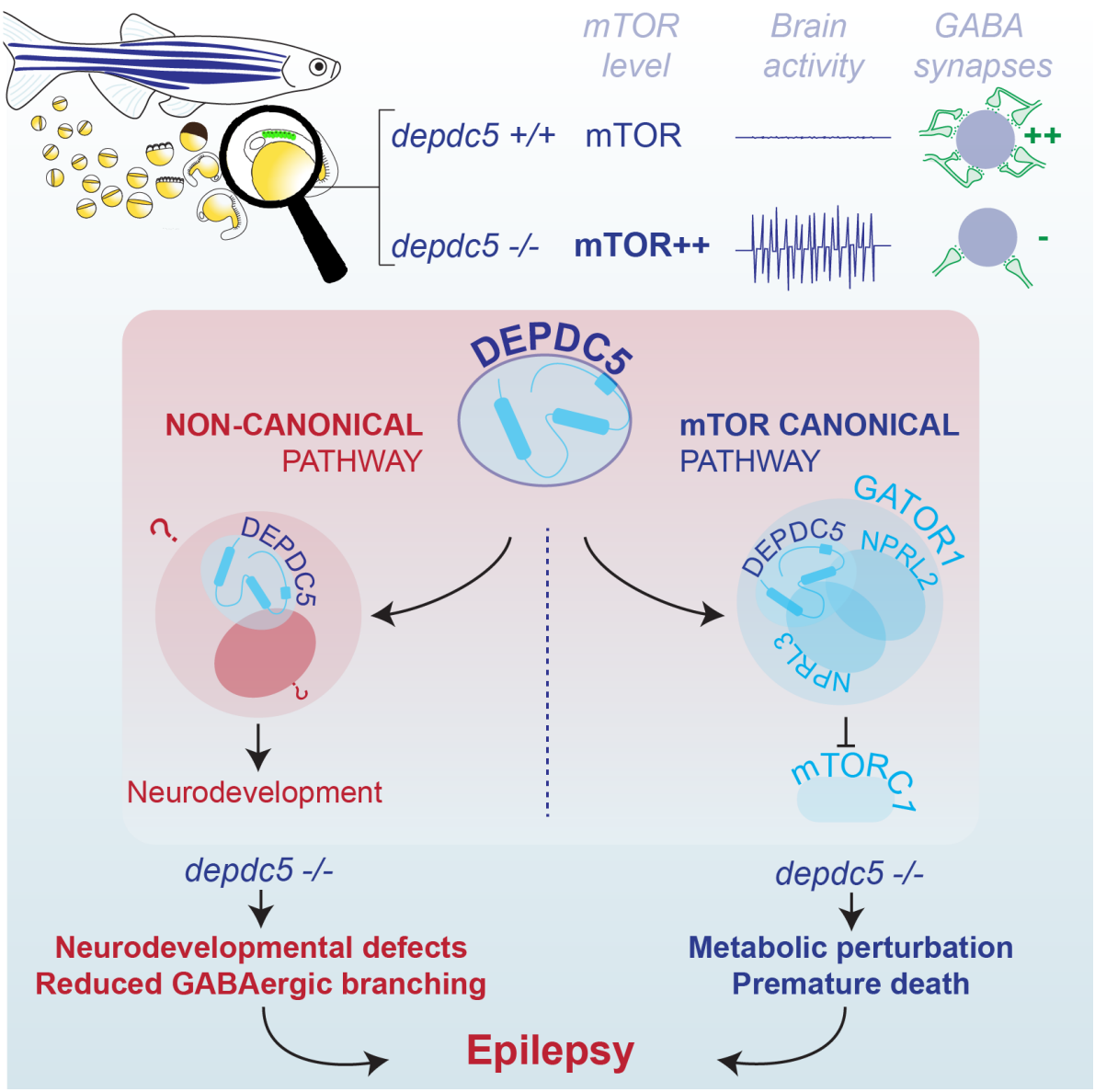
Topic: B.10. Epilepsy

Support: FRQS
Savoy Foundation for Epilepsy

Title: Non-canonical mTOR-independent role of DEPDC5 in regulating GABAergic network development

Authors: *E. SAMARUT[1], A. SWAMINATHAN[2], R. HASAN-ABDI[3], S. RENAULT[3], A. SIEKIERSKA[4], R. RICHÉ[2], M. LIAO[2], P. A. M. DE WITTE[5], C. YANICOSTAS[3], N. SOUSSI-YANICOSTAS[3], P. DRAPEAU[2]
[1]Neurosciences, [2]Crchum, Montreal, QC, Canada; [3]Inserm, Paris, France; [4]Lu Leuven, Leuven, Belgium; [5]Ku Leuven, Leuven, Belgium

Abstract:



Mutations in *DEPDC5* are causal factors for a broad spectrum of focal epilepsies, but the underlying pathogenic mechanisms are still largely unknown. To address this question, a zebrafish *depdc5* knockout model showing spontaneous epileptiform events in the brain, increased drug-induced seizure susceptibility, general hypoactivity and premature death at 2-3 weeks post fertilization as well as the expected hyperactivation of mTOR signaling was developed. Using this model, the role of DEPDC5 in brain development was investigated using an unbiased whole transcriptomic approach. Surprisingly, in addition to mTOR-associated genes, many genes involved in synaptic function, neurogenesis, axonogenesis and GABA network activity were found to be dysregulated in larval brains. Consistently, although no gross defects in brain morphology/neuron loss were observed, immunostaining of *depdc5*-/- brains for several GABAergic markers revealed specific defects in the fine branching of GABAergic network.

Consistently, some defects in *depdc5-/-* could be compensated by treatment with GABA, corroborating that GABA signaling is indeed involved in DEPDC5 pathogenicity. Interestingly, the mTOR-independent nature of the neurodevelopmental defects was demonstrated by the inability of rapamycin to rescue the defects of GABAergic networks observed in *depdc5-/-* brains and conversely, the inability of GABA to rescue the hypoactivity in another genetic model showing mTOR hyperactivation. This study hence provides the first *in vivo*evidence that DEPDC5 plays previously unknown roles apart from its canonical function as an mTOR inhibitor. Moreover, these results propose that defective neurodevelopment of GABAergic network could be a key factor in epileptogenesis when *DEPDC5* is mutated.

Disclosures: E. Samarut: None. **A. Swaminathan:** None. **R. Hasan-abdi:** None. **S. Renault:** None. **A. Siekierska:** None. **R. Riché:** None. **M. Liao:** None. **P.A.M. De witte:** None. **C. Yanicostas:** None. **N. Soussi-yanicostas:** None. **P. Drapeau:** None.

Nanosymposium

012. Animal Models of Epilepsy

Location: SDCC 1

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 012.05

Topic: B.10. Epilepsy

Support: Institute of Translational Health Sciences -
National Center For Advancing Translational Sciences of the National Institutes of Health under Award Number UL1 TR002319
University of Washington School of Pharmacy

Title: Effect of epileptogenesis on mitochondrial dynamics-regulating proteins in two mouse models of temporal lobe epilepsy

Authors: *M. L. BARKER-HALISKI[1], C. KINOSHITA[2], H. S. WHITE[1], R. S. MORRISON[2]
[1]Dept. of Pharm., [2]Dept Neurolog. Surgery, Univ. of Washington, Seattle, WA

Abstract: Healthy mitochondria underlie neuronal health, function and connectivity. Impairment of mitochondrial function can contribute to nervous system disease. Temporal lobe epilepsy (TLE) is the most common form of acquired epilepsy. The 60 Hz corneal kindled mouse model (CKM) of TLE is commonly used in the pursuit of new antiseizure drugs (ASDs). The Theiler's murine encephalomyelitis virus (TMEV) mouse model of TLE is suitable for the discovery of ASDs with novel mechanisms (Barker-Haliski et al, *Epilepsia* 2016b). While much is known about epileptogenesis and response to ASDs in these models, very little is understood about their CNS pathophysiology, despite seemingly similar phenotypic outcomes, e.g. chronic seizures and behavioral comorbidities. The TMEV model exhibits hippocampal sclerosis and mitochondria-dependent oxidative stress; whether mitochondrial dysfunction coincides with neurodegeneration

in the TMEV model is unknown. CKM do not demonstrate hippocampal neurodegeneration; thus, whether and when CKM also exhibit mitochondrial dysfunction is unknown and thus a study goal. Oxidative stress and mitochondrial dysfunction may promote neurodegeneration by directly inducing apoptosis or necrosis; aberrant neuronal loss can then precipitate seizure susceptibility. Further characterization of the CKM and TMEV models may identify novel therapeutic targets for epilepsy. The relative levels of expression of mitochondrial proteins were quantified by western blot in the isolated hippocampus of CKM and TMEV models during and after epileptogenesis. Mitochondrial dynamics-regulating proteins assessed were: dynamin-related protein 1 (Drp1), mitochondrial fission factor (Mff), mitofusin 2 (Mfn2), endophilin B1 (Endo-B1; which is protective in neurons), histone deacetylase 2 (HDAC2; which regulates Endo-B1), and Opa1 (a mitochondrial dynamin-like GTPase). We report significant, time-dependent decreases in hippocampal expression of Endo-B1 b/c, Drp1, and Opa1 (long isoform), 7 days post-TMEV infection; a time of peak acute seizures during the active infection. Conversely in CKM, there were significant, time-dependent increases in the expression of Drp1, Opa1 (short and long isoforms), Mfn2, and Mff at 7 days post-kindling acquisition, a time when mice experience secondarily generalized seizures. This study demonstrates that mitochondrial integrity or function may be differentially affected during epileptogenesis in two etiologically-relevant models of TLE. These data suggest that mitochondrial dysfunction may underlie epileptogenesis and further differentiates the utility of the TMEV model to identify novel ASD mechanisms.

Disclosures: M.L. Barker-Haliski: A. Employment/Salary (full or part-time):; University of Washington. **C. Kinoshita:** A. Employment/Salary (full or part-time):; University of Washington. **H.S. White:** A. Employment/Salary (full or part-time):; University of Washington. **R.S. Morrison:** A. Employment/Salary (full or part-time):; University of Washington.

Nanosymposium

012. Animal Models of Epilepsy

Location: SDCC 1

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 012.06

Topic: B.10. Epilepsy

Support: INPRFM NC123240.1

Title: Randomization of the interpulse interval of low frequency electrical stimulation delays seizure generalization and modifies the spectral power of epileptiform activity in rats

Authors: *F. SANTOS-VALENCIA[1], S. ALMAZAN-ALVARADO[2], A. RUBIO-LUVIANO[2], E. URBINA-TREJO[2], V. MAGDALENO-MADRIGAL[2], A. VALDES-CRUZ[2], D. MARTINEZ-VARGAS[2]

[1]Dept. de Neurociencia, [2]Lab. de Neurofisiologia del Control y la Regulacion, Inst. Nacional de Psiquiatría Ramón de La Fuen, Ciudad de México, Mexico

Abstract: Epilepsy is a common neurological disorder that affects 1-2% of the global population. 30% of epileptic patients do not respond to conventional treatment with anti-epileptic drugs and surgical resection of the epileptic foci is a viable alternative only for a minority. Deep brain stimulation has become a viable treatment proposal, but the optimal parameters are still debated. The objective of the present work was to study the effect of temporal interpulse interval randomization of electrical deep brain stimulation over epileptogenesis. 45 male Wistar rats were implanted with an electrode in the right basolateral amygdala for the induction of electrical amygdaloid kindling (AK), randomized interval non-periodic stimulation (NPS) and electrographic recording. Five groups were formed: 1) AK control (KC), where rats were daily stimulated with AK (train duration 1s, 60Hz, pulses 1ms) until they exhibited three generalized convulsive seizures; 2) NPS (train duration 20 min, 4Hz mean, pulses 0.1ms) delivered before AK stimulus (NPS+K); 3) NPS delivered immediately after AK stimulus (K+ENPR); 4) NPS delivered five minutes after the termination of the afterdischarge (K+NPS) and 5) Periodic stimulation delivered five minutes after the termination of the afterdischarge (K+PS). After the behavioral studies, electrode locations were histologically verified in all rats. It was found that the groups ENP+K and K+ENP had a delay in the development of AK, requiring more stimuli to achieve seizure generalization ($p<0.05$ & $p<0.01$), furthermore seizure severity was diminished, noting a reduction in the relative spectral power of the electrographic recordings of the generalized seizures from 8-12 Hz ($p<0.05$) and absolute spectral power of 0-40 bands ($p<0.01$), on the other hand an increment in the relative spectral power of 12-20 Hz band ($p<0.05$) was noted. Additionally, a reduction of the duration of the clonic phase, the daily afterdischarge duration and a delay in the the behavioral seizure stage progression was observed ($p<0.05$ & $p<0.001$). Interestingly no changes were found when comparing K+PS to KC rats. These results bolster the hypothesis that NPS exerts its anti-epileptogenic effect due to the random interpulse interval and not to other parameters such as mean frequency or intensity. In conclusion, NPS delivered during the development of AK delays the epileptogenic processes and diminished the severity of the seizures, possibly by interfering with their mechanisms of generalization.

Disclosures: F. Santos-Valencia: None. **S. Almazan-Alvarado:** None. **A. Rubio-Luviano:** None. **E. Urbina-Trejo:** None. **V. Magdaleno-Madrigal:** None. **A. Valdes-Cruz:** None. **D. Martinez-Vargas:** None.

Nanosymposium

012. Animal Models of Epilepsy

Location: SDCC 1

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 012.07

Topic: B.10. Epilepsy

Support: NINDS NS 079274

Title: Pharmacogenetic control of status epilepticus and epileptiform discharges in an animal model of temporal lobe epilepsy

Authors: *A. ZAYACHKIVSKY, M. W. COULDWELL, F. DUDEK
Neurosurg., Univ. of Utah, Salt Lake City, UT

Abstract: This study aimed to test the hypothesis that inhibiting the electrical activity of excitatory hippocampal neurons with a Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) system will suppress both status epilepticus (SE) and subsequent epileptiform activity in an animal model of temporal lobe epilepsy. Transgenic DREADD mice, R26-LSL-hM3Di-DREADD for neuronal silencing were crossed with mice that expressed cre recombinase in EMX1-positive cells, a gene specifically expressed in glutamatergic cells in cortex and hippocampus. The cross of EMX1-cre with R26-LSL-hM3Di-DREADD resulted in strong expression of DREADD receptors in excitatory neurons and their processes in the hippocampus, but not in cortex or other brain areas. The expression spanned the entire length of both hippocampi. To obtain proof-of-concept data for efficacy of silencing, the intrahippocampal kainate (KA) model was used to induce epilepsy. KA was injected into the right hippocampus (CA1,n=8), and the mice were implanted with telemetry for EEG recording. The treatment resulted in bilateral electrographic SE with acute and sub-acute seizures that lasted for 48-72 h. CNO (20 mg/kg) was administered 24 h after KA injection, which caused cessation of SE in all mice. Administration of CNO to Emx1-IRES-Cre mice without DREADD receptor did not affect electrical activity (n=2). Administration of vehicle to Emx1-IRES-Cre mice expressing DREADD receptor also did not suppress EEG activity (n=2). To test the effect on epileptiform discharges, we injected several more mice (n=5) with intrahippocampal KA. All mice soon developed brief epileptiform discharges that occurred several times per hour and have been described by others as surrogate markers for epilepsy. Administration of CNO in drinking water (10 mg/kg/day) to three of animals suppressed the epileptiform discharges and normalized the background EEG. The data from these proof-of-concept experiments so far support the hypothesis that DREADD-mediated inhibition of excitatory hippocampal neurons can suppress KA-induced acute and subacute seizure activity and can also reduce subsequent epileptiform discharges. Future studies will aim to determine if CNO selectively decreases spontaneous recurrent seizures in DREADD-expressing mice.

Disclosures: A. Zayachkivsky: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **M.W. Couldwell:** None. **F. Dudek:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Epitel, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Epitel, Inc. F. Consulting Fees (e.g., advisory boards); Epitel, Inc.

Nanosymposium

013. Alzheimer's Disease and Other Dementias: Genetic Analyses

Location: SDCC 25

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 013.01

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

Support: R01 AG O36400
U01 AG046139
U01AG046170

Title: Use of brain homogenate RNA expression data to identify novel cell-type specific alterations in Alzheimer's disease

Authors: *I. S. PIRAS[1], P. D. COLEMAN[2], M. J. HUENTELMAN[1]
[1]Translational Genomics Res. Inst., Phoenix, AZ; [2]ASU-Banner Neurodegenerative Res. Ctr., Tempe, AZ

Abstract: Cell type resolution gene expression changes are critical to assess in neurological disease due to the heterogeneity within the brain. The generation of such data requires labor and cost intensive approaches (i.e laser capture microdissection, LCM) typically at the sacrifice of sample size. We describe herein a bioinformatics approach that is able to leverage expression profiling data from brain homogenate to derive cell type specific differential expression. Our approach is able to identify expression differences that were previously only seen using LCM, demonstrating the utility of our method to expand the knowledge of brain disease gene expression changes without the need for generation of additional cell specific data.
We utilized an LCM-derived RNA expression database from mouse cortex (Zhang et al. J Neurosc 34, 11929-47) to create a cell type enrichment expression score for each gene in the transcriptome. The database includes RNA profiling of 22,458 genes in 6 cell types: astrocytes (*A*), neurons (*N*), microglia (*M*), endothelial (*E*), and Oligodendrocytes (O). We classified the DEGs from: middle temporal gyrus (MTG), temporal cortex (TCX), BA22, BA10, BA44, hippocampus (HIP), and cerebellum (CBE) in AD and controls.
We classified 11,994 DEGs detecting 50 gene classes. The "Mixed" genes (not specific cell expression), were the most represented (67.7%), followed by N (9.1%), E (5.8%), M (5.7%), A (4.6%) and O (3.1%). "N" genes were mostly downregulated in AD cases, and "E" genes were mostly upregulated, especially in the temporal area. "M" genes were upregulated in the temporal area and BA44, and slightly downregulated in BA10, HIP and CBE. "N" genes were especially enriched with the "*GABAergic"* pathway (MTG, TCX, HIP). Specific pathways for EC were: "*Angiogenesis" and "Hemostasis"* (MTG and TCX). "M" genes were enriched for Immune Pathways (MTG, TCX, BA44, CBE). "O" genes were enriched for Glycosaminoglycan metabolism in TCX, MTG, and CBE.

We detected class of genes cell-specific functionally related, and we found novel pathways not identifiable from the bulk homogenate results. We observed a deregulation of N genes, with the prevalence of “GABAergic” pathway. The upregulation of “M” seems specific to temporal area and BA44, as well as the enrichment in Immune System genes. We detected in Oligodendrocytes, only in specific regions, an enrichment of genes involved in Glycosaminoglycan metabolism, involved in amyloid formation in AD. Our approach affords the advantage of cell type level interrogation of the transcriptome using bulk RNA profiling which lends itself to more cost and time effective studies that should have increased statistical power.

Disclosures: I.S. Piras: None. **P.D. Coleman:** None. **M.J. Huentelman:** None.

Nanosymposium

013. Alzheimer's Disease and Other Dementias: Genetic Analyses

Location: SDCC 25

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 013.02

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

Title: Structural study of PSEN1 mutations close to active site to explain loss-of-function in Alzheimer's disease

Authors: *M. CORREDOR[1], P. ARAQUE-MARIN[2]
[1]Biol. Inst., Univ. of Antioquia, Medellin, Colombia; [2]Univ. EIA, Envigado, Colombia

Abstract: Mutations in proteins associated with neurodegeneration are the cause of heterogeneous diseases, producing various symptoms, disorders and disease, from motor to cognitive levels. Alzheimer's disease (AD) is an excellent example. The enzymatic complex of γ-secretase is responsible for the transmembrane cleavages of approximately 91 substrates, among them the amyloid precursor protein (APP), generates a peptide with a size of 40 to 42 amino acids, to develop Aβ-amyloid peptide (Aβ), being oligomerized to generate senile plaques. The AD may be familial FAD or sporadic SAD. FAD mutations have been identified in the genes that translate to proteins: presenilin-1 (PSEN1), presenilin-2 (PSEN2) and amyloid precursor protein (APP) [1]. Therefore, this type of AD does not have a defined pathogenic mechanism and is presumed the gain of function when cutting the APP by PSEN1 in the active site of the enzyme γ-secretase, producing the toxic peptide (β Amyloid) and subsequently forming senile plaques. Notwithstanding it occurs faster compared with patients with load for late-onset AD (LOAD), but still do not have clearness about it [2], [3].
In this investigation, we have analyzed in silico several mutations of subunit presenilin-1 (PSEN1), exactly the amino acids near to catalytic site in both TM6 and TM7 α-helix. Using computational chemistry, more specifically, the hybrid of Quantum Mechanics/Molecular Mechanics (QM/MM), we examined A246E, L248P, L248R, L250V, Y256S, A260V, V261F mutations belong to TM6 and L381V, G384A, F386I, F386S, F388L mutations belong to TM7.

Those mutations cause AD and APP precipitation, suggesting that they are critical for structural stability and crucial in the efficiency of enzymatic activity on APP. We suggest in those analyzed mutation the change of conformational structure, affecting the active site, previous the access of APP, preventing the normal cleavage of protein. The results support that structural alterations in PSEN1 affect protease activity in AD.
References [1] Berezovska, Oksana, et al. "Familial Alzheimer's disease presenilin 1 mutations cause alterations in the conformation of presenilin and interactions with amyloid precursor protein." Journal of Neuroscience 25.11 (2005): 3009-3017. [2] Shen, Jie, and Raymond J. Kelleher. "The presenilin hypothesis of Alzheimer's disease: evidence for a loss-of-function pathogenic mechanism." Proceedings of the National Academy of Sciences 104.2 (2007): 403-409. [3] Bentahir, Mostafa, et al. "Presenilin clinical mutations can affect γ-secretase activity by different mechanisms." Journal of neurochemistry 96.3 (2006): 732-742.

Disclosures: M. Corredor: None. **P. Araque-Marin:** None.

Nanosymposium

013. Alzheimer's Disease and Other Dementias: Genetic Analyses

Location: SDCC 25

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 013.03

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

Support: Tietze Foundation-UW
Ellison Foundation-UW
NIH AG005136
BrightFocus Foundation: A2018656S

Title: Probing the role of SORL1 and endocytic network dysfunction in AD pathogenesis using human neuronal models

Authors: *J. E. YOUNG[1], A. KNUPP[1], R. MARTINEZ[1], S. ROSE[1], B. ROLF[2], C. KEENE[1], S. JAYADEV[2]
[1]Pathology, [2]Neurol., Univ. of Washington, Seattle, WA

Abstract: The purpose of this study is to determine whether genetic variants associated with AD risk in the *SORL1* gene lead to endosomal network dysfunction and cellular AD phenotypes in human neurons. Endosomal abnormalities are documented in post-mortem AD brain tissue and multiple endocytic regulatory genes are associated with increased AD risk in population studies. *SORL1* is a vesicular trafficking gene that functions in transporting cargo between endosomes, Golgi, lysosomes, and the plasma membrane. *SORL1* plays an integral in trafficking amyloid beta and the amyloid precursor protein through the endocytic network and loss of *SORL1* is documented in AD brain tissue. Previously, we have used human induced pluripotent stem cell

(hiPSC)-derived neurons to show that deficiencies in *SORL1* expression induction correlate with the presence of AD-associated variants in non-coding regions of *SORL1*. Here, we show that in hiPSC-derived neural cells either expressing a *SORL1* shRNA or CRISPR/Cas9 edited for complete loss of SORL1 we observe increased amyloid beta peptides, reduced transferrin recycling, and increased size of Rab5+ endosomes. In collaboration with the UW Alzheimer's Disease Research Center, we have identified AD patients with *SORL1* coding variants and are generating hiPSCs from these patients. We will assay hiPSC-derived neurons from *SORL1* variant carriers for endosomal phenotypes and use CRISPR/Cas9 gene-editing to correct the variants to determine whether the predicted pathogenic variant leads to endocytic dysfunction in human neurons. To assess whether cumulative burden of AD risk variants in the endocytic pathway predict endocytic phenotypes, we will derive hiPSC-neurons from cases of autopsy confirmed late-onset AD with high risk burdens of AD-associated SNPS in loci involving endocytic genes. We hypothesize that a higher endocytic risk burden will lead to stronger cellular phenotypes in derived neurons. This work will investigate a functional genotype-phenotype relationship of genetic variants in the endosomal network, which is known to be disrupted early in AD pathogenesis. Investigating this driver of disease pathogenesis and how it relates to human genetic variation is critical in the development of new and precision treatments for AD.

Disclosures: J.E. Young: None. **A. Knupp:** None. **R. Martinez:** None. **S. Rose:** None. **B. Rolf:** None. **C. Keene:** None. **S. Jayadev:** None.

Nanosymposium

013. Alzheimer's Disease and Other Dementias: Genetic Analyses

Location: SDCC 25

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 013.04

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

Support: F31 AG055264
K99/R00 AG044469
R01 AG055581
R01 AG056622
NIRG-15-362799
A2017457S
P30AG049638

Title: Brain-specific repression of AMPKα1 alleviates memory deficits and synaptic failure in a mouse model of Alzheimer's disease

Authors: *H. R. ZIMMERMANN[1], W. YANG[3], T. MA[2]
[1]Wake Forest Sch. of Med., Winston-Salem, NC; [2]Intrnl. Medicine-Geriatrics, Wake Forest Sch. of Med., Winston Salem, NC; [3]Wake Forest Baptist Med. Ctr., Winston Salem, NC

Abstract: Alzheimer's disease (AD) is the most common form of dementia, and the molecular mechanisms that underlie AD pathophysiology remain unclear. AMP-activated protein kinase (AMPK) is a Ser/Thr kinase that functions as a central energy sensor to maintain cellular energy homeostasis. Furthermore, AMPK integrates several signaling pathways controlling *de novo* protein synthesis (mRNA translation) which is vital for long-term synaptic plasticity and memory formation. Dysregulation of energy homeostasis and *de novo* protein synthesis are both implicated in AD. AMPK is a heterotrimeric protein with a catalytic α subunit and regulatory β/γ subunit. The α subunit of AMPK exists in two isoforms: α1 and α2, and their roles in AD are unknown. Analysis of *Post Mortem* brain tissue from human AD and a transgenic mouse model revealed significant increases in AMPKα1 expression in AD conditions. To investigate if restoration of AMKα1 levels can improve AD pathophysiology, AMPKα1 protein levels were selectively reduced in late development in the forebrain of Tg19959 AD model mice to generate AMPKα1(+/-)/Tg19959 double mutant mice. All experiments were blinded and replicates were based on previously published studies. Cognitive assessment by Morris Water Maze (MWM) and Novel Object Recognition (NOR) tasks of these mice aged (6-9 m) revealed AD-associated impairments of cognition were alleviated by AMPKα1 reduction. Consistently, hippocampal long term potentiation (LTP) failure in the Tg19959 condition was prevented in by AMPKα1 supression. Analysis of dendritic spine morphology revealed the hippocampal abnormalities in theTg19959 model mice were restored with genetic reduction of AMPKα1, and Transmission electron microscopy (TEM) showed a restoration of the AD-associated deficits in post-synaptic density (PSD) and polyribosome counts in double mutant mice. Additionally, Surface SEnsing of Translation (SUnSET) and western blot assays show that AMPKα1 reduction ameliorates the AD-associated impairments of *de novo* protein synthesis. Our results demonstrate that restoration of AMPKα1 levels ameliorates the behavioral and synaptic plasticity impairments in a mouse model of AD, as well as restore AD associated abnormal synaptic morphology. Our findings indicate AMPKα1 dysregulation as a molecular mechanism underlying AD pathophysiology, and providing insights into a potential novel therapeutic strategy.

Disclosures: H.R. Zimmermann: None. **W. Yang:** None. **T. Ma:** None.

Nanosymposium

013. Alzheimer's Disease and Other Dementias: Genetic Analyses

Location: SDCC 25

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 013.05

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

Support: R01 AG030142
R01 AG030142
AARF-16-433173

Title: Role of Unc5c, an Alzheimer's risk gene in late-onset Alzheimer's disease in a novel mouse model

Authors: *D. KARUNAKARAN[1], K. R. SADLEIR[1], S. KEMAL[1], L. K. CUDDY[1], J. POPOVIC[1], R. J. WATTS[2,3], J. K. ATWAL[2], R. J. VASSAR[1]
[1]Northwestern Univ., Chicago, IL; [2]Dept. of Neurosci., Genentech, South San Francisco, CA; [3]Denali Therapeut. Inc., South San Francisco, CA

Abstract: Alzheimer's disease (AD) is characterized by amyloid plaques, neurofibrillary tangles, and synaptic and neuronal loss. Recently, a rare autosomal dominant coding mutation, T835M, was discovered in the Un-coordinated 5c (*UNC5C*) netrin receptor gene that segregated with late-onset AD (LOAD). T835M alters a conserved amino acid in the hinge region of the UNC5C death domain, suggesting the mutation may increase apoptosis. Indeed, in primary hippocampal neurons, overexpression of UNC5C T835M increased cell death in response to neurotoxic stimuli including beta-amyloid (Aβ). These results suggest a mechanism by which UNC5C T835M may confer increased risk of LOAD, however the effects of this mutation in an AD animal model have not yet been explored. We hypothesize that the T835M mutation predisposes to LOAD by exacerbating neuronal death, as observed in the 5XFAD brain, via increased sensitivity to Aβ-induced neurotoxicity and UNC5C death domain activation. Toward this end, we generated a mouse knock-in (KI) model of Unc5c T835M and crossed it with the 5XFAD mouse model of amyloid pathology and neuron loss. Our preliminary results show that homozygous KI mice are very similar to WT littermate controls in terms of the histology, protein and RNA expression or in cell death. However, proteomics analysis of KI and wildtype mice brains showed upregulation of apoptotic proteins and down-regulation of neuronal proteins. Moreover, when neurons were counted in NeuN-stained brain sections of $Unc5c^{KI/KI}$;5XFAD mice, we observed that ~40% of neurons were lost in cortical layer 5 of $Unc5c^{KI/KI}$;5XFAD compared to $UNC5C^{+/+}$;5XFAD mice. Neuron loss in $Unc5c^{KI/KI}$;5XFAD mice correlated strongly with the presence of Aβ deposits in layer 5. Primary KI neurons showed an increased cell death in the presence of cytotoxic stressors. We are further investigating mechanisms of cell death and distal phenotypes in 5XFAD; Unc5c T835M KI mice by biochemical, cellular, and behavioral approaches. Although neuron loss is a cardinal feature of AD, the molecular mechanism of cell death in AD is still unclear. We expect our results to provide valuable insight into the role of UNC5C T835M mutation in Aβ-associated cell death, and thereby identify novel therapeutic targets to prevent neuron loss in AD.

Disclosures: D. Karunakaran: None. **K.R. Sadleir:** None. **S. Kemal:** None. **L.K. Cuddy:** None. **J. Popovic:** None. **R.J. Watts:** None. **J.K. Atwal:** None. **R.J. Vassar:** None.

Nanosymposium

013. Alzheimer's Disease and Other Dementias: Genetic Analyses

Location: SDCC 25

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 013.06

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

Support: Legacy Research Foundation Grant

Title: A role for decreased DNA methylation in mediating high-fat diet and diabetic effects on hippocampal and cortical neurodegeneration

Authors: *D. M. OSBORNE, J. W. VANDER VELDEN, D. BOISON
Legacy Hlth. Res., Portland, OR

Abstract: Obesity and Type 2 Diabetes (T2D) are leading predisposing environmental factors for the development of neurodegenerative diseases, like Alzheimer's disease (AD). A nutritional environment heavily comprised of fat and sugar may alter epigenetics, specifically decrease methylation, resulting in increased expression of genes related to neurodegeneration that would otherwise be repressed. We used a chronic high-fat/high-sugar diet to examine its impact on methylation and neurodegenerative markers in 6-month and 13-month old male mice with T2D. We found a chronically hypomethylated state in the hippocampus by way of decreased 5-methylcytosine (5mc) staining in both 6- and 13-month old mice, with similar results found in the cerebral and entorhinal cortices of 6-month old mice. These mice also had increased microglial activation in these regions, with preliminary data supporting a trending correlation between 5mc and microglial activation in the CA1. Additionally, 13-month old mice, showed a significant 23% increase in amyloid beta 1-42, compared to age-matched chow-fed mice. We hypothesized that the skew toward inflammatory and neurodegenerative pathologies was due to chronic hypomethylation; therefore, we sought to limit the progression of these neurodegenerative hallmarks by administering the methyl donor, s-adenosylmethionine (SAMe; ~300-400μg/day) to half of the 13-month old mice. After 6 weeks of SAMe treatment, our exploratory study, will examine brain tissues taken for advanced Methyl-seq analysis to determine emerging changes in methylation resulting from the significant life-long decrease in 5mc levels in the brain, with the goal of confirming, and isolating new, molecular targets related to the increased incidence of AD in those with T2D.

Disclosures: D.M. Osborne: None. **J.W. Vander Velden:** None. **D. Boison:** None.

Nanosymposium

013. Alzheimer's Disease and Other Dementias: Genetic Analyses

Location: SDCC 25

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 013.07

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

Support: NICHD/NIH R01HD067731

Title: Non-alzheimer's aging brain, behavior and biomarkers in down syndrome and mouse

Authors: *L. DAI[1], J. SCHIEVING[2], J. TIPPETTS[2], O. ABDULLAH[2], M. C. BURBACK[2], A. VAN HOEK[2], A. RAMIREZ[2], J. O. EDGIN[5], M. PRIGGE[3], J. S. ANDERSON[4], J. R. KORENBERG[2]
[1]Brain Institute/Department of Pediatrics, Univ. of Utah Brain Inst., Salt Lake Cty, UT; [2]Dept. of Pediatrics, Brain Inst., [3]Dept. of Paediatric Neurol., Univ. of Utah, Salt Lake City, UT; [4]Dept. of Radiology, Univ. of Utah, Salt Lake Cty, UT; [5]Dept. of Psychology, Univ. of Arizona, Tucson, AZ

Abstract: One of the major challenge for therapeutics of the aging at risk worldwide is to determine the mechanisms of normal aging, accelerated aging versus Alzheimer's disease (AD). Down syndrome (DS) is a major cause of genetic imbalances causing brain disease throughout the lifespan: intellectual disabilities due to developmental perturbations in the young through premature aging and AD in the old, and therefore provides an important genetic model to study aging and AD. Previous reports (Le Becker 1985 and Mann 1988) show basal ganglia calcification in both DS and AD patients, while more severe with increased age in DS but not in AD. However, the genetic and neural basis as well as the Non-AD related consequences of the pathology are unknown. To fill the gap, we first applied MRI in a young aged DS cohort (n=22; 21.5 ± 6.4 years), and show that lesions in globus pallidus (GP) are found in 23% of full trisomy 21 DS subjects, showing and confirming early onset of GP lesions in DS. In order to determine cognitive effects, of the lesions, in this report we show significant correlation between the Intra-Extra Dimensional Set Shift test (IED) and those with and without lesions in the GP in DS suggesting a non-AD deficit related to the lesions, possibly related to DS. Third, analysis of an individual, age 22 with partial trisomy revealed a GP lesion, defining a subset of gene candidates located between APP and MX1, whose overexpression led to the lesions. Fourth, we asked whether the lesions were related to the AD genetic risk alleles, apolipoprotein E (APOE). Our results showed no significant correlation between the lesions and the APOE genotyping results, suggesting that APOE is not the cause of the lesion found in DS. Finally, we performed MRI and CT on the Ts65Dn mouse model of DS, aged (12-27 months). The unexpected results revealed mild to severe lesions in thalamus in all Ts65Dn mice, with minor lesions present only in aged litter mate wild type controls. Finally histological calcium staining using the Von Kossa method

revealed and defined the lesions as calcium bearing. This is the first report of calcification in the anterior nucleus of the thalamus of the Ts65Dn mouse, of interest because it is the target of the GPi regions found in DS. Taken together, our results establish new genetic mechanisms for the cognitive deficits in DS at young ages, that could also affect the non-AD accelerated aging seen in DS. In addition, the prominent thalamic calcification in the Ts65Dn mouse provides an opportunity to study the genetic and neural mechanisms of accelerated aging and possibly its interaction with AD.

Disclosures: L. Dai: None. **J. Schieving:** None. **J. Tippetts:** None. **O. Abdullah:** None. **M.C. Burback:** None. **A. Van Hoek:** None. **A. Ramirez:** None. **J.O. Edgin:** None. **M. Prigge:** None. **J.S. Anderson:** None. **J.R. Korenberg:** None.

Nanosymposium

013. Alzheimer's Disease and Other Dementias: Genetic Analyses

Location: SDCC 25

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 013.08

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

Support: NIH Grant R01HD057939

Title: Identification of Tip60 interacting transcription factors involved in Alzheimer's disease

Authors: *M. BEAVER, P. PANIKKER, F. ELEFANT
Biol., Drexel Univ., Philadelphia, PA

Abstract: Disruption of epigenetic gene control mechanisms in the brain involving reduced histone acetylation levels causes cognitive deficits that are a debilitating hallmark of most neurodegenerative disorders, including Alzheimer’s disease (AD). Accordingly, histone acetylation has been unequivocally linked to facilitating cognition by regulating neuroplasticity gene expression programs *via* chromatin packaging control in neurons. Our laboratory has published a compendium of studies demonstrating that the histone acetyltransferase (HAT) Tip60 is critical for cognitive processes based on its role in neural epigenetic gene control and protects multiple cognitive neural circuits impaired in the brain during early AD neurodegenerative progression. Nevertheless, a fundamental question that remains to be addressed is how does Tip60 acquire specificity towards specific neuroplasticity gene loci? While Tip60 associates with DNA-binding transcription factors (TFs) to control gene transcription, the identity of TFs involved in Tip60 neural gene control remains unknown. To identify TFs involved in recruitment of Tip60 neuroplasticity genes that are epigenetically impaired in AD, we first identified Tip60 gene targets whose expression levels, Tip60 binding and cognition linked acetylation marks are disrupted in the AD *Drosophila* brain and restored by increasing Tip60 brain levels. We next analyzed these gene promoter regions for conserved TF

DNA binding site motifs using a tightly controlled bioinformatics analysis. This analysis reveals that clusters of these genes have significant enrichment for binding motifs for the same TFs, and that these TFs are all linked to neural function, supporting a model by which Tip60 controls neuroplasticity genes in concert *via* its recruitment by certain common neural TFs. We have recently developed a rapid functional screen in *Drosophila* that enables us to identify whether these TFs modulate neurotoxicity caused by human $A\beta_{42}$ and/or human Tau. Using this strategy, we can rapidly screen and identify those putative Tip60 interacting TFs that protect against Tau and/or Aβ induced neurotoxicity simply by assessing modification of a rough $A\beta_{42}$ or Tau induced neurodegenerative eye phenotype. Together, these studies should provide insight into the mechanisms underlying specificity of Tip60 recruitment to neuroplasticity genes.

Disclosures: M. Beaver: None. **P. Panikker:** None. **F. Elefant:** None.

Nanosymposium

013. Alzheimer's Disease and Other Dementias: Genetic Analyses

Location: SDCC 25

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 013.09

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

Support: Marato-TV3 Foundation, Catalunya, Spain.

Title: Identification of astrocytic gene signatures in Alzheimer’s disease by bioinformatic compartmentalization of human brain transcriptomes into cell-specific gene clusters

Authors: *E. GALEA[1,2], L. D. WEINSTOCK[3], R. LARRAMONA[1], R. MASGRAU[1], L. WOOD[3]
[1]Univ. Autònoma, Inst. Neurosci., Dept. Bioquímica, Bellaterra, Spain; [2]ICREA, Barcelona, Spain; [3]Mechanical Engin. and Inst. for Bioengineering and Biosci., Georgia Inst. of Technol., Atlanta, GA

Abstract: PROBLEM STATEMENT. Astrocytes carry out homeostatic and computational functions. The clustering of GFAP-overexpressing astrocytes around amyloid-β plaques in Alzheimer’s disease (AD) points to major phenotypical and hence functional alterations in astrocytes. However, to what extent loss of cognition in AD is due to astrocyte malfunction, and which dysregulated astrocyte pathways have an impact on disease pathogenesis, hallmarks and clinical symptoms has not been established. Progress on knowledge about the contribution of astrocytes to AD has been hampered, in part, by a lack of human data. OBJECTIVES. To undertake computerized discovery of pathway dysregulation in astrocytes in AD using human data in order to help clarify the contribution of astrocytes to the disease and to inform systems-biology-based therapeutics. METHODS. First, we established the cellular specificity of brain gene clusters by applying the univariate cell-type enrichment score Tau (1) together with

hierarchical clustering to RNAseq data from astrocytes, neurons, microglia, endothelial cells and oligodendrocytes isolated from aged human cortices (2). Second, we defined the functions of such gene clusters using both open-access gene-ontology platforms and manual curation. Third, we used gene set enrichment analysis (GSEA) to evaluate changes of astrocyte-specific clusters in AD using microarray and RNAseq datasets from post-mortem AD tissues and age-matched controls. Neuronal clustering served as a positive control. RESULTS. Neuron-specific clusters related to synaptic structure, synaptic plasticity and neurotransmission were, as expected, down-regulated in AD. At the time of writing this piece the most salient changes detected in the astrocyte-specific clusters in AD imply energy-metabolism-related genes; specifically, down-regulation of glycolysis, the electron transfer chain and the Krebs cycle, and up-regulation of mitochondrial fatty-acid oxidation. CONCLUSION. Cellular compartmentalization of genes differentially expressed in human AD brains with respect to healthy controls suggests that neurodegeneration correlates with dysfunction of energy metabolism in astrocytes. *Supported by Marato-TV3 foundation, Barcelona.* 1. Kryuchkova-Mostacci N et al. Briefings in Bioinformatics 18, 205-214, 2017. 2. Zhang et al. Neuron 89, 37-53, 2016.

Disclosures: E. Galea: None. **L.D. Weinstock:** None. **R. Larramona:** None. **R. Masgrau:** None. **L. Wood:** None.

Nanosymposium

013. Alzheimer's Disease and Other Dementias: Genetic Analyses

Location: SDCC 25

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 013.10

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

Support: Council of Scientific and Industrial Research (CSIR), India
Department of Biotechnology (BT/PR3996/MED/97/57/2011), Government of India
International Society for Neurochemistry

Title: Identification of Arc interacting proteins during amnesia

Authors: *A. GAUTAM[1], S. KAUL[2], M. THAKUR[3]
[1]Univ. of Hyderabad, Hyderabad, India; [2]Natl. Inst. of Advanced Industrial Sci. & Technol., Ibaraki, Japan; [3]Banaras Hindu Univ., Varanasi, India

Abstract: Activity-regulated cytoskeleton-associated protein (Arc) has been shown to be involved in memory dysfunction as well as in its restoration through different studies, 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 bio-informatical 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 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.

Disclosures: A. Gautam: None. **S. Kaul:** None. **M. Thakur:** None.

Nanosymposium

013. Alzheimer's Disease and Other Dementias: Genetic Analyses

Location: SDCC 25

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 013.11

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

Support: NIH/NIA RF1AG056976
Kwanjeong Educational Foundation Overseas Scholarship

Title: Upregulation of protein prenylation is associated with aging and Alzheimer's disease

Authors: *A. JEONG[1], D. A. BENNETT[2], M. DISTEFANO[3], L. LI[4]
[1]Exptl. and Clin. Pharmacol., Univ. of Minnesota-Twin Cities, Minneapolis, MN; [2]Rush Alzheimer's Dis. Ctr., Chicago, IL; [3]Univ. of Minnesota, Chemistry, MN; [4]Exptl. and Clin. Pharmacol., Univ. of Minnesota, Minneapolis, MN

Abstract: Alzheimer’s disease (AD) is the number one cause of age-related dementia, yet there is no effective cure or treatment for this disease. Recently, several lines of evidence suggest that impaired regulation of protein prenylation is associated with brain aging and AD pathology. Ras family GTPases including Ras, Rho, Rab, Rheb subfamilies undergo prenylation by the catalytic action of farnesyl transferase (FT) and geranylgeranyl transferases (GGT-1 and GGT-2), and these small GTPases play important roles in regulating various important cellular processes. Epidemiological studies have shown that the level of isoprenoids including farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) are elevated in brains from

patients with AD. Moreover, studies using cell and animal models of AD reported that inhibition of FT or GGT-1 ameliorated AD pathology. However, the scope of changes of protein prenylation in normal aging and AD has not been thoroughly investigated. This study aims to investigate the altered dynamics of prenylation of various small GTPases in normal aging and in AD. For the AD study, postmortem cortical tissues (BA46/BA9) from the participants of the Religious Orders Study were obtained. These samples were from age- and sex-matched human subjects with a spectrum of cognitive function from no cognitive impairment (NCI), mild cognitive impairment (MCI), to AD dementia. For aging study, postmortem frozen cortical tissues (BA46/BA9) from cognitively normal individuals from different age groups were obtained through the NIH NeuroBioBank. The brain tissue samples were undergone analytical ultracentrifugation or Triton x-114 phase extraction followed by immuoblotting. Our preliminary data suggests that both FT and GGT levels increase along with aging. However, significantly elevated FT level was observed in AD group compared to age- and sex-matched NCI group. In addition, membrane-associated (farnesylated) H-Ras as well as p-ERK/ERK in both MCI and AD brains compared to NCI indicating activation of H-Ras/ERK pathway may be involved in AD pathogenesis. These findings indicate that upregulation of protein prenylation is involved in brain aging, and abnormal upregulation in protein farnesylation, and overactivation of downstream signaling pathways such as H-Ras/ERK may contribute to the pathogenic cascade of AD.

Disclosures: A. Jeong: None. **D.A. Bennett:** None. **M. Distefano:** None. **L. Li:** None.

Nanosymposium

014. Parkinson's Disease: Diagnostics and Clinical Trials

Location: SDCC 5

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 014.01

Topic: C.03. Parkinson’s Disease

Title: Implementation of a smartphone as a wearable and wireless inertial sensor platform for determining efficacy of deep brain stimulation for Parkinson’s disease tremor through machine learning

Authors: *R. C. LEMOYNE[1], T. J. MASTROIANNI[2]
[1]Independent, Running Springs, CA; [2]Cognition Engin., Pittsburgh, PA

Abstract: The treatment of Parkinson's disease is a subject of considerable interest. Deep brain stimulation (DBS) offers a robust treatment strategy especially in the event that intervention through medication has become intractable. Quantified feedback enabled through a smartphone functioning as a wearable and wireless inertial sensor platform could augment clinical acuity for the optimization DBS parameters. The inertial sensor system of the smartphone provides insight as to the potential of the Internet of Things for the movement disorder community, since the

inertial sensor data can be transmitted wirelessly as an email attachment to a post-processing location anywhere in the world. The inertial sensor signal data can be consolidated into a feature set. Considerable machine learning classification for distinguishing between DBS in 'on' and 'off' status with regards to Parkinson's disease tremor has been successfully achieved.

Disclosures: R.C. LeMoyne: None. **T.J. Mastroianni:** None.

Nanosymposium

014. Parkinson's Disease: Diagnostics and Clinical Trials

Location: SDCC 5

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 014.02

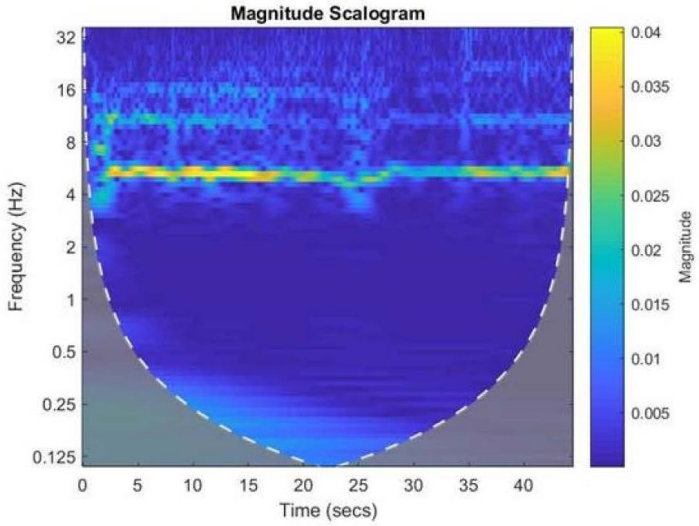
Topic: C.03. Parkinson's Disease

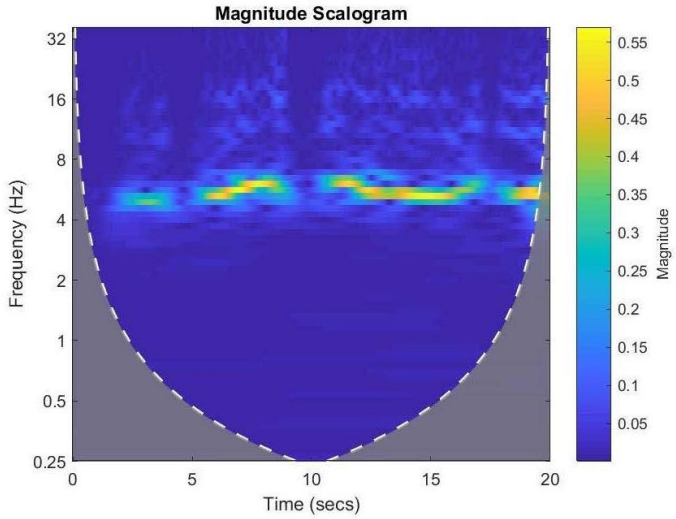
Title: Quantitative continuous measurement of tremor

Authors: *J. R. BRASIC[1], G. N. MCKAY[3], T. P. HARRIGAN[4], A. Y. PANTELYAT[2], K. A. MILLS[2], B. J. HWANG[5], J. Y. A. BANG[2], C. MISHRA[3], L. ROSENTHAL[2], E. MOUKHEIBER[2], K. KITZMILLER[3], A. MATHUR[3], J. ROBERTS[3], D. F. WONG[3]
[1]The Russell H. Morgan Dept. of Radiology and Radiological Sci., [2]Neurol., Johns Hopkins Sch. of Med., Baltimore, MD; [3]The Russell H. Morgan Dept. of Radiology and Radiological Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [4]Applied Physics Lab., Johns Hopkins Univ., Laurel, MD; [5]Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Objective: To correlate output of an accelerometry-based device for the measurement of motor function of people with Parkinson's disease (PD) with visual observations of trained raters in person and on video. **Rationale:** Drawbacks to the ratings by observation include the reliance on real-time human vision to quantify small differences in motion and significant inter-rater variability due to inherent subjectivity in scoring the procedures. **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 without PD. The participant moved his hands to simulate the pill-rolling tremor of PD. Signal processing algorithms utilizing the "bump" waveform in the MATLAB wavelet toolbox 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 varying amplitudes. (Upper panel) A mild tremor demonstrates a relatively stable representation at around 6 Hz with harmonics at 12 and 16 Hz. (Lower panel) A severe tremor demonstrates disorganized representations at around 6 Hz with harmonics at 12 and 16 Hz. The irregularities demonstrated in the output indicate subtleties that could be overlooked in clinical examinations. **Conclusions:** An accelerometry-based device with signal processing differentiates 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. **T.P. Harrigan:** None. **A.Y. Pantelyat:** None. **K.A. Mills:** None. **B.J. Hwang:** None. **J.Y.A. Bang:** None. **C. Mishra:** None. **L. Rosenthal:** None. **E. Moukheiber:** None. **K. Kitzmiller:** None. **A. Mathur:** None. **J. Roberts:** None. **D.F. Wong:** None.

Nanosymposium

014. Parkinson's Disease: Diagnostics and Clinical Trials

Location: SDCC 5

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 014.03

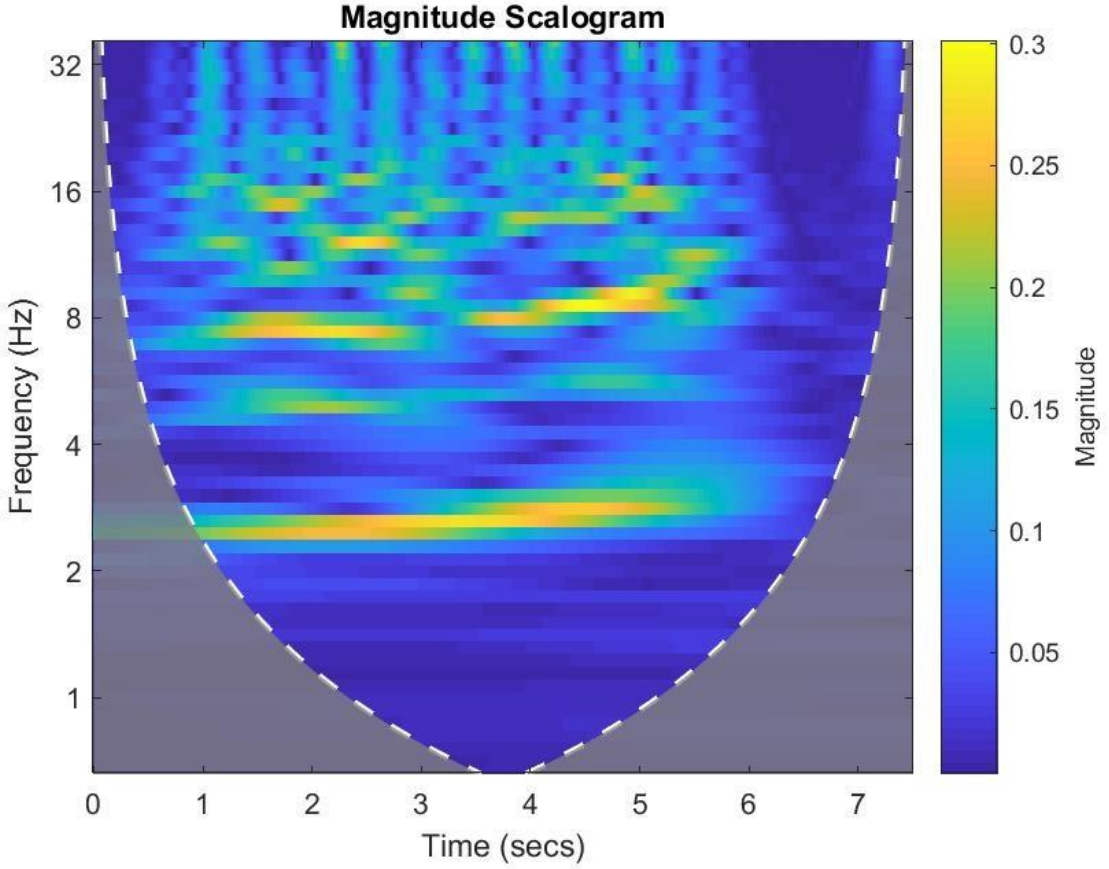
Topic: C.03. Parkinson’s Disease

Support: Tuve Part-time Sabbatical from JHUAPL

Title: Wavelet investigation of accelerometry in Parkinson's disease

Authors: *T. HARRIGAN[1], J. R. BRASIC[2], G. N. MCKAY[4], K. A. MILLS[7], J. Y. A. BANG[5], B. J. HWANG[8], C. MISHRA[3], A. PANTELYAT[9], L. FAYAD[6], D. F. WONG[6]
[1]REDD, Johns Hopkins Univ. Applied Physics Laborator, Laurel, MD; [2]Radiology and Radiological Sci., [3]Johns Hopkins Sch. of Med., Baltimore, MD; [5]Neurol., [6]Radiology and Radiological Sci., [4]Johns Hopkins Univ. Med. Sch., Baltimore, MD; [7]Neurol., [8]Neurosci., Johns Hopkins Univ., Baltimore, MD; [9]Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Clinical grading of the changes in movement in Parkinson’s disease and similar disorders is based on several factors, including tremor, slowness, and features such as halting. Accelerometry offers the chance to standardize observations or to provide data for remote diagnosis. The purpose of this study is to assess how well acceleration histories can be used to standardize or augment clinical observations**. Methods:** In this study 21 patients with Parkinson’s disease were instrumented with tri-axial accelerometers on the upper and lower extremities during 12 modified segments of the of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) (Goetz, 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 using the “bump” wavelet transform in the Matlab toolbox. The major frequency component and change in frequency component was correlated to the clinical observations. **Results:** Figure 1 shows typical results in a 76 year old patient with mild impairment the upper extremity finger tapping test. Colors reflect frequency component magnitude. The lower bright line shows the major frequency component for this motion and shows a small change in base frequency during the test. At the top, the high-frequency components for each tap can be observed. **Conclusions:** The wavelet components reflect clinical observations and provide data to quantify measures such as rhythm, slowing, and interruptions. This procedure can show subtleties that are not perceived by clinical examination. will likely facilitate obtaining objective data to monitor movements in people with Parkinson’s disease during clinical trials and other interventions, and it can clarify the specific components of movement that influence a clinical assessment.



Disclosures: **T. Harrigan:** Other; Tuve Part-time Sabbatical from JHUAPL. **J.R. Brasic:** None. **G.N. McKay:** None. **K.A. Mills:** None. **J.Y.A. Bang:** None. **B.J. Hwang:** None. **C. Mishra:** None. **A. Pantelyat:** None. **L. Fayad:** None. **D.F. Wong:** None.

Nanosymposium

014. Parkinson's Disease: Diagnostics and Clinical Trials

Location: SDCC 5

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 014.04

Topic: C.03. Parkinson’s Disease

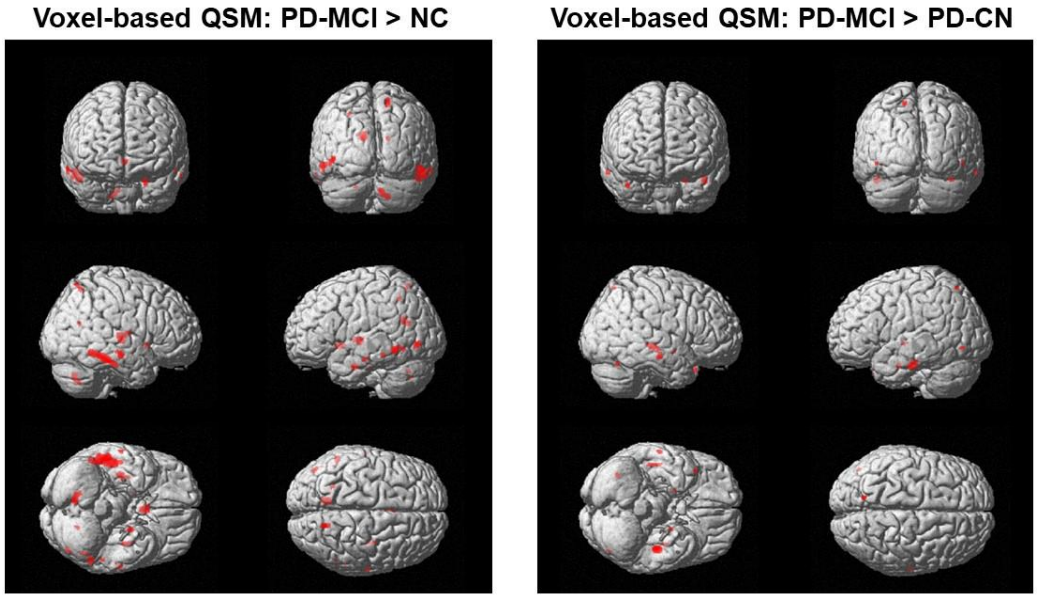
Support: KAKENHI Grant 16H06403

Title: Mild cognitive impairment in Parkinson's disease: The voxel-based QSM analysis

Authors: ***Y. UCHIDA**[1], H. KAN[2], N. ARAI[2], Y. UEKI[3], N. MATSUKAWA[4]
[1]Neurol., Nagoya City Univ. Grad. Sch. of Med., Nagoya / Aichi, Japan; [2]Radiology, Nagoya

City Univ. Hosp., Nagoya, Japan; [3]Nagoya Citiy Univ., Nagoya, Japan; [4]Nagoya City Univ., Nagoya-Shi, Japan

Abstract: Objective: Mild cognitive impairment (MCI) in Parkinson's disease (PD) frequently occurs in association with aging, disease duration, and/or disease severity. Although iron accumulation has been proposed as one of the pathomechanisms in PD, the association of its accumulation with cognitive dysfunction is not entirely cleared. Here, we applied quantitative susceptibility mapping (QSM), a magnetic resonance imaging method which is sensitive to tissue iron, to PD-MCI subjects. **Methods:** Patients with PD, aged 60 or older and Hoehn & Yahr staging 2-4, and normal elderly controls (NC) were recruited for this study. The diagnosis of PD-MCI was made based on the Movement Disorder Society Task Force criteria for PD-MCI. By using the combined method of QSM and voxel-based morphometry (VBM), voxel-based susceptibility of whole brain was analyzed among three groups. **Results:** 20 PD-MCI, 18 PD with cognitively normal (PD-CN), and 17 NC participated in this study. The PD-MCI subjects were on average older and had lower mean Montreal Cognitive Assessment score and higher mean Unified Parkinson's Disease Rating Scale Part III score than the PD-CN subjects. There were no volumetric differences among these groups. By contrast, voxel-based QSM analyses demonstrated that the PD-MCI group had more cortical areas with significant difference of susceptibility, concordant with known distributions of α-synuclein pathology, compared to the NC and PD-CN group. **Conclusions:** This study suggests that cognitive decline in PD might be associated with cerebral iron burden and that QSM might have the potential for monitoring as a cognitive biomarker in PD.



Disclosures: H. Kan: None. **N. Arai:** None. **Y. Ueki:** None. **N. Matsukawa:** None.

Nanosymposium

014. Parkinson's Disease: Diagnostics and Clinical Trials

Location: SDCC 5

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 014.05

Topic: C.03. Parkinson's Disease

Title: Microphysiological systems to study human neurodegenerative disease

Authors: *S. SANCES[1], D. WEST[1], A. MEYER[1], A. WOODBURY[1], A. LAPERLE[1], R. HO[1], V. DARDOV[1], W. SPIVIA[2], J. E. VAN EYK[2], C. N. SVENDSEN[1]
[1]Board of Governors Regenerative Med. Inst., [2]Advanced Clin. Biosystems Inst., Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: The physiological, molecular and cellular changes that underlie amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD) are complex. Rare monogenetic forms of these diseases, while informative, do not reflect the approximately 90% of ALS and PD cases with no known genetic mutations (termed sporadic). The greater prevalence of sporadic ALS and PD cases prompts the immediate need to develop sporadic disease models. Working with the Cedars-Sinai's Induced Pluripotent Stem Cell (iPSC) Core to generate large cohorts of ALS and PD lines, we have developed advanced differentiation techniques for cell types relevant to central nervous system function. Among these are robust methods to derive spinal motor neurons (spMNs) and dopaminergic neurons (DANs) that are uniquely susceptible in ALS and PD, respectively. From iPSCs, we can derive other cell types that are also affected in disease, including astrocytes and microglia, as well as brain microvascular endothelial cells (BMECs) that replicate blood brain barrier (BBB) function. Here we have combined these iPSC-derived cells with highly scalable microphysiological systems (MPS), also known as Organ-Chips (Emulate Inc.). Through co-culture of either spMNs or DANs with astrocytes, microglia and BMECs, we have developed highly physiological models of ALS and PD on Organ-Chips referred to as ALS-Chip and PD-Chip. Importantly, each cell type is derived from the same sporadic ALS or PD patient and therefore carry identical genetic background. To uncover disease-specific pathophysiology in the ALS-Chip or PD-Chip and to generate novel biomarkers for both diseases, we have developed a comprehensive array of genomic, proteomic, metabolomic, and electrophysiological assays. The primary outcome of this project is the establishment of reproducible disease-specific phenotypes of both sporadic ALS and PD that will then be used as physiological biomarkers to screen for novel pathological-mitigating drugs.

Disclosures: S. Sances: None. **D. West:** None. **A. Meyer:** None. **A. Woodbury:** None. **A. Laperle:** None. **R. Ho:** None. **V. Dardov:** None. **W. Spivia:** None. **J.E. Van Eyk:** None. **C.N. Svendsen:** None.

Nanosymposium

014. Parkinson's Disease: Diagnostics and Clinical Trials

Location: SDCC 5

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 014.06

Topic: C.03. Parkinson's Disease

Title: Results of the first cohort of an open label dose escalating phase 1 study evaluating the safety of a human neural stem cell based therapy in Parkinson's disease

Authors: 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], G. NAIR[2], A. EVANS[2], *R. A. KERN[1,3]
[1]Intl. Stem Cell Corp, Carlsbad, CA; [2]Royal Melbourne Hosp., Parkville, Australia; [3]Cyto Therapeut., Melbourne, Australia

Abstract: Available treatment options for Parkinson's disease (PD) do not restore the damaged nigrostriatal pathway. Cell based therapies have the potential to restore the nigrostriatal pathway and have shown significant clinical improvements for several years in some patients. In preclinical PD models, intra-nigrostriatal transplantation of human parthenogenetic derived neural stem cells (ISC-hpNSC) has shown to promote behavioral recovery and increase dopamine (DA) levels, DA neuron innervation and number. Intra-nigrostriatal administration of clinical grade ISC-hpNSC is safe, well tolerated, provides neurotrophic support and restores the damaged nigrostriatal pathway. Here we show interim clinical data of a First-In-Human study evaluating the safety and functional activity of ISC-hpNSC, which is the world's first pluripotent stem cell based therapy for PD (ClinicalTrials.gov: NCT02452723). In this is a single-arm, open-label, Phase I study, escalating doses of 30, 50 and 70 million ISC-hpNSC are evaluated in 12 patients divided into 3 cohorts of 4 patients each. Patients receive immunosuppression and stereotactic bilateral injections into the caudate nucleus, putamen and substantia nigra. In this 12-month study with a 5 year long-term follow-up the primary endpoint is safety and secondary endpoints evaluate efficacy with different neurological assessments. A total of eight patients have successfully been transplanted with ISC-hpNSC, four patients from the first cohort received 30 million cells and four from the second cohort received 50 million cells. No tumor, inflammation or serious adverse events (SAE) associated with ISC-hpNSC have been reported. Six month interim analysis of the first cohort shows improvements of 24% in the % OFF-Time and 19% in the % ON-Time without dyskinesia compared to baseline.

Disclosures: I. Garitaonandia: A. Employment/Salary (full or part-time):; International Stem Cell Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Stem Cell Corporation. **R. Gonzalez:** A. Employment/Salary (full or part-time):; International Stem Cell

Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Stem Cell Corporation. **G. Sherman:** A. Employment/Salary (full or part-time):; International Stem Cell Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Stem Cell Corporation. **A. Noskov:** A. Employment/Salary (full or part-time):; International Stem Cell Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Stem Cell Corporation. **D. Cardiff:** A. Employment/Salary (full or part-time):; International Stem Cell Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Stem Cell Corporation. **T. Christiansen-Weber:** A. Employment/Salary (full or part-time):; International Stem Cell Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Stem Cell Corporation. **A. Semechkin:** A. Employment/Salary (full or part-time):; International Stem Cell Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Stem Cell Corporation. **E. Braine:** None. **G. Nair:** 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.; International Stem Cell Corporation. **A. Evans:** 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.; International Stem Cell Corporation. **R.A. Kern:** A. Employment/Salary (full or part-time):; International Stem Cell Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Stem Cell Corporation.

Nanosymposium

014. Parkinson's Disease: Diagnostics and Clinical Trials

Location: SDCC 5

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 014.07

Topic: C.03. Parkinson’s Disease

Support: Philanthropy
Novartis Pharmaceuticals

Title: Nilotinib increases dopamine metabolism and reduces oligomeric:total alpha-synuclein ratio in Parkinson’s disease

Authors: *C. E. MOUSSA[1], M. HEBRON[3], Y. TORES-YAGHI[2], A. LAWALER[2], J. ALLERANO[2], T. KIMBASON[2], B. WILMURTH[2], N. STARR[2], A. SHEKOYAN[2], E. MUNDEL[2], N. YASUF[2], J. AHN[2], F. L. PAGAN[4]
[1]Neurol., Georgetown Univ. Med. Ctr., Washington, DC; [2]Georgetown Univ. Med. Ctr., Washington DC, DC; [3]Georgetown Univ., Washington, DC; [4]Georgetown Univ. Hosp. Neurol. Dept., Medstar Georgetown Univ. Hosp., Washington, DC

Abstract: Parkinson's disease (PD) is a neurodegenerative disorder that affects motor and non-motor functions. PD results in loss of dopaminergic neurons as a result of oligomerization and accumulation of alpha-synuclein. Our pre-clinical and open label phase I data indicate that the tyrosine kinase inhibitor (TKI) Nilotinib may improve motor symptoms and cognition, reverse dopamine loss and reduce brain alpha-synuclein. Nilotinib is FDA-approved for the treatment of chronic myeloid leukemia (CML) at 800mg oral dose twice daily. This is a phase II, open label, random single dose (RSD) study in mid-stage PD patients with mild cognitive impairment (MCI) to evaluate the effects of Nilotinib on disease biomarkers of PD. Cerebrospinal fluid (CSF) from 75 patients was examined to assess changes in the levels of CSF alpha-synuclein and the dopamine metabolite homovanillic acid (HVA) and **3,4**-Dihydroxyphenylacetic **acid** DOPAC as primary disease biomarkers. A total of 15 patients in each of 5 randomized study groups, including placebo, 150mg, 200mg, 300mg and 400mg Nilotinib had lumbar puncture at 1-4 hours after a single time oral drug administration. CSF biomarkers analyses showed a statistically significant increase in the level of CSF HVA and DOPAC. No change was detected in total levels of CSF total alpha-synuclien, but lower dose (150mg and 200mg) resulted in a significant decrease of oligomeric;total CSF alpha-synuclein. Further analysis will be performed to compare plasma and CSF levels of these biomarkers between this single time administration and 52-week treatment. These data suggest that a single time oral administration of Nilotinib may increase brain dopamine levels and metabolism. All patients were receiving a maximum dose of 800mg per day Levodopa therapy and were not receiving any MOA-B inhibitors (selegeline/rasagiline) that may affect HVA levels for at least 6 weeks. These results suggest Nilotinib, in a dose dependent manner, may have a symptomatic effect through modulation of brain dopamine levels. Additionally, the significant reduction of oligomeric alpha-synuclein, which is expected to increase in the CSF of PD patients as the disease progresses, suggests that Nilotinib may reduce misfolded alpha-synuclein accumulation and have a long-term disease modifying effect. Importantly, the dose response of oligomeric alpha-synuclein and HVA changes to nilotinib suggests that the dose administered may depend on the stage of disease to potentially halt PD progression.

Disclosures: C.E. Moussa: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Moussa is amn inventor of an issued patent to use tyrosine kinase inhbitors as a treatment for neurodegenerative diseases, Georgetown University. **M. Hebron:** None. **Y. Tores-Yaghi:** None. **A. Lawaler:** None. **J. Allerano:** None. **T. Kimbason:** None. **B. Wilmurth:** None. **N. Starr:** None. **A. Shekoyan:** None. **E. Mundel:** None. **N. Yasuf:** None. **J. Ahn:** None. **F.L. Pagan:** None.

Nanosymposium

015. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: SDCC 2

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 015.01

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Air Force Material Command, USAF, under grant number FA8655-05-1-3065
Air Force Office of Scientific Research (EOARD, London, UK),
Alzheimer's Association (IIRG-09- 132087),
National Institutes of Health (R01 AG028679)
Dr. Robert M. Kohrman Memorial Fund
Swedish Medical Research Council (Nr 2710-HSS),
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),

Title: Concussive head injury exacerbates Alzheimer's disease pathophysiology. Neuroprotection by TiO2-nanowired cerebrolysin with neuronal nitric oxide synthase antibodies and mesenchymal stem cells

Authors: *H. S. SHARMA[1], D. F. MURESANU[3], J. V. LAFUENTE[4], A. OZKIZILCIK[5], Z. R. TIAN[6], R. PATNAIK[7], A. NOZARI[8], H. MOESSLER[9], R. J. CASTELLANI[10], A. SHARMA[2]
[2]Surgical Sciences, Anesthesiol. & Intensive Care Med., [1]Uppsala Univ., Uppsala, Sweden; [3]The Fndn. of the Society for the Study of Neu, Cluj Napoca, Romania; [4]Univ. of Basque Country, Bilbao, Spain; [5]Biomed. Engin., [6]Chem. & Biochem., Univ. of Arkansas, Fayetteville, AR; [7]Sch. of Biomed. Engin., Indian Inst. of Technology, Banaras Hindu Univ., Varanasi, India; [8]Anesthesia and Critical Care, Massachusetts Gen. Hosp., Boston, MA; [9]Drug Develop. & Discovery, Ever NeuroPharma, Mondsee, Austria; [10]Pathology, Univ. of Maryland, Baltimore, MD

Abstract: Military personnel are prone to develop Alzheimer’s disease (AD) because of combat stress or due to mild to moderate degree of traumatic brain injury. Previous experiments from our laboratory showed that a mild concussive head injury (CHI) leads to exacerbation of brain pathology following amyloid beta peptide (AβP) infusion model of AD. Thus, there was a significant increase in AβP deposition and tau phosphorylation (p-tau) in the brain and in the cerebrospinal fluid (CSF) as compared to normal rats after identical AβP infusion. Since AD induced pathophysiology, oxidative stress could play key roles. We examined the role of nitric oxide in AD by immunohistochemical evaluation of neuronal nitric oxide synthase (nNOS) in the brain. Furthermore, we evaluated the influence of cerebrolysin-a multimodal drug with a balanced composition of several neurotrophic factors and active peptide fragment either alone or together with mesenchymal stem cells (MSCs) administration to reduce CHI induced exacerbation of AD brain pathology. AD like symptoms were induced in male Sprague-Dawley

rats (age 15 to 20 wks) by administering AβP (1-40, 150 ng/10 µl) into the left lateral ventricle once daily for 4 weeks. In another group of rats, CHI was inflicted by delivering an impact of 0.224 N on the right parietal bone under Equithesin anesthesia by dropping a tapered iron cylinder (114.6 g) from a 20 cm height using a guide tube. A pronounced increase in nNOS immunoreactivity was seen in normal rats after AβP infusion that was prominent in the cerebellum, cortex, hippocampus and the thalamus. The magnitude and intensity of nNOS expression was significantly enhanced in CHI rats after identical AβP infusion. The nNOS expression in neurons was present in the areas showing neuronal injury, edematous expansion and AβP deposition. The biochemical measurement of AβP and p-tau exhibited 40 to 58 % higher levels in the brain and in the CSF of CHI rats after AβP infusion as compared to naïve animals. TiO2-nanowired delivery of cerebrolysin (5 ml/kg, i.v.) together with antibodies of nNOS (1:20, 20 µl/min, i.c.v.) and MSCs (10^6cells) significantly reduced nNOS expression, AβP and p-tau levels in AD model with CHI and induced marked neuroprotection. These observations are the first to show that blockade of nNOS expression in AD induces neuroprotection, not reported earlier. Further studies using nanodelivery of NOS inhibitors are needed to understand the role of nitric oxide in AD.

Disclosures: H.S. Sharma: None. **D.F. Muresanu:** None. **J.V. Lafuente:** None. **A. Ozkizilcik:** None. **Z.R. Tian:** None. **R. Patnaik:** None. **A. Nozari:** None. **H. Moessler:** None. **R.J. Castellani:** None. **A. Sharma:** None.

Nanosymposium

015. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: SDCC 2

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 015.02

Topic: C.07. 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;
Air Force Material Command, USAF Grant nr FA8655-05-1-3065;
Swedish Medical Research Council (Nr 2710-HSS)
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
The University Grants Commission, New Delhi, India
India-EU Grant Support, Ministry Of Biotechnology, Govt. of India
Indian Medical Research Council, New Delhi, India (HSS/AS)

Title: Nanowired delivery of antibodies to tau and neuronal nitric oxide synthase together with cerebrolysin reduces exacerbation of brain pathology in Parkinson's disease after traumatic brain injury

Authors: *A. OZKIZILCIK[1], A. SHARMA[2], D. F. MURESANU[3], J. V. LAFUENTE[4], A. NOZARI[5], R. PATNAIK[6], Z. TIAN[7], H. MOESSLER[8], H. S. SHARMA[2]
[1]Biomed. Engin., Univ. of Arkansas, Fayetteville, AR; [2]Surgical Sciences, Anesthesiol. & Intensive Care Med., Uppsala Univ., Uppsala, Sweden; [3]Clin. Neurosciences, THE FOUNDATION OF THE SOCIETY FOR THE STUDY OF NEU, CLUJ NAPOCA, Romania; [4]Neurosciences, Univ. of Basque Country, Bilbao, Spain; [5]Anesthesia and Critical Care, Massachusetts Gen. Hosp., Boston, MA; [6]Sch. of Biomed. Engin., Indian Inst. of Technology,Banaras Hindu Univ., Varanasi, India; [7]Chem. & Biochem., Univ. of Arkansas Fayetteville, Fayetteville, AR; [8]Drug Develop. & Discovery, Ever Neuropharma, Mondsee, Austria

Abstract: Previous studies from our laboratory showed that Parkinson's disease (PD) induced brain pathology is exacerbated following traumatic brain injury (TBI), a feature very common in military personnel during combat operations. In such situations, exacerbation of tau-phosphorylation (p-tau) and alpha-synuclein (ASNC) occurred in the cerebrospinal fluid (CSF) and in several brain areas associated with brain pathology. Moreover upregulation of neuronal nitric oxide synthase (nNOS) was also seen in the brain areas in PD that exhibited enhanced overexpression following TBI. Thus, it would be interesting to explore whether neuroprotective agents e.g., cerebrolysin (CBL)-a balanced composition of several neurotrophic factors and active peptide fragment may have further superior effects when combined with antibodies of p-tau and nNOS antibodies in PD following TBI. PD like symptoms was produced in mice by administration of 1-metyl-4-fenyl-1,2,3,6-tetrahydropyridin (MPTP, 20 mg/kg, i.p.) daily within 2-h intervals for 5 in normal animals or following TBI. Mild penetrating TBI was inflicted in anaesthetized rats after making burr hole in both parietal cerebral cortex (4 mm^2). About 3 mm deep and 4 mm long incision was made on the right parietal cortex in normal or PD rats. On the 8^{th} day brain pathology was examined. Our observations showed 150 to 220 % higher increase in the blood-brain barrier (BBB) permeability to Evans blue albumin (EBA) and radioiodine in PD rats after TBI that was most marked in injured hemisphere. Exacerbation of p-tau and ASNC levels by 1.5 to 2.3 fold in the CSF as well as in the right traumatized hemisphere was seen. The untraumatized half also showed a higher increase in p-tau and ASNC after PD but the values were significantly lower than the inured half. Immunohistological studies showed higher expression of nNOS, neuronal or glial cell injuries in the traumatized half in PD as compared to the uninjured half. Nanodelivery of CB (2.5 ml/kg, i.v.) together with monoclonal p-tau antibodies (phospho S396, 1:20, 30 µl, i.c.v.) with nNOS antibodies (EP1855Y, 1.20 40 µl, i.c.v.) into the left lateral cerebral ventricle 5 days after MPTP significantly reduced BBB disruption in both hemispheres after TBI in PD as compared to CBL given alone. The biochemical levels of p-tau and ASNC were also significantly reduced in the whole brain. The nNOS expression and brain pathology markedly reduced in PD after TBI. These changes were most marked in the uninjured half. These observations are the first to show that p-tau and nNOS antibodies if given with CBL has remarkably enhanced neuroprotective ability in PD after TBI, not reported earlier.

Disclosures: A. Ozkizilcik: None. **A. Sharma:** None. **D.F. Muresanu:** None. **J.V. Lafuente:** None. **A. Nozari:** None. **R. Patnaik:** None. **Z. Tian:** None. **H. Moessler:** None. **H.S. Sharma:** None.

Nanosymposium

015. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: SDCC 2

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 015.03

Topic: C.07. 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;
Air Force Material Command, USAF Grant nr FA8655-05-1-3065;
Swedish Medical Research Council (Nr 2710-HSS)
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
Swedish Strategic Foundation, Stockholm, Sweden (HSS/AS)
Astra Zeneca, Mölndal, Sweden (HSS/AS),
Alzheimer's Association (IIRG-09- 132087),

Title: Nanodelivery of hitamine H3/H4 receptor modulators with antibodies to amyloid beta peptide in combination with alpha synuclein reduces brain pathology in Parkinson's disease

Authors: *R. PATNAIK[1], A. SHARMA[2,3], J. V. LAFUENTE[4], D. F. MURESANU[5], A. NOZARI[6], R. J. CASTELLANI[7], P. K. MENON[8], A. OZKIZILCIK[9], R. TIAN[10], H. S. SHARMA[2,3]
[1]Sch. of Biomed. Engin., Indian Inst. of Technology,Banaras Hindu Univ., Varanasi, India; [2]Surgical Sciences, Anesthesiol. & Intensive Care Med., Uppsala Univ., Uppsala, Sweden; [3]Int. Exp. CNS Injury & Repair (IECNSIR), Uppsala Univ. Hosp., Uppsala, Sweden; [4]neurosciences, Univ. of Basque Country, Bilbao, Spain; [5]Clin. Neurosciences, THE FOUNDATION OF THE SOCIETY FOR THE STUDY OF NEU, CLUJ NAPOCA, Romania; [6]Anesthesia and Critical Care, Massachusetts Gen. Hosp., Boston, MA; [7]Pathology, Univ. of Maryland, Baltimore, MD; [8]Biomaterials, Biomed. Engin., Banaras Hindu Univ., Varnasi, India; [9]Biomed. Engin., Univ. of Arkansas, Fayetteville, AR; [10]Chem. & Biochem., Univ. of Arkansas Fayetteville, Fayetteville, AR

Abstract: Parkinson’s disease (PD) is often associated with traumatic brain injury (TBI) due to trauma-induced increase of phosphorylation of tau (p-tau) and alpha synuclein (ASNC) in the brain or cerebrospinal fluid (CSF). Postmortem studies show deposition of amyloid beta peptide (AbP) in several brain areas in PD. This suggests an intricate connection between that AbP, p-tau and ASNC is responsible for the development of brain pathology in PD. Obviously, military personnel are highly vulnerable to TBI and due to this reason, instances of PD is quite common

in them with advancing age. Thus, novel treatment strategies are required to reduce or alleviate the consequences of PD induced brain pathology for enhanced quality of life.
Previous reports from our laboratory showed that a potent histaminergic H3 receptor inverse agonist BF-2549 and clobenpropit a partial histamine H4 agonist with H3 receptor antagonistic activity reduced pathophysiology in a mouse model of PD. Since PD is also associated with elevation of ASNC and AbP, it would be interesting to see whether nanodelivery antibodies to AbP and ASNC together with histaminergic drugs could induce superior neuroprotection in PD in our mouse model.
Administration of 1-metyl-4-fenyl-1,2,3,6-tetrahydropyridin (MPTP, 20 mg/kg, i.p.) in mice daily within 2-h intervals for 5 days induced PD like symptoms. This is confirmed by significant decreases in tyrosine hydroxylase (TH) positive cells in the substantia niagra pars Compacta (SNpc) and striatum (STr) together with dopamine (DA) and its metabolites 3,4-Dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) on the 8^{th} day. At this time, ASNC and tau proetins increased profoundly in the CSF. Treatment with TiO2-nanowired BF 2649 (1 mg/kg, i.p.) or Clobenpropit (1 mg/kg, i.p.) once daily for 1 week together with monoclonal antibodies (50 µl, 1:20 in PBS, in left lateral ventricle, i.c.v.) to AbP (AbP1-40, Tocris 1119, UK) and ASNC (Syn211, ab80627) resulted in significant reduction in brain pathology, and restored DA and DOPAC levels and TH immunoreactivity in the SNpc, STr by more than 68 to 82 % that the normal values. Interestingly, CSF levels of ASNC, AbP and p-tau were also decreased by 75 to 80 % from the untreated PD mouse. When histaminergic drugs were given alone in PD, the magnitude of biochemical or immunohistochemical changes together with brain pathology were much less evident. Taken together our observations are the first to point a prominent interrelationship among AbP, ASNC and p-tau in the pathophysiology of PD together with histaminergic modulation of H3/H4 receptors, not reported earlier.

Disclosures: R. Patnaik: None. **A. Sharma:** None. **J.V. Lafuente:** None. **D.F. Muresanu:** None. **A. Nozari:** None. **R.J. Castellani:** None. **P.K. Menon:** None. **A. Ozkizilcik:** None. **R. Tian:** None. **H.S. Sharma:** None.

Nanosymposium

015. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: SDCC 2

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 015.04

Topic: C.07. 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;
Air Force Material Command, USAF Grant nr FA8655-05-1-3065;
Swedish Medical Research Council (Nr 2710-HSS)
Swedish Strategic Research Foundation, Stockholm, Sweden

Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
India-EU Co-operation Program (RP/AS/HSS)
Astra Zeneca Mölndal, Mölndal, Sweden

Title: Co-administration of nanowired antibodies to inducible nitric oxide synthase and tumor necrosis factor-alpha with cerebrolysin reduces SiO2-nanoparticles induced exacerbation of spinal cord pathophysiology following trauma

Authors: *P. K. MENON[1], A. SHARMA[2,3], R. PATNAIK[4], J. V. LAFUENTE[5], D. F. MURESANU[6,7], A. NOZARI[8], A. OZKIZILCIK[9], R. TIAN[10], H. MOESSLER[11], H. S. SHARMA[2,3]
[1]Banaras Hindu Univ., Varnasi, India; [2]Surgical Sciences, Anesthesiol. & Intensive Care Med., Uppsala Univ., Uppsala, Sweden; [3]Int. Exp. CNS Injury & Repair (IECNSIR), Uppsala Univ. Hosp., Uppsala, Sweden; [4]Sch. of Biomed. Engin., Indian Inst. of Technology,Banaras Hindu Univ., Varanasi, India; [5]Neurosciences, Univ. of Basque Country, Bilbao, Spain; [6]Clin. Neurosciences, THE FOUNDATION OF THE SOCIETY FOR THE STUDY OF NEU, CLUJ NAPOCA, Romania; [7]Neurol., "RoNeuro'' Inst. for Neurolog. Res. and Diagnostic,, Cluj-Napoca, Romania; [8]Anesthesia and Critical Care, Massachusetts Gen. Hosp., Boston, MA; [9]Biomed. Engin., [10]Chem. & Biochem., Univ. of Arkansas, Fayetteville, AR; [11]Drug Develop. & Discovery, Ever NeuroPharma, Mondsee, Austria

Abstract: Spinal cord injury (SCI) is quite prevalent in military personnel during combat operations across the hot and/or desert environments where they are additionally exposed to silica dust (SiO2-nanoparticles, SiO2 NPs) and hyperthermia. Previous reports from our laboratory show that SiO2 NPs exacerbate SCI induced tissue destruction and functional disabilities. We have also shown earlier that SCI alone induces marked upregulation of neuronal nitric oxide synthase (nNOS) in the cord associated with cord pathology that was significantly neutralized by topical application of nNOS antibodies alone or together with tumor necrosis factor-alpha (TNF-a) antibodies. Moreover, SCI was shown to enhance amyloid beta peptide (AbP) and tau proetins (p-tau) in the cerebrospinal fluid (CSF) that correlates with cord pathology seen at 24 h after trauma. Since AbP is known to induce neurotoxicity and stimulates inducible NOS (iNOS) production, a possibility exists that antibodies to iNOS together with TNF-a could result in superior neuroprotection in SCI compounded with SiO2 NPs. In this investigation, we explored the effects of co-administration of nanowired iNOS and TNF-a antibodies together with a known neuroprotective agent cerebrolysin (CBL-a balanced composition of several neurotrophic factors and active peptide fragments) SiO2 NPs induced exacerbation of SCI pathology in a rat model.
SCI was inflicted in Equithesin (3 ml/Kg, i.p.) anesthetized rats by making a longitudinal incision in the right dorsal horn of the T10-11 segments (2 mm deep and 4 mm long) in normal or SiO2 NPs intoxicated (50 mg/kg, i.p. once daily for 1 week) rats and allowed to survive 24 h after trauma. Our observations showed pronounced upregulation of iNOS expression after SCI that was 60 to 98 % higher in SiO2 NPs exposed rats associated with higher neuronal damage. The AbP and p-tau levels in the CSF showed 120 to 280 % higher elevation in SCI with SiO2 NPs. Co-administration of TiO2-nanowired monoclonal antibodies to iNOS and TNF-a (1:20, 30

µl each, i.t. 1 h after injury) together with nanowired CBL (5 ml/kg, i.v. 4 or 8 h after injury) significantly attenuated iNOS expression and cellular injuries in the cord as well as AbP and p-tau levels in CSF in SCI with SiO2 NPs at 24 h after trauma, a feature not observed by individual treatment strategies with either agents alone. These observations are the first to show that AbP and p-tau could induce neurotoxicity through upregulation of iNOS in SCI and combined treatment with iNOS and TNF-a antibodies together with CBL has an added value in enhancing neuroprotection in SCI after SiO2 NPS intoxication, not reported earlier.

Disclosures: P.K. Menon: None. **A. Sharma:** None. **R. Patnaik:** None. **J.V. Lafuente:** None. **D.F. Muresanu:** None. **A. Nozari:** None. **A. Ozkizilcik:** None. **R. Tian:** None. **H. Moessler:** None. **H.S. Sharma:** None.

Nanosymposium

015. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: SDCC 2

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 015.05

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CIHR
Weston Brain Institute
NIH

Title: Neuronal plasticity mediated by the modulation of the blood-brain barrier using focused ultrasound and the delivery of therapeutics

Authors: *I. AUBERT[1], S. DUBEY[1], K. XHIMA[1], H. SARAGOVI[2], K. HYNYNEN[1]
[1]Sunnybrook Res. Inst., Toronto, ON, Canada; [2]Lady Davis Institute-Jewish Gen. Hosp., Montreal, QC, Canada

Abstract: Rationale. New treatment strategies for Alzheimer's disease (AD) are worth exploring. Focused ultrasound (FUS) combined with microbubbles is known to transiently and non-invasively increase the permeability of the blood-brain barrier (BBB) and it has recently entered clinical trials for AD. In preclinical studies, we are evaluating treatment efficacy of FUS combined with the delivery of therapeutics to the brain.
Research Objective. We aim to evaluate the potential of FUS-induced BBB permeability to deliver therapeutic antibodies or molecules targeting neurotrophin receptors, affording neuroprotective signaling, neuronal growth, survival and plasticity. **Methods.** These studies were conducted in non-transgenic (non-Tg) mice and in a transgenic mouse model of AD (Tg-AD). Anesthetized mice were treated with FUS under MRI guidance, targeting brain areas of interests in presence of microbubbles and gadolinium administered intravenously. A subgroup of mice also received therapeutic agents injected intravenously. Time-points post-FUS ranged from 90

min to 21 days, evaluating early and lasting effects of treatments, respectively. Outcome measures included quantification of RNAs and of protein signaling pathways, to characterize hippocampal neurogenesis, pro- and anti-inflammatory cytokines, and signaling related to cell survival, proliferation and regeneration. **Results:** The entry of endogenous antibodies from the bloodstream was restricted to sites of BBB opening identified under MRI-guidance. Effectors implicated in neuronal growth, survival and plasticity were increased by FUS including the phosphorylation of Akt and CREB. These effects were further potentiated in presence of therapeutics. Neuronal apoptosis or red blood cell extravasation were not detected in sonicated areas, indicating the safety of the ultrasound treatment paradigm. Hippocampal neurogenesis reached a 400% increase with two FUS treatments, given weekly, in combination with therapeutic antibodies. This response was independent of amyloid load, and it was observed in Tg-AD and non-Tg mice. Interleukins which are generally considered pro-inflammatory were decreased. **Conclusion:** FUS-induced BBB permeability by itself can stimulate effectors involved in neuronal plasticity which can be further potentiated in the presence of therapeutics.

Disclosures: I. Aubert: None. **S. Dubey:** None. **K. Xhima:** None. **H. Saragovi:** None. **K. Hynynen:** None.

Nanosymposium

015. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: SDCC 2

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 015.06

Topic: C.07. 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;
Air Force Material Command, USAF Grant nr FA8655-05-1-3065;
Swedish Medical Research Council (Nr 2710-HSS)
IT 794/13 (JVL), Govt. of Basque Country and UFI 11/32 (JVL)
Government of Basque Country and UFI 11/32 (JVL) University of Basque Country, Spain
India-EU Co-operation Program (RP/AS/HSS)
Indian Medical Research Council, New Delhi, India (HSS/AS)

Title: Nanowired delivery of mesenchymal stem cells with cerebrolysin reduces exacerbation of methamphetamine neurotoxicity in hot environment

Authors: *J. V. LAFUENTE[1], A. SHARMA[2], R. PATNAIK[3], D. F. MURESANU[4], L. FENG[5], A. OZKIZILCIK[6], R. TIAN[7], H. MOESSLER[8], H. S. SHARMA[2]
[1]Univ. of Basque Country, Bilbao, Spain; [2]Surgical Sciences, Anesthesiol. & Intensive Care Med., Uppsala Univ., Uppsala, Sweden; [3]Sch. of Biomed. Engin., Indian Inst. of

Technology,Banaras Hindu Univ., Varanasi, India; [4]Clin. Neurosciences, THE FOUNDATION OF THE SOCIETY FOR THE STUDY OF NEU, CLUJ NAPOCA, Romania; [5]Neurol., Bethune Intl. Peace Hosp., Hebi Province, China; [6]Biomed. Engin., Univ. of Arkansas, Fayetteville, AR; [7]Chem. & Biochem., Univ. of Aekansas Fayetteville, Fayetteville, AR; [8]Drug Develop. & Discovery, Ever NeuroPharma, Mondsee, Austria

Abstract: Methamphetamine (METH) is widely abused drug for recreation across the World. Previous experiments from laboratory showed that consumption of METH at hot environment leads to exacerbation of neurotoxicity. Breakdown of blood-brain barrier (BBB), edema formation and cellular injuries were 2- to 3 fold greater after METH administration (20 mg/kg, i.p.) at 30°C as compared to identical dose given at room temperature (21°C). Biochemical measurement of serotonin (5-HT) and tumor necrosis factor-alpha (TNF-a) showed 70 to 80 % higher accumulation in the brain and in CSF of METH exposed rats at hot environment as compared to room temperature. Since METH exposure reduces neurotrophic factors in the brain and enhances 5-HT and cytokine levels, it would be possible to reduce neurotoxicity of METH by exogenous supplement of cerebrolysin-a balanced composition of several neurotrophic factors with active peptide fragments in hot environment. Few reports suggest that combination of cerebrolysin with mesenchymal stem cells (MSCs) induce superior neuroprotection in traumatic brain injury. Thus, in this investigation we explored the role of MSCs and cerebrolysin in METH induced neurotoxicity at hot environment. METH (20 mg/kg, i.p.) was administered in male rats (Age 20 to 25 weeks) at 21°C or 30°C and neurotoxicity was examined 4 h after exposure. Profound BBB disruption to Evans blue albumin (EBA) and radioiodine in several brain areas associated with brain edema and neuronal injuries were seen with METH at 30°C. TiO2-nanowired administration of cerebrolysin (2.5 ml/kg, i.v.) together with nanowired MSCs (10^6) given 30 min after METH, significantly attenuated BBB breakdown, brain edema formation and neuronal injuries at 30°C. In these rats, 5-HT and TNF-a levels were also significantly reduced. Interestingly, cerebrolysin or MSCs alone were able to reduce METH neurotoxicity at room temperature together with elevation of 5-HT and TNF-a in brain or CSF. Immunohistochemical investigation exhibited significantly higher upregulation of heat shock protein 72 (HSP-72) in the areas showing brain damage after METH administration at 30°C. Nanodelivery of cerebrolysin with MSCs significantly thwarted upregulation of HSP-72 expression induced by METH at 30°C. Taken together these observations for the first to show that MSCs and cerebrolysin could reduce METH toxicity by reducing cellular stress associated with elevated 5-HT and TNF-a levels, not reported earlier. It remains to be seen whether nanodelivery of TNF-a or 5-HT antibodies together with cerebrolysin may have additional advantages in reducing METH neurotoxicity at hot environment require further investigation.

Disclosures: J.V. Lafuente: None. **A. Sharma:** None. **R. Patnaik:** None. **D.F. Muresanu:** None. **L. Feng:** None. **A. Ozkizilcik:** None. **R. Tian:** None. **H. Moessler:** None. **H.S. Sharma:** None.

Nanosymposium

015. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: SDCC 2

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 015.07

Topic: C.07. 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;
Air Force Material Command, USAF Grant nr FA8655-05-1-3065;
Alzheimer's Association (IIRG-09- 132087),
National Institutes of Health (R01 AG028679)
Dr. Robert M. Kohrman Memorial Fund (MAS, RJC);
Swedish Medical Research Council (Nr 2710-HSS),
Swedish Strategic Research Foundation

Title: Co-administration of nanowired cerebrolysin with neprilysin combined with antibodies to amyloid beta peptide thwarted exacerbation of brain pathology and tau protein accumulation following concussive head injury at hot environment

Authors: *A. NOZARI[1], A. SHARMA[2], D. F. MURESANU[3], J. V. LAFUENTE[4], R. PATNAIK[5], I. MANZHULO[6,7], R. J. CASTELLANI[8], A. OZKIZILCIK[9], R. TIAN[10], H. MOESSLER[11], H. S. SHARMA[2]
[1]Anesthesia and Critical Care, Massachusetts Gen. Hosp., Boston, MA; [2]Surgical Sciences, Anesthesiol. & Intensive Care Med., Uppsala Univ., Uppsala, Sweden; [3]Clin. Neurosciences, THE FOUNDATION OF THE SOCIETY FOR THE STUDY OF NEU, CLUJ NAPOCA, Romania; [4]Neurosciences, Univ. of Basque Country, Bilbao, Spain; [5]Sch. of Biomed. Engin., Indian Inst. of Technology,Banaras Hindu Univ., Varanasi, India; [6]Far Eastern Branch, Russian Acad. of Sciences,, Natl. Scientific Ctr. of Marine Biol., Vladivostok, Russian Federation; [7]Sch. of Biomedicine, Far Eastern Federal Univ., Vladivostok, Russian Federation; [8]Pathology, Univ. of Maryland, Baltimore, MD; [9]Biomed. Engin., Univ. of Arkansas, Fayetteville, AR; [10]Chem. & Biochem., Univ. of Arkansas Fayetteville, Fayetteville, AR; [11]Drug Develop. & Discovery, Ever NeuroPharma, Mondsee, Austria

Abstract: Previous reports from our laboratory showed that concussive head injury (CHI) when inflicted at hot environment (HE) induces exacerbation of brain pathology and higher accumulation of amyloid beta peptide (AbP) and tau levels in the cerebrospinal fluid (CSF) as compared to identical CHI at room temperature (RT). Co-administration of nanowired cerebrolysin with antibodies to tau was able to thwart brain pathology and AbP and tau levels in the CSF following CHI at HE. This suggests that CHI could induce AbP and tau pathology leading to brain damage at HE. Since AbP and tau pathology are interlinked in brain pathology

in several neurodegenerative diseases e.g., Alzheimer's and Parkinson's, it would be interesting to see whether nanowired delivery of cerebrolysin together with antibodies to AbP could equally induce neuroprotection and reduce tau levels in the CSF in CHI at HE.
CHI was inflicted by dropping a weight of 114.6 g from 20 cm height on the exposed parietal skull bone in Equithesin anaesthetized rats either acclimatized at RT (21±1°C) or at HE (34°C for 4 h per day for 2 weeks in biological oxygen demand incubator (BOD, relative humidity 45-47 %, wind speed 20-25 cm/sec). HE alone did not result in BBB breakdown, edema formation or changes in AbP or tau levels. However, CHI in HE resulted in 250 to 285 % higher breakdown of the BBB to Evans blue albumin and radioiodine ($^{[131]}$-I) and exhibited neuronal, glial and axonal damage as compared to identical CHI at RT after 24 trauma. The AbP and tau in CHI at HE increased by 3- to 6-fold in the CSF (control AbP 0.23±0.04; CHI-RT 0.82±0.05; CHI-HE 2.34±0.12 ng/ml); (Control tau 20±2; CHI-RT 34±6; CHI-HE 76±8 pg/ml). Nanodelivery of cerebrolysin (2.5 ml/kg, i.v.) together with 50 µl 1:20 AbP antibodies i.c.v. 4 h after CHI resulted in significant reductions in AbP levels and brain pathology in CHI at HE. Interestingly the tau levels also showed marked reduction in the CSF in these groups. Immunohistochemical analysis of heat shock protein 72 (HSP-72) showed pronounced overexpression in CHI at HE as compared to identical injury at RT. Treatment with cerebrolysin and AbP antibodies also thwarted HSP-72 upregulation at after CHI at HE. Since HSP-72 isoform is normally an inducible one, it appears that cellular stress induced by AbP and tau could further contribute to exacerbation of trauma induced brain pathology. Furthermore, our studies show that cerebrolysin and antibodies to AbP also reduced tau levels in CSF indication an intricate connections between AbP and tau in exacerbation of brain damage following CHI, not reported earlier.

Disclosures: A. Nozari: None. **A. Sharma:** None. **D.F. Muresanu:** None. **J.V. Lafuente:** None. **R. Patnaik:** None. **I. Manzhulo:** None. **R.J. Castellani:** None. **A. Ozkizilcik:** None. **R. Tian:** None. **H. Moessler:** None. **H.S. Sharma:** None.

Nanosymposium

015. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: SDCC 2

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 015.08

Topic: C.07. 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;
Air Force Material Command, USAF Grant nr FA8655-05-1-3065;
Institut Henri Beaufour-IPSEN, 75116 Paris, France
Ministry of Science & Technology, People Republic of China
Swedish Strategic Foundation, Stockholm, Sweden (HSS/AS)

Swedish Medical Research Council (Nr 2710-HSS),
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),

Title: TiO2-nanowired delivery of Chinese extract of Gingko biloba EGB-761 and BN-52021 enhanced neuroprotective effects of cerebrolysin in spinal cord injury at cold environment

Authors: *A. K. PANDEY[1], A. SHARMA[2,3], K. DRIEU[4], R. PATNAIK[5], Z. ZHANG[6], C. LI[6], D. F. MURESANU[7], J. V. LAFUENTE[8], A. NOZARI[9], A. OZKIZILCIK[10], R. TIAN[11], H. MOESSLER[12], H. S. SHARMA[2,3]
[1]Senior Res. Fellow, IIT-BHU, Ballia, India; [2]Surgical Sciences, Anesthesiol. & Intensive Care Med., Uppsala Univ., Uppsala, Sweden; [3]Int. Exp. CNS Injury & Repair (IECNSIR), Uppsala Univ. Hosp., Uppsala, Sweden; [4]Drug Develop. & Discovery, Inst. Henri Beaufour-IPSEN, Paris, France; [5]Sch. of Biomed. Engin., Indian Inst. of Technology,Banaras Hindu Univ., Varanasi, India; [6]Dept. of Neurosurg., Chinese Med. Hosp. of Guangdong Province, The Second Affiliated Hospital, Univ. of Chinese Med. in Guangzhou, Guangzhou, China; [7]Clin. Neurosciences, The Fndn. of the Society for the Study of NEU, CLUJ NAPOCA, Romania; [8]Neurosciences, Univ. of Basque Country, Bilbao, Spain; [9]Anesthesia and Critical Care, Massachusetts Gen. Hosp., Boston, MA; [10]Biomed. Engin., Univ. of Arkansas, Fayetteville, AR; [11]Chem. & Biochem., Univ. of Arkansas Fayetteville, Fayetteville, AR; [12]Drug Develop. & Discovery, Ever NeuroPharma, Mondsee, Austria

Abstract: Spinal cord injury (SCI) induces lifetime disability and depending on the magnitude and severity results in loss of functional activity due to paraplegia or quadriplegia of the victims. Military personnel during combat operation are more prone to SCI for which no suitable therapeutic strategies have been developed so far. Thus, exploration of novel therapeutic strategies with novel compounds either alone or in combination is required to enhance the therapeutic efficacy in SCI. Also, nanodelivery of compounds are needed for superior neuroprotective ability and long-lasting effects for added therapeutic values. We have earlier shown that traumatic brain injury (TBI) when performed at hot or cold environments results in exacerbation of brain pathology. However, effects of cold environment (CE) on SCI are not well known. SCI induces severe oxidative stress and results in decrease in several neurotrophic factors in the cord causing lack of regenerative ability after trauma. Since military personnel often inflicted with SCI at high altitude and CE, in this investigation we examined SCI induced cord pathology in CE. In addition, we evaluated the effects of nanowired delivery of cerebrolysin (CBL-a balanced composition of several neurotrophic factors and active peptide fragments) in combination with extracts of Gingko biloba the well-known antioxidant compounds EGB-761 or bilobalide BN-52021 in SCI. SCI was inflicted in Equithesin anesthetized rats by making a longitudinal incision of the right dorsal horn of the T10-11 segments (2 mm deep and 4 mm long) and allowed to survive 24 h after trauma in rats at room temperature (RT 21±1°C) or animals reared at CE (5±1°C in BOD incubator 2 h daily for 1 week). Our observations show that SCI at CE resulted in marked enhancement of blood-spinal cord barrier (BSCB) breakdown to protein tracers by 75 to 89 %, edema formation (1.5 to 2.8 %) and neuronal injury (60 to 85 %) as compared to identical SCI at RT. Nanodelivery of CBL (5 ml/kg, i.v.) together with nanowired EGb-761 (50 mg/kg, i.p.) and BN-52021 (80 mg/kg, i.p.) 4 h and 8 h after SCI

resulted in profound neuroprotection after trauma at CE. However, when these agents were delivered alone in identical conditions, the magnitude of neuroprotection was much less evident after 24 SCI at CE. Nanowired CBL together with either EGb-761 or BN-52021 were able to reduce SCI induced cord pathology significantly at RT. It appears that EGb-761 is more potent in inducing neuroprotection in SCI as compared to BN-52021. Taken together our observations are the first to show that EGb-761 together with BN-52021 has potentiated the neuroprotective effcst of CBL in SCI at CE, not reported earlier.

Disclosures: A.K. Pandey: None. **A. Sharma:** None. **K. Drieu:** None. **R. Patnaik:** None. **Z. Zhang:** None. **C. Li:** None. **D.F. Muresanu:** None. **J.V. Lafuente:** None. **A. Nozari:** None. **A. Ozkizilcik:** None. **R. Tian:** None. **H. Moessler:** None. **H.S. Sharma:** None.

Nanosymposium

015. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: SDCC 2

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 015.09

Topic: C.07. 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;
air Force Material Command, USAF Grant nr FA8655-05-1-3065;
Swedish Medical Research Council (Nr 2710-HSS)
Swedish Strategic Research Foundation, Stockholm, Sweden
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
National Institutes of Health (R01 AG028679)
IT 794/13 (JVL), Government of Basque Country

Title: Nanodelivery of curcumin attenuates methamphetamine neurotoxicity and elevates dopamine and brain derived neurotrophic factors

Authors: *G. TOSI[1], A. SHARMA[2,3], B. RUOZI[1], F. FORNI[1], M. A. VANDELLI[1], J. V. LAFUENTE[4], A. NOZARI[5], D. F. MURESANU[6,7], H. S. SHARMA[2,3]
[1]Te.far.t.I, Dept of Life Sciences, Univ. of Modena and Reggio Emilia, Modena, Italy; [2]Surgical Sciences, Anesthesiol. & Intensive Care Med., Uppsala Univ., Uppsala, Sweden; [3]Int. Exp. CNS Injury & Repair (IECNSIR), Uppsala Univ. Hosp., Uppsala, Sweden; [4]Neurosciences, Univ. of Basque Country, Bilbao, Spain; [5]Anesthesia and Critical Care, Massachusetts Gen. Hosp., Boston, MA; [6]Clin. Neurosciences, The Fndn. of the Society For the Study of Neu, Cluj Napoca, Romania; [7]Neurol., ‘‘RoNeuro’’ Inst. for Neurolog. Res. and Diagnos., Cluj-Napoca, Romania

Abstract: Curcumin is well known antioxidant that is used as traditional medicine in China and India since ages to treat variety of inflammatory ailments and as a food supplement. Curcumin

has anti-tumor effects [1] as well as a neuroprotective effects in Alzheimer's disease. Curcumin elevates brain derived neurotrophic factor (BDNF) and elevates dopamine (DA) level in the brain indicating its role in substance abuse. Methamphetamine (METH) is one of the most abused substances in the World that induces profound neurotoxicity by inducing breakdown of the blood-brain barrier (BBB) to albumin causing vasogenic edema and cellular injuries. However, influence of curcumin on METH induced neurotoxicity is still not investigated. In this investigation we examined METH induced neurotoxicity in rats and its modification with curcumin alone or following its nanodelivery. METH (20 mg/kg, i.p.) induces neurotoxicity in rats after 4 h that is evident with 130 to 158 % increase in the BBB permeability to Evans blue albumin in the cerebral cortex, hippocampus, cerebellum, thalamus and hypothalamus as compared to saline control. Vasogenic brain edema as measured using water content was seen in all these regions showing BBB leakage Nissl attaining showed profound neuronal injuries or damage in the above areas exhibiting BBB leakage. Normal curcumin (2 mg/kg, i.v.) 1 h after METH administration was able to reduce BBB breakdown and brain edema partially in some of the above brain regions. However, when nanodelivery of curcumin (2 mg/kg, i.v.) was done significantly attenuated brain edema formation, neuronal injuries and the BBB leakage to Evans blue in all the above brain areas. Measurement of BDNF showed a significant higher level in the cerebral cortex, hippocampus, cerebellum and thalamus of METH treated rats that received nanodelivery of curcumin as compared to saline treated METH animals. Nanodelivery of curcumin was also able to significantly enhance DA levels in the cortex, hippocampus and cerebellum in METH treated rats, whereas normal curcumin was able to slightly elevate DA and BDNF levels in the cerebral cortex and thalamus. Taken together our observations are the first to show that nanodelivery of curcumin induces superior neuroprotection in METH neurotoxicity and this could be largely due to enhanced BDNF and DA levels in the brain caused by curcumin, not reputed earlier.

1. Zhang Z, Li C, Tan Q, Xie C, Yang Y, Zhan W, Han F, Sharma HS, Sharma A. **Curcumin** Suppresses Tumor Growth and Angiogenesis in Human Glioma Cells Through Modulation of Vascular Endothelial Growth Factor/ Angiopoietin-2/Thrombospondin-1 Signaling. CNS Neurol Disord Drug Targets. 2017;16(3):346-350.

Disclosures: G. Tosi: None. **A. Sharma:** None. **B. Ruozi:** None. **F. Forni:** None. **M.A. Vandelli:** None. **J.V. Lafuente:** None. **A. Nozari:** None. **D.F. Muresanu:** None. **H.S. Sharma:** None.

Nanosymposium

015. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: SDCC 2

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 015.10

Topic: C.07. 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;
Air Force Material Command, USAF, under grant number FA8655-05-1-3065;
Alzheimer's Association (IIRG-09- 132087),
National Institutes of Health (R01 AG028679)
Dr. Robert M. Kohrman Memorial Fund (MAS, RJC);
Swedish Medical Research Council (Nr 2710-HSS),
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),

Title: Nanowired delivery of antibodies to amyloid beta peptide, phosphorylated tau and serotonin together with cerebrolysin induces superior neuroprotection following sleep deprivation induced exacerbation of Alzheimer's disease pathophysiology

Authors: *A. SHARMA[1], R. J. CASTELLANI[3], D. F. MURESANU[4], J. V. LAFUENTE[5], A. OZKIZILCIK[6], Z. R. TIAN[7], A. NOZARI[8], R. PATNAIK[9], H. MOESSLER[10], H. S. SHARMA[2]
[2]Surgical Sciences, Anesthesiol. & Intensive Care Med., [1]Uppsala Univ., Uppsala, Sweden; [3]Dept. of Pathology, Univ. of Maryland, Baltimore, MD; [4]Clin. Neurosciences, The Fndn. of The Society for the Study of Neu, Cluj Napoca, Romania; [5]Neurosciences, Univ. of Basque Country, Bilbao, Spain; [6]Biomed. Engin., Univ. of Arkansas, Fayetteville, AR; [7]Chem. & Biochem., Univ. of Arkansas Fayetteville, Fayetteville, AR; [8]Anesthesia and Critical Care, Massachusetts Gen. Hosp., Boston, MA; [9]Sch. of Biomed. Engin., Indian Inst. of Technology,Banaras Hindu Univ., Varanasi, India; [10]Drug Develop. & Discovery, Ever NeuroPharma, Mondsee, Austria

Abstract: Military personnel are often quite susceptible to sleep deprivation (SD) and related mental abnormalities such as attention deficit or decision-making abilities. Previous experiments from our laboratory show that sleep deprivation (SD) itself induces neuronal damage and further exacerbates traumatic brain injury induced pathology. It is likely that increased levels of serotonin in the brain and in plasma following SD contributes to blood-brain barrier (BBB) and blood-cerebrospinal fluid barriers (BCSFB) breakdown and cell injuries. Breakdown of the BBB and BCSFB will allow passage of proetins and other harmful agents into the fluid compartment of the brain causing brain edema and cellular damage. Since SD is also associated with upregulation of amyloid beta protein (AβP) and phosphorylated tau (p-tau) it appears that breakdown of the BBB and BCSFB could enhance the their transport into the brain fluid compartment resulting in exacerbation of AD pathology. Thus, it is quite likely that infusion of antibodies to AβP, p-tau and serotonin together to neutralize their actions in vivo with a known neuroprotective agent-cerebrolysin (a balanced composition of several neurotrophic factors and active peptide fragments) using TiO2 nanodelivery could induce superior neuroprotection in AD following SD. AD like pathology was induced in Male Sprague-Dawley rat (Age 30-35 weeks) by infusion AβP (1-40 human, soluble in water) intraventricularly (i.c.v.) in the left lateral ventricle (250 ng/10 µl once daily for 4 weeks. SD was induced by inverted flowerpot method in rat for 48 h. Our results showed 190 to 264 % increase in AβP and p-tau in different brain areas along with 250 to 310 % elevation of plasma and brain serotonin levels in AβP administration in SD as compared to AβP infusion alone. The BBB and BCSFB showed 230 to 290 % increase to radioiodine in AD with SD from AD alone. Nanowired delivery of cerebrolysin (25 µl),with

antibodies (dilution 1:10) to AβP (10 µl), p-tau (10 µl) and serotonin (20 µl) given i.c.v. 10 days after AβP infusion for 1 week significantly reduced AβP and p-tau levels in the brain and thwarted serotonin accumulation in the plasma and brain. This treatment also restored BBB and BCSFB function to radioiodine by 85 to 90%. Neuronal damages, astrocytic activation and axonal injuries were also significantly reduced by the combined treatment in AD with SD. These observations are the first to show that co-administration of TiO2-nanowired cerebrolysin with antibodies to AβP, p-tau and serotonin has remarkably superior neuroprotective effects in AD following SD, not reported earlier.

Disclosures: A. Sharma: None. **R.J. Castellani:** None. **D.F. Muresanu:** None. **J.V. Lafuente:** None. **A. Ozkizilcik:** None. **Z.R. Tian:** None. **A. Nozari:** None. **R. Patnaik:** None. **H. Moessler:** None. **H.S. Sharma:** None.

Nanosymposium

015. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: SDCC 2

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 015.11

Topic: C.07. 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;
Air Force Material Command, USAF Grant nr FA8655-05-1-3065;
Swedish Medical Research Council (Nr 2710-HSS)
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
Astra Zeneca, Mölndal, Sweden (HSS/AS)
India-EU Co-operation Program (RP/AS/HSS)
Ministry of Science & Technology, Govt. of India (HSS/AS),

Title: Nanowired delivery of cerebrolysin with mesenchymal stem cells attenuates heat stress induced exacerbation of brain pathology following blast brain injury

Authors: *D. F. MURESANU[1,2], A. SHARMA[3,4], R. PATNAIK[5], J. V. LAFUENTE[6], A. D. BUZOIANU[7], I. MANZHULO[8,9], A. NOZARI[10], A. OZKIZILCIK[11], R. TIAN[12], L. FENG[13], Z. ZHANG[14], C. LI[14], H. MOESSLER[15], H. S. SHARMA[3,4]
[1]The Fndn. of the Society for the Study of NEU, Cluj Napoca, Romania; [2]Neurol., ‘‘RoNeuro’’ Inst. for Neurolog. Res. and Diagnos., Cluj-Napoca, Romania; [3]Surgical Sciences, Anesthesiol. & Intensive Care Med., Uppsala Univ., Uppsala, Sweden; [4]Int. Exp. CNS Injury & Repair (IECNSIR), Uppsala Univ. Hosp., Uppsala, Sweden; [5]Sch. of Biomed. Engin., Indian Inst. of Technology,Banaras Hindu Univ., Varanasi, India; [6]Clin. Neurosciences, Univ. of Basque Country, Bilbao, Spain; [7]Dept. of Pharmacology, Fac. of Med., Univ. of Med. and Pharmacy, “Iuliu Haţieganu”, Cluj-Napoca, Romania; [8]Far Eastern Branch, Russian Acad. of Sciences,,

Natl. Scientific Ctr. of Marine Biol., Vladivostok, Russian Federation; [9]Sch. of Biomedicine, Far Eastern Federal Univ., Vladivostok, Russian Federation; [10]Anesthesia and Critical Care, Massachusetts Gen. Hosp., Boston, MA; [11]Biomed. Engin., Univ. of Arkansas, Fayetteville, AR; [12]Chem. & Biochem., Univ. of Arkansas Fayetteville, Fayetteville, AR; [13]Neurol., Bethune Intl. Peace Hosp., Hebi Province, China; [14]Dept. of Neurosurg., Chinese Med. Hosp. of Guangdong Province, The Second Affiliated Hospital, Univ. of Chinese Med. in Guangzhou, Guangzhou, China; [15]Drug Develop. & Discovery, Ever NeuroPharma, Mondsee, Austria

Abstract: Military personnel are prone to blast brain injury (bBI) duirng combat operations across the world where hyperthermia or hot environment is prevalent. The bBI is a combination of pressure, rotation, penetration of sharp objects and chemical exposure causing laceration, perforation and tissue loss in the brain. Moreover, this is still unknown whether hot environment (HE) could exacerbate brain pathology after bBI. The bBI was examined in a rat model at normal or HE. For neurorepair, nanodelivery of cerebrolysin (CBL, a multimodal drug comprising neurotrophic factors and active peptide fragments) and/or mesenchymal stem cells (MSCs) were examined on the pathological outcome of bBI. Equithesin (3 ml/kg, i.p.) anesthetized rats head was exposed to overpressure blast in a shock tube where compressed air-and helium-induced membrane rupture results in pressure waves (100, 150 or 200 kPa) with a shockwave velocity of ca. 400 to 450 m/sec and the animals were allowed to survive 8 and 12 h after trauma. Identical bBI was induced to rats exposed to HE at 38°C for 2 h daily for 1 week. In both group of bBI blood-brain barrier (BBB) breakdown to Evans blue albumin and radioiodine, brain edema formation and neuronal, glial and axonal injuries were evaluated. In addition, regional cerebral blood flow (rCBF) was also examined using radiolabelled microspheres.
Our observations showed a progressive BBB breakdown in the cerebral cortex, hippocampus, cerebellum, thalamus, hypothalamus and brain stem that correlates well with the blast overpressure strength. In these brain areas rCBF reduced by -30 to -58 % associated with increased edema formation resulting in 8 to 16 % higher volume swelling. Expansion of neuropil, sponginess and neuronal, glial and myelin damages are quite frequent. These pathophysiological changes were 2-to 3-fold higher after identical bBI in rats at HE. Nanodelivery of CBL or MSCs (10^6 cells, i.v.) alone either 30 min or 1 h after bBI (5 ml/kg, i.v.) significantly reduced brain pathology in normal animals but this effect was much less evident in rats after bBI at HE. However, when TiO2 nanodelivery of CBL (5 ml/kg, i.v.) together with MSCs (10^6 cells, i.v.) was administered, significant neuroprotection in bBI was observed in animals at HE. These observations are the first to show that (i) bBI induced brain pathology is exacerbated at HE, (ii) nanodelivery of CBL or MSCs has the potential to reduce brain pathology of normal animals after bBI, (iii) whereas, a combination of nanowired CBL and MSCs is needed to induce neuroprotection after bBI in heat exposed animals, not reported earlier.

Disclosures: D.F. Muresanu: None. **A. Sharma:** None. **R. Patnaik:** None. **J.V. Lafuente:** None. **A.D. Buzoianu:** None. **I. Manzhulo:** None. **A. Nozari:** None. **A. Ozkizilcik:** None. **R. Tian:** None. **L. Feng:** None. **Z. Zhang:** None. **C. Li:** None. **H. Moessler:** None. **H.S. Sharma:** None.

Nanosymposium

015. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: SDCC 2

Time: Saturday, November 3, 2018, 1:00 PM - 4:00 PM

Presentation Number: 015.12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Ministry of Science and Technology of the People's Republic of China
Air Force Material Command, USAF Grant nr FA8655-05-1-3065;
Air Force Office of Scientific Research (EOARD, London, UK),
Swedish Medical Research Council (Nr 2710-HSS),
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
India-EU Co-operation Program (RP/AS/HSS)
IT 794/13 (JVL), Government of Basque Country

Title: Co-administration of TiO2 DL-3-n-butylphthalide (DL-NBP) with mesenchymal stem cells enhanced neuroprotection in Parkinson's disease after concussive head injury

Authors: *L. FENG[1], A. SHARMA[2,3], N. FENG[4], A. NOZARI[5], J. V. LAFUENTE[6], D. F. MURESANU[7,8], R. PATNAIK[9], A. OZKIZILCIK[10], R. TIAN[11], H. S. SHARMA[2,3]
[1]Bethune Intl. Peace Hosp., Hebi Province, China; [2]surgical Sciences, Anesthesiol. & Intensive Care Med., Uppsala Univ., Uppsala, Sweden; [3]Int. Exp. CNS Injury & Repair (IECNSIR), Uppsala Univ. Hosp., Uppsala, Sweden; [4]Drug Develop. & Discovery, CSPC NBP Pharmaceut. Med., Shijiazhuang, China; [5]Anesthesia and Critical Care, Massachusetts Gen. Hosp., Boston, MA; [6]Neurosciences, Univ. of Basque Country, Bilbao, Spain; [7]Clin. Neurosciences, THE FOUNDATION OF THE SOCIETY FOR THE STUDY OF NEU, CLUJ NAPOCA, Romania; [8]Clin. Neurosciences, ‘‘RoNeuro’’ Inst. for Neurolog. Res. and Diagnostic,, Cluj-Napoca, Romania; [9]Sch. of Biomed. Engin., Indian Inst. of Technology,Banaras Hindu Univ., Varanasi, India; [10]Biomed. Engin., Univ. of Arkansas, Fayetteville, AR; [11]Chem. & Biochem., Univ. of Arkansas Fayetteville, Fayetteville, AR

Abstract: DL-3-n-butylphthalide (DL-NBP) is one of the constituents of Chinese celery extract that is used to treat stroke, dementia and ischemic diseases. Since NBP has powerful antioxidative effects, the compound has shown powerful neuroprotective effects in Alzheimer’s disease (AD), Amyolateral sclerosis (ALS) and other neurodegenerative diseases. However, role of NBP in Parkinson’s disease (PD) is not well known. Few studies in cell culture showed neuroprotective effects of NBP in PD. Thus, efforts should be made to understand the role of NBP in PD in great details. Recent research shows that traumatic brain injury (TBI) is one of the key factors inducing PD like symptoms in human populations and particularly in military personnel who are prone to TBI. There are many similarities in AD and PD cases as both exhibit deposition of amyloid beta peptide (AbP), tau phosphorylation (p-tau) as well as alpha synuclein

(ASNC) disturbances. Previous reports from our laboratory showed that nanowired-NBP are capable to induce profound neuroprotection following concussive head injury (CHI). Thus, it would be interesting to explore the possible neuroprotective effects of NBP in PD following CHI in a rat model. It has been shown that a combination of NBP and mesenchymal stem cells (MSCs) reduces brain pathology following carbon monoxide poisoning in human cases. Thus, we also examined a combination of MSCs and NBP in our model of PD with CHI. PD like symptoms was induced in naive or CHI rats by administration of 1-metyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP, 20 mg/kg) daily within 2-h intervals for 5 days. CHI was inflicted under anesthesia by dropping a weight of 114.6 g from a height of 20 cm inducing an impact of 0.224 N on right parietal skull. PD symptoms e.g., loss of tyrosine hydroxylase (TH) activity in substantia niagra pars compacta (SNpc) and striatum (STr) and decrease in dopamine (DA) and dopamine decarboxylase (DOPAC) levels were exacerbated by CHI. The p-tau in the cerebrospinal fluid (CSF) showed greater enhancement in CHI with PD.
Treatment with TiO2-nanowired delivery of NBP (40 mg/kg, i.p.) together with MSCs (10^6) 4 h after CHI in PD significantly reduced the p-tau levels in the cerebrospinal fluid (CSF) and restored the TH immunoreactivity in SNpc and STr. The levels of DA and DOPAC were also significantly elevated in CHI rats with PD as compared to the untreated group. Neuronal damages were also significantly reduced in PD after CHI by a combination of NBP and MSCs. These observations are the first to show that a combination of NBP with MSCs when delivered using nanowired technology has superior neuroprotective effects in PD exacerbated by CHI, not reported earlier.

Disclosures: L. Feng: None. **A. Sharma:** None. **N. Feng:** None. **A. Nozari:** None. **J.V. Lafuente:** None. **D.F. Muresanu:** None. **R. Patnaik:** None. **A. Ozkizilcik:** None. **R. Tian:** None. **H.S. Sharma:** None.

Nanosymposium

016. Somatosensation: Cortical Mechanisms

Location: SDCC 23

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 016.01

Topic: D.04. Somatosensation: Touch

Support: NSF GRFP #2014177995
NIH F31 NS101843
HMS Neurobiology Stuart H.Q. & Victoria Quan Fellowship

Title: Corticospinal modulation of somatosensory circuit processing

Authors: *M. SPRINGEL, D. D. GINTY
Harvard Med. Sch., Boston, MA

Abstract: While corticospinal motor neurons are often studied due to their importance in executing voluntary movement, corticospinal neurons residing in somatosensory cortex are less appreciated and not as well understood. Decades-old work from neuroanatomists traced these long-range descending projections from somatosensory cortex to the spinal cord dorsal horn, where they were hypothesized to exert top-down control over somatosensory circuits. But two major questions persist regarding top-down control of mechanosensory circuits: 1) how does descending corticospinal input modulate somatosensory signals as they are processed in the mechanosensory dorsal horn, and 2) what role does this descending input play in influencing tactile perception? To address these questions, we integrated molecular genetic and viral approaches to explore corticospinal anatomy, with electrophysiological approaches in slice and in vivo to investigate corticospinal modulation of mechanosensory circuits. To probe changes in mechanical sensitivity upon corticospinal manipulation, we trained animals to report perception of simple indentation stimuli using a tactile detection task. Preliminary data suggests that somatosensory corticospinal neurons are a heterogeneous population that may evoke top-down control by distinct mechanisms.

Disclosures: M. Springel: None. **D.D. Ginty:** None.

Nanosymposium

016. Somatosensation: Cortical Mechanisms

Location: SDCC 23

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 016.02

Topic: F.01. Neuroethology

Support: CIHR

Title: Closed- and open-loop control of voluntary whisker movements

Authors: *M. ELBAZ, C. ETHIER, M. DESCHENES
CERVO - Laval Univ., Quebec, QC, Canada

Abstract: Neural activities in the motor cortex and in the cerebellum are correlated with whiskers' position (Hill et al., 2011; Chen et al., 2016). Yet, the functional significance of these central modulations remains unknown. We designed a behavioral task to clarify their role in voluntary movements. Head-restrained rats were rewarded if they maintained their vibrissae protracted for up to 1 second, within an angular range getting narrower as training progressed. Both the angular precision and the ability to adapt to moving angular windows can thus be quantified. We found that rats are able to perform this task in the dark without any vibrissa contact. As facial muscles that move the vibrissae are devoid of proprioceptors (Moore et al., 2015), the question arises as to how rats perform the task. One possibility is that vibrissa position is signaled by receptors that also encode changes in the external environment (i.e., re-afference).

Another possibility is that information about vibrissa position derives from a central copy of the motor commands for the intended vibrissa position; this is denoted corollary discharge. We found that rats still perform the task after sensory de-afferentation, except when the motor cortex is inactivated or lesioned. Therefore, in the absence of sensory feedback, the motor cortex is crucially involved in dexterous whisker movements, as part of a corollary discharge network. On the other hand, inactivating the motor cortex in non-deafferented rats does not impair performance. Thus, in the presence of sensory feedback, a pathway which does not require motor cortical activity permits dexterous whisker movements: we are currently experiencing on this residual, possibly cerebellar, pathway.

Disclosures: M. Elbaz: None. **C. Ethier:** None. **M. Deschenes:** None.

Nanosymposium

016. Somatosensation: Cortical Mechanisms

Location: SDCC 23

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 016.03

Topic: D.04. Somatosensation: Touch

Support: R01NS08286505
NIHF31NS09695203

Title: Neural dynamics in S1 and M1 underlying arm and hand movements

Authors: *A. K. SURESH[1], J. GOODMAN, JR[1], S. LEE[2], N. G. HATSOPOULOS[1], S. J. BENSMAIA[2]
[2]Dept. of Organismal Biol. and Anat., [1]Univ. of Chicago, Chicago, IL

Abstract: Reaching movements are associated with oscillatory neural dynamics in primary motor cortex, which may reflect a fundamentally different representational scheme than that posited by traditional neural coding hypotheses. We investigate whether these oscillatory neural dynamics are also observed in the cortical representation of finger and wrist movements. To this end, we record the time-varying kinematics of the hand using a camera-based motion tracking system and the population activity in somatosensory and motor cortices using chronically implanted electrode arrays, while monkeys grasp thirty-five objects varying in shape and size. We then analyze the population responses in primary motor cortex and in proprioceptive areas of somatosensory cortex, namely Brodmann's areas 3a and 2. We find that the neural dynamics underlying hand movements in both somatosensory and motor cortices do not exhibit the strong rotational dynamics seen in motor cortex during proximal limb movements and consider the functional significance of this difference in neural representation.

Disclosures: A.K. Suresh: None. **J. Goodman:** None. **S. Lee:** None. **N.G. Hatsopoulos:** None. **S.J. Bensmaia:** None.

Nanosymposium

016. Somatosensation: Cortical Mechanisms

Location: SDCC 23

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 016.04

Topic: D.04. Somatosensation: Touch

Support: NIH Grant NS101325

Title: Temporal spiking patterns in somatosensory cortex convey information about surface texture

Authors: *K. H. LONG[1], J. D. LIEBER[2], S. J. BENSMAIA[3]
[1]Interdisciplinary Scientist Training Program, sp. Computat. Neurosci., [2]CNS, [3]Dept. of Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL

Abstract: We have an exquisite sensitivity to the microstructure and material properties of surfaces, allowing us to differentiate satin from silk and sense surface features across six orders of magnitude, from tens of nanometers to tens of millimeters. In the peripheral nerves, two separate mechanisms convey information about textures: coarse features are encoded in the spatial pattern of activation of slowly adapting type 1 (SA1) fibers, and fine features are encoded in the precise spike timing of rapidly adapting (RA) and Pacinian corpuscle (PC) fibers. Having previously shown that this precise temporal patterning is informative at the periphery, we tested the extent to which these temporal patterns are still present and informative in somatosensory cortex. To this end, we scanned a diverse set of everyday textures at a controlled speed and contact force across the fingertip of awake, behaving macaques while collecting single unit recordings from somatosensory cortex, including Brodmann's areas 3b, 1, and 2. We then wished to assess the degree to which neuronal responses convey information about texture identity, and whether spike timing conveyed complementary information (above and beyond that carried by rates).
To this end, we classified textures based on cortical spiking patterns at various temporal resolutions, from millisecond precision to spike count. We found that temporal patterning in the spiking responses of cortical neurons carries texture information, but this temporal code is less reliable and informative than is its counterpart in the nerve. Furthermore, the temporal resolution varies across cortical cells and depends in part on the submodality composition of their peripheral inputs, with neurons dominated by PC input exhibiting the highest temporal resolution and those dominated by SA1 input exhibiting the lowest. At the population level, a combination of rate and timing is more informative than each neural code in isolation. We conclude that

temporal spiking patterns do carry information about texture in somatosensory cortex and reflect a progressive conversion from temporal to rate code that is not yet complete.

Disclosures: K.H. Long: None. **J.D. Lieber:** None. **S.J. Bensmaia:** None.

Nanosymposium

016. Somatosensation: Cortical Mechanisms

Location: SDCC 23

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 016.05

Topic: D.04. Somatosensation: Touch

Support: Chinese FRFCU 2016QN81017
Chinese NSF 61673346
Chinese NSF 81600982
Chinese NSF 81527901

Title: The ultra-high field functional MRI reveals the vibrotactile frequency of primary somatosensory cortex in human

Authors: *B. QU[1,2], X. YU[1,3], Y. JIANG[1], M. XIN[1,2], H.-Y. LAI[1,2]
[1]Interdisciplinary Inst. of Neurosci. and Technology, QAAS, [2]Col. of Biomed. Engin. and Instrument Sci., [3]Dept. of Neurobiology, Sch. of Med., Zhejiang Univ., Zhejiang, China

Abstract: Mapping functional location of the primary somatosensory cortex (S1) is necessary for understanding of the properties of tactile perception in human. Generally, the ultra-high field functional magnetic resonance imaging (fMRI) could provide the reliable cortical responses of digits in the S1 because of the higher sensitivity and spatial resolution in blood-oxygen-level dependent (BOLD) signals. However, the effect of vibrotactile frequency responded to the cortical function in S1 remained unclear. Here, we used 7T fMRI to explore the frequency dependency of neural activity in S1 by implementing various vibrotactile frequencies at the digit tip. The lab-designed MR-compatible stimulator is consist of a piezoelectric device connected to a 2 mm in diameter round plastic probe, and the probe brings the vibrotactile stimulation to the tip of middle finger. The stimulation parameters include five vibrotactile stimulus frequencies (1 Hz, 6 Hz, 12 Hz, 24 Hz and 48 Hz) with 15 ms pulse duration. The tactile stimulus paradigm was one block design with OFF-ON-OFF, where OFF = 40 s and ON = 30 s. BOLD-fMRI signals were acquired by a GE-EPI sequence (TR = 2000 ms, TE = 21 ms, Voxel size: 1.5×1.5×1.5 mm3). The results showed that the lowest vibration frequency, 1 Hz, didn't produce BOLD response while the others, 6 Hz, 12 Hz, 24 Hz and 48 Hz, obtained BOLD responses in the Brodmann area 3b and 1 with respect to middle finger. There is no significant difference in the amplitude of BOLD in 6 Hz, 12 Hz, 24 Hz and 48 Hz stimulation frequencies.

Disclosures: B. Qu: None. **X. Yu:** None. **Y. Jiang:** None. **M. Xin:** None. **H. Lai:** None.

Nanosymposium

016. Somatosensation: Cortical Mechanisms

Location: SDCC 23

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 016.06

Topic: D.04. Somatosensation: Touch

Support: MOST106-2314-B-182-001
CMRPG5F0092
CMRPG5H0051

Title: Neural code in barrel cortex following partial neurorrhaphy in infraorbital nerve

Authors: *J. J. TSENG[1], M. C. CHIANG[1], H. P. CHEN[3,4], H. T. LIN[5,4], C. H. LIN[1,5,4], J. J. HUANG[1,3,4], Y. C. PEI[1,2,3,4]
[1]Sch. of Med., [2]Healthy Aging Res. Ctr., Chang Gung Univ., Taoyuan, Taiwan; [3]Dept. of Physical Med. and Rehabil., [4]Ctr. of Vascularized Tissue Allograft, [5]Dept. of Plastic & Reconstructive Surgery, Chang Gung Mem. Hospital, Linkou, Taoyuan, Taiwan

Abstract: Neuroplasticity has been considered as the major mechanism underlying the recovery of sensory function following a nerve reconstruction, but its cortical mechanism remains unknown. In this study, we evaluated the change of tuning to whisker stimulation in neurons in the barrel cortex (S1BF). Sprague-Dawley rats received hemi-neurorrhaphy surgery, a novel aberrant reinnervation model in which the connection in the infraorbital nerve was reconnected with a 50% spatial offset and 50% of the inputs were lost, yielding a systematic aberrant reinnervation following spontaneous regeneration. This animal model allows us to observe the temporal changes of neural code mediated by neuroplasticity. The single-units evoked by whisker stimulation were recorded in anesthetized rats from the sham control (SC) group and 1 (1-m) and 2 month (2-m) post hemi-neurorrhaphy groups. To characterize the direction tuning in S1BF neurons, the whiskers were stimulated in one of the eight directions using the piezo-motor based stimulator. Our results showed that neuronal firing decreased in the 1-m and 2-m groups (69±11% and 47±9%, respectively) as compared with the SC group. Surprisingly, the majority of neurons in the 1-m group had extremely strong direction selectivity and we dubbed such tuning as “nascent tuning”. Interestingly, the nascent tuning was less observed in the 2-m group, implying that nascent tuning occurs when distorted sensory input ascends from the reinnervated periphery. In summary, chronological changes of neuronal activities showed the cortical mechanisms underlying the recovery of sensation following an aberrant nerve regeneration.

Disclosures: J.J. Tseng: None. **M.C. Chiang:** None. **H.P. Chen:** None. **H.T. Lin:** None. **C.H. Lin:** None. **J.J. Huang:** None. **Y.C. Pei:** None.

Nanosymposium

016. Somatosensation: Cortical Mechanisms

Location: SDCC 23

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 016.07

Topic: D.03. Somatosensation: Pain

Support: NIH grants GM115384
NIH grants NS100016
NSF-CRCNS grant IIS-130764
China Scholarship Council 201606370208
National Natural Science Foundation of China 81771101

Title: Ketamine reduces hyperactivity of the anterior cingulate cortex to provide enduring relief of chronic pain

Authors: *H. ZHOU[1,3], Q. ZHANG[1], E. MARTINEZ[1], J. DALE[1], S. HU[2], E. ZHANG[1], K. LIU[1], D. HUANG[3], Z. CHEN[2], G. YANG[1], J. WANG[1]
[1]Dept. of Anesthesiology, Perioperative Care and Pain Med., [2]Dept. of Psychiatry, New York Univ. Sch. of Med., New York, NY; [3]Dept. of Pain, The Third Xiangya Hosp. and Inst. of Pain Med., Central South Univ., Changsha, China

Abstract: Pain has sensory and affective dimensions. Chronic pain not only causes sensory hypersensitivity, but it can also induce an amplified aversive reaction to peripheral nociceptive inputs. This specific enhancement of the affective response constitutes a key pathologic feature of chronic pain syndromes such as fibromyalgia. However, the neural mechanisms that underlie this important pain phenotype remain poorly understood, resulting in a lack of specific treatments. Here, we show that a single dose of ketamine can produce a persistent reduction in the aversive response to noxious stimuli in a rodent chronic pain model, long after the termination of its anti-nociceptive effects. Furthermore, combining *in vivo* electrophysiology with optogenetics and pharmacology, we demonstrated that this anti-aversive property is mediated by prolonged suppression of the hyperactivity of neurons in the anterior cingulate cortex, a brain region well-known to regulate pain affect. Therefore, our results show that it is feasible to dissociate the affective from the sensory component of pain, and demonstrate the potential for low-dose ketamine to be an important therapy for a variety of chronic pain syndromes.

Disclosures: H. Zhou: None. **Q. Zhang:** None. **E. Martinez:** None. **J. Dale:** None. **S. Hu:** None. **E. Zhang:** None. **K. Liu:** None. **D. Huang:** None. **Z. Chen:** None. **G. Yang:** None. **J. Wang:** None.

Nanosymposium

017. Vision: Representation of Objects and Scenes

Location: SDCC 32

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 017.01

Topic: D.07. Vision

Support: NIH Intramural Research Program

Title: The amygdala responds to the intermediate visual features of threatening animals

Authors: V. ZACHARIOU[1], A. C. DEL GIACCO[1], M. GHANE[1], L. G. UNGERLEIDER[1], *X. YUE[2]
[1]LBC:Section on Neurocircuitry, NIH/NIMH, Bethesda, MD; [2]NIH, Bethesda, MD

Abstract: Recent studies have demonstrated that differences in the amount of curvilinear and rectilinear visual features of animals and man-made objects are sufficient for animate/inanimate categorization (e.g. Perrinet and Bednar, 2015; Long et al. 2016). Here we explored (in humans) whether these intermediate visual features can also convey information associated with how threatening an animal is. Using the International Affective Picture System (IAPS; Lang et al. 2008) as a guide, we created two sets of stimuli. One consisted of animal images with high arousal and low valance IAPS ratings (threatening set) and the other of animal images with high valance and low arousal IAPS ratings (non-threatening set). The images that comprised these two sets were selected so that on average the threatening and non-threatening animal images were matched in the amount of image-based and perceived curvilinear and rectilinear features. Additionally, we matched stimuli on lower-level features such as mean luminance and root-mean-square contrast. Then, using an algorithm (Portilla and Simoncelli, 2000; Freeman and Simoncelli, 2011), we generated synthesized versions of the animal images in each set which maintained the intermediate visual features of the original images but made them unrecognizable. Global shape information was not preserved in these synthesized images and they appeared as texture patterns. We then presented these synthesized stimuli to a group of participants (n=20) within the context of a one-back memory task, inside an MRI scanner. Participants were told the synthesized images depicted abstract patterns. We found that bilateral amygdala was significantly more active in response to the threatening synthesized images compared to the non-threatening ones. In contrast, fMRI activity in control, affect-agnostic brain regions, such as V1 and fusiform face area, did not differ for the two sets of images. Importantly, during an image rating session which followed each scan, participants rated the threatening set of synthesized images as significantly more threatening compared to the non-threatening set, which is consistent with the fMRI findings. Lastly, these threat ratings significantly predicted the magnitude of activation in the amygdala; participants who rated the threatening stimuli as more threatening had greater amygdala activation in response to these stimuli. We conclude that the

intermediate visual features of animals convey information associated with how threatening they are and this information is processed by the amygdala.

Disclosures: V. Zachariou: None. **A.C. Del Giacco:** None. **M. Ghane:** None. **L.G. Ungerleider:** None. **X. Yue:** None.

Nanosymposium

017. Vision: Representation of Objects and Scenes

Location: SDCC 32

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 017.02

Topic: D.07. Vision

Support: Estonian Research Council PUT438
Estonian Research Council PUT1476

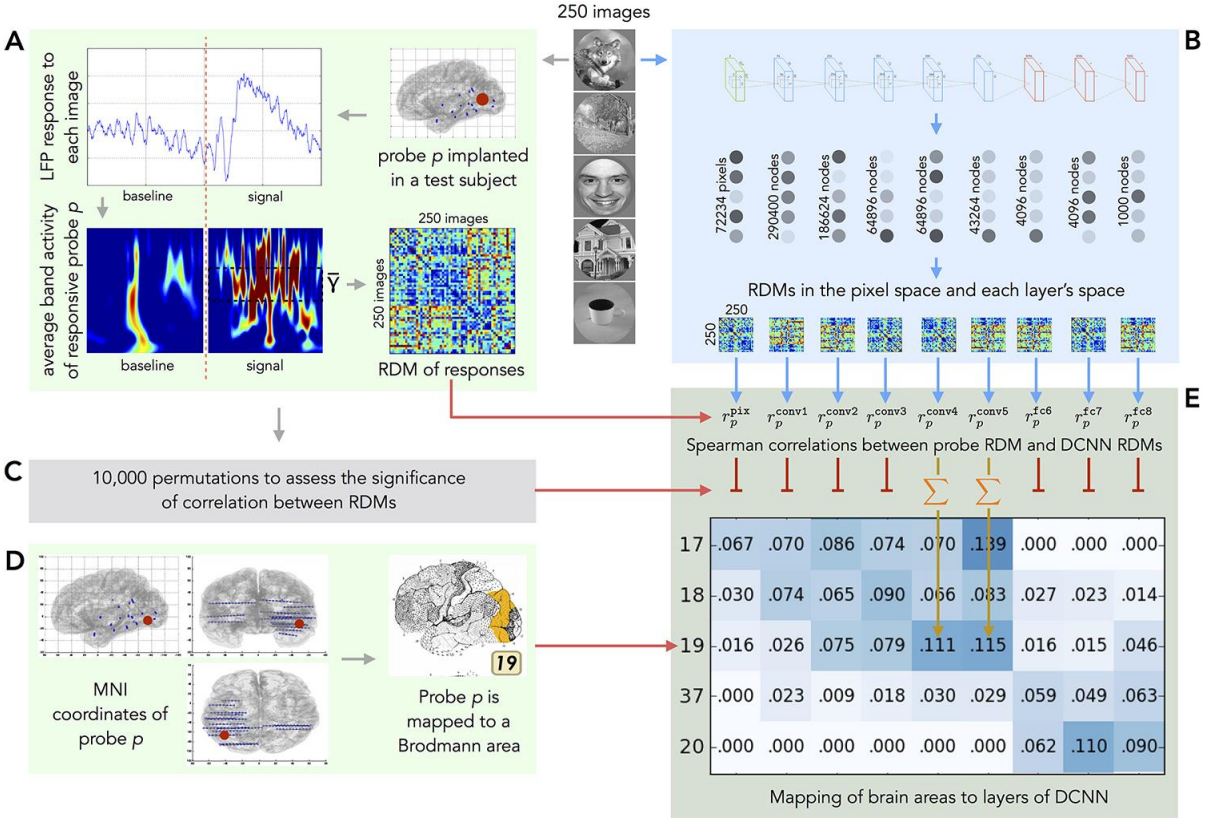
Title: Activations of deep convolutional neural network are aligned with gamma band activity of human visual cortex

Authors: *I. KUZOVKIN[1], R. VICENTE[1], M. PETTON[2,3], J.-P. LACHAUX[2,3], M. BACIU[4,5], P. KAHANE[6,7], S. RHEIMS[2,8,9], J. R. VIDAL[10,5,11], J. ARU[1]
[1]Inst. of Computer Sci., Univ. of Tartu, Tartu, Estonia; [2]Lyon Neurosci. Res. Ctr., INSERM U1028, Lyon, France; [3]Univ. Claude Bernar, Lyon, France; [4]LPNC, Univ. Grenoble-Alpes, Grenoble, France; [5]Lpnc, CNRS, Grenoble, France; [6]INSERM U1216, Grenoble, France; [7]Neurol. Departmen, CHU de Grenoble, Grenoble, France; [8]Dept. of Functional Neurol. and Epileptology, Hospices Civils de Lyon and Univ. Lyon, Lyon, France; [9]Epilepsy Inst., Lyon, France; [10]LPNC, Univ. Grenoble Alpes, Grenoble, France; [11]Catholic Univ. of Lyon, Lyon, France

Abstract: The rise of artificial intelligence fuelled by artificial neural networks puts the synergy between Neuroscience and AI in the spotlight. Advances in AI have revealed principles about neural processing, in particular about vision. Previous work demonstrated a direct correspondence between the hierarchy of the human visual areas and layers of deep convolutional networks (DCNN) trained on visual object recognition. We used DCNNs to investigate which frequency bands correlate with feature transformations of increasing complexity along the ventral visual pathway. By capitalizing on intracranial depth recordings from 100 patients and 11293 electrodes we assessed the alignment between the DCNN and signals at different frequency bands in different time windows.
To map human visual areas to layers of DCNN we calculate dissimilarity matrices in those two representation spaces for every brain area and every layer of DCNN and compute the mapping based on correlation scores between the pairs of RDM matrices. By observing the correlation scores ranked, on one hand, by the order of visual areas along the ventral stream and on the other

hand by the hierarchy of DCNN we compute an alignment between the two hierarchies -- one biological another artifical. By running this experiment on the activity from various temporal and spectral regions of interest we identify at what times and at which frequencies the hierarchies are aligned the most.

We have found that the gamma activity, especially in the low gamma-band (30-70 Hz), matched the increasing complexity of visual feature representations in the DCNN. Previous research has shown that in terms of anatomical location the activity of DCNN maps best to the activity of visual cortex and this mapping follows the propagation of activity along the ventral stream in time. With this work we have confirmed these findings and have additionally established at which frequency ranges the activity of human visual cortex correlates the most with the activity of DCNN, providing the full picture of alignment between these two systems in spatial, temporal and spectral domains.



Disclosures: I. Kuzovkin: None. **R. Vicente:** None. **M. Petton:** None. **J. Lachaux:** None. **M. Baciu:** None. **P. Kahane:** None. **S. Rheims:** None. **J.R. Vidal:** None. **J. Aru:** None.

Nanosymposium

017. Vision: Representation of Objects and Scenes

Location: SDCC 32

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 017.03

Topic: D.07. Vision

Support: Intramural Research Program

Title: Curved features are critical for animate/inanimate categorization in macaques

Authors: *M. YETTER[1], M. ELDRIDGE[2], G. MAMMARELLA[2], L. G. UNGERLEIDER[1], X. YUE[1]
[1]Lab. of Brain and Cognition, [2]Lab. of Neuropsychology, NIMH/NIH, Bethesda, MD

Abstract: In an earlier fMRI study, we showed that multivoxel activity patterns, measured with support vector machine classification, encoded animate vs. inanimate categories in the macaque inferior temporal cortex. However, the classification accuracy was reduced to chance after removing the variance in the fMRI activity patterns that were explained by the curvlinear and rectilinear image features, as quantified using curved and straight Gabor filters. These results indicate that categorization in the macaque inferior temporal cortex might not stem from acquired semantic knowledge of the characteristics that distinguish animate from inanimate object categories, but rather from their unique image-based features. The current experiment was designed to directly examine those two possibilities using behavioral tests. Three rhesus macaques were trained to categorize images of 20 animate and 20 inanimate objects, until their performance reached 85% accuracy for two consecutive days. Then, the monkeys were tested on novel trial-unique image sets of 100 animate and 100 inanimate objects across multiple days to assess whether the original training generalized to unfamiliar objects. We found that the animals' average classification accuracy for these unfamiliar objects was significantly above chance on the first day of testing, and performance continued to improve across the testing days, achieving an average of 83.82% ($p<0.001$), 75.34% ($p<0.001$), and 74.62% correct ($p<0.001$) for each monkey respectively. Taken together, our results support our fMRI conclusion that animate/inanimate categorization does not stem from acquired semantic knowledge of animate vs. inanimate categories. Next, we tested whether image features that differ substantially between the two object categories, such as curvilinear and rectilinear information, contribute to the monkeys' classification accuracy. Two of the three animals were tested across five days on sets of synthetic animate and inanimate images that were created using an algorithm that significantly distorted the global shape of the original images, while maintaining the original images' intermediate features (e.g. curvilinear and rectilinear information). We found that the animals' classification accuracy on these synthesized images was significantly above chance (62.45% ($p<0.001$), 58.63% correct ($p<0.001$) for each monkey, on average, across five days),

suggesting that unique image-based features, such as curvilinear features, distinguish animate from inanimate objects to some extent and contribute to the formation of animate/inanimate categorization in macaques.

Disclosures: M. Yetter: None. **M. Eldridge:** None. **G. Mammarella:** None. **L.G. Ungerleider:** None. **X. Yue:** None.

Nanosymposium

017. Vision: Representation of Objects and Scenes

Location: SDCC 32

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 017.04

Topic: D.07. Vision

Support: NIH R90DA023420
NIH R01MH107797
NIH R21MH103592
NSF Award 1734907

Title: Endogenous pre-stimulus activity modulates category tuning in ventral temporal cortex and influences behavior

Authors: *Y. LI[1], M. J. WARD[3], R. M. RICHARDSON[3], M. G. G'SELL[2], A. S. GHUMAN[3]
[1]Ctr. for the Neural Basis of Cognition, [2]Dept. of Statistics and Data Sci., Carnegie Mellon Univ., Pittsburgh, PA; [3]Dept. of Neurolog. Surgery, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Perception of sensory inputs is modulated by shifts in endogenous, ongoing brain activity. Specifically, previous studies have tied endogenous, pre-stimulus neural activity to behavior in sensory tasks. However, it remains unclear whether the endogenous activity modulates neural coding and category tuning in visual processing, and if this modulation of tuning provides a neural pathway for behavioral modulation. To address these questions, we collected intracranial electroencephalography (iEEG) data from a large cohort of 32 patients while viewing visual images. We analyzed the iEEG data recorded from 230 channels in ventral temporal cortex (VTC) showing category-selectivity for 5 different categories of visual stimuli: faces, human bodies, words, places, and tools. We hypothesized that pre-stimulus activity modulates the degree of category tuning in response to visual stimuli and the aspect of pre-stim activity that modulates category tuning correlates with behavior. To test this, a generalized linear model was trained to classify the category of the stimuli, and the accuracy was compared for a model that used the post-stimulus activity alone and one that conditioned the post-stimulus classification on the pre-stimulus activity. The results showed that the inclusion of pre-stimulus activity improved the classification accuracy, indicating that category-selectivity was modulated by pre-stimulus activity in VTC. Furthermore, the aspect of the pre-stimulus activity that

modulated category tuning correlated with behavior in a 1-back task. We then examined the temporal and spatial specificity of the pre-stimulus effects. Pre-stimulus modulation were seen to be very localized, suggesting the effect seen was not due to fluctuations in overall arousal or global attention. They were also seen to fluctuate greatly from trial-to-trial, suggesting the effects were not related to slow fluctuations in neural activity, such as infra-slow fluctuations seen in resting state. Taken together, these results demonstrate that endogenous activity modulates category tuning in a regionally specific manner on a trial-to-trial basis in VTC. This modulation provides a potential neural basis for perceptual variation arising from shifts in endogenous ongoing activity.

Disclosures: Y. Li: None. **M.J. Ward:** None. **R.M. Richardson:** None. **M.G. G'Sell:** None. **A.S. Ghuman:** None.

Nanosymposium

017. Vision: Representation of Objects and Scenes

Location: SDCC 32

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 017.05

Topic: D.07. Vision

Support: DST Cognitive Science Research Initiative, Government of India (HK)
Wellcome Trust - DBT India Alliance, Intermediate and Senior Fellowships (SPA)

Title: Monkeys can’t read but their brains can: Compositionality and CAPTCHA decoding in IT neurons

Authors: *H. KATTI, S. P. ARUN
Indian Inst. of Sci., Bangalore, India

Abstract: Primates excel at object recognition. An every day example of this is the distorted letter tests that we see on websites. These tests – known as CAPTCHAs (Completely Automated Public Turing test to tell Computers and Humans Apart) – are used to deny access to malicious computer programs. What makes us so good at reading distorted letters? One possibility is that we may have specialized, invariant letter detectors that combine systematically to represent words. Alternatively, we may have specialized detectors not only for single letters but also for combinations of letters, thereby leading to efficient decoding. Either representation may exist *de facto* in the primate visual system, or may emerge as a consequence of learning to read.
We investigated this issue by characterizing the representation of single Latin letters and combinations of letters in the inferior temporal (IT) cortex of monkeys. We selected English letters as well as numbers and combined them systematically into strings up to 6 characters long. From these, we obtained 432 unique stimuli by applying applied local, global as well as CAPTCHA-like shape distortions. We recorded multi-channel extracellular activity from 141

visually responsive neurons from two monkeys and used 50 neurons with high response consistency for further analysis. We investigated two broad questions: First, can the population activity of monkey IT neurons be used to solve CAPTCHAs? Yes, linear classifiers trained to identify characters at every retinal location in CAPTCHAs, showed above-chance decoding accuracy. This accuracy increased with the number of neurons, suggesting that near-perfect CAPTCHA decoding with sufficiently large population. Second, can the neural response to letter strings be predicted from single-letter responses, or do neurons respond to novel combinations of letters in a manner that is not predictable from the responses to the individual letters? We trained linear models to predict neural responses to longer strings using single characters and obtained very good fits suggesting pure compositionality, although yielding mis-predicted strings. However the mis-prediction occurrence rate was not significantly different from that observed in a population of simulated compositional neurons with matched shape tuning and noisy Poisson firing. Thus, word representations are entirely predictable from letter representations in IT neurons.
Taken together, our results show for the first time that generic object recognition mechanisms in the primate brain suffice to process and decode CAPTCHAs, and that this ability arises from simple compositional rules that govern how word responses relate to letters.

Disclosures: H. Katti: None. **S.P. Arun:** None.

Nanosymposium

017. Vision: Representation of Objects and Scenes

Location: SDCC 32

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 017.06

Topic: D.07. Vision

Support: National Key Basic Research Program of China 2014CB846101
National Natural Science Foundation of China 31500851
National Natural Science Foundation of China 31671079
National Natural Science Foundation of China 91432102
Gatsby Charitable Foundation
111 Project B07008
Fundamental Research Funds for the Central Universities of China 2017XTCX04

Title: Bottom-up saliency and top-down learning in the primary visual cortex

Authors: *Y. YAN[1], L. ZHAOPING[2], W. LI[1]
[1]State Key Lab. of Cognitive Neurosci. and Learning, Beijing Normal Univ., Beijing, China; [2]Univ. Col. London, London, United Kingdom

Abstract: The pop-out effect in perception, such as a vertical bar within many horizontal bars (i.e. an orientation singleton), has been thought to be related to V1 responses representing the feature contrast. But it is still a matter of debate whether the feature contrast signals are of V1 origin and whether they are actually used for the behavior of singleton detection. Here we explore the behavioral relevance of neuronal responses in V1 of monkeys trained to detect an orientation singleton with various orientation contrasts against a background of uniformly oriented bars. Using chronically implanted microelectrodes, we measured V1 activities while the monkeys were required to quickly saccade to the singleton. A neuron's responses to the singleton within its receptive field had an early and a late component, both increased with the orientation contrast. The early component of orientation contrast signals started from the outset of neuronal responses and it remained unchanged before and after training on the singleton detection. The late component started ~40 ms after the early one; it emerged and evolved with practicing the detection task. Training increased the behavioral accuracy and speed of singleton detection and increased the amount of information in the late response component about a singleton's presence or absence. Furthermore, fluctuations in the detection performance correlated with fluctuations in both the early and late V1 responses. Training increased this correlation for the early component but decreased it for the late component. Hence, V1's early responses have an immediate impact on behavior and therefore represent the bottom-up saliency signals. Learning promotes the utilization of these saliency signals to make task performance more reflexive and less top-down driven.

Disclosures: Y. Yan: None. **L. Zhaoping:** None. **W. Li:** None.

Nanosymposium

017. Vision: Representation of Objects and Scenes

Location: SDCC 32

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 017.07

Topic: D.07. Vision

Support: NSF NCS
Simons Foundation

Title: A slow drift of macaque V4 population activity: Implications for perceptual decision-making

Authors: *B. R. COWLEY[1], A. C. SNYDER[1], K. ACAR[2], R. C. WILLIAMSON[1,2], B. M. YU[1], M. A. SMITH[2]
[1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: In visual cortex, fluctuations of neural activity have been observed across different time scales, but it is unclear how these fluctuations affect perception and decision-making. We

recorded from populations of V4 neurons in macaque monkeys performing a change detection task, and found that the activity of many neurons slowly drifted over the course of hours. This slow drift covaried with slow changes in decision criterion, pupil diameter, and reaction time, suggesting the slow drift is a cognitive signal of arousal, alertness, or motivation and may arise from brain-wide neuromodulators. In support of this, we simultaneously recorded neurons in V4 and prefrontal cortex, and found that activity in both areas drifted together.
A slow drift in V4 activity is puzzling because it can corrupt sensory information, yet the subject still performs the task proficiently. One possibility is that downstream areas do not read out the slow drift. However, we found that the slow drift overlapped with axes of population activity along which V4 responses to natural images varied most, and thus are likely read out by downstream areas to decode image features. Another possibility is that the slow drift is a byproduct of a pathway, independent of perception, that induces slow changes in decision criterion. If such a pathway influenced sensory neurons directly, it could impair the reliability of perceptual processing. Instead, we found evidence for a model in which the slow drift was removed from the perceptual readout but induced slow changes in decision criterion via an independent pathway. The model reproduced the finding that the slow drift and changes in criterion covaried, as well as the finding that V4 activity predicted the moment-by-moment occurrence of false alarms only when we removed the slow drift. Overall, this work demonstrates that a key consideration in understanding the role of neural variability in perception and decision-making is the degree to which downstream readout areas may access and remove such variability.

Disclosures: B.R. Cowley: None. **A.C. Snyder:** None. **K. Acar:** None. **R.C. Williamson:** None. **B.M. Yu:** None. **M.A. Smith:** None.

Nanosymposium

018. Timely Insights in Circadian Regulation

Location: SDCC 4

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 018.01

Topic: F.08. Biological Rhythms and Sleep

Support: Alzheimer's Association grant AARF-16-443613
NIH grant NS084582-01A1
NIH grant HL00701-15
Harold and Leila Y. Mathers Foundation
NIH grant NS072337
NIH grant NS085477
NIH grant AG09975

Title: A hypothalamic circuit for the circadian control of aggression and its implications for sundowning in dementia and Alzheimer's disease

Authors: *W. D. TODD, III[1], C. B. SAPER[2]
[1]Dept. of Neurol., Harvard Med. School/Beth Israel Deaconess Med. Ctr., Boston, MA; [2]James Jackson Putnam Prof, Harvard Med. Sch. Dept. of Neurol., Boston, MA

Abstract: Intro: "Sundowning syndrome" is a poorly understood clinical phenomenon exhibited by dementia and Alzheimer's disease (AD) patients which has been described in medical literature for over 70 years and is characterized by agitation, aggression, and delirium during the early evening. Whether dysfunction of the central circadian clock, the suprachiasmatic nucleus (SCN), underlies sundowning is unclear, and direct circadian modulation of behavioral aggression had previously never been demonstrated. We recently showed that aggression propensity in mice follows a daily rhythm that is regulated by GABAergic neurons in the subparaventricular zone (SPZ). We further demonstrated that these SPZ neurons receive functional input from the SCN, are active in a phase-dependent manner, and project to neurons within the ventromedial hypothalamus (VMH) that drive attack behavior, altogether suggesting a novel circuit by which the central circadian clock gates aggression propensity across the 24h day. Here we assessed rhythms of aggression propensity and locomotor activity (LMA) in mice that develop both hallmarks of AD neuropathology, amyloid-beta (a-beta) plaques and tau neurofibrillary tangles.
Methods: We utilized the TAPP mouse model, which carries the transgene for the 695-amino acid isoform of human AD a-beta protein and the transgene for the human P301L mutation of the microtubule-associated protein tau gene (MAPT). Double wild-type (WT) controls were non-mutant mice from the same genetic background. We assessed aggressive propensity using resident intruder tests at four time points and LMA rhythms using biotelemetry. Experiments occurred at ages known to be relevant milestones in the development of neuropathology in this strain. We are also examining the specific effects of this neuropathology on the SCN-SPZ-VMH pathway.
Results: Our preliminary findings show that TAPP mice exhibit increased aggression during the early daytime compared to WT controls and blunted nighttime LMA. These behavioral abnormalities are similar to that seen following SPZ GABAergic disruption in our previous studies, suggesting that the SCN-SPZ-VMH pathway may be specifically compromised in TAPP mice.
Conclusion: Both TAPP mutants and mice with SPZ GABAergic disruption show increased propensity for behavioral aggression during the early resting phase (morning for mice), which is temporally consistent with the increased aggressive symptoms reported in patients with dementia and AD. This suggests that the SCN-SPZ-VMH pathway could be a promising therapeutic target for treating circadian dysfunction and aggression in patients who display sundowning syndrome.

Disclosures: W.D. Todd: None. **C.B. Saper:** None.

Nanosymposium

018. Timely Insights in Circadian Regulation

Location: SDCC 4

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 018.02

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant K99NS101065

Title: Clock-generated temporal codes determine synaptic plasticity to control sleep

Authors: *M. TABUCHI[1], J. D. MONACO[2], G. DUAN[1], B. BELL[1], S. LIU[3], K. ZHANG[2], M. N. WU[1]
[1]Dept. of Neurol., [2]Dept. of Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [3]Ctr. for Brain and Dis. Res. and Dept. of Neurosci., VIB, Leuven, Belgium

Abstract: It has long been postulated that temporal coding in neurons is important for encoding responses to stimuli or effecting changes in behavior. However, this hypothesis has been challenging to rigorously test, owing to the difficulty of studying temporal coding in the absence of rate coding. Here, in our investigations of the circadian clock-dependent mechanisms regulating sleep quality, we show that temporal coding alone in clock neuron drives changes in sleep quality. Sleep quality is reduced during midday, compared to the middle of the night, which is correlated with greater irregularity of spike timing, in the absence of changes in firing rate. This cycling of sleep quality and spike timing irregularity depends on an intact circadian clock and a recently identified molecule WIDE AWAKE (WAKE). Using computational modeling approaches, we generated daytime and nighttime synthetic temporal codes. In vivo optogenetic manipulation of spike timing of these clock neurons using these synthetic temporal codes, while holding firing rate constant, reveal that temporal coding of these neurons is sufficient to induce changes in sleep quality. To delineate the molecular mechanisms by which WAKE effectuates changes in temporal coding, we conducted a genetic interaction screen. From this screen of ~1,200 RNAi lines, we identified two proteins—the Ca2+-dependent K+ channel binding protein (SLOB) and a novel Na+/K+ pump beta-subunit that regulate the cycling of different aspects of membrane potential dynamics. Knockdown of SLOB in these clock neurons decreased afterhyperpolarization amplitude and reduced sleep quality at night. Loss of NaK beta in these clock neurons resulted in slower spike risetimes and decreased sleep quality. Finally, we show that changes in spike timing regularity in the circadian clock circuit is transformed into persistent changes in firing rates in downstream arousal-promoting neurons, elucidating a mechanism by which temporal coding induces synaptic plasticity to drive a persistent change in rate coding to impact behavior.

Disclosures: M. Tabuchi: None. **J.D. Monaco:** None. **G. Duan:** None. **B. Bell:** None. **S. Liu:** None. **K. Zhang:** None. **M.N. Wu:** None.

Nanosymposium

018. Timely Insights in Circadian Regulation

Location: SDCC 4

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 018.03

Topic: F.08. Biological Rhythms and Sleep

Support: NIH GRANT NSR01094571

Title: Characterization of mWAKE; a novel circadian modulator of arousal in mammals

Authors: *B. J. BELL[1], A. WANG[3], Q. LIU[2], S. LEE[2], M. TABUCHI[2], M. N. WU[2]
[1]Human Genet., [2]Neurol., Johns Hopkins Sch. of Med., Baltimore, MD; [3]Johns Hopkins Univ., Baltimore, MD

Abstract: Introduction: The mechanisms by which the circadian clock regulates sleep and arousal states remain poorly understood. In *Drosophila*, WIDE AWAKE (WAKE) acts downstream of the clock to increases GABA sensitivity in arousal-promoting neurons to promote sleep onset at dusk. Here, we characterize the expression pattern of mWAKE, the mammalian homolog of WAKE, as well as the behavioral and physiological consequences of loss of mWAKE both globally and its role within specific circuits.
Methods: We characterized the mWAKE expression pattern using RNAscope *in situ* hybridization and genetically inserted tagged proteins. To assess behavior and arousal state of both constitutive and spatiotemporally-restricted conditional mWAKE mutants, we used a combination of EEG/EMG recordings, beam break locomotion, and open field assays. Additionally, we manipulated local and global mWAKE circuits via chemogenetics and observed behavioral and electrophysiological outcomes.
Results: mWAKE expression is more widespread than anticipated in the mouse brain, and labels a distinct subset of glutamatergic neurons intermingled throughout numerous arousal circuits, including the noradrenergic locus coeruleus, serotonergic periaqueductal gray, and histaminergic and orexinergic lateral hypothalamus. Constitutive knockout of mWAKE results in significant circadian-dependent hyperactivity, as well as increases in other measures of arousal such as anxiety and stereotypic behaviors, and fragmentation of sleep architecture including bout length decreases and REM reduction. Manipulation of individual mWAKE circuits via global or conditional knockouts or with chemogenetic activation via DREADD's perturbs behavior and alters the electrophysiological properties of mWAKE+ neurons.
Conclusions: Similar to WIDE AWAKE in *Drosophila*, mWAKE appears to act as a circadian modulator of sleep and arousal. However, in mammals, its prominent expression throughout numerous arousal centers suggests a broader role in mediating circadian modulation of arousal state. Furthermore, we are addressing the specific molecular and circuit-based mechanisms by

which mWAKE effects mammalian behavior via projection-mapping, patch-clamp recordings and exogenous activation and inhibition of $mWAKE^{+}$ cells.

Disclosures: B.J. Bell: None. **A. Wang:** None. **Q. Liu:** None. **S. Lee:** None. **M. Tabuchi:** None. **M.N. Wu:** None.

Nanosymposium

018. Timely Insights in Circadian Regulation

Location: SDCC 4

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 018.04

Topic: F.08. Biological Rhythms and Sleep

Support: T32 HL-007901

Title: Glutamatergic output of the dorsomedial hypothalamus controls the release of corticosteroids

Authors: *D. H. EGHLIDI[1], W. D. TODD, III[2], M. A. KHANDAY[3], Y. LV[4], N. L. MACHADO[5], P. M. FULLER[6], J. LU[8], R. VETRIVELAN[7], E. ARRIGONI[9], C. B. SAPER[10]
[1]Div. of Sleep Med. and Dept. of Neurol., Harvard Med. Sch. and Beth Israel Deaconess M, Boston, MA; [2]Dept. of Neurol., [3]Neurol., Harvard Med. School/Beth Israel Deaconess Med. Ctr., Boston, MA; [4]Harvard Med. School/Beth Israel Deaconess Med. Center/ The First Hosp. of Jilin Univ., Boston and Changchun, MA; [5]Federal Univ. of Minas Gerais, Boston, MA; [7]Dept. of Neurol., [6]Harvard Med. Sch., Boston, MA; [8]Dept. of Neurol. and Div. of Sleep Med., Beth Israel Deaconess Mededical Ctr., Boston, MA; [9]Dept Neurol., [10]James Jackson Putnam Prof, Harvard Med. Sch. Dept. of Neurol., Boston, MA

Abstract: Abstract Corticosteorids (Cort) have a 24-hour rhythm that play an integral role in allowing an individual to meet the physiological and behavioral demands of the active, waking period. Lesions of the dorsomedial hypothalamus (DMH), which receives circadian information via a suprachiasmatic nucleus (SCN) to subparaventricular zone (SPZ) to DMH pathway, result in continuous Cort levels typical of the daily nadir. However, it is unknown how the paraventricular hypothalamus corticotropin-releasing hormone (CRH) neurons receive inputs from the DMH. Here, we determined whether glutamatergic inputs to PVH^{CRH} contribute to the timed daily rhythm of corticosteroid production by the adrenal glands. First, using tracing methods we show that DMH^{Glut} neurons project directly and make contact on or near PVH^{CRH} neurons with DMH microinjections of a cre dependent Synaptophysin-mCherry in *Vglut2-Ires-Cre* mice. Using targeted genetic deletion experiments, we found that eliminating DMH^{Glut} to PVH^{CRH} in $Vglut2^{fl/fl}$ with DMH microinjections of Venus-2A-Cre significantly dampens the subjective early light period peak in Cort relative to control GFP microinjection in the DMH. Finally, using excitatory DREADDs we found that stimulating DMH^{Glut} with CNO using DMH

microinjections of Hm3dq in *Vglut2-Ires-Cre* mice significantly increased Cort levels during the typical nadir (subjective morning to afternoon) as compared to saline treated *Vglut2-Ires-Cre* and wild-type litter mate CNO treated controls. Together, these data suggest that excitatory output of the circadian neural circuit contribute to the timed daily production of Cort, which may play roles in mediating homeostatic and behavioral responses.

Disclosures: D.H. Eghlidi: None. **W.D. Todd:** None. **M.A. Khanday:** None. **Y. Lv:** None. **N.L. Machado:** None. **P.M. Fuller:** None. **J. Lu:** None. **R. Vetrivelan:** None. **E. Arrigoni:** None. **C.B. Saper:** None.

Nanosymposium

018. Timely Insights in Circadian Regulation

Location: SDCC 4

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 018.05

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant NS091234

Title: Sex differences in $GABA_A$ signaling modulate molecular rhythms in the master circadian clock

Authors: *J. A. EVANS, C. KAROW, A. TELEGA
Biomed. Sci., Marquette Univ., Milwaukee, WI

Abstract: Neuronal responses to $GABA_A$ signaling depend on the electrochemical gradient of chloride, which is regulated by the chloride co-transporters, NKCC1 and KCC2. Early in development, NKCC1 drives a depolarizing chloride reversal potential, but up-regulation of KCC2 during brain maturation causes a switch to the hyperpolarizing GABA response typical in adulthood. Sex differences in $GABA_A$ signaling occur during development, but whether divergent responses persist into adulthood has received less attention. Here we test whether $GABA_A$ signaling is sexually diergic in the master circadian clock of the suprachiasmatic nucleus (SCN), which has been shown to display excitatory GABA responses in adult males. Using a bioluminescence reporter of molecular clock function, we examined sex differences in the SCN response to inhibition of KCC2, NKCC1, or bicarbonate regeneration, which drives excitatory GABA responses. The SCN of male and female mice displayed similar responses to KCC2 inhibition, but differed in the response to NKCC1 inhibition. Further, blocking excitatory $GABA_A$ signaling by inhibiting bicarbonate regeneration altered SCN function in males, but not females. These results suggest that $GABA_A$ circuits in the SCN are sexually dimorphic. Differential responses to NKCC1 inhibition may be driven by sex differences in SCN chloride co-transporter expression and/or function, which is the focus of ongoing work. Given that GABA

is the primary neurotransmitter produced by SCN neurons, it will be important to determine consequences of this sexual dimorphism for neuronal excitability and master clock circuitry.

Disclosures: J.A. Evans: None. **C. Karow:** None. **A. Telega:** None.

Nanosymposium

018. Timely Insights in Circadian Regulation

Location: SDCC 4

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 018.06

Topic: F.08. Biological Rhythms and Sleep

Support: Veterans Affairs Merit Award (I01 BX001146) to DKW
KAVLI Award (2016-038) to DD
UCSD CRES (2018) to AP

Title: Photoperiod-induced neurotransmitter switching in the suprachiasmatic nucleus

Authors: *A. PORCU, M. RIDDLE, D. K. WELSH, D. DULCIS
Dept. of Psychiatry, Univ. of California, La Jolla, CA

Abstract: Light, circadian clocks, and rhythmic behaviors interact to produce a temporal order essential for the survival of living organisms. In mammals, the principal circadian pacemaker in the brain is the suprachiasmatic nucleus (SCN), which receives direct retinal input synchronizing it to the day-night cycle. Disrupted circadian rhythms are associated with impaired cognitive function and mood, and bright light is therapeutic for humans with winter depression. Altering day length (photoperiod) induces changes in neurotransmitter (NT) phenotype in the hypothalamic paraventricular nucleus (PVN), leading to depression-like behavior in adult rodents (Dulcis et al., 2013).
We hypothesize that altering photoperiod also changes NT expression in SCN neurons, which then control the activity of PVN neuronal circuits shown to induce depression-like behavior. Mice were exposed to 19L:5D (19 hours light, 5 hours dark) or 5L:19D photoperiods for 15 days. Then SCN were processed for immunohistochemistry to investigate whether NT plasticity occurs in response to photoperiod, as well as to determine the role of circadian clock genes in this process.
We found substantial differences in the number of SCN neurons expressing either vasoactive intestinal polypeptide (VIP) or neuromedin-S (NMS) in response to short- or long-day photoperiod. Consistent with neurotransmitter switching, co-expression ratios of these neuropeptides was also affected. Using a reporter mouse line for NMS-Cre expression, we found an increase in NMS-expressing SCN projections onto PVN dopaminergic neurons, indicating a potential increase of NMS synaptic release sites. Such photoperiod-dependent NT plasticity was retained in *Bmal1-KO* mice, suggesting that circadian clock function is not required for

photoperiod-induced changes in NMS and VIP expression. Further experiments will be performed to manipulate clock genes in selected classes of SCN neurons.
We then used a chemogenetic approach (DREADDs) aimed at selectively activating NMS neurons during the dark phase. This manipulation shifted the timing of locomotor activity onset, suggesting that activation of NMS neurons can affect behavior.
Our findings provide new insights into seasonal NT plasticity of SCN neurons. Further studies will reveal the role of SCN NT switching in depression-like behavior.

Disclosures: A. Porcu: None. **M. Riddle:** None. **D.K. Welsh:** None. **D. Dulcis:** None.

Nanosymposium

018. Timely Insights in Circadian Regulation

Location: SDCC 4

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 018.07

Topic: F.08. Biological Rhythms and Sleep

Support: NIH: MH103361
NSF: 1354612

Title: Cellular-level analysis of circadian timing in the hippocampal neurons

Authors: *K. H. OBRIETAN[1], K. R. HOYT[2]
[1]Dept Neurosci, Ohio State Univ. Dept. of Neurosci., Columbus, OH; [2]Pharmaceutics and Pharmaceut. Chem., Ohio State Univ., Columbus, OH

Abstract: Circadian (i.e., 24 hr) timing is an organism-wide, distributed, process, where the suprachiasmatic nucleus (SCN) serves as the master pacemaker that generates a phasing cue to entrain peripheral oscillator populations found in all organs systems. Within the brain, oscillatory capacity has been reported in a number of extra-SCN regions; however, data regarding the inherent (i.e., autonomous) oscillatory capacity of extra-SCN forebrain neurons is limited. To address this question, we utilized cellular imaging based approaches to test for hippocampal neuronal rhythms, and then to test for the functional relevance of these rhythms. Here we report that hippocampal neurons exhibit weak and intermittent oscillatory activity. Rhythmic activity was markedly longer than the circadian period, however, these long, stochastic oscillations were dependent on transcriptional drive from the CLOCK/BMAL1 complex. Interestingly, these oscillatory properties were not dependent on synaptic input; however, strong neuronal activity was capable of resetting this weak rhythmic activity. Further, the limited rhythmic activity of hippocampal neurons was not affected by co-culturing with SCN explants, thus indicating that these damped oscillations are a defining feature of hippocampal neuronal populations. Next, to complement the cell culture-based profiling approach, we examined cellular-level oscillatory capacity within organotypic slices of hippocampal tissue. In specific, this approach was used to

test whether, in contrast to the cell culture format, hippocampal neurons are capable of robust oscillatory capacity within an *in situ* model system. Profiling of postnatal day 1 hippocampal slices cultured for 10 days revealed that CA1 neurons exhibit limited oscillatory capacity, similar to the profile of cultured hippocampal neurons. Current work is focused on an in vivo examination of the rhythm generating capacity of hippocampal neurons, and on the potential functional roles that these forebrain oscillations play in cognition.

Disclosures: K.H. Obrietan: None. **K.R. Hoyt:** None.

Nanosymposium

018. Timely Insights in Circadian Regulation

Location: SDCC 4

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 018.08

Topic: F.08. Biological Rhythms and Sleep

Support: NIH grant R01NS091234

Title: SCN heterogeneity revealed through developmental patterning of neuropeptide expression

Authors: *V. CARMONA-ALCOCER, K. E. ROHR, J. JOHN, F. SAABEDRA, J. A. EVANS
Biomed. Sci. Deparment, Marquette Univ., Milwaukee, WI

Abstract: Neuropeptide signaling modulates the function of master clock neurons in the suprachiasmatic nucleus (SCN). Both arginine vasopressin (AVP) and vasoactive intestinal peptide (VIP) regulate the SCN network, but when these two neuropeptides are first expressed during development has been difficult to establish precisely. To address this important issue, we used a transgenic approach to define the developmental patterns of neuropeptide expression across the SCN network. Specifically, we crossed *Avp-Cre*$^{+/-}$ or *Vip-Cre*$^{+/+}$ males to Ai9$^{+/+}$ females that express floxed tdTomato. In the offspring of this genetic cross, the fluorescent protein tdTomato is stably expressed after initiation of *Avp or Vip* transcription. Here we use this approach to profile the spatiotemporal patterning of neuropeptide expression by examining tdTomato expression at critical developmental time points spanning mid-embryonic age to adulthood. Preliminary results indicate that neuropeptide expression is initiated at different developmental time points in clusters of SCN neurons located in different locations within the network. Notably these spatial clusters display distinct molecular clock function in adulthood. These data suggest that SCN neurons can be distinguished into further subtypes based on the developmental patterning of neuropeptide expression, which may relate to their functional differences in the mature network.

Disclosures: V. Carmona-Alcocer: None. **K.E. Rohr:** None. **J. John:** None. **F. Saabedra:** None. **J.A. Evans:** None.

Nanosymposium

018. Timely Insights in Circadian Regulation

Location: SDCC 4

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 018.09

Topic: F.08. Biological Rhythms and Sleep

Support: Swiss National Science Foundation
Human Frontiers Science Program
USZ CRPP "Sleep & Health"

Title: Circadian neurons control siesta sleep and wake maintenance

Authors: *S. BROWN[1], B. COLLINS[1], S. PIERRE FERRER[1], C. MUHEIM[1], A. SPINNLER[1], C. G. HERRERA[2], A. R. ADAMANTIDIS, Dr[3]
[1]Inst. of Pharmacol. and Toxicology, Univ. of Zürich, Zürich, Switzerland; [2]Dept of Neurol., Inselspital Univ. of Bern, Bern, Switzerland; [3]Dept of Neurol., Univ. of Bern, Bern, Switzerland

Abstract: Both human cultures and rodent species divide their active zone into an initial time of high activity, a following period of lower alertness or sleep - a daily siesta - and a subsequent period of wake maintenance. Genetic and epidemiological studies in humans and mice indicate that nighttime sleep duration and siesta behaviour are dependent on sleep pressure. Here we show that in fact siesta sleep and subsequent wake maintenance are driven by a specific population of neurons within the suprachaismatic nuclei (SCN) - the circadian “master clock” -- that is active when most SCN neurons are silent. Using optogenetic and chemogenetic approaches, we show that silencing these neurons delays the daily siesta, while activating them or mistiming them can create a siesta at will. Thus, the daily siesta is a “hard-wired” property encoded by the biological clock. This is the first demonstration of an acute effect of clock neuron activity on sleep, and the first step in understanding how the neural circuits of the mammalian circadian clock modulate daily sleep-wake cycles.

Disclosures: S. Brown: None. **B. Collins:** None. **S. Pierre Ferrer:** None. **C. Muheim:** None. **A. Spinnler:** None. **C.G. Herrera:** None. **A.R. Adamantidis:** None.

Nanosymposium

018. Timely Insights in Circadian Regulation

Location: SDCC 4

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 018.10

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant MH106460
IMHRO
NARSAD

Title: Using optogenetics to determine the role of the suprachiasmatic nucleus in mood regulation

Authors: *C. A. VADNIE[1], H. ZHANG[2], R. W. LOGAN[1], L. A. EBERHARDT[1], M. A. HILDEBRAND[1], D. BECKER-KRAIL[1], C. N. HEISLER[1], C. A. MCCLUNG[1]
[1]Dept. of Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; [2]Tsinghua Univ., Beijing, China

Abstract: Individuals suffering from mood disorders often display circadian rhythm disruptions, including dampened and/or phase shifted rhythms. Recent work indicates that disrupting molecular rhythms in the suprachiasmatic nucleus (SCN) affects mood-like behavior, suggesting that the SCN plays a causal role in mood disorders. However, it is unknown whether disrupting SCN neural activity rhythms affects mood or anxiety-like behaviors. Here our goal was to determine whether chronically dampening or advancing SCN neural activity rhythms affects depression and anxiety-like behavior. Channelrhodopsin-2 (ChR2) expression in the SCN was obtained by crossing mice expressing Cre recombinase in GABAergic neurons with mice expressing Cre-dependent ChR2. Optic fibers were implanted above the SCN and mice were individually housed to measure activity and/or body temperature rhythms by telemetry or piezoelectric sensors. To determine the effects of SCN-mediated dampening of rhythms, we unpredictably stimulated (1 h, 10 ms pulse width, 8 Hz) the SCN during the dark phase. To determine the effects of chronically advancing rhythms, free-running mice received stimulations every three days, late (CT21) into their active phase. Depression and anxiety-like behaviors were assessed using a battery of tests. Unpredictable stimulation of the SCN during the dark phase dampened the amplitude of activity and body temperature rhythms. Interestingly, chronic unpredictable stimulation of the SCN during the dark phase increased anxiety-like behavior. Stimulating the SCN at CT21 decreased the period and dampened the amplitude of activity rhythms. Consistent with the unpredictable stimulations, correlations were observed between the amplitude of rhythms and behavior in chronically phase-advanced mice. Overall, our findings thus far suggest that dampened SCN neural activity rhythms increase anxiety-like behavior. Ongoing studies will determine the effects of chronically delaying SCN neural activity rhythms.

Disclosures: C.A. Vadnie: None. **H. Zhang:** None. **R.W. Logan:** None. **L.A. Eberhardt:** None. **M.A. Hildebrand:** None. **D. Becker-Krail:** None. **C.N. Heisler:** None. **C.A. McClung:** None.

Nanosymposium

018. Timely Insights in Circadian Regulation

Location: SDCC 4

Time: Saturday, November 3, 2018, 1:00 PM - 3:45 PM

Presentation Number: 018.11

Topic: F.08. Biological Rhythms and Sleep

Title: Parallel retina-brain circuits drive the effects of light on mood and learning

Authors: *D. FERNANDEZ, S. HATTAR
Section on Light and Circadian Rhythms (SLCR), Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Light exerts profound effects on behavior. It is well known that alterations in the regular lighting conditions lead to cognitive impairment and depressive symptoms. Thus, mapping the neural circuits by which light negatively affects mood and learning is a promising step towards new treatments for affective disorders associated with abnormal light exposure. In mammals, light detection occurs exclusively in the retina. The recent discovery of novel photoreceptors in the mammalian retina, which are projection neurons that send widespread brain projections, extended enormously the spectrum of potential targets that could be directly modulated by photic information. These atypical photoreceptors constitute a subpopulation of retinal ganglion cells (RGCs), which express the photopigment melanopsin, making them intrinsically photosensitive (ip)RGCs. One of the principal targets of ipRGCs is the suprachiasmatic nucleus (SCN), which houses a central pacemaker that orchestrates circadian functions. Several neuropsychiatric disorders, including major depression and seasonal affective disorder, are characterized by alterations in circadian rhythms and sleep architecture. These observations led to the assumption that mood/cognitive alterations induced by light are secondary effects of circadian and/or sleep disruptions. However, recent studies have challenged this view, raising the possibility that ipRGCs can directly affect mood-regulating and learning centers in the brain, without altering circadian activity. Here we reveal that the direct effects of light on learning and mood utilize distinct ipRGC output streams. The SCN is sufficient for driving ipRGC-mediated effects of light on learning, and this occurs independently of the SCN's pacemaker function. Mood regulation by light, on the other hand, requires an SCN-independent pathway linking ipRGCs to a previously unrecognized thalamic region, termed perihabenular nucleus (PHb). The PHb is integrated in a distinctive circuitry with mood-regulating centers, and is both necessary and sufficient for driving the light effects on affective behavior. Together, these results provide new insights into the neural basis required for light to influence mood and learning.

Disclosures: D. Fernandez: None. **S. Hattar:** None.

Nanosymposium

019. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms

Location: SDCC 30B

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 019.01

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust (090954/Z/09/Z; 102409/Z/13/A)

Title: Spatial memory engram in the mouse retrosplenial cortex

Authors: M. M. MILCZAREK[1], S. D. VANN[1], *F. SENGPIEL[2]
[1]Sch. of Psychology, [2]Cardiff Univ., Cardiff, United Kingdom

Abstract: It is nearly 100 years since Richard Semon coined the term 'engram' for a memory trace in the brain, but only a handful of studies have so far been able to identify engrams for specific situations. The retrosplenial cortex (RSC) is a key brain area supporting spatial memory and navigation. It receives strong inputs from the hippocampus as well as sensory, in particular visual, cortical areas. Dysgranular RSC is densely connected with dorsal stream visual areas and contains place-like and head-direction cells, making it a prime candidate for integrating navigational information. We present for the first time evidence of a relationship between the emergence and stability of retrosplenial engrams and the acquisition and retention of spatial memory over several weeks. We employed mice expressing a short-lived version of the enhanced green fluorescent protein (eGFP) under the control of the *c-fos* gene promoter. Cranial windows were implanted over the dorsal (dysgranular) RSC of eight mice which we trained on a spatial memory task in a radial arm maze (RAM). We used in-vivo two-photon imaging to analyse patterns of activity of over 6000 neurons within dysgranular RSC and link them to behaviour. Mice were imaged repeatedly over a 6-week period which comprised the acquisition of a reference memory in the RAM at three-day intervals over 19 days, two sessions on days 25 and 43 testing the retention of long-term memory; and three control sessions including two negative control sessions involving placement in the dark, and a positive control session involving exposure to a novel environment. Training sessions led to an 80% reduction in visits to non-baited arms and the formation of stable engrams which showed high levels of overlap between each other but not with control conditions. Testing after a delay of 6 and 24 days revealed deterioration of the spatial memory (50% and 150% more errors, respectively) which did, nevertheless, remain above naïve levels. The stability of the memory engrams was predictive of the degree of forgetting; when tested 24 days later, mice with neuronal representations most similar to those on the final day of training achieved the best behavioural scores. Our results provide direct evidence for the interdependence of spatial memory consolidation and retrosplenial engram formation and demonstrate the participation of the retrosplenial cortex in the encoding and storage of spatial memories at the level of neuronal ensembles.

Disclosures: M.M. Milczarek: None. **S.D. Vann:** None. **F. Sengpiel:** None.

Nanosymposium

019. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms

Location: SDCC 30B

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 019.02

Topic: H.01. Animal Cognition and Behavior

Support: DARPA BTO TNT / SPAWAR Cooperative Agreement No. N66001-17-2-4019

Title: Vagus nerve stimulation epigenetically modulates learning and memory

Authors: *T. H. SANDERS[1,2], J. WEISS[2], R. LIFER[2], C. M. PATON[2], J. D. SWEATT[2]
[1]Vanderbilt Univ., Nashville, TN; [2]Pharmacol., Vanderbilt Univ. Sch. of Med., Nashville, TN

Abstract: Vagus Nerve Stimulation (VNS) is known to enhance learning and memory in rodents and humans. However, the mechanisms behind these cognitive improvements are unclear. Here, we present evidence that epigenetic modulation of stress response signaling and plasticity plays a prominent role in VNS-enhanced learning and memory. In this study, rats that received 30 minutes of intermittent VNS bursts on 4 consecutive days showed improved learning and memory, along with changes in cortical, hippocampal, and blood transcription profiles and epigenetic marks. Many of the significantly changed transcripts correlated with behavioral performance in an object recognition memory task. Interestingly, similar transcriptional changes occurred in a cohort of rats that did not participate in any behavioral task, suggesting that VNS stimulation alone is sufficient to drive the changes. Significant VNS-induced cortical changes included decreased stress response signaling (NF-κB) and increased neural-remodeling (ARC) and translation elongation-related (DPH1) transcripts, while the most significant hippocampal changes included reduced potassium channel (KCNH5), phospholipase (HRASLS), and calcium release inhibition (CAR-8) transcripts. Despite differences in the overall transcription-change landscape between the cortex and hippocampus, tissue from both regions showed reductions in stress response signaling (including NF-κB), and changes in immediate early gene (IEG) and histone-related transcripts. Reduced NF-κB signaling during VNS has been assumed to be a downstream effect of reduced inflammatory cytokines. However, in our study, we observed few changes in inflammatory markers, yet identified significant effects of epigenetic modulation and stress response signaling that correlated with behavioral performance. Our results indicate that VNS-induced learning and memory effects may be primarily mediated through non-inflammatory, epigenetically-driven NF-κB signaling and associated effects such as double strand break (DSB) repair at γH2A.X-marked sites. This is consistent with our transcriptional profiling evidence and finding that DSBs were decreased in the brain tissue of stimulated rats. Taken together, the results demonstrate that epigenetic modulation plays a prominent role in VNS-enhanced learning and memory by 1) altering neural signaling and plasticity gene

expression through DNA methylation and histone modifications, 2) reducing stress response signaling, and 3) promoting efficient repair of double strand breaks that occur during transcription of plasticity genes.

Disclosures: T.H. Sanders: None. **J. Weiss:** None. **R. Lifer:** None. **C.M. Paton:** None. **J.D. Sweatt:** None.

Nanosymposium

019. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms

Location: SDCC 30B

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 019.03

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant AG025894
NIH Grant NS086960
NIH Grant NS045855
NIH Grant NS057558

Title: An identified neocortical ensemble within a distributed neocortical circuit encodes some of the essential information for performing visual shape discrimination learning

Authors: *A. I. GELLER[1], H. ZHAO[2], E. CHOI[2], M. SVESTKA[2], X. WANG[2], A. NAGAYACH[3], A. SINGH[3], R. G. COOK[4], G.-R. ZHANG[2]
[1]LSUHSC, New Orleans, LA; [2]W. Roxbury VA Hospital/Harvard Med. Sch., W. Roxbury, MA; [3]Ophthalmology, Louisiana State Univ. Hlth. Sci. Ctr., New Orleans, LA; [4]Tufts Univ., Medford, MA

Abstract: Synaptic plasticity and neural network theories hypothesize that essential information for specific advanced cognitive tasks is encoded in specific neuronal ensembles, within distributed neocortical networks. But these hypothesized ensembles remain to be identified. Suggesting that such ensembles may exist, specific subcortical areas, such as the amygdala or hippocampus, contain specific ensembles that encode simple learning tasks. Here, using a genetically-modified circuit that encodes essential information for an advanced cognitive task, we showed that an identified neocortical ensemble can encode specific visual shape discriminations.
We examined a distributed neocortical circuit that contains a critical multimodal associative area, postrhinal (POR) cortex, for encoding visual learning. Several hundred glutamatergic or GABAergic neurons in POR cortex received a constitutively active protein kinase C (PKC) (J Neurosci 2005 25 8468-81). This intervention activated specific PKC substrates that play important roles in synaptic plasticity, and increased activation-dependent neurotransmitter release. Importantly, this intervention enhanced accuracy for specific visual shape

discriminations.
Some of the essential information for performance is encoded in the genetically-modified circuit (PNAS 2010 107 14478–83). After gene transfer and then learning new image sets, ~21 % of POR cortex, centered on the injection site, was ablated by lesioning, and the lesions reduced performance selectively for the discriminations learned after gene transfer. Correlatively, during the learning, activity was increased in the genetically-modified circuit, as shown by activity-dependent gene imaging. The critical circuit is sparse coded and small, ~500 neurons.
Now, we show that both learning and recall require fast neurotransmitter release from an identified ensemble within this circuit, the transduced neurons. We blocked fast release from these neurons by coexpressing a Synaptotagmin I siRNA and the constitutively active PKC. During learning or recall, particular signaling pathways that are required for learning are activated in this ensemble, including dendritic protein synthesis, MAP kinase, calcium/calmodulin-dependent protein kinase II, and CREB. Further, activity in this ensemble during learning is required to recruit the circuit. Additionally, for image presentation after learning, blocking the activity of this ensemble reduces accuracy, even though the remainder of the circuit is activated. Thus, an identified ensemble within a neocortical circuit encodes essential information for performing an advanced cognitive task.

Disclosures: **A.I. Geller:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkermes Inc.. **H. Zhao:** None. **E. Choi:** None. **M. Svestka:** None. **X. Wang:** None. **A. Nagayach:** None. **A. Singh:** None. **R.G. Cook:** None. **G. Zhang:** None.

Nanosymposium

019. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms

Location: SDCC 30B

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 019.04

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 5R01MH106617
NARSAD /BBRF

Title: Updated prefrontal neural ensembles of context-fear relationship control fear discrimination learning

Authors: A. CORCHES[1], *E. KORZUS[2], T. W. BAILEY[3], A. HIROTO[4], J. H. SPEIGEL, III[3], M. R. MAYFORD[5]
[1]Biomed. Sci., [2]Departments of Psychology, Biomed Sci. & Neurosc Program, [3]Program in Neurosci., [4]Dept. of Psychology, Univ. of California Riverside, Riverside, CA; [5]Psychiatry, Univ. of California San Diego, LA Jolla, CA

Abstract: Fear discrimination is critical for survival while fear generalization is effective for recalling and avoiding dangerous situations. Overgeneralized fear is a typical symptom of anxiety-related disorders including generalized anxiety disorder and posttraumatic stress disorder (PTSD). Previous research has demonstrated that fear discrimination learning is mediated by prefrontal mechanisms. To get insight into the circuit mechanisms underlying context-dependent fear discrimination we investigated murine prefrontal neuronal ensembles representing distinct experiences associated with learning to distinguish between dangerous and similar yet distinct harmless stimuli. We evaluate large-scale neuronal activity patterns in response to dangerous and safe contextual stimuli within prelimbic (PL) and infralimbic (IL) subdivisions of the medial prefrontal cortex (mPFC) during different phases of fear discrimination learning to uncover the neural mechanisms underlying the ability to distinguish between danger and safety. Tagging neural ensembles of contextual fear memories was performed using an immediate early gene *Arc* -based tetTag bi-transgenic genetic system in mouse mice. Neuronal activity at a population level can be effectively studied the learning brain using the tetTAG system, in which neuronal activities can be persistently labeled during two specific experiences. Here we show profoundly distinct quantitative activation differences in response to dangerous and non-dangerous experiences as well as modulation of neuronal ensembles associated with successful fear discrimination learning. Our study suggests that fear discrimination learning is associated with modulation of prefrontal memory representations in a subregion- and experience-specific fashion, while appropriate responses to dangerous and non-dangerous experiences are driven by updated and re-balanced prefrontal ensembles of context-fear functional relationships.

Disclosures: A. Corches: None. **E. Korzus:** None. **T.W. Bailey:** None. **A. Hiroto:** None. **J.H. Speigel:** None. **M.R. Mayford:** None.

Nanosymposium

019. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms

Location: SDCC 30B

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 019.05

Topic: H.01. Animal Cognition and Behavior

Support: NIH R21MH105746 to XC
K01AG054729 to XC
NIH P20GM113131 to XC
NIH MH095840 to XZ
NIH MH073601 to DS
NIH MH094536 to LZ

Title: *In vivo* imaging of memory formation: Highly sensitive CA1 neurons in the hippocampus are preferably recruited to encode trace fear memory

Authors: *X. CHEN, L. ZWEIFEL[1], S. LU[1], L. QIU[2], D. STORM[1], Z. XIA[1]
[1]Univ. of Washington, Seattle, WA; [2]Dept. of Molecular, Cell. and Biomed. Sci., Univ. of New Hampshire, Durham, NH

Abstract: Memory is thought to be encoded by sparsely distributed neuronal ensembles in memory-related regions. However, it is unclear how neurons are selected to encode a memory and how they react during learning and memory recall. We implemented fiber-optic fluorescence confocal endomicroscopy to directly visualize calcium dynamics in hippocampal CA1 neurons in freely behaving mice, which are subject to a paradigm of trace fear conditioning. Here we report that a portion of highly active CA1 neurons (~13 %) prior to training, coined "Lead Neurons" henceforth, play a critical role in memory formation. Lead Neurons exhibited high sensitivity to external stimuli and were very labile to modify their activity pattern. After 3-4 cycles of tone and foot-shock paired training, the activity dynamic of Lead Neurons was drastically modified from a random active pattern to a pattern in which activities were elicited by (or in phase with) tone and foot shock. Intriguingly, the modification of activity pattern coincided with the appearance of freezing behavior of mice. Further, Lead Neurons preferably re-activated in a manner that their activity pattern was also modified responding to an unconditional stimulus (tone) during recall. Repetitive trainings also caused some moderately active neurons (~22% of total) to modify their activity pattern in response to a tone in learning, however, these neurons' re-activation was much more difficult to observe in recall. The remaining approximate 65% CA1 neurons were silent: they failed to respond to tone and foot-shock throughout the learning and recall cycles. We conclude that the engram of trace fear memory preferably recruit Lead Neurons, which are highly active prior to training, and whose activity pattern is readily modified by external cues during learning.

Disclosures: L. Zweifel: None. **S. Lu:** None. **L. Qiu:** None. **D. Storm:** None. **Z. Xia:** None.

Nanosymposium

019. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms

Location: SDCC 30B

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 019.06

Topic: H.01. Animal Cognition and Behavior

Support: IDRC 108191-001

Title: Selective reduction of eIF2α phosphorylation in excitatory neurons enhances learning and memory

Authors: *V. SHARMA
McGill Univ., Montreal, QC, Canada

Abstract: MJE and MA contributed equally to this work.
mRNA translation regulation is pivotal for memory formation. A key molecule regulating protein synthesis on the initiation level is eukaryotic initiation factor 2 (eIF2). We have shown before that genetic or pharmacological reduction of eIF2α phosphorylation on Ser 51 enhances the formation of long term memory (LTM) and late phase LTP (Costa-Mattioli et al 2007). Here we aim at extending these findings to identify the specific cell types in which eIF2a dephosphorylation subserve the behavioral and electrophysiological phenotype. We used the conditional eIF2α $Ser51^{A/A}$;fTg^{+} mutant mice with cre expression under cell-type specific promoters to study the molecular mechanisms by which eIF2 regulates brain function. We found that selective reduction of eIF2α phosphorylation (p-eIF2α) in excitatory neurons of the dorsal hippocampus enhanced spatial learning and contextual fear conditioning. In addition, the reduced p-eIF2α facilitated the conversion of a transient early long-term potentiation (E-LTP) into a sustained late phase LTP (L-LTP) in hippocampal sections. Moreover, local reduction of p-eIF2α in excitatory neurons in the insular cortex or basolateral complex of the amygdala, two brain regions that are critically involved in the acquisition and consolidation of conditioned taste aversion (CTA), enhanced CTA memory. These findings provide evidence that modulating p-eIF2α levels specifically in excitatory neurons regulates memory consolidation in different brain regions. Deciphering the mechanisms by which levels of eIF2a phosphorylation controls cognitive functions advances our understanding of the molecular basis of memory formation in the healthy and disease brain.

Disclosures: V. Sharma: None.

Nanosymposium

019. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms

Location: SDCC 30B

Time: Saturday, November 3, 2018, 1:00 PM - 2:45 PM

Presentation Number: 019.07

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Grant R15-MH110876

Title: The role of mediodorsal thalamus for the development of cortical response types in rats learning the DNMTP task

Authors: *M. J. FRANCOEUR, E. KRELL, N. MONTEIRO, L. CALDERAZZO, K. HOWARD, A. HAYES, A. MCALLISTER, B. M. GIBSON, R. G. MAIR
Psychology, Univ. of New Hampshire, Durham, NH

Abstract: Medial prefrontal cortex (mPFC) supports flexible goal-directed behavior. Recordings of mPFC in awake, behaving rats have revealed a wide range of task-related responses, including activity related to preparation, movements, task-dependent actions, anticipation and delivery of

reinforcement, errors, memory delay, behavioral rule, and spatial context. Subcortical structures such as the thalamus likely interact with mPFC to control executive functions. There is little known about how high-order nuclei in central thalamus, including the mediodorsal (MD) nucleus, shape information sent to mPFC. Lesion and inactivation studies indicate that interactions between MD and mPFC support the acquisition of new information. Previously, we have examined the effects of unilateral pharmacologic inactivation of MD on the activity of mPFC neurons in rats performing a delayed non-match to position task (DNMTP). Our results show that thalamic inactivation disrupts signal-to-noise properties of mPFC neurons independent of whether overall activity increases or decreases in firing rate during the inactivation period. Pharmacological inactivation, chemogenetic and optogenetic manipulations all support a role for MD in influencing cortical activity, but is MD critical for the acquisition of complex decision-making tasks? To investigate if MD shapes the response types that develop in mPFC to support task-relevant behavior we lesioned MD in one hemisphere before exposing rats to the DNMTP task. The unilateral lesions did not interfere with the ability of rats to learn the DNMTP task. Once trained to criterion we implanted driveable tetrode arrays in both hemispheres of mPFC (4 tetrodes in each hemisphere). Types of event-related responses, firing rate, and signal-to-noise properties of mPFC neurons were compared between the ipsilateral and contralateral hemispheres. Cortical neurons collected from ipsilateral mPFC showed restricted event-related response types and differences in the onset/ offset of critical activity periods. Our results support the hypothesis that MD is important for the acquisition of neural responses in mPFC that mediate performance on complex decision-making tasks.

Disclosures: M.J. Francoeur: None. **E. Krell:** None. **N. Monteiro:** None. **L. Calderazzo:** None. **K. Howard:** None. **A. Hayes:** None. **A. McAllister:** None. **B.M. Gibson:** None. **R.G. Mair:** None.

Nanosymposium

020. Human Cognition and Behavior: Timing and Temporal Processing

Location: SDCC 7

Time: Saturday, November 3, 2018, 1:00 PM - 3:30 PM

Presentation Number: 020.01

Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI Grant Number 16H01866

Title: Constant stimulus intervals elongate subjective duration of the auditory stimulus sequence

Authors: *K. KANNAGA[1], M. MIYAZAKI[1,2]
[1]Dept. of informatics, Grad. Sch. of Integrated Sci. and Technol., [2]Fac. of Informatics, Shizuoka Univ., Hamamatsu-Shi, Japan

Abstract: The perceived durations of sensory stimuli are modulated by various physical factors of the stimuli (e.g., intensity, size, or number). In the present study, we investigated the effects of constancy/randomness of time intervals in auditory stimulus sequences on the perceived duration of the stimulus sequences. Participants (N = 24) received two consecutive auditory stimulus sequences and judged whether the duration of the second sequence (comparison stimulus sequence, C) was longer or shorter than that of the first sequence (standard stimulus sequence, S). Each stimulus sequence comprised pure tones (1000 Hz, 10-ms duration). The number of tones was fixed at 17 for S but varied between trials from 11 to 23 for C. For the time intervals between the tones, we set two conditions: constant and random. In addition, the time intervals were fixed at 39.375 ms in the constant condition (duration of S: 800 ms) but varied from 12 to 66 ms in the random condition (durations of C: 503.75 - 1096.25 ms). We calculated the points of subjective equality (PSEs) from the ratios of "C was longer than S" responses as a function of the durations of C. The PSE results (Fig. 1) indicated that the participants perceived the durations as being longer for the stimulus sequences with the constant time intervals than for those with random time intervals, even though these durations were actually identical. Recently, Sasaki and Yamada (2017) reported that the perceived durations were longer for visual stimuli with regular dot patterns than for those with random dot patterns, suggesting a similarity of the constancy (regularity)/randomness effect on duration perception between time and space. We discuss possible neural bases of the constancy/randomness effect on subjective duration, based on the neural energy model (Eagleman and Pariyadath, 2009).

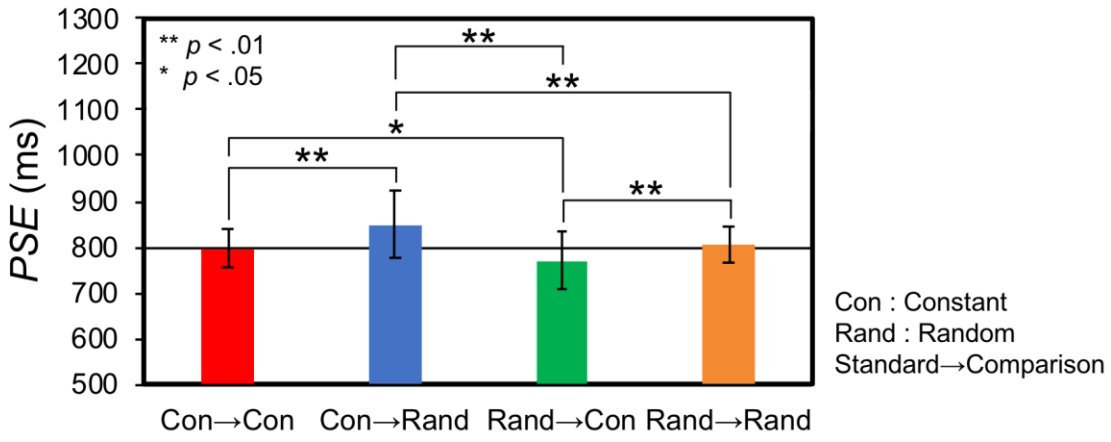


Fig. 1. Points of subjective equality (PSEs) calculated from the ratios of “C was longer than S” responses as a function of the durations of C (S: standard stimulus sequence, C: Comparison stimulus sequence). The shorter (longer) PSEs imply that participants perceived C as being longer (shorter) than S. Error bars denote the standard error of the mean (SEM). The paired t-test with the Holm correction was used for the multiple comparisons.

Disclosures: K. Kannaga: None. **M. Miyazaki:** None.

Nanosymposium

020. Human Cognition and Behavior: Timing and Temporal Processing

Location: SDCC 7

Time: Saturday, November 3, 2018, 1:00 PM - 3:30 PM

Presentation Number: 020.02

Topic: H.02. Human Cognition and Behavior

Support: HHMI predoctoral fellowship
NINDS R37NS21135
SURF Berkeley
NIMH Silvio O. Conte Center 1PO MH109429-01
NIH/NICHD R25-HD088157
NIH/NIBIB P41-EB018783
US Army Research Office grant W911NF-14-1-0440

Title: Contributions of auditory posterior STG to signaling temporal violations and salience: Evidence from broadband gamma and ERPs in a combined EEG/ECoG study

Authors: *Y. M. FONKEN[1], E. L. KOSIK[2], L. J. CROWTHER[4], J. LIN[5], P. BRUNNER[6], G. SCHALK[7], R. T. KNIGHT[3]
[1]Knight Lab. - Univ. of California, Berkeley, Berkeley, CA; [2]Cognitive Sci., [3]Psychology, Univ. of California, Berkeley, Berkeley, CA; [4]Natl. Ctr. for Adaptive Neurotechnologies, Wadsworth Ctr., Albany, NY; [5]Dept. of Neurol., Univ. of California, Irvine, Irvine, CA; [6]Ctr. for Adaptive Neurotechnology, Albany Med. Col. / Wadsworth Ctr., Albany, NY; [7]Wadsworth Ctr, NYSDOH, Albany, NY

Abstract: The current study aimed to investigate the influence of predictions generated by the brain on auditory processing using scalp-recorded electroencephalography (EEG) and subdurally recorded electrocorticography (ECoG). Recent literature suggests that predictions modulate sensory activations. To investigate how predictions are implemented, we recorded signals from STG directly from the cortex. Subjects were patients with medically refractory epilepsy who were implanted with electrodes (spaced between 3 and 10 mm) covering STG. ECoG signals were recorded while subjects listened to a sequence of phonemes in a regular pattern La-La-Ba; La-La Ga with fixed ISI. The ‘Ba’ and ‘Ga’ phonemes were infrequently omitted from the sequence, enabling us to isolate internal prediction processes in the absence of stimulus-evoked activity. The prediction literature suggests that omission signals would be maximal in sites that were active to auditory stimuli. However, our analyses confirmed broadband gamma (70-150 Hz) responses to omissions that overlapped with only a posterior subset of auditory reactive electrodes in the superior temporal gyrus (STG) and -sulcus (STS), during a time-window of 100-300ms ($p<0.05$, cluster permutation corrected). In overlapping electrodes on the posterior STG, we also measured a negative potential ERP peaking around 200ms ($p<0.05$ cluster

permutation corrected). This intracranial ERP overlaps with previous source-modeling approaches in MEG using an omission paradigm (Raij et al, 1997), and may be related to the omission N2 (Naatanen & Picton, 1986). In a parallel EEG study in healthy subjects performing the same task, we revealed a clear P3a ERP response to omissions. The ECoG broadband gamma and ERP activations occur in a region previously indicated in (auditory) salience detection (Downar et al, 2000). Together with the P3a response measured in EEG, our results suggest that these ECoG activations may be a signature of an important node in auditory salience detection signaling. Overall, this dataset provides a unique insight relating broadband gamma activations to ECoG and scalp ERPs. We propose that the posterior STG is central for implementing predictions and signaling mis-predictions in the auditory environment.

Disclosures: Y.M. Fonken: None. **E.L. Kosik:** None. **L.J. Crowther:** None. **J. Lin:** None. **P. Brunner:** None. **G. Schalk:** None. **R.T. Knight:** None.

Nanosymposium

020. Human Cognition and Behavior: Timing and Temporal Processing

Location: SDCC 7

Time: Saturday, November 3, 2018, 1:00 PM - 3:30 PM

Presentation Number: 020.03

Topic: H.02. Human Cognition and Behavior

Support: Intramural Research Program of the NIH/NINDS
Klingenstein-Simons Neuroscience Fellowship
Leon Levy Neuroscience Fellowship

Title: Neural time windows of auditory integration scale flexibly based on rate of information

Authors: *J. L. LEE[1], B. MANISCALCO[3], M. W. FLOUNDERS[2], T. BAUMGARTEN[2], B. J. HE[2]
[1]Ctr. for Neural Sci., [2]Langone Med. Ctr., New York Univ., New York, NY; [3]Neurosci., UC Riverside, Riverside, CA

Abstract: How much of the past does the brain use in order to predict the future? The brain continuously monitors the history of environmental sounds it receives in order to make predictions about those to come, allowing individuals to detect sudden, unexpected changes that might be important to survival. However, natural environments vary drastically in their temporal richness-- integrating auditory history over a rigid time window might afford more or less prediction-relevant information, depending on the speed at which new information arrives. What determines the amount of stimulus history integrated by the brain for the purpose of prediction: a period of time, or a quantity of information? We investigated whether temporal windows of sensory information adjust flexibly to different speeds of stimulus presentation, or whether this integration is limited by a fixed time window (e.g., due to the low-level biological time constants

which govern signalling in circuits and single neurons). We used magnetoencephalography (MEG) to record the neural activity of human subjects in response to naturalistic auditory sequences which were sped up or slowed down. These sequences were tone series whose pitch fluctuations follow the power spectral patterns found in the statistical structure of many natural soundscapes. Using sequences with three distinct presentation speeds, we asked whether history-tracking neural activity carried information about a fixed number of previous tones or a fixed previous time window. We found that humans are indeed capable of exploiting the naturalistic statistical structure of an auditory sequence in order to make valid predictions about an upcoming stimulus, and that slow, arrhythmic neural activity continuously integrates past information in a moving-window fashion to form the neural basis of such predictions. Importantly, we found that the amount of stimulus history integrated by neural activity at a given time point is limited by the quantity of informational units presented (i.e., the number of tones), rather than the time period over which they are presented (i.e., the number of seconds). Our findings therefore suggest that the neural activity underlying naturalistic sensory predictions is built on a window of history integration which adjusts flexibly in time, depending on the rate of information arrival.

Disclosures: J.L. Lee: None. **B. Maniscalco:** None. **M.W. Flounders:** None. **T. Baumgarten:** None. **B.J. He:** None.

Nanosymposium

020. Human Cognition and Behavior: Timing and Temporal Processing

Location: SDCC 7

Time: Saturday, November 3, 2018, 1:00 PM - 3:30 PM

Presentation Number: 020.04

Topic: H.02. Human Cognition and Behavior

Support: European Research Council Grant (ERC) to DB (Grant Agreement 682117 ERC-2015-CoG)

Title: Effective connectivity in a duration selective cortical network

Authors: *D. BUETI[1], F. PROTOPAPA[1], M. J. HAYASHI[2], R. KANAI[3]
[1]Neurosci., Intl. Sch. for Advanced Studies (SISSA), Trieste, Italy; [2]Global Ctr. for Med. Engin. and Informatics, Osaka Univ., Suita, Japan; [3]Dept. of Neuroinformatics, Araya Brain Imaging, Tokyo, Japan

Abstract: How long does it take for a tennis ball to reach the opposite side of the court once hit it? And how long does it take for a music note or a dance movement to be executed? The answer to these questions is likely different and concerns a time range spanning from hundreds of milliseconds to a few seconds. The neurophysiological mechanisms underlying the capacity of producing and decoding such a variety of temporal information remain unclear. In a recent fMRI study, we measured human brain activity at ultra-high field (7T) while asking participants to

discriminate visual stimuli of four different durations (ranging from 0.2 to 1 second).
The results identified the existence, in the Supplementary Motor Area (SMA), and in the medial and lateral Inferior Parietal Lobule (IPL) of the left hemisphere, of neuronal units maximally responsive to each of the four different durations ("duration selective"). To investigate the functional relationship between IPL and SMA in processing the four different durations we employed dynamic causal modeling (DCM) and assessed the effective connectivity between duration selective portions of SMA, IPL medial and lateral in a 12-nodes network (i.e., 4 durations by 3 areas).
We compared 18 networks, which, according to their connections, their modulation by stimulus presentation as well as their input-region, could be classified in 3 main families: a) stimulus-duration independent, b) only partially stimulus-duration dependent or c) totally stimulus-duration dependent. The Bayesian model selection of these networks models identified as the best, the model that had all connections between the 12 nodes of the network but whose connections and input regions were modulated in a duration-specific fashion. These findings identify duration-sensitive tuning as a neural mechanism underlying the perception of time and shed light into the directionality and specificity of the connections between IPL and SMA in time processing.

Disclosures: D. Bueti: None. **F. Protopapa:** None. **M.J. Hayashi:** None. **R. Kanai:** None.

Nanosymposium

020. Human Cognition and Behavior: Timing and Temporal Processing

Location: SDCC 7

Time: Saturday, November 3, 2018, 1:00 PM - 3:30 PM

Presentation Number: 020.05

Topic: H.02. Human Cognition and Behavior

Support: NSFC Grant 31700993

Title: Rapid temporal dynamics of stimuli modulate multi-voxel activation patterns in the ventral and dorsal visual pathways

Authors: *B. GUO, J. LI, S. WANG, M. MENG
South China Normal Univ., Guangdong, China

Abstract: It is well-known that faces lead to greater fMRI activity than non-faces in several areas along the ventral visual pathway, whereas tools lead to greater activity than non-tools in the dorsal pathway. Moreover, multi-voxel pattern analyses (MVPA) of fMRI activation have shown reliable encoding of various object categories including faces and tools in the ventral pathway. By contrast, the dorsal pathway is often hypothesized to be the perception-for-action pathway, and therefore less sensitive to visual object categories but quicker in processing the temporal dynamics of stimulus change. However, little is known about how activation patterns in both

pathways may change according to the temporal dynamics of stimulus change. Here we compared the temporal bottleneck of face versus tool MVPA in the two visual pathways. By using a slow event-related design, we measured fMRI activation patterns corresponding to three stimulus presentation conditions: 1) a face was shown the first followed by a tool; 2) a tool was shown the first followed by a face; 3) overlapping face and tool were shown simultaneously. Participants were asked to classify the three stimulus presentation conditions. Moreover, in the first two conditions, the inter-stimulus interval (ISI) between the first and second stimulus varied at 5 levels (0, 33, 67, 133, 267 ms). Regions of interest (ROIs) in both visual pathways were functionally localized with separate scan runs by contrasting brain activation corresponding to an independent set of faces images versus tools images that were not used in the main experimental runs. In addition, we anatomically localized the V1 (BA17) for comparison by using Talairach coordinates. MVPA of these ROIs were conducted to classify the three stimulus presentation conditions, revealing that ISI significantly modulated activation pattern change that also correlated with behavioral response accuracy results. Specifically, longer ISI led to better behavioral response accuracy corresponding to higher classification accuracy in both the ventral and dorsal pathways, but different ROIs differ in responses as a function of the ISI. These results are the first to show how temporal dynamics of stimulus change as rapid as <50 ms modulated multi-voxel fMRI activation pattern change. And such temporal dynamic response function in different ROIs along the two visual pathways may shed lights on understanding functional relationship and organization of these ROIs.

Disclosures: B. Guo: None. **J. Li:** None. **S. Wang:** None. **M. Meng:** None.

Nanosymposium

020. Human Cognition and Behavior: Timing and Temporal Processing

Location: SDCC 7

Time: Saturday, November 3, 2018, 1:00 PM - 3:30 PM

Presentation Number: 020.06

Topic: H.02. Human Cognition and Behavior

Support: Natural Sciences and Engineering Research Council of Canada (NSERC)
Canadian Foundation for Innovation (CFI)
Oculus Research

Title: Virtual reality exposure affects performance in a motor time perception task

Authors: *S. WEECH, A. BANSAL, S. KENNY, M. BARNETT-COWAN
Dept. of Kinesiology, Univ. of Waterloo, Waterloo, ON, Canada

Abstract: Although virtual reality is a valuable tool for mimicking real-world conditions, the complex dynamics of incoming sensory information are often poorly replicated in the virtual space. The effects of exposure to these unlearned sensory correlations are not well understood,

particularly with respect to the impact on sensorimotor processing and time perception. This work focuses on performance in motor and non-motor time perception tasks following virtual reality use. We asked 18 participants to reproduce the interval of a rotating probe whose duration and velocity varied over trials. The task consisted of two variations: Participants reproduced the spatiotemporal trajectory of the probe with a mouse in the 'motor' task, and they pressed a button to signal the start and end of the interval in the 'non-motor' task. These time perception tasks were completed pre- and post-exposure to dynamic virtual reality content in a block-counterbalanced order. In addition to experiencing the standard virtual reality task, one group of participants also had their movements coupled to the speed of events that occurred in the virtual space. We expected this novel action-perception relationship to affect motor time perception performance. Highlights of our findings include a motor-specific adaptation effect that varied depending on the duration and velocity of the probe motion. We also identified an interaction between the probe dynamics and spatiotemporal movement coupling in virtual reality. The findings provide valuable insights into the impact of virtual reality on time perception, which is of timely interest given the impending growth of the virtual reality user-base.

Disclosures: S. Weech: None. **A. Bansal:** None. **S. Kenny:** None. **M. Barnett-Cowan:** None.

Nanosymposium

020. Human Cognition and Behavior: Timing and Temporal Processing

Location: SDCC 7

Time: Saturday, November 3, 2018, 1:00 PM - 3:30 PM

Presentation Number: 020.07

Topic: H.02. Human Cognition and Behavior

Support: JSPS Research Fellowships for Young Scientists
KAKENHI JP17K20006
KAKENHI JP18H01101
NIH Grant NS092079

Title: Repetition suppression in the right parietal cortex mediates psychophysical duration aftereffects

Authors: *M. J. HAYASHI[1,2], R. IVRY[2]
[1]Global Ctr. for Med. Engin. and Informatics, Osaka Univ., Suita, Japan; [2]Univ. California, Berkeley, CA

Abstract: Psychophysical studies demonstrate that our sense of time can be altered by perceptual and cognitive factors such as stimulus repetition, motion, and stimulus size or number. For example, repeated exposure to a stimulus of a specific duration produces negative aftereffects when people are asked to judge the duration of stimuli of varying duration: Stimulus durations are over-estimated following exposure to a short adaptor and under-estimated

following exposure to a long adaptor. In a recent fMRI study, the BOLD response in the right supramarginal gyrus (SMG) showed duration-specific repetition suppression, suggesting that neural populations in the right SMG are tuned to specific durations (Hayashi et al., 2015 PLoS Biology). However, it is unclear whether the duration-specific repetition suppression in the right SMG is associated with changes in subjective time following psychophysical adaptation. Here, we show evidence that these two phenomena are linked. In an fMRI adaptation experiment, duration perception was assessed by having participants (n = 18) judge if a visual stimulus of variable duration (test duration = 350-650 ms) was shorter or longer than an auditory stimulus of fixed duration (reference duration = 500 ms). In adaptation blocks, the duration judgments were preceded by an adaptation period in which a visual stimulus of 250 ms duration ('Short' block) or 750 ms duration ('Long' block) was repeatedly presented for 30 times. In baseline blocks, there was no adaptation period. We opted to use a cross-modal comparison so that the effects of adaptation from a visual adaptor would be limited to the test stimulus. Relative to the baseline block, we obtained robust negative aftereffects (mean shifts in point of subjective equality ($p < 0.05$): Short = 487 ms; Baseline = 533 ms; Long = 568 ms). In a region-of-interest analysis focusing on right SMG, the BOLD response time-locked to the offset of the test stimuli showed context-dependent repetition suppression: Activation was smaller (suppressed) to stimulus durations that were most similar to the adaptor duration. Moreover, individual differences in the size of the behavioral aftereffects correlated with the magnitude of the repetition suppression effect in the right SMG. In a whole-brain analysis, repetition suppression effects were also found in the bilateral middle occipital gyrus; however, the changes here were not correlated with the behavioral changes. These results suggest that population coding of duration in the right SMG reflects subjective time. Whether this representation is reflective of absolute or relative time remains a question for future study.

Disclosures: M.J. Hayashi: None. **R. Ivry:** None.

Nanosymposium

020. Human Cognition and Behavior: Timing and Temporal Processing

Location: SDCC 7

Time: Saturday, November 3, 2018, 1:00 PM - 3:30 PM

Presentation Number: 020.08

Topic: H.02. Human Cognition and Behavior

Support: Gordon and Marilyn Macklin Foundation
Margaret Q. Landenberger Research Foundation

Title: Timing and Sequencing in Cerebellar Ataxia

Authors: *M. SLAPIK[1], O. MORGAN[1], J. CREIGHTON[1], S. M. LACONTE[2], J. LISINSKI[2], C. L. MARVEL[1]

[1]Dept. of Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Virginia Tech. Carilion Res. Inst., Roanoke, VA

Abstract: Background:
Similar to its role in the fine-tuning of motor skills, the cerebellum may also contribute to cognition through sub-second time perception, probabilistic sequence learning, and organization of strategy. Problems with timing and coordination in cognition may underlie a variety of cognitive deficits observed in people cerebellar ataxia, a disorder caused by progressive cerebellar degeneration, yet few studies have investigated into this area. In this study, we combined several tasks to assess timing and sequencing aspects of cerebellar cognitive function.
Methods:
Three tests were administered to 18 cerebellar ataxia patients and 20 matched healthy controls:
1) Tapping to Cued Frequencies: Participants were asked to tap in time with a flashing cross. Four frequencies were tested (1, 2, 3, and 4 Hz) with 3 blocks at each speed, and the order of the blocks was randomized. Speed was then compared to target frequencies, and participants were asked to report the number of frequencies.
2) Implicit Sequence Learning: In each trial, a star appeared in one of four quadrants on a computer screen, and participants pressed a corresponding button on the keyboard. There were 12 blocks of 102 trials, in which the first and last blocks represented entirely random locations, and the middle 10 blocks contained random moves and pattern moves, where the pattern was based on directions rather than locations. Reaction times were recorded for each trial.
3) Tower of London: Participants rearranged three circles on a row of pegs in order to match a pictured goal state. There were 10 trials; each required a minimum of 4 to 7 moves to complete. Number of moves and time to complete were recorded.
Results:
Tapping to Cued Frequencies: Ataxia patients tapped with less accuracy than controls. They were faster than controls at 1 Hz but slower at 4 Hz.
Implicit Sequence Learning: Both groups improved reaction time across blocks, indicating general motor learning. However, only the control group showed sequence learning, as revealed by a separation in RT between pattern and random trials.
Tower of London: The ataxia patients made more excess moves, and took more time to complete trials, than did controls.
Correlations: In ataxia patients, greater sequence learning was associated with precise timing while tapping and with fewer excess moves on Tower of London. These associations were not observed in controls.
Conclusions:
These preliminary results suggest that cerebellar ataxia patients have a reduced ability to perform accurate timing and sequencing as a part of cognition, and this mechanism may underlie the various cognitive deficits reported in people with cerebellar damage.

Disclosures: M. Slapik: None. **O. Morgan:** None. **J. Creighton:** None. **S.M. LaConte:** None. **J. Lisinski:** None. **C.L. Marvel:** None.

Nanosymposium

020. Human Cognition and Behavior: Timing and Temporal Processing

Location: SDCC 7

Time: Saturday, November 3, 2018, 1:00 PM - 3:30 PM

Presentation Number: 020.09

Topic: H.02. Human Cognition and Behavior

Title: A kernel density inspired bayesian model of interval timing: Predicting and accounting for prior distribution and likelihood function of expected durations effects on temporal bisection performance

Authors: *C. W. DANIELS, T. A. GUPTA, F. SANABRIA
Dept. of Psychology, Arizona State Univ. - Tempe Campus, Tempe, AZ

Abstract: Interval timing refers to the entrainment of behavior in the range of seconds-to-minutes. Interval timing is often studied in humans using a temporal bisection task. In this task, individuals are trained to respond 'short' following a short-anchor (e.g., 2 s) and 'long' following a long anchor (e.g., 8 s). After this training, individuals are typically tested with arithmetically or logarithmically spaced non-reinforced intermediate durations. Interestingly, the duration at which individuals respond 'long' equally as often 'short' (the point of subjective equality, or PSE) appears to depend on the spacing of these intermediate durations. Accounting for these shifts is not trivial: Bayesian models that have yielded important insights on human interval timing are often constructed under simplifying assumptions that are analytically convenient, but do not easily allow for exploration of likelihood functions (spacing of intermediate durations) or priors (generated during anchor training). We outline a simple Bayesian pacemaker-accumulator model of interval timing that constructs the prior distribution, likelihood function, and posterior distribution (from which choice behavior is derived) of expected durations on a trial-by-trial basis via kernel density algorithms. This results in a bimodal posterior distribution of expected durations, with a mode centered near the short-anchor, and the other mode centered near the long-anchor. The model then chooses 'short' or 'long' by setting the response threshold at the interval associated with the minimum probability between the two modes; if the interval is below that threshold the model chooses 'short'; if the interval is above that threshold the model chooses 'long'. This simple model accounts for the effect of differences in likelihood functions (e.g., anti-logarithmic, super-logarithmic, logarithmic, and arithmetic spacing of intermediate durations) on temporal bisection performance in humans. Additionally, the model makes predictions about the effect of prior distributions and the abruptness of the transition between training and testing on temporal bisection performance in humans. Thus, this model provides a new test bed in which to formulate and test hypotheses about the sensitivity of temporal bisection performance to the mean and variance of anchor durations and the spacing of intermediate intervals.

Disclosures: C.W. Daniels: None. **T.A. Gupta:** None. **F. Sanabria:** None.

Nanosymposium

020. Human Cognition and Behavior: Timing and Temporal Processing

Location: SDCC 7

Time: Saturday, November 3, 2018, 1:00 PM - 3:30 PM

Presentation Number: 020.10

Topic: H.02. Human Cognition and Behavior

Support: EN464266, Edgar J Marston Professorship of Psychology, Brown University
R01EY019466, NIH

Title: Specificity and generalization of temporal perceptual learning

Authors: *R. XU[1], R. M. CHURCH[2], T. WATANABE[3]
[1]Cognitive, Linguistic and Psychological Sci., [3]Cognitive, Linguistic, and Psychological Sci., [2]Brown Univ., Providence, RI

Abstract: Perceptual learning (PL) constitutes one of the most ubiquitous and profound forms of plasticity in the adult nervous system. Despite evidence in support of PL in multiple sensory systems, a long-standing controversy is whether PL reflects changes in the intrinsic representation of a sensory stimulus (e.g., sharpening of tuning functions) or updated higher level neural changes that is specific to the trained task (e.g., optimization of behavior). Here using a two-stage temporal discrimination task, we sought to address this dichotomy in the domain of time perception. If learning of a temporal interval occurs only due to changes in the inherent representation of a temporal stimulus, performance improvements on one task (e.g., increased sensitivity to the trained interval) should completely transfer to a secondary task. If learning results from changes in neural structures specific to the trained task, improvement on one task should be largely confined to the trained task structure, no transfer to a secondary task should occur. In the present study, participants were trained for five days on a 2AFC task comparing the duration of a short auditory tone with a reference interval from memory. Before and after training, a threshold estimate was also obtained on a separate (secondary) task, involving the comparison between two auditory intervals. The intervals used during the training and testing stages were identical. If PL of a temporal interval reflects changes in the intrinsic representation of the stimulus, learning of the interval itself should occur and result in a complete transfer between the training and testing stages. On the other hand, if PL of temporal interval depends on optimization of higher level neural structures, improvements on the training task should not transfer to the testing phase, due to differences in task demand. Using a fitted logistic regression, individual sensitivity thresholds during the five training days were estimated, revealing a significant improvement in performance across days. In contrast, a comparison of performance on the secondary task during pretest (Day 1) and posttest (Day 7) sessions revealed no changes in performance. These results are the first to demonstrate a lack of task-independent learning of time and suggest that PL of temporal intervals at least partially reflects higher-level reweighting

or decision unit changes. Our findings provide grounds for constructing a unifying framework of PL and address a critical dichotomy between associative and representational learning at a systematic level.

Disclosures: R. Xu: None. **R.M. Church:** None. **T. Watanabe:** None.

Nanosymposium

102. Axon and Dendrite Development: Axon Growth and Guidance: Adhesion, Cytoskeletal Dynamics, and Transport

Location: SDCC 33

Time: Sunday, November 4, 2018, 8:00 AM - 9:45 AM

Presentation Number: 102.01

Topic: A.05. Axon and Dendrite Development

Support: Australian Research Council (ARC) through a Discovery Project Grant DP170103704
Australian National Health and Medical Research Council (NHMRC) Project Grant APP1083209

Title: Overexpression of tropomyosin Tpm3.1 enhances neurite outgrowth in an inhibitory environment for neurite growth

Authors: *T. FATH[1], H. STEFEN[2], A. HASSANZADEH-BARFOROUSHI[3], T. TOMANIC[2], M. BRETTLE[2], S. FOK[2], N. TEDLA[2], T. BARBER[3], M. WAKIANI[4]
[1]Dept. of Biomed. Sci., Macquarie Univ., Macquarie Park, Australia; [2]Sch. of Med. Sci., [3]Sch. of Mechanical and Manufacturing Engin., UNSW Sydney, Sydney, Australia; [4]Ctr. for Hlth. Technologies (CHT) & Inst. for Biomed. Materials & Devices (IBMD), Univ. of Technol. Sydney, Sydney, Australia

Abstract: Inhibitory guidance cues limit regeneration of injured neurites by preventing their normal outgrowth and extension. The actin cytoskeleton, playing a central role in growth cone protrusion, has been identified as an important target to enhance neurite regeneration and neurite extension. Targeting different isoforms of the actin-associated tropomyosin proteins, key regulators of actin filament dynamics, enables us to manipulate specific aspects of neuronal morphogenesis. Here, we investigated manipulating expression levels of tropomyosin isoform Tpm3.1 as a potential candidate for overcoming inhibitory effects of the substrate Nogo-66 in a novel microfluidic device-based assay system. The designed microfluidic device allows wild-type and human Tpm3.1 (hTpm3.1)-overexpressing mouse hippocampal neurons to grow in close proximity to the inhibitory substrate Nogo-66. We show that neurons that overexpress hTpm3.1 have a 2-fold greater ability to extend neurites into and past the area coated with Nogo-66. Our research is further establishing isoform-specificity in impacting neurite growth. In conclusion, we propose Tpm3.1 as a potential target for overcoming inhibitory environments for

neurite growth in the central nervous system, promoting advancement of neurite outgrowth, and restauration of connectivity in the brain after injury or in neurological conditions.

Disclosures: T. Fath: None. **H. Stefen:** None. **A. Hassanzadeh-Barforoushi:** None. **T. Tomanic:** None. **M. Brettle:** None. **S. Fok:** None. **N. Tedla:** None. **T. Barber:** None. **M. Wakiani:** None.

Nanosymposium

102. Axon and Dendrite Development: Axon Growth and Guidance: Adhesion, Cytoskeletal Dynamics, and Transport

Location: SDCC 33

Time: Sunday, November 4, 2018, 8:00 AM - 9:45 AM

Presentation Number: 102.02

Topic: A.05. Axon and Dendrite Development

Support: R03 NS084386
R03 NS092024
OVPRED

Title: Evidence for Presenilin and Glycogen synthase kinase 3 beta (GSK3β)-mediated regulation of molecular motors during axonal transport

Authors: *R. BANERJEE[1], Z. RUDLOFF[2], C. NAYLOR[2], M. YU[2], S. GUNAWARDENA[2]
[1]Univ. At Buffalo,State Univ. of New York, Buffalo, NY; [2]Biol. Sci., Univ. at Buffalo, State Univ. at New York, Buffalo, NY

Abstract: Long distance transport within axons is essential for neuronal function and viability, and transport defects have been implicated in Alzheimer's disease. Defects in transport could occur due to improper regulation of molecular motors. Previously we found that reduction of Presenilin (PS) stimulated APP vesicle motility and decreased active GSK3β and motor binding to membranes. Reduction of GSK3β also showed a similar effect, while excess GSK3β caused axonal blockages likely via increased motor binding to membranes. Together, these observations indicate that PS and GSK3β are functionally coupled during axonal transport. Here, using *Drosophila* genetics, we report findings to suggest that PS likely functions as a scaffold, whereby it uses its loop region to sequester GSK3β away from motors for proper regulation of motor functions. We found that functional PS with an intact loop was essential to rescue GSK3β-mediated axonal transport defects. Further, active GSK3β associated with and phosphorylated kinesin-1 *in vitro*. To test whether GSK3β-mediated phosphorylation of kinesin-1 is required for motor function we are generating phospho-active and phospho-inactive KHC mutant lines. Therefore, our work highlights a key role for PS and GSK3β in controlling motor activity during axonal transport.

Disclosures: R. Banerjee: None. **Z. Rudloff:** None. **C. Naylor:** None. **M. Yu:** None. **S. Gunawardena:** None.

Nanosymposium

102. Axon and Dendrite Development: Axon Growth and Guidance: Adhesion, Cytoskeletal Dynamics, and Transport

Location: SDCC 33

Time: Sunday, November 4, 2018, 8:00 AM - 9:45 AM

Presentation Number: 102.03

Topic: A.05. Axon and Dendrite Development

Support: NINDS NS047484
NINDS NS046357
NINDS NS095615

Title: LRRK2 regulates growth cone signaling and axon guidance mediated by Wnt/Planar cell polarity pathway

Authors: *K. ONISHI, Y. ZOU
Div. of Biol. Sci., Univ. of California San Diego, La Jolla, CA

Abstract: Leucine-rich repeat kinase 2 (LRRK2), a multi-domain protein, is a one of the causal factors in Parkinson's disease. Numerous studies revealed that LRRK2 regulates membrane trafficking, including synaptic vesicle endocytosis. We discovered a novel function of LRRK2 in axon guidance. We found previously that Wnts provide directional cues for axon growth through the planar cell polarity (PCP) pathway. We also showed that phosphorylation of Frizzled3, a key component of PCP signaling in axon guidance, regulates its trafficking. While searching for kinases that regulate Frizzled3 phosphorylation, we found that LRRK2 promotes phosphorylation of Frizzled3. To determine the role of LRRK2 in axon guidance during development, we generated *LRRK1* and *LRRK2* knockout mice using CRISPR/Cas9 system. In *LRRK1/2* DKO embryos, surprisingly, we observed defects of axon guidance events regulated by Wnt/PCP signaling. These findings reveal the previous unknown functions of LRRK2 in axon guidance through regulating Wnt/PCP signaling.

Disclosures: K. Onishi: None. **Y. Zou:** None.

Nanosymposium

102. Axon and Dendrite Development: Axon Growth and Guidance: Adhesion, Cytoskeletal Dynamics, and Transport

Location: SDCC 33

Time: Sunday, November 4, 2018, 8:00 AM - 9:45 AM

Presentation Number: 102.04

Topic: A.05. Axon and Dendrite Development

Support: NIH Intramural Research grant

Title: TP5 enhances survival of the neurons insulted by overexpression of DAPK1

Authors: *M. BHASKAR[1], S. P. YADAV[2], N. D. AMIN[2], S. SKUNTZ[2], C. WINTERS[2], H. C. PANT[2]
[1]NINDS/ NIH, Bethesda, MD; [2]NINDS, NIH, Bethesda, MD

Abstract: DAPK1 is an ER stress-responsive S/T kinase, responsible for caspase activation and autophagy, resulting in cell death. It regulates both type I apoptotic (caspase-dependent) and type II autophagic (caspase-independent) cell death signals and act as a tumor suppressor gene, by promoting autophagy and apoptosis. Cerebral ischemia recruits DAPK1 to NMDA receptor complex subunit NR2B by direct binding to its carboxyl terminus, triggering phosphorylation of NR2B subunit at Ser-1303, inducing Ca^{2+}influx through NMDA receptor channels, resulting in an irreversible neuronal death. Increased Ca^{2+} level induces cleavage of CDK5 regulator p35 into p10 and p25 leading to hyperactivation of CDK5. Here we report that both normal (CDK5/p35) and hyperactive (CDK5/p25); can phosphorylate DAPK1 derived peptides. We also showed that DAPK1 overexpression induced the death of cortical neurons and this can be rescued by treatment with TP5, a peptide inhibitor of the hyperactive CDK5. Using NetPhos 3.1 server we analyzed the predicted phosphorylation sites in DAPK1 and identified seven putative CDK5 phosphorylation sites. We designed small peptides spanning to these seven regions and tested their activity using normal and hyperactive CDK5 *in vitro*. All the seven DAPK1 derived peptides were phosphorylated by normal CDK5, however, we noted an increased phosphorylation of three peptides (T480, T579 and T612) with CDK5 compared to other peptides. Further studies on phopshorylation of theses peptides using hyperactive CDK5 revealed an increase in their phopshorylation compared to normal CDK5. These results suggest a critical role of residues T480, T579 and T612 in the modulation of DAPK1 activity in pathological conditions where CDK5 is hyperactive. We have not seen any phosphorylation activity with peptides with alanine substitution of S/T residues of the respective sites. To test the DAPK1 mediated neuronal death we overexpressed DAPK1 in cortical neurons in addition to GFP reporter. Treatment of cultured neurons either with 500nM of TP5 peptide or with 1X PBS as control, we followed their morphology at day *in vitro* (DIV) 6, 12 and 17. Over expression of DAPK1 in cortical neurons shrunken their morphology in the transfected cells. However

treatment of neuronal cultures with 500nM of the TP5 rescued the shrunken morphology to normal level. These observations indicate a role of CDK5 mediated phosphorylation of DAPK1 that was inhibited by TP5.

Disclosures: M. Bhaskar: None. **S.P. Yadav:** None. **N.D. Amin:** None. **S. Skuntz:** None. **C. Winters:** None. **H.C. Pant:** None.

Nanosymposium

102. Axon and Dendrite Development: Axon Growth and Guidance: Adhesion, Cytoskeletal Dynamics, and Transport

Location: SDCC 33

Time: Sunday, November 4, 2018, 8:00 AM - 9:45 AM

Presentation Number: 102.05

Topic: A.05. Axon and Dendrite Development

Title: Cannabinoid-induced axonal elongation and growth cone remodeling depend on kinesin1-mediated axonal transport of CB1 receptors

Authors: T. M. SAEZ, I. FERNANDEZ BESSONE, M. ALLOATTI, S. SARGIOTO, *T. L. FALZONE
Univ. of Buenos Aires, Buenos Aires, Argentina

Abstract: The endocannabinoid (eCB) system plays crucial roles in brain wiring during development, particularly in modulating axonal pathfinding and fasciculation. These processes are significantly highlighted due to the cortical wiring defects and neurodevelopmental disorders generated by abnormal eCB stimulation during pregnancy. Interestingly, humans disorders such as intellectual disability, cerebral cortical malformations, autism and epilepsy have been recently associated with somatic mutations in genes encoding the kinesin-1 molecular motor complex. Therefore, we dive into a relevant question directed to unravel whether axonal transport mechanism of cannabinoid receptors has a role in wiring and pathfinding processes that are necessary for normal neuronal development. Here, using genetically modified mice with KLC1 deletion and a combination of axonal tracing staining techniques in mice brain, live-cell imaging analysis of fluorescent CB1 receptor axonal transport, biochemistry, and immunofluorescence we tested whether KLC1 motor subunit has a functional significance in eCB signaling. Our main conclusions are that: 1) axonal transport supported by kinesin-1 is necessary for axonal pathfinding and fasciculation of corticofugal and thalamocortical axons; 2) kinesin-1 mediates the axonal transport, localization and presentation of CB1R in growth cones; 3) defects in CB1R axonal transport triggers dysfunctions in eCB-dependent axonal growth cone rearrangement and outgrowth; and 4) actin remodeling defects and impaired cofilin activation due to abnormal CB1R signaling mediate the pathfinding impairments in $KLC1^{-/-}$ neurons. All together, we demonstrated that kinesin-1 motor function is necessary for brain wiring of eCB-dependent pathways and the brain wiring abnormalities in KLC1 mutant are proposed through CB1R

axonal transport defects that impair it signaling. Our work stress a novel and relevant proposition directed to understand how trafficking of guidance receptors that depend on motor proteins, contributes to the complex process of brain wiring. These results shed light towards understanding the mechanistic underlying of several human brain wiring developmental diseases in which kinesin-1 mutations lead to severe failures in neuronal connectivity.

Disclosures: T.M. Saez: None. **I. Fernandez Bessone:** None. **M. Alloatti:** None. **S. Sargioto:** None. **T.L. Falzone:** None.

Nanosymposium

102. Axon and Dendrite Development: Axon Growth and Guidance: Adhesion, Cytoskeletal Dynamics, and Transport

Location: SDCC 33

Time: Sunday, November 4, 2018, 8:00 AM - 9:45 AM

Presentation Number: 102.06

Topic: A.05. Axon and Dendrite Development

Support: NIH RO1 Grant EY020496-07

Title: Constitutive interleukin-6 influences axon structure and transport in the optic projection

Authors: *L. K. WAREHAM[1], F. D. ECHEVARRIA[3], C. R. FORMICHELLA[1], R. M. SAPPINGTON[2]
[2]Dept. Ophthalmology and Visual Sci., [1]Vanderbilt Univ. Med. Ctr., Nashville, TN;
[3]Neurosciences, Case Western Reserve Univ., Cleveland, OH

Abstract: The pleotropic cytokine interleukin-6 (IL-6) is implicated in neuronal viability and proper CNS development. IL-6 is constitutively expressed in murine retina and changes in IL-6 expression are associated with a variety of ocular disorders and injuries, including retinal ganglion cell (RGC) degeneration. The role of constitutive IL-6 signaling in retina and its impact on visual function and retinal physiology is currently unknown. Here we examined outcomes of structural and functional physiology in the early visual pathway of mice with germline IL-6 deficiency (IL-$6^{-/-}$). Neonatal (P3, P7, P21) or adult (2-3 mo) male and female IL-$6^{-/-}$ mice (B6.129S2-$IL6^{tm1kopf}$/J) and respective genomic controls (B6129SF2/J) were used in all experiments. *In situ* hybridization studies indicated that IL-6 is expressed by RGCs throughout post-natal development and in maturity. IL-$6^{-/-}$ mice exhibited alterations in the amplitude and latency of the N1 depolarization event of visual-evoked potentials ($p<0.05$ for both) that did not translate to altered visual acuity ($p>0.05$). IL-6 deficiency had the greatest impact on function and structure of RGC axons. Histological and neural tracing studies revealed enlargement of the RGC axoplasm ($p<0.05$), a reduction in the rate of anterograde axon transport ($p<0.05$) and disruption of microtubule morphology in IL-$6^{-/-}$ mice, as compared to WT. The latter was also noted elsewhere in the CNS, suggesting that IL-6 may modulate axon structure in neurons more

generally. Protein expression studies showed differential spatial expression of microtubule proteins and microtubule-associated proteins in the retina vs optic nerve in IL6$^{-/-}$ mice compared to WT mice. Acute IL-6 replacement largely mitigated axon transport and microtubule phenotypes, suggesting that IL-6 likely influences RGC axons both during development and in maturity. Our findings identify, for the first time, the structural and functional aspects of RGCs and their axons that are influenced by constitutive IL-6 signaling and provide indications for how IL-6 may promote RGC growth and repair. These findings have significant implications for our understanding of constitutive functions for IL-6 as well as for therapeutic targeting of IL-6 in the retina and optic nerve and elsewhere in the CNS.

Disclosures: L.K. Wareham: None. **F.D. Echevarria:** None. **C.R. Formichella:** None. **R.M. Sappington:** None.

Nanosymposium

102. Axon and Dendrite Development: Axon Growth and Guidance: Adhesion, Cytoskeletal Dynamics, and Transport

Location: SDCC 33

Time: Sunday, November 4, 2018, 8:00 AM - 9:45 AM

Presentation Number: 102.07

Topic: A.05. Axon and Dendrite Development

Support: NSF Award 1656463
NIH Grant P20GM103650

Title: Dscam1 extended 3′ UTR transcripts are essential for axon guidance

Authors: *P. MIURA, Z. ZHANG, R. PETERSON, K. SO, M. BAUER, H. NG, Y. ZHANG, J. H. KIM, T. KIDD
Univ. of Nevada, Reno, Reno, NV

Abstract: In the *Drosophila* nervous system, hundreds of genes express alternative mRNA isoforms with extended 3′ UTRs. However, the functions of extended 3′ UTR isoforms in neural development remain unclear. The *Dscam1* gene is essential for neural development, and generates short (*Dscam1-S*) and long (*Dscam1-L*) 3′ UTR isoforms. We found that *Dscam1-L* biogenesis is controlled by the neuronal RNA-binding protein Embryonic Lethal Abnormal Visual System (Elav). Specific knockdown of *Dscam1-L* in neurons caused death in early adulthood and impaired axon guidance. Using long-read nanopore sequencing, we found that extended 3′ UTR transcripts preferentially skipped exon 19. This alternative splicing event was found to be also controlled by Elav. Thus, Elav controls *Dscam1* processing at both the levels of alternative splicing and alternative polyadenylation to generate mRNA isoforms that are essential for neural development.

Disclosures: P. Miura: None. **Z. Zhang:** None. **R. Peterson:** None. **K. So:** None. **M. Bauer:** None. **H. Ng:** None. **Y. Zhang:** None. **J.H. Kim:** None. **T. Kidd:** None.

Nanosymposium

103. Animal Models of Neurodevelopmental Disease

Location: SDCC 32

Time: Sunday, November 4, 2018, 8:00 AM - 10:15 AM

Presentation Number: 103.01

Topic: A.07. Developmental Disorders

Support: SFARI 344904

Title: Sex-specific behavioral and neuronal circuit disruptions in a 16p11.2 microdeletion model of autism

Authors: *J. GIOVANNIELLO, S. AHRENS, B. LI
Bo Li Lab., Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Autism Spectrum Disorders (ASD) refers 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 Variant (CNV) found in patients with ASD - 16p11.2 microdeletion - on learning, behavioral flexibility, motivation, and innate behaviors like feeding. We hypothesize that disruption of circuitry controlling these fundamental processes may give rise to the repetitive behaviors, deficits in inhibition learning, anxiety and obesity characterized in patients with the microdeletion. Our data suggests that mice harboring 16p11.2 microdeletion exhibit repetitive behaviors, are less flexible in learning new behavioral contingencies, and have generalization in fear learning. Further, electrophysiological data in these animals suggest that specific amygdala circuitry involved in these behaviors may have elevated activity. Importantly, we have identified several non-overlapping behavioral phenotypes in male and female 16p11.2 microdeletion animals. These differences in behavior across sexes may provide insight for understanding sex-specific phenotypes of Autism Spectrum Disorders in humans.

Disclosures: J. Giovanniello: None. **S. Ahrens:** None. **B. Li:** None.

Nanosymposium

103. Animal Models of Neurodevelopmental Disease

Location: SDCC 32

Time: Sunday, November 4, 2018, 8:00 AM - 10:15 AM

Presentation Number: 103.02

Topic: A.07. Developmental Disorders

Support: JSPS KAKENHI Grant (#16H06524)

Title: Paternal aging affects trajectory of developmental patterns of ultrasonic vocalization syllables induced by maternal separation in C57BL6/J mice

Authors: *L. MAI[1], R. KIMURA[1], K. KANNO[2], H. INADA[1], N. OSUMI[1]
[1]Dept. of Developmental Neurosci., Tohoku University, Grad. Sch. of Med., Sendai, Japan; [2]Fac. of Law, Econ. and Humanities, Kagoshima Univ., Kagoshima, Japan

Abstract: Autism Spectrum Disorder (ASD) is one of neurodevelopmental disorders and characterized with persistent impairments in social communication and social interactions as the core symptoms. Epidemiological studies suggest significant association between paternal aging and the ASD in offspring. However, how paternal aging makes an impact on the offspring's early communicative behavior is enigmatic. With the aim of detecting ASD, we measured body weight and ultrasonic vocalization (USV) induced by maternal separation of pups derived from young (3 months) or aged (>12 months) fathers at postnatal day 3 (P3), P6, P9 and P12. Then we further analyzed the duration,maximum frequency and maximum amplitude of USV syllables that were classified into 12 types according to Scattoni et al. (PLoS One, 2008) with minor modifications. Our results demonstrated a general delay in body weight gain across early postnatal developments. A trajectory of syllable development in pups derived from aged fathers showed reduction in the number, duration and sum duration of total syllables during the period we observed. Furthermore, detailed syllable analyses indicated a delay in the number of syllable types during developments because of paternal aging. Pups derived from aged fathers emitted significantly less types of syllables from P3 to P12. A complex type of syllable "wave" was absent in the pups from aged fathers at P3. We also found a significantly different composition of the syllable number and percentage of 12 different types between the pups derived from young and aged fathers. The pups derived from aged fathers showed increased percentages of the simple syllables such as "downward", "flat" and "short", conversely decreased percentage of complex syllables such as "wave", "chevron", "one jump" and "more jump". Moreover, the pups derived from aged fathers emitted the syllables of "upward", "short", "chevron", "wave" and "one jump" with lower maximum frequency. Overall, our results reveal for the first time a significant influence of paternal aging on USV development in the early postnatal days with qualitative and quantitative aspects.

Disclosures: L. Mai: None. **R. Kimura:** None. **K. Kanno:** None. **H. Inada:** None. **N. Osumi:** None.

Nanosymposium

103. Animal Models of Neurodevelopmental Disease

Location: SDCC 32

Time: Sunday, November 4, 2018, 8:00 AM - 10:15 AM

Presentation Number: 103.03

Topic: A.07. Developmental Disorders

Support: U54-HD087011 IDDRC @ Washington University

Title: Zika virus infection produces extensive neurodegeneration in brain and spinal cord of developing mouse central nervous system

Authors: *K. K. NOGUCHI[1], S. L. WILLIAMS[2], J. N. HUFFMAN[3], B. S. SWINEY[2], P. SALINAS-CONTRERAS[2], H. S. WANG[2], K. DIKRANIAN[2]
[1]Psychiatry, Washington Univ. St. Louis, Saint Louis, MO; [2]Psychiatry, Washington Univ. in St Louis, St Louis, MO; [3]Univ. of Missouri-St. Louis, Saint Louis, MO

Abstract: The Zika virus (ZIKV) has gone from a little known pathogen to a confirmed human teratogen resulting in the most difficult emergency health response ever undertaken by the Centers for Disease Control. Infection of pregnant women has been linked to a constellation of fetal abnormalities (called Congenital Zika Syndrome; CZS) including microcephaly, calcifications, perivascular cuffing, parenchymal hemorrhage, epileptic seizures, reduced spinal cord volume, and arthrogryposis. In order to investigate the neuropathological consequences of ZIKV infection, neonatal mouse pups were inoculated with 10^3 focus forming units of a French Polynesian clinical isolate (H/PF/2013) and sacrificed approximately two week later. Since mice are born neurodevelopmentally immature compared to humans, this would roughly translate to an infant with CZS following infection early in the second trimester. ZIKV infection produced neuropathology mirroring clinical symptoms including calcification, parivascular cuffing, and parenchymal hemorrhage. Histology revealed two types of neurodegeneration: excitotoxicity (toxicity produced by the overstimulation of neurons) and apoptosis (programmed cell death). Excitotoxic neurodegeneration could be seen in large portions of the brain including the lateral geniculate nucleus, cortex, hippocampus, striatum, superior colliculus, and cerebellum. Apoptotic degeneration mirrored excitotoxicity but occurred far less frequently. Interestingly, the spinal cords showed apoptosis in scattered cells in the funiculus and heavy focal degeneration in the axons of the corticospinal tract. While previous research suggests the ZIKV can infect neural progenitor cells (NPCs) earlier in gestation, it is unknown what occurs as the brain matures and most NPCs are naturally eliminated. This research suggests neuropathology continues after this point and can be just as devastating. The presence of excitotoxicity suggests the ZIKV infected brain may suffer from constant overstimulation and is consistent with a study reporting seizures

are the most common complication in the first 4 months of life for CZS sufferers. Corticospinal apoptosis may also explain why ZIKV infection can produce arthrogryposis: joint contractures that occur when weakness of muscles lead to joint deformities due to a fixed position in utero. It has been suggested that ZIKV infection may produce diminished corticospinal tract activation of motor neurons leading to muscle weakness and arthrogryposis. Taken as a whole, this research suggest the devastating effects of ZIKV infection are not restricted to NPCs and can continue unabated throughout gestation.

Disclosures: K.K. Noguchi: A. Employment/Salary (full or part-time):; Washington University St Louis. 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.; NICHD U54-HD087011/R01-HD083001. **S.L. Williams:** A. Employment/Salary (full or part-time):; Washington University St Louis. **J.N. Huffman:** A. Employment/Salary (full or part-time):; University of Missouri-St. Louis. **B.S. Swiney:** A. Employment/Salary (full or part-time):; Washington University St Louis. **P. Salinas-Contreras:** None. **H.S. Wang:** A. Employment/Salary (full or part-time):; Washington University St Louis. **K. Dikranian:** A. Employment/Salary (full or part-time):; Washington University St Louis.

Nanosymposium

103. Animal Models of Neurodevelopmental Disease

Location: SDCC 32

Time: Sunday, November 4, 2018, 8:00 AM - 10:15 AM

Presentation Number: 103.04

Topic: A.07. Developmental Disorders

Support: 5P50MH106438-04
2R01MH097236-06A1

Title: Altered dendritic morphology in dorsolateral prefrontal cortex of nonhuman primates prenatally exposed to maternal immune activation

Authors: *C. M. SCHUMANN[1], R. K. WEIR[2], A. IOSIF[3], J. VAN DE WATER[4], C. S. CARTER[6], A. K. MCALLISTER[5], M. D. BAUMAN[7]
[1]Dept. of Psychiatry, UC Davis MIND Inst., Davis, CA; [2]Psychiatry, UC Davis MIND Inst., Sacramento, CA; [3]Publ. Hlth., [4]Med., UC Davis, Sacramento, CA; [5]Ctr. for Neurosci., UC Davis, Davis, CA; [6]Imaging Res. Ctr., Univ. of California Davis, Sacramento, CA; [7]Univ. California, Davis, Sacramento, CA

Abstract: Maternal infection during pregnancy may increase the risk for neurodevelopmental disorders in offspring. Rhesus monkeys (Macaca mulatta) prenatally exposed to maternal immune activation (MIA) develop atypical behaviors, including increased repetitive behaviors

and atypical social interactions. Here we present evidence of underlying brain pathology. Pregnant rhesus monkeys were injected with a modified form of the viral mimic polyI:C (poly ICLC) at the end of the first trimester (n=5) or second trimester (n=4). Brain tissue was collected from MIA-treated (n=9) male offspring or control (n=4) male offspring at 4 years of age. Blocks of dorsolateral prefrontal cortex (DLPFC/BA46) were processed with the Golgi-Cox impregnation method to analyze neuronal dendritic morphology and spine density. The DLPFC was traced utilizing Neurolucida software (MBF Bioscience) and further subdivided into supra- (II/III) and infra- (V/VI) granular cell layers. For each case in each of the two regions, 10 pyramidal cells were traced in their entirety, including all apical, oblique and basal dendrites, and their spines. Somal size and apical dendrite trunk diameter were measured on 30 cells per case per region. Apical dendrite diameter was collected over a 30µm section located 100±10 µm from the soma. Nonparametric statistics were applied to assess group differences in these summary measures. Compared to controls, MIA-treated offspring exhibit a greater number of oblique dendrites (infra- $p<.01$, supra- $p<.01$). There were no differences detected in spine density or soma size in either DLPFC region. However, apical dendrites of MIA-treated offspring were smaller in diameter in infragranular layers ($p<.01$) and trend difference in supragranular layers. These data provide evidence that prenatal exposure to MIA alters dendritic morphology in a nonhuman primate MIA model, which may have profound implications for revealing the underlying neuropathology of neurodevelopmental disorders related to maternal infection.

Disclosures: C.M. Schumann: None. **R.K. Weir:** None. **A. Iosif:** None. **J. Van de Water:** None. **C.S. Carter:** None. **A.K. McAllister:** None. **M.D. Bauman:** None.

Nanosymposium

103. Animal Models of Neurodevelopmental Disease

Location: SDCC 32

Time: Sunday, November 4, 2018, 8:00 AM - 10:15 AM

Presentation Number: 103.05

Topic: A.07. Developmental Disorders

Support: Brain Canada Foundation

Title: Neurodevelopmental impact of prenatal exposure to non-infectious inflammation

Authors: *M.-E. BRIEN[1,2,3], I. BOUFAIED[3], S. GIRARD[1,2,3]
[1]Microbiology, Infectiology and Immunol., Univ. De Montreal, Montreal, QC, Canada; [2]Obstetrics and Gynecology, Univ. de Montreal, Montreal, QC, Canada; [3]Ste-Justine Hosp. Res. Ctr., Montreal, QC, Canada

Abstract: INTRODUCTION: Prenatal inflammation alters placental function which has a negative impact on fetal development and is associated with an increased risk of neurodevelopmental disorders such as cerebral palsy and autism. Infectious stimuli are most

often used in animals model; however, infections are often undetectable during pregnancy whilst inflammation is still observed. The effects of prenatal exposure to non-infectious inflammatory mediators on brain development are still mostly unknown. We developed an animal model of prenatal non-infectious inflammation, induced by uric acid crystals, leading to fetal growth restriction (FGR) (Brien et al., 2017). In this model, we observed placental inflammation and immune cells infiltration within the placenta. Our objective was to further study the effect of prenatal exposure to non-infectious inflammation on the developing brain. METHODS: We used our published model of prenatal inflammation leading to FGR. The impact of *in utero* exposure to inflammation was determined on the developing brain at different time point from gestational day 22 (GD22) to postnatal day 21 (PND21). Immunohistological analysis were performed to evaluate microglial and astroglial activation as well as myelin formation. RESULTS: Prenatal exposure to inflammation led to microglial activation characterised by increased number of microglial cell and staining intensity for Iba1 in the hippocampus (CA3 and DG) as well as in the corpus callosum at PND21, but not earlier. Astrogliosis was observed transiently in the white matter (both cc and cg), in the motor cortex and in the hippocampus (CA3 and DG) at PND7. Altered myelination was also observed in later developmental stages. These neurodevelopmental alterations were associated with smaller growth weight, which was maintained from birth until PND21 in both sexes. CONCLUSION: Prenatal exposure to non-pathogenic inflammation, mimicking the most frequent clinical situation, has important negative impact on brain development. Futures studies are needed to evaluate the functional impact of these structural changes and investigate the potential of prenatal anti-inflammatory intervention to protect the placenta and the developing brain.

Disclosures: M. Brien: None. **I. Boufaied:** None. **S. Girard:** None.

Nanosymposium

103. Animal Models of Neurodevelopmental Disease

Location: SDCC 32

Time: Sunday, November 4, 2018, 8:00 AM - 10:15 AM

Presentation Number: 103.06

Topic: A.07. Developmental Disorders

Support: NIH Grant NS064079
NUH Grant MH109795

Title: Structural and functional whole-brain mapping in a model of Syngap1-related brain disorders

Authors: *T. VAISSIÈRE[1], D. FURTH[2], K. MELETIS[3], C. A. MILLER[4], G. RUMBAUGH[5]
[1]Neurosci., The Scripps Res. Institue, Jupiter, FL; [2]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [3]Karolinska Inst., Stockholm, Sweden; [4]Mol. Med. and Neurosci., [5]Neurosci., The Scripps Res. Inst., Jupiter, FL

Abstract: MRD5, which is caused by SYNGAP1 haploinsufficiency, is among the most common genetically defined causes of intellectual disability (ID) with epilepsy and autism spectrum disorder. Mouse models of *Syngap1* haploinsufficiency recapitulate key behavioral and neurophysiological phenotypes observed in MRD5 patients, including cognitive impairment, abnormal social interactions and seizure. *Syngap1* regulates a critical period during development by coordinating dendrite elongation and synaptic maturation/plasticity in forebrain areas. This process is believed to promote the proper assembly of circuits necessary for executing higher brain functions. To understand how circuit assembly is impacted by *Syngap1* mutations, we are employing cell-type specific trans-synaptic tracing technology to understand how brain-wide long-range inputs into distinct classes of cortical neurons are affected in MRD5 models. To understand how impaired circuit assembly may lead to neural dysfunction, we are also performing whole-brain mapping of neural activation in *Syngap1* mutants. Indeed, we have developed methods that enable rapid digital reconstructions and subsequent analysis of cellular data within dozens of mouse brains. This method can identify brain areas in Syngap1 mice that respond abnormally during a novel social experience. Importantly, the mapping and visualization software enables the superimposition of both anatomical and functional whole-brain data sets. Our initial studies have identified abnormalities in specific lamina linked to higher forms of cortical processing. Together, our approaches provide a systematic and comprehensive way of investigating cell-type and region-specific circuit impairments in animal models of brain disorders. These approaches are expected to reveal how variants linked to genetically-defined human brain disorders disrupt neural circuit structure and function at the mesoscale.

Disclosures: T. Vaissière: None. **D. Furth:** None. **K. Meletis:** None. **C.A. Miller:** None. **G. Rumbaugh:** None.

Nanosymposium

103. Animal Models of Neurodevelopmental Disease

Location: SDCC 32

Time: Sunday, November 4, 2018, 8:00 AM - 10:15 AM

Presentation Number: 103.07

Topic: A.07. Developmental Disorders

Support: Howard Hughes Medical Institute

Title: PB transposon based genome-wide screening system in mice

Authors: *H. CHANG[1], Y. PAN[2], T. XU[1]
[1]Genet., Yale Univ., New Haven, CT; [2]Yeda Inst., Taizhou, China

Abstract: Forward genetic screens have been widely used in lower model organisms such as flies, worms and yeast. However, cost and time associated with generating large scale mutant animals and mapping these mutations are still major limitations of achieving a genome-wide

screen in mammalian systems. Here, we established a highly efficient *piggyBac* (PB) transposon-mediated first generation dominant screen system in mice, which makes it possible for an individual investigator to conduct a genome-wide phenotypic screen within a year with less than 300 cages and 80,000$ in total cost. Using this elegant PB F1 system, we conducted a pilot screen for growth retardation. Growth retardation affects 3-10% of first-time pregnancies, increases 4-8 times higher for infants' perinatal mortality rates (IUGR) and will also leads to many serious diseases such as Costello syndrome and human dwarfism (PGR). After examining 2036 F1s with new PB insertions, five growth retardation associated mutants were isolated, including both IUGR and PGR related genes. Furthermore, characterization of the BFDM/4PB/+ mutants revealed a novel role in milk intake behavior. The mutant animals exhibit abnormalities in nipple recognition and milk ingestion in breastfeeding period. Adult BFDM/4PB/+ mutants also show defects in predatory-hunting and pasta-eating.

Disclosures: H. Chang: None. **Y. Pan:** None. **T. Xu:** None.

Nanosymposium

103. Animal Models of Neurodevelopmental Disease

Location: SDCC 32

Time: Sunday, November 4, 2018, 8:00 AM - 10:15 AM

Presentation Number: 103.08

Topic: A.07. Developmental Disorders

Support: JSPS KAKENHI Grant Number 16H06524

Title: Paternal aging affects offspring's behavior and gene expression possibly through transmission of hypomethylated DNA regions in NRSF/REST binding sites

Authors: *R. KIMURA[1], T. KIKKAWA[1], K. YOSHIZAKI[2], T. KOIKE[3], S. OKI[5], H. KOBAYASHI[4], H. J. INADA[1], K. MOCHIZUKI[1,6], N. AOKI[6], T. KONO[3], Y. MATSUI[6], N. OSUMI[1]
[1]Dept. of Developmental Neurosci., Tohoku Univ. Grad. Sch. of Med., Sendai, Japan; [2]Dept. of Pathology, Inst. for Developmental Res., Aichi, Japan; [3]Dept. of Biosci., [4]NODAI Genome Res. Ctr., Tokyo Univ. of Agr., Tokyo, Japan; [5]Dept. of Developmental Biol., Kyushu Univ. Grad. Sch. of Med. Sci., Fukuoka, Japan; [6]Cell Resource Ctr. for Biomed. Res., Tohoku Univ. Inst. of Development, Aging and Cancer, Sendai, Japan

Abstract: Paternal age has deleterious effects on the transmission of phenotypes to offspring such as higher prevalence of major psychiatric and neurodevelopmental disorders. We have found that F1 offspring of aged fathers showed impairment in pup's vocalization, sensorimotor gating and spatial learning. Here we analyzed molecular mechanisms underlying behavioral changes due to paternal aging. Since we found reduction of thickness in the neocortex, especially in the deep layer, at postnatal day 6, when vocalization defects were observed, we profiled gene

expression of developing brains at embryonic day 11.5 (E11.5) and E14.5 by RNA-seq. Gene Set Enrichment Analysis (GSEA) showed in brains of aged-father derived offspring at E14.5, but not in E11.5, enrichment of "Late-fetal genes" and conversely, that of "Early-fetal genes" in those derived from young father. Interestingly, "NRSF/REST motif genes" and "SFARI genes (autism-related)" were found to be highly enriched in the brains derived from aged father. A possible scenario is that paternal aging may induce in the offspring's brain precocious neurogenesis via dis-regulation of gene expression by NRSF/REST, a pivotal transcription factor for neurogenesis. Our parallel analyses on sperm DNA methylation at the whole genome level also suggest involvement of hypo-methylation in aged sperm and NRSF/REST as a common motif in hypo-methylated regions. We are currently examining relationship between DNA de-methylation and gene expression within the developing brain.

Disclosures: R. Kimura: None. **T. Kikkawa:** None. **K. Yoshizaki:** None. **T. Koike:** None. **S. Oki:** None. **H. Kobayashi:** None. **H.J. Inada:** None. **K. Mochizuki:** None. **N. Aoki:** None. **T. Kono:** None. **Y. Matsui:** None. **N. Osumi:** None.

Nanosymposium

103. Animal Models of Neurodevelopmental Disease

Location: SDCC 32

Time: Sunday, November 4, 2018, 8:00 AM - 10:15 AM

Presentation Number: 103.09

Topic: A.07. Developmental Disorders

Support: Canadian Institue for Health Research
Brain Canada
Ontario Brain Institute

Title: Animal population imaging - An update on clustering mouse models related to autism based on their neuroanatomy

Authors: *J. ELLEGOOD, L. R. QIU, B. C. DARWIN, R. M. HENKELMAN, J. P. LERCH
Mouse Imaging Ctr., Hosp. For Sick Children, Toronto, ON, Canada

Abstract: Background – Autism is complex and still poorly understood. It is highly heritable, yet no single gene accounts for more than 1-2% of known cases (Abrahams and Geschwind, 2010). Currently, 800+ genes are associated with Autism in humans (gene.sfari.org), and while autism is associated with communication and social deficits, as well as repetitive behaviours, individual clinical presentations are highly heterogeneous (Reiss, 2009). Over the past 10 years, we have established a large cohort of mouse models related to autism, which allows for a neuroanatomical investigation of a large autism population in the mouse.
Objectives – The purpose here is to build upon our previous work, which included 26 different mouse models of autism (Ellegood et al. 2015), in an effort to further characterize and cluster our

current dataset with 70+ mouse models.
Methods – The data used in this study was accumulated over a period of 10 years with more than 70 different autism related mouse-lines and includes over 2000 mice. Ex vivo imaging was done using a 7T MRI with a T2 weighted, 3D fast spin echo sequence which acquires data at a current isotropic resolution of 40 μm (Spencer Noakes et al. 2017).
Data Analysis – To visualize and compare any differences, the images were registered together (Lerch et al., 2011). From this the volumes of 182 different regions (Dorr et al. 2008, Ullmann et al. 2013, and Steadman et al. 2014, Richards et al. 2011, Qiu et al. 2018, Beera et al. 2017) were calculated. Group differences in each of the 182 regions across the different mouse models were calculated and used to group the different models using hierarchical clustering algorithms.
Results – Across all models the most affected regions were the trunk of the arbor vita (white matter) in the cerebellum, hypothalamus, striatum, and the granular layer of the hippocampus. Three distinct groups were formed. Increases in the frontal and cingulate cortices, as well as decreases in the cerebellum and medulla defined group 1 (consisting of Arid1b, Chd8, En2, Fmr1, NRXN1α, Shank3 mutations). Conversely, decreases in large white matter structures, the granular layer of the hippocampus, the globus pallidus, and increases in the cerebellum defined group 2 (consisting of 15q11-13, Arhgef6, BTBR, Nlgn3, and Ube3a). A mixture of differences including decreases in the amygdala and anterior commissure and increases in the cerebellum and colliculi defined group 3 (consisting of 16p11, Cntnap2, Mecp2, Slc6a4 ala56 KI, and Nhs). This all suggests that the autistic phenotype both preferentially affects key regions of the brain, but also divides into distinct clusters based on directionality and localization of the differences in the brain.

Disclosures: J. Ellegood: None. **L.R. Qiu:** None. **B.C. Darwin:** None. **R.M. Henkelman:** None. **J.P. Lerch:** None.

Nanosymposium

104. Parkinson's Disease: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 4

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 104.01

Topic: C.03. Parkinson’s Disease

Support: This work was supported by the Worth Family Fund, The Perry & Ruby Stevens Charitable Foundation and The Robert J., Jr. and Helen C. Kleberg Foundation.
The NIH primate center base grant (Office of Research Infrastructure Programs/OD P51 OD011133)
The National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1 TR001120

Title: Charting the onset of motor and non-motor dysfunctions in nonhuman primate model of Parkinson's disease

Authors: *M. DAADI, G. CHOUDHURY
Texas Biomed. Res. Inst., San Antonio, TX

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disease increasingly affecting our aging population. Remarkable advances have been made in developing novel therapies to control symptoms, halt or cure the disease ranging from physiotherapy and small molecules to cell and gene therapy. This progress was enabled by the existence of reliable animal models. The nonhuman primatemodel of PDemulates the cardinal symptoms of PD including tremor, rigidity, bradykinesia, postural instability, freezing and cognitive impairment. However, this model is established through the specific loss of midbrain dopaminergic neurons, while our current knowledge reflects the reality of PD as a multisystem disease. PD involves both motor (MS) and non-motor symptoms (NMS), such as sleep disturbance, olfaction, gastrointestinal dysfunctions, depression and cognitive deficits. Some of the NMS emerge earlier at the prodromal phase and worsen with the disease progression, yet in basic and translational studies, they are rarely considered as endpoints. In this study, we set to characterize an ensemble of less described motor and non-motor dysfunctions in the marmoset MPTP model. We provide evidence that this animal model expresses postural head tremor and a progressive worsening offine motor skills, movement coordination and cognitive abilities over a 6-month period. We report for the first time a non-invasive approach showing detailed analysis of daytime and nighttime sleep and circadian rhythm disturbance remarkably similar to PD patients. This study describes the incidence of tremors, motor and non-motor dysfunctions in a preclinical model and highlights the need for their consideration in translating effective new therapeutic approaches for PD.

Disclosures: M. Daadi: None. **G. Choudhury:** None.

Nanosymposium

104. Parkinson's Disease: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 4

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 104.02

Topic: C.03. Parkinson's Disease

Support: MUSC Barmore Foundation
LivaNova PLC

Title: The anti-inflammatory effect of vagus nerve stimulation as a therapeutic approach for Parkinson's disease

Authors: *H. A. BOGER[1], A. FARRAND[2], R. VERNER[3], R. MCGUIRE[3]
[1]Neurosciences, Med. Univ. of South Carolina Dept. of Neurosciences, Charleston, SC; [2]Neurosciences, Med. Unversity of South Carolina, Charleston, SC; [3]Neuromodulation Div., LivaNova PLC, Houston, TX

Abstract: Vagal control of the inflammatory reflex is an exciting new area of research with vast clinical potential. Recent studies have focused on vagal attenuation of systemic inflammatory response to chemical or biological insults. Conditions such as Parkinson's and Alzheimer's Disease have neuroinflammatory components, and prior investigation using a dual lesion (DSP-4/6-OHDA) rat Parkinson's model demonstrated that brief periods of VNS could reduce Parkinson's Disease symptom severity and bolster dopaminergic neuron health through neuroprotective effects. Specifically, this model revealed improved locomotion, elevated tyrosine hydroxylase expression in striatum, substantia nigra, and locus coeruleus, and decreased substantia nigra alpha-synuclein expression in response to twice daily VNS. The dependence of these outcomes on more broadly selected VNS dosing parameters is currently not known. In the present work, we aim to characterize therapeutic waveform features of VNS using the DSP-4/6-OHDA dual lesion model to better understand important physiological circuits that affect disease progression. Modulation of inflammatory circuits and the extrapyramidal motor pathway are hypothesized to be differentially controlled by VNS of different stimulation frequencies, and may be characterized experimentally by modulated levels of serum cortisol and acetylcholine, as well as norepinephrine levels in the central nervous system. In capturing these biomarkers, along with assessing motor dysfunction and neuropathological changes that occur as a result of Parkinson's Disease, we will assess the therapeutic potential of each physiological pathway on disease pathology.

Disclosures: H.A. Boger: None. **A. Farrand:** None. **R. Verner:** Other; Employee of LivaNova. **R. McGuire:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock Holder of LivaNova. Other; Employee of LivaNova.

Nanosymposium

104. Parkinson's Disease: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 4

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 104.03

Topic: C.03. Parkinson’s Disease

Support: Axovant Sciences
Emerald Foundation

Title: Discoidin domain receptors are potential targets to treat neurodegenerative diseases

Authors: *A. J. FOWLER[1,2], C. E. H. MOUSSA[1], M. L. HEBRON[1]
[1]Neurol., [2]Interdisciplinary Program in Neurosci., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Human Parkinson's disease pathogenesis is characterized by prominent loss of dopaminergic neurons within the Substantia Nigra pars compacta and accumulation of misfolded α-synuclein, which contributes to the formation of intraneuronal proteinaceous inclusions termed Lewy Bodies. Although there have been a number of studies which explored targeting α-synuclein at its various stages of production and dysfunction none so far has led to a successful therapy for use in humans. Tyrosine kinases (TK) have increased activation in multiple neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's Disease (PD). Specific TKs, Abelson and Discoidin Domain Receptors 1 and 2 (DDR) are upregulated in the midbrain and hippocampus in post-mortem PD and AD brains, respectively. We have shown in preclinical models that Nilotinib, an Abl inhibitor, penetrates the brain and activates parkin leading to Beclin-1 mediated autophagic clearance of aggregated α-synuclein. In the A53T mouse model of α-synucleinopathy we have shown that knockdown of DDR2 via shRNA leads to a reduction in the levels of α-synuclein, inflammation, and microglial activity without a change in cell number. LCB-03-0110 has been reported to be a potent DDR inhibitor. In neuronal cell culture models LCB administration inhibited DDR1 and DDR2 activation. In the triple mutant APP mouse, a low dose of LCB reduced amyloid-β;;, phosphorylated tau, inflammation, and increased cognition. In a viral-vector gene-transfer model, where human α-synuclein is expressed in the substantia nigra of C57BL/6J mice, a low dose of LCB decreased α-synuclein load and prevented dopamine metabolism within the midbrain of these animals. This was repeated in a Preformed Fibril mouse model of Parkinson's disease. Future studies aim to better understand the role of DDRs in neurodegeneration and develop LCB as a potential new therapy for these diseases.

Disclosures: A.J. Fowler: None. **C.E.H. Moussa:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Georgetown University. **M.L. Hebron:** None.

Nanosymposium

104. Parkinson's Disease: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 4

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 104.04

Topic: C.03. Parkinson's Disease

Support: CIHR Grant PJT 148736

Title: Viral knockdown of alpha-synuclein expression prevents spreading synucleinopathy

Authors: *S. MENON[1], F. NABBOUH[1], K. XHIMA[2], P. SARDI[3], L. S. SHIHABUDDIN[3], H. MOUNT[1], I. AUBERT[2], J. C. WATTS[1], A. TANDON[1]
[1]Tanz Ctr. for Res. in Neurodegenerative Dis., Univ. of Toronto, Toronto, ON, Canada; [2]Sunnybrook Res. Inst., Toronto, ON, Canada; [3]Neurosci., Sanofi, Framingham, MA

Abstract: α-Synuclein (α-syn) is a key factor in neurodegenerative disorders known as synucleinopathies, which include Parkinson's disease (PD), Dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Synucleinopathy brains feature progressive accumulation of insoluble, aggregated and phosphorylated α-syn, resulting in neuronal death. A prion-like mechanism is proposed to underlie the spreading of α-syn pathology, whereby misfolded α- syn recruits normal α-syn to a self-perpetuating conversion into aberrant conformations along specific neuronal tracts. Silencing of the α-syn gene could therefore provide long-lasting therapeutic benefits by reducing the requisite substrate and disrupting the neuronal cascade of spreading aggregation. The rapid and reproducible phenotype of MSA-inoculated hemizygous M83 (Tg M83$^{+/-}$) mice is a unique model of synucleinopathy that provides an ideal disease platform to assess the therapeutic benefits of α-synuclein knockdown. Stereotaxic injection of adeno-associated virus serotype 1 bearing α-syn shRNA unilaterally into Tg M83$^{+/-}$ brains reduced α-syn expression and prevented the spread of phosphorylated α-syn. Our study combines biochemical, immunohistochemical and behavioral data to assess the efficacy of α-synuclein knockdown in preventing the spread of pathological α –synuclein.

Disclosures: S. Menon: None. **F. Nabbouh:** None. **K. Xhima:** None. **P. Sardi:** None. **L.S. Shihabuddin:** None. **H. Mount:** None. **I. Aubert:** None. **J.C. Watts:** None. **A. Tandon:** None.

Nanosymposium

104. Parkinson's Disease: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 4

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 104.05

Topic: C.03. Parkinson's Disease

Support: CIHR Grant PJT148736

Title: Suppression of alpha-synuclein gene expression prevents spreading synucleinopathy

Authors: *A. TANDON[1], S. MENON[2], F. NABBOUH[3], K. XHIMA[4], S. SARDI[5], L. S. SHIHABUDDIN[6], H. T. MOUNT[7], I. AUBERT[4], J. C. WATTS[2]
[1]Tanz Ctr. for Res. in Neurodegenerative Dis., [3]Inst. of Med. Sci., [2]Univ. of Toronto, Toronto, ON, Canada; [4]Sunnybrook Res. Inst., Toronto, ON, Canada; [6]Neurosci., [5]Sanofi, Framingham, MA; [7]Thurston County Publ. Hlth. and Social Services, Toronto, ON, Canada

Abstract: Synucleinopathies such as Parkinson's disease (PD), Dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) are distinguished by progressive accumulations of insoluble and aggregated alpha-synuclein (asyn). Although the pattern of affected brain regions is unique to each disorder, the underlying spread of asyn pathology is thought to share a common prion-like mechanism, whereby misfolded asyn molecules template normal asyn into conformationally rigid species that can spread along connected neuronal tracts. Suppression of asyn levels may be a viable therapeutic approach to delay or block the spreading pathology. In this study, we evaluated the benefits of asyn knockdown in hemizygous M83 (Tg M83$^{+/-}$) mice which overexpress human A53T asyn. When these animals are inoculated with MSA-derived brain lysate, they develop a widespread progressive synucleinopathy with diminishing motor function over 100 days. Unilateral stereotaxic brain injections of adeno-associated virus serotype 1 bearing asyn shRNA into the Tg M83$^{+/-}$ animals 30 days before inoculation with MSA lysate reduced asyn expression and conferred resistance against the pathological spread of phosphorylated asyn and motor impairments in these mice. Our study provides biochemical, immunohistochemical and behavioural data on the neuroprotection afforded by asyn knockdown in a mouse model of spreading synucleinopathy.

Disclosures: A. Tandon: None. **S. Menon:** None. **F. Nabbouh:** None. **K. Xhima:** None. **S. Sardi:** None. **L.S. Shihabuddin:** None. **H.T. Mount:** None. **I. Aubert:** None. **J.C. Watts:** None.

Nanosymposium

104. Parkinson's Disease: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 4

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 104.06

Topic: C.03. Parkinson's Disease

Support: MSA Coalition Grant 20170367
NIH Grant AG050721; Administrative Supplement to Promote Diversity in the Workforce

Title: Treatment with the molecular tweezer, CLR01, shows positive efficacy in a multiple system atrophy mouse model

Authors: *D. BOUQUIO[1], K. BIGGS[1], G. NAIR[1], T. SCHRADER[2], N. STEFANOVA[3], G. BITAN[1]
[1]Dept. of Neurol., Univ. of California Los Angeles, Los Angeles, CA; [2]Inst. for Organic Chem., Univ. of Duisburg-Essen, Essen, Germany; [3]Dept. of Neurol., Med. Univ. of Innsbruck, Innsbruck, Austria

Abstract: Multiple System Atrophy (MSA) is a rare synucleinopathy characterized by fibrillary alpha-synuclein (a-syn) deposits in oligodendrocytes, therefore, preventing a-syn aggregation is a prominent target for treatment. The molecular tweezer, CLR01, is a novel, broad-spectrum protein-aggregation inhibitor with a unique mechanism that works in a process-specific manner, instead of a protein specific one, by binding to exposed lysine residues and disrupting the weak forces that facilitate the early steps of aggregation. CLR01 previously has been shown to prevent a-syn aggregation *in vitro,* inhibit a-syn-induced toxicity *in cellulo,* rescue zebrafish embryo death caused by a-syn overexpression, and improve behavioral deficits in a Parkinson's disease (PD) mouse model, Thy1-aSyn. Based on these observations, we hypothesized that CLR01 would exhibit similar anti-aggregation properties and ameliorate disease phenotype in an MSA mouse model. In this proof-of-concept study, we administered CLR01 in two doses via intracerebroventricular (ICV) infusion to transgenic mice overexpressing human a-syn in oligodendroglia under the proteolipid protein promoter (PLP-aSYN) for one month. Mice were evaluated in open-field activity and dissected brain regions were analyzed for neuropathological a-syn-positive glial cytoplasmic inclusion (GCI) density. Fractioned brain samples were assessed for total, pS129- and oligomeric a-syn by ELISA and Western blot, and for seeding activity using a HEK293T FRET biosensor cell assay. The results demonstrate a dose-dependent response to CLR01 treatment in behavioral, pathological, and biochemical measurements. We report an improvement in anxiety-like behavior, reduction in GCI density, breakdown of toxic a-syn oligomers, and decrease in seeding activity with CLR01 treatment. This study provides the first functional readout for the therapeutic use of CLR01 in MSA mice.

Disclosures: D. Bouquio: None. **K. Biggs:** None. **G. Nair:** None. **T. Schrader:** None. **N. Stefanova:** None. **G. Bitan:** None.

Nanosymposium

104. Parkinson's Disease: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 4

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 104.07

Topic: C.03. Parkinson's Disease

Support: The Michael J. Fox Foundation for Parkinson's Research

Title: IkT-148009 a c-Abl inhibitor: Target engagement in Parkinson's disease model

Authors: *S. S. KARUPPAGOUNDER[1,2,6], H. WANG[1,2,7], S. BISEN[8], F. AKKENTLI[2], N. SLOAN[8], A. SIGMON[8], H. LEE[8], S. BRAHMACHARI[1,2,6], M. KUMAR[1,2,6], T. M. DAWSON[1,2,3,4,6], M. H. WERNER[9], V. L. DAWSON[1,2,4,5,6]
[1]Neurol., [2]Neuroregeneration and Stem Cell Programs, Inst. for Cell Engin., [3]Pharmacol. and Mol. Sci., [4]Neurosci., [5]Physiol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [6]Adrienne Helis Malvin Med. Res. Fndn., New Orleans, LA; [7]Diana Helis Henry Med. Res. Fndn., New

Orleans, LA; [8]Krieger Sch. of Arts and Sci., Johns Hopkins Univ., Baltimore, MD; [9]Inhibikase Therapeut., Atlanta, GA

Abstract: c- Abl activation is linked to the pathology of Parkinson's disease. Mitochondrial dysfunction results in oxidative stress which leads to c-Abl activation, a molecular sensor of oxidative stress. c-Abl activation leads to the inactivation of parkin, the activation of p38α, NLRP3-inflammasome-mediated NF-κB activation in microglia, and α-synuclein phosphorylation at Y39. Previously, we have shown that Parkin inactivation causes the accumulation of pathogenic parkin substrates PARIS and AIMP2 and subsequently leads to Parthanatos-mediated neuronal death. PD patients and MPTP intoxicated mice show c-Abl activation in the brain. Conditional knockout of c-Abl in mice protects against MPTP toxicity. Current therapies are focused on the symptoms of the disease, but none of the existing drugs are appropriate for disease-modifying therapy. Target engagement therapeutic approaches will be beneficial in halting or preventing the progression of the disease. Current limitations with small molecule inhibitors are mainly due to poor brain penetration, a lack of efficacy, and other adverse effects. Thus, developing a c-Abl inhibitor with safer, and better efficacy is a major requirement for the therapeutic treatment of PD. In the present study, we evaluated the lead candidate, IkT-148009, which is a highly potent inhibitor, first-in-class, small-molecule drug designed and engineered to target c-Abl specifically. The primary aim of this current study is to evaluate the target engagement of this new generation c-Abl inhibitor in the MPTP-induced PD mouse model. The results demonstrate significant inhibition of activated c-Abl in the MPTP intoxicated mouse brain. Pharmacokinetics of IkT-148009 shows a steady state concentration of the drug in the brain. Co-administration of P-glycoprotein inhibitor prevents the efflux and maintains the steady state of IkT-148009 in the brain. This study could provide the rationale for the development of an oral medication that targets an underlying biological mechanism that leads to Parkinson's disease, with the goal of reversing disease progression.

Disclosures: S.S. Karuppagounder: None. **H. Wang:** None. **S. Bisen:** None. **F. Akkentli:** None. **N. Sloan:** None. **A. Sigmon:** None. **H. Lee:** None. **S. Brahmachari:** None. **M. Kumar:** None. **T.M. Dawson:** None. **M.H. Werner:** None. **V.L. Dawson:** None.

Nanosymposium

104. Parkinson's Disease: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 4

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 104.08

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS NS38377
NIH/NINDS NS082205
NS098006

JPB Foundation
Adrienne Helis Malvin Medical Research Foundation and the Diana Helis Henry Medical Research Foundation

Title: Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease

Authors: *T.-I. KAM[1], S. YUN[2], N. PANICKER[2], Y. OH[2], J.-S. PARK[2], S.-H. KWON[2], S. KARUPPAGOUNDER[2], H. PARK[2], S. A. LIDDELOW[3], B. BARRES[4], V. L. DAWSON[5], S. LEE[2], H. KO[2], T. M. DAWSON[6]
[1]Inst. for Cell Engineering/ Dept. of Neurol., Johns Hopkins Univ. Sch. of Med., Ellicott City, MD; [2]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Neurobio., [4]Dept. of Neurobiology,, Stanford Univ., Stanford, CA; [5]Inst. Cell Engin., Johns Hopkins Univ. Sch. Med., Baltimore, MD; [6]Inst. for Cell Engin., Johns Hopkins Univ. Inst. for Cell Engin., Baltimore, MD

Abstract: Activation of microglia leads to the conversion of resting astrocytes to toxic A1 type astrocytes in a variety of neurologic disorders including Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Laterals Sclerosis (ALS), Huntington's disease (HD), and Multiple Sclerosis (MS). Development of agents that could inhibit the formation of A1 reactive astrocytes could have profound therapeutic potential since they could be used to treat a variety of neurologic disorders for which there currently are no disease modifying therapies. Glucagon-like peptide-1 receptor (GLP-1R) agonists have been touted as potential neuroprotective agents for AD and PD, and for traumatic brain injury (TBI). However, the mechanisms of how GLP-1R agonist elicits these actions is not known. Here we show that a potent, brain penetrant long acting GLP-1R agonist NLY01, is profoundly neuroprotective in models of PD. We found that NLY01 protects against the loss of dopamine neurons and behavioral deficits in the α-synuclein preformed fibril (α-syn PFF) model of sporadic PD. NLY01 also prolongs the life, reduces the behavioral deficits and neuropathologic abnormalities in the human A53T α-synuclein (hA53T) transgenic (Tg) model of α-synucleinopathy induced neurodegeneration. We found that NLY01 is a potent GLP-1 agonist with favorable properties that is neuroprotective via the direct prevention of microglial mediated conversion of resting astrocytes to neurotoxic A1 reactive astrocytes. We anticipate that NLY01 will have favorable properties in the treatment of PD and related neurologic disorders characterized by microglial activation.

Disclosures: T. Kam: None. **S. Yun:** None. **N. Panicker:** None. **Y. Oh:** None. **J. Park:** None. **S. Kwon:** None. **S. Karuppagounder:** None. **H. Park:** None. **S.A. Liddelow:** None. **B. Barres:** None. **V.L. Dawson:** None. **S. Lee:** None. **H. Ko:** None. **T.M. Dawson:** None.

Nanosymposium

105. Vision: Visual Cortex: Functional Architecture and Circuits

Location: SDCC 23

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 105.01

Topic: D.07. Vision

Support: NRF-2016R1C1B2016039
NRF-2016R1E1A2A01939949

Title: A unified developmental model of functional maps in the primary visual cortex

Authors: *J. JANG[1], M. SONG[1,2], G. KIM[3], S.-B. PAIK[1,2]
[1]Dept. of Bio and Brain Engin., [2]Program of Brain and Cognitive Engin., KAIST, Daejeon, Korea, Republic of; [3]Dept. of Physics, Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: In higher mammals, the primary visual cortex (V1) is organized into various functional maps representing preferred orientation, direction, and spatial frequency. These cortical functional maps are thought to play an important role in visual information processing; therefore, they have been extensively studied for decades. Interestingly, it was reported that the topography of these functional maps is correlated across the cortical surface (Nauhaus et al., 2016). For example, the contours of the orientation and the spatial frequency maps intersect orthogonally, implying an efficient tiling of functional domains (Nauhaus et al., 2012). However, it is still unclear how this systematic organization of multiple maps can arise in the cortex. To address this issue, we introduce a model in which the functional maps can be seeded altogether from the regularly structured retinal afferents, and this unified process can result in the observed topographical correlations among the maps. Our developmental model is based on the previous notion that a quasi-periodic orientation map can be seeded by the moiré interference between hexagonal lattices of ON and OFF retinal ganglion cells (RGCs) (Paik and Ringach, 2011). The key assumption was that the orientation tuning of a V1 neuron can be generated by the anisotropic receptive fields from the ON and OFF RGCs afferents. Expanding this developmental model of orientation maps, we suggest that the ON and OFF RGC afferents from the retina can also induce other types of stimulus tuning in V1. We found that the regularly structured ON and OFF retinal inputs could result in the observed quasi-periodic variation of direction preference and ocular dominance. Also, the competition between contra- and ipsilateral inputs to V1 neurons could generate the preference for higher spatial frequency in binocular regions (Nauhaus et al., 2016). As a result, we found that each feature preference changes in relation to the orthogonal direction across the retinal mosaics. Also, we successfully reconstructed the orthogonal relationships between orientation, ocular dominance, and spatial frequency maps, as reported in previous experiments (Hübener et al., 1997; Nauhaus et al.,

2012). In addition, using published animal data (Crair et al., 1997; Hübener et al., 1997; Issa et al., 2000; Swindale et al., 2000; Kisvarday et al., 2001; Xu et al., 2005), we validated the prediction of our model that iso-domains with the same feature preference are arranged in a hexagonal lattice in each type of functional map. Our results suggest a unified developmental model of various functional maps in the visual cortex.

Disclosures: J. Jang: None. **M. Song:** None. **G. Kim:** None. **S. Paik:** None.

Nanosymposium

105. Vision: Visual Cortex: Functional Architecture and Circuits

Location: SDCC 23

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 105.02

Topic: D.07. Vision

Support: Leon Levy
National Science Foundation

Title: Adaptive processing and top-down influences in areas V1 and V4

Authors: *G. L. ASTORGA[1], Y. YAN[2], W. LI[3], C. D. GILBERT[4]
[1]Lab. of Neurobio., The Rockefeller Univ., New York, NY; [2]Sch. of Brain and Cognitive Sci., [3]State Key Lab. of Cognitive Neurosci. and Learning, Beijing Normal Univ., Beijing, China; [4]Rockefeller Univ., New York, NY

Abstract: Top-down influences have profound effects on the functional properties of cortical neurons. To determine the relative effects of perceptual task on multiple areas along the ventral visual pathway we made chronic implantations of electrode arrays in visual cortical areas V1 and V4. To distinguish response properties due to stimulus context from those conferred by behavioral context, we trained monkeys on a dual task paradigm, where they were cued to perform either of two discrimination tasks with the identical visual stimulus. The stimulus consisted of a central line segment with two parallel flankers and two collinear flankers. With this stimulus configuration the monkey performed either a 3-line bisection task or a vernier discrimination task. We found that the responses of neurons in both V1 and V4 showed differential tuning to the identical stimulus attributes as the animal alternated between perceptual tasks, with strong modulation by task-relevant inputs and weak modulation by task-irrelevant stimulus components. In both V1 and V4 the task-dependent differences in response originated from the outset of the visual responses, and were seen first in V1 and then in V4 after a 45 ms delay. Since the animal is cued to perform a specific task in advance of the stimulus presentation, it is likely that V1 receives a signal as to task identity at trial onset, setting the matrix of effective connectivity to enable neurons in each area to carry task-relevant information. As with the tuning measured by spiking activity to the 5-line stimuli, the LFPs at each recorded site showed task-

dependent modulation. Within a recording session the task-dependent tuning of spiking activity was highly reproducible with little variability and substantial effect size, but the tuning appeared to change between different sessions. The LFP tuning did not show such changes between sessions, suggesting that while the firing patterns of individual neurons are not fixed, the integrated activity of neuronal populations remains stable.
Overall, our results show that visual cortical neurons are adaptive processors, carrying different information according to the behavioral requirements of the task at hand.

Disclosures: G.L. Astorga: None. **Y. Yan:** None. **W. Li:** None. **C.D. Gilbert:** None.

Nanosymposium

105. Vision: Visual Cortex: Functional Architecture and Circuits

Location: SDCC 23

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 105.03

Topic: D.07. Vision

Support: NIH RO1 EY 08372
NIH RO1 EY 018897
NIH EY 01876
The Whitehall Foundation

Title: The distribution and spatial organization of significant hue and orientation tuning in macaque area V4

Authors: *D. J. FELLEMAN, A. PARAJULI
NBA, Univ. Texas Med. Sch., Houston, TX

Abstract: Intrinsic cortical imaging has revealed many aspects of the functional architecture of area V4, but the spatial organization, underlying periodicity, and relative proportion of V4 domains that are quantitatively tuned to hue or orientation, alone, or in combination, is largely unknown. We performed quantitative intrinsic imaging to determine the distribution and organization of pixel clusters that exhibit statistically significant tuning for hue and orientation in foveal and parafoveal V4 on the prelunate gyrus. Significant tuning was determined by the dot-product method that evaluated the trial-by-trial set variability of the direction and magnitude of hue or orientation vectors compared to the across trial summed vector components. The across session reliability of pixel tuning was tested using the multivariate Hotelling's T^2 statistic.
We found significant ($p<0.05$) pixel tuning for hue or orientation across a large proportion of V4 on the prelunate gyrus. Across sessions and cases, V4 domains significantly tuned for hue occupied ~35% of the imaged cortex and V4 domains significantly tuned for orientation occupied ~ 30% of imaged parafoveal V4. When compared within and/or across trial datasets, about 15% of V4 pixels exhibited significant ($p<0.05$) tuning for both hue and orientation.

Overall, approximately 65% of the imaged pixels in foveal and parafoveal V4 on the prelunate gyrus were significantly tuned to these extended stimuli. Thus, about 35% of the imaged cortex were not significantly tuned to these simple stimuli. Perhaps these responsive but not significantly tuned V4 domains may be tuned to other stimulus features, may exhibit greater surround suppression than observed in previous imaging studies in V1 and V2, or they may exhibit more variable responses as compared to lower cortical areas.
Selectivity for hue or orientation is not randomly distributed across V4, but appears to be inter-digitated across the prelunate gyrus without an explicit antero-posterior bias. We determined the underlying periodicity of the highly selective, significant hue and orientation domains using the 2D-autocorrelation and 2D-Fourier transform to identify the low spatial frequency and corresponding pixel distances that describes the periodicity of the peak hue or orientation responses. These data revealed ~2.0 mm periodic representations for both hue and orientation selectivity in V4. Future investigations will determine how higher-order shapes are represented in V4 and will determine whether these, or other, feature representations, are contained within the ~35% of V4 not significantly tuned to simple hue and shape stimuli.

Disclosures: D.J. Felleman: None. **A. Parajuli:** None.

Nanosymposium

105. Vision: Visual Cortex: Functional Architecture and Circuits

Location: SDCC 23

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 105.04

Topic: D.07. Vision

Support: National Science Foundation of China Outstanding Young Researcher Award 30525016
Project 985 Grant of Peking University
Beijing Municipal Commission of Science and Technology under contract No. Z151100000915070

Title: Perceptual color representation in awake macaque primary visual cortex

Authors: *M. LI[1], N. JU[2], F. LIU[1], H. JIANG[1], S. TANG[1]
[2]Sch. of Life Sci., [1]Peking Univ., Beijing, China

Abstract: Dimensions of color perception is quite different with the spectrum information input into eyes. It is a big misery of how the transformation formed in the brain, even where the representation of perceptual color dimensions happens in the visual cortex is not clear. Previous study show that monkey V4 forms systematic representation of hue and lightness using intrinsic optical imaging, however, electrophysiology study revealed that V1 have many cells response to different hues and lightness. Whether or not V1 forms systematic representation of perceptual

color dimensions is still not known, due to shortage of high resolution technique available on awake macaque cortex. Using long-term two photon imaging with genetically encoded calcium indicator and systematic chosen of color stimulus from perceptual uniform Munsell color space, we discovered that neuropil function map of hues in most color modules of primary visual cortex forms pinwheel like patterns, while lightness representation form cluster like patterns, which is orthogonal to the hue representation. Moreover, we found that signal strength of 5 main Munsell hues are almost the same, while the spatial patterns between representation of red and purple are more separated. Signal strength of different lightness level are almost the same when using achromatic mosaic background. Achromatic stimulus evoked maps highly correlated with green, which coincidence with the spectral distribution of luminance perception. So it's amazing that even in V1 our perceptual aspect of color was precisely represented, these fine structures are far more than expected. As color and orientation are quite different aspect of visual inputs, the similarity and difference of their representation and the formation of these structures may supply important general construct and computing rules of primate visual neural system.

Disclosures: M. Li: None. **N. Ju:** None. **F. Liu:** None. **H. Jiang:** None. **S. Tang:** None.

Nanosymposium

105. Vision: Visual Cortex: Functional Architecture and Circuits

Location: SDCC 23

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 105.05

Topic: D.07. Vision

Support: NIH Grant F32 EY025523
NIH Grant R01 EY011379
NIH Grant EY12196

Title: Cortical feedback strongly influences brain rhythms in primary visual cortex

Authors: *T. S. HARTMANN[1], S. RAJA[1], S. G. LOMBER[2], R. T. BORN[1]
[1]Dept. of Neurobio., Harvard Med. Sch., Boston, MA; [2]Dept. of Physiol. and Pharmacol., Univ. of Western Ontario, London, ON, Canada

Abstract: Gamma-band oscillations (30-80 Hz) in the local field potential (LFP) are a fascinating phenomenon whose functional interpretation is controversial. While some investigators have made the case for a computational role in sensory coding (Buzsáki and Chrobak, 1995; Fries, 2009), others have argued that they are simply an epiphenomenon produced by local interactions between excitation and inhibition (Ray and Maunsell, 2015). Several groups have adduced evidence that gamma oscillations are a unique signature of feedforward processing, whereas slower rhythms, like alpha (5-15 Hz), are a marker of feedback signals (van Kerkoerle et al., 2014; Bastos et al., 2015). Regardless of their function, gamma

rhythms are believed to be generated locally through strong excitation-inhibition interactions, even though they may become synchronized across relatively large regions of cortex (Tiesinga and Sejnowski, 2009; Buzsáki and Wang, 2012). We examined the influence of cortico-cortical feedback on the LFP and on multi-unit activity (MUA) by reversibly inactivating areas V2 and V3 while recording visually evoked activity in primary visual cortex (V1) of alert macaque monkeys. We were able to produce profound effects on the LFP and rhythmicity of the MUA recorded in V1. During control conditions, the MUA and the LFP exhibited strong gamma oscillations; these were completely abolished during feedback inactivation, even though spike rates were not significantly changed. The results indicate that gamma is not a simple signature of feed forward processing. Our experiments reveal a strong influence of cortico-cortical feedback on rhythms previously believed to be of purely local origin.

Disclosures: T.S. Hartmann: None. **S. Raja:** None. **S.G. Lomber:** None. **R.T. Born:** None.

Nanosymposium

105. Vision: Visual Cortex: Functional Architecture and Circuits

Location: SDCC 23

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 105.06

Topic: D.07. Vision

Support: Bernstein Award Udo Ernst, BMBF Grant 01GQ1106
Priority Program 1665, DFG Grant ER 324/3-2

Title: How well do critical dynamics perform information integration in cortical networks?

Authors: *U. A. ERNST, M. SCHÜNEMANN, N. TOMEN
Theoretical Physics, Univ. Bremen, Bremen, Germany

Abstract: Cortical networks have been shown to exhibit critical dynamics, a state between order and chaos characterized by scale-free distributions of synchronized events. However, it is still unclear if criticality really supports cortical function, in particular in inhomogeneous systems subject to a strong external drive - such as the brain when actively processing a sensory stimulus. Since a critical dynamics is theoretically able to engage large groups of neurons in a rapid and flexible manner, we hypothesize that especially the visual system might greatly profit from such a state. Typically, visual information is represented by a large number of neurons which can signal the presence of elementary and local features, but for perceiving a visual scene, the brain has to quickly and flexibly integrate those features which might indicate the presence of a contour, a texture, a shape or, summarized in a more abstract term, an 'object'. To investigate our hypothesis, we analysed a structured, recurrently coupled network of leaky integrate-and-fire neurons with excitatory and inhibitory interactions. Each unit can be activated by the presence of an elementary feature in a visual scene. Excitatory connections link neurons representing feature

conjunctions which are typical for an object, while inhibitory connections suppress uninformative feature combinations. When driven by an external input, we required that our network realizes three fundamental computations important for cortical function: detecting the presence of a target in a background of distracters, discriminating between two or more targets presented simultaneously, and balancing a representation of equally salient targets. For detection and discrimination, we assume a coincidence detection readout mechanism which can easily be realized by integrate-and-fire neurons. We found that both detection and discrimination are very fast and that performance increases with increasing excitatory coupling strength, however, the representation also becomes less balanced. The optimum between these two counteracting factors depends on system parameters but lies almost always in the vicinity of the state where the subnetwork activated by the ensemble of features defining an object becomes critical. For a network with non-leaky units, we analytically determined its capacity to represent multiple objects in dependence on system and object size. Surprisingly, it turns out that computational performance is still high even for large overlaps between object representations, thus demonstrating that our paradigm is a viable scenario for visual cortical networks with their dense excitatory connectivity.

Disclosures: U.A. Ernst: None. **M. Schünemann:** None. **N. Tomen:** None.

Nanosymposium

105. Vision: Visual Cortex: Functional Architecture and Circuits

Location: SDCC 23

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 105.07

Topic: D.07. Vision

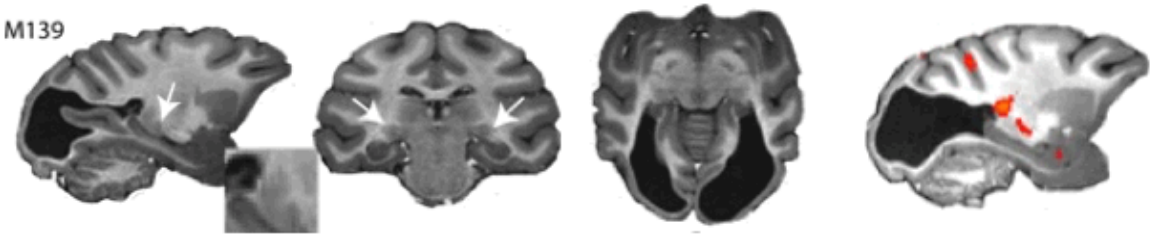
Support: Wellcome Trust 101092/Z/13/Z
BBSRC BB/H016902/1

Title: Intact extrastriate visual network without primary visual cortex: A case study of naturally occurring Blindsight in a Rhesus macaque

Authors: K. KRUG[1], A. H. BELL[1], M. AINSWORTH[1], J. SALLET[1], E. PREMEREUR[3], B. AHMED[1], A. S. MITCHELL[1], M. J. BUCKLEY[1], *A. J. PARKER[2], H. BRIDGE[1]
[2]Physiology, Anat. and Genet., [1]Univ. of Oxford, Oxford, United Kingdom; [3]KU Leuven, Leuven, Belgium

Abstract: Lesions of human primary visual cortex (V1) can lead to Blindsight with loss of conscious visual perception. We investigated a female Rhesus macaque (S) with bilaterally enlarged lateral ventricles, expanding into space usually occupied by V1, which was missing. The deficit is likely congenital, with no injury recorded. Monkey S was identified as unremarkable but unmotivated in behavioural tests with coloured squares on a touch screen.

We compared structural, diffusion-weighted (DW) and functional magnetic resonance (MR) images of monkey S collected at 3T under general anesthesia (0.8-1.6% isoflurane) to those of up to seven typical adult macaques. Outside affected brain regions, sulcal patterns of monkey S appeared normal. T1/T2-weighted MR images indicated a pattern of thick myelination near presumed visual motion area V5/MT. Visual stimulation with a checkerboard gave activation in lateral geniculate nucleus (LGN) of monkey S, but not in pulvinar nucleus or in V5/MT as seen in typical monkeys. In contrast, full-field moving dots did activate pulvinar in monkey S, as strongly as for the best typical animal. For moving dots, there was BOLD activation bilaterally in dorsal STS, not strictly located to V5/MT, and activation near visual areas V2 and V3. For face stimuli, we saw activations of anterior and posterior face patches along ventral STS. Time-series analysis revealed a typical network of bilateral dorsal visual areas and area FEF correlated with the temporal pattern of BOLD activity in V5/MT. DW MR images and probabilistic tractography showed significantly weaker connectivity (fewer streamlines) between pulvinar or LGN and V5/MT, although all were present.
Overall, there is an intact extrastriate visual network of cortical areas, despite the absence of primary visual cortex, but little evidence for strengthened pulvinar-V5/MT or LGN-V5/MT connectivity that could potentially support residual visual function. Other cortical inputs must be considered.



Disclosures: K. Krug: None. **A.H. Bell:** None. **M. Ainsworth:** None. **J. Sallet:** None. **E. Premereur:** None. **B. Ahmed:** None. **A.S. Mitchell:** None. **M.J. Buckley:** None. **A.J. Parker:** None. **H. Bridge:** None.

Nanosymposium

105. Vision: Visual Cortex: Functional Architecture and Circuits

Location: SDCC 23

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 105.08

Topic: D.07. Vision

Support: The Gatsby Chariable Foundation

Title: Top-down feedback to peripheral visual field is weaker: Motivation and experimental test

Authors: *L. ZHAOPING
Univ. Col. London, London, United Kingdom

Abstract: Visual attention selects a visual location, and, by eye movements, places it in the central visual field for further processing. Hence peripheral vision not only has a lower spatial acuity, but is also likely to be inferior in other aspects of processing for recognition, particularly in the ventral visual pathway. From ambiguous perception for dichoptic visual input gratings, Zhaoping (2017) inferred, and thus hypothesized, a weaker or absent top-down feedback from higher visual cortical areas to the primary visual cortex (V1) in the peripheral visual field. Such feedbacks, presumed more abundant in central visual field, serve the computation of analysis-by-synthesis; they are particularly useful in noisy and challenging situations when external visual inputs can only ambiguously suggest candidate visual scenes (e.g., a face or a house) for perception. To disambiguate, higher visual areas generate or synthesize hypothetical visual inputs for the candidate scenes according to internal knowledge of image formation in the visual world, and feed these synthesized inputs back to V1 to verify whether they match the actual visual input; a candidate scene becomes the perceptual outcome or is vetoed, respectively, when the corresponding synthesized input sufficiently matches or mismatches the actual sensory input. To test this central-peripheral difference in top-down feedback, I use anti-correlated random dot stereograms (RDSs). Such RDSs cannot evoke depth perception in central visual field, even though they do activate V1 neurons. However, V1 neurons invert their disparity tuning curves to such RDSs so that non-preferred disparities evoke higher responses than preferred disparities (Cumming and Parker 1997). Hence, for anti-correlated RDSs, V1 reports reversed depth values (e.g., seeing a near surface as a far surface) to higher visual areas. Top-down feedback for analysis-by-synthesis should veto such reversed depths reported by feedforward inputs from V1, since the synthesized inputs are correlated and would match neither the anti-correlation nor the input disparities of the sensory inputs. This not only explains the lack of depth perception in anti-correlated RDSs in central vision (where top-down feedback should be abundant), but also predicts that the reversed depth should be more likely perceived in the peripheral field where the top-down feedbacks maybe too weak or absent to veto the feedforward report. This prediction was confirmed experimentally (Zhaoping & Ackermann 2018). I will discuss the central-peripheral dichotomy in cortical feedback in relation to other behavioural, physiological, and anatomical data to motivate future studies.

Disclosures:

Nanosymposium

105. Vision: Visual Cortex: Functional Architecture and Circuits

Location: SDCC 23

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 105.09

Topic: D.07. Vision

Support: NIH Grant R01EY022605 to DMB MF GG

Title: The role of feedback to early visual cortex in visual awareness: A TMS-EROS investigation

Authors: *R. S. KNIGHT[1], G. GRATTON[2], M. FABIANI[2], D. M. BECK[2]
[1]Beckman Inst., Univ. of Illinois at Urbana-Champaign, Urbana, IL; [2]Psychology Dept., Beckman Institute, Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Early visual cortex plays a critical role in visual awareness; however, it is unclear whether that role stems purely from its function as a critical input to the visual system or whether it is also necessary during continued cortical dynamics. During normal visual processing, V1 of the occipital cortex serves as the primary input of visual information into the cortex. This information is then transmitted to later visual areas, as well as frontoparietal cortex. After this initial feedforward sweep of information from early visual cortex (V1-V3), its continued role in generating visual awareness has been difficult to assess, in part because it is difficult to dissociate input from later processing; that is, most visual experiences originate in the eye and enter the cortex via V1.

Here, we bypass V1 input functions by using single-pulse transcranial magnetic stimulation (TMS) over left posterior parietal cortex (PPC) to produce visual experiences in the form of a phosphene. We simultaneously recorded activity in bilateral occipital cortex and under the TMS coil using the event-related optical signal (EROS) to ask whether activity in early visual areas or in PPC is predictive of visual awareness. Critically, since TMS to PPC served as the primary input of visual information into the cortex, any downstream activations in early visual cortex that predict awareness would be due to feedback rather than feedforward mechanisms.

Each participant's (N=12) phosphene threshold (PT) was measured in order to determine the TMS intensity needed to evoke a phosphene in 50% of the experimental trials. PT intensity was held constant throughout the session to allow EROS comparisons of phosphene-present versus phosphene-absent trials in both V1-V3 and under the TMS coil (PPC). Since the TMS intensity in the coil was equivalent in all trials, any modulations of awareness must be due to the underlying neural activity.

Results indicate that visual cortex activity rather than PPC activity predicts the likelihood of perceiving a phosphene. There are two temporal intervals in which early visual cortex activity predicts awareness. 0-24 ms after the TMS pulse, activity in V1-V2 predicted phosphene perception, the timing of which is consistent with the state of early visual cortex at the time of input being predictive of awareness. Additionally, 38-101 ms after the TMS pulse, activity in V3 predicted phosphene perception, consistent with a role of feedback dynamics. Taken together, the current data provide evidence that both the feedforward and feedback functions of early visual cortex are critical to visual awareness.

Disclosures: R.S. Knight: None. **G. Gratton:** None. **M. Fabiani:** None. **D.M. Beck:** None.

Nanosymposium

105. Vision: Visual Cortex: Functional Architecture and Circuits

Location: SDCC 23

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 105.10

Topic: D.07. Vision

Title: Is visual cortex a selforganized recurrent spiking deep convolutional network?

Authors: *K. R. PAWELZIK, D. ROTERMUND
Univ. Bremen, Inst. Theoretical Physics, Bremen, Germany

Abstract: The visual cortex of primates contains more than 30 mutually linked areas each of which represents different features in a given visual stimulus.
The rationale of this organization is not known. In particular, it is neither known how the networks of neuronal modules flexibly perform varying cognitive tasks including recognition, classification, detection, and decision making nor how the inter-module connections become organized during learning.
We propose an understanding of the dynamics and the structure of recurrently connected systems of neuronal modules in terms of first principles. Despite reproducing some responses of neurons in the visual system, the relevance of deep convolutional networks (DCNs) for understanding the real neuronal networks in the visual system remains questionable. In contrast to the unidirectional architecture of DCNs cortical areas in mammal brains are cyclically connected and exchange signals dominantly by brief pulses, the action potentials. Furthermore, learning in natural neuronal networks occurs locally by changes of synaptic efficacies, in stark contrast to technical optimization methods used for DCNs which require error signals to unrealistically bridge several layers of neurons.
A novel biologically plausible framework for deep recurrent networks is presented that is based on realistic spiking neurons and employs only local synaptic mechanisms to self-organize synaptic connections between neuronal modules.
Computations of mathematically well defined functions in networks comprising many modules are shown to require only few action potentials per neuron. Applying the framework to more realistic problems demonstrate that the framework can approach the performance of their technical cousins deep convolutional networks. Selforganization of networks from natural images without using any error signal but biologically plausible synaptic mechanisms reproduces the increasingly complex receptive fields in the visual system. The proposed framework provides testable hypothesis about the functional rôles of feedback connections in attention and learning.

Disclosures: K.R. Pawelzik: None. **D. Rotermund:** None.

Nanosymposium

106. Vision: Representation of Faces and Bodies

Location: SDCC 24

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 106.01

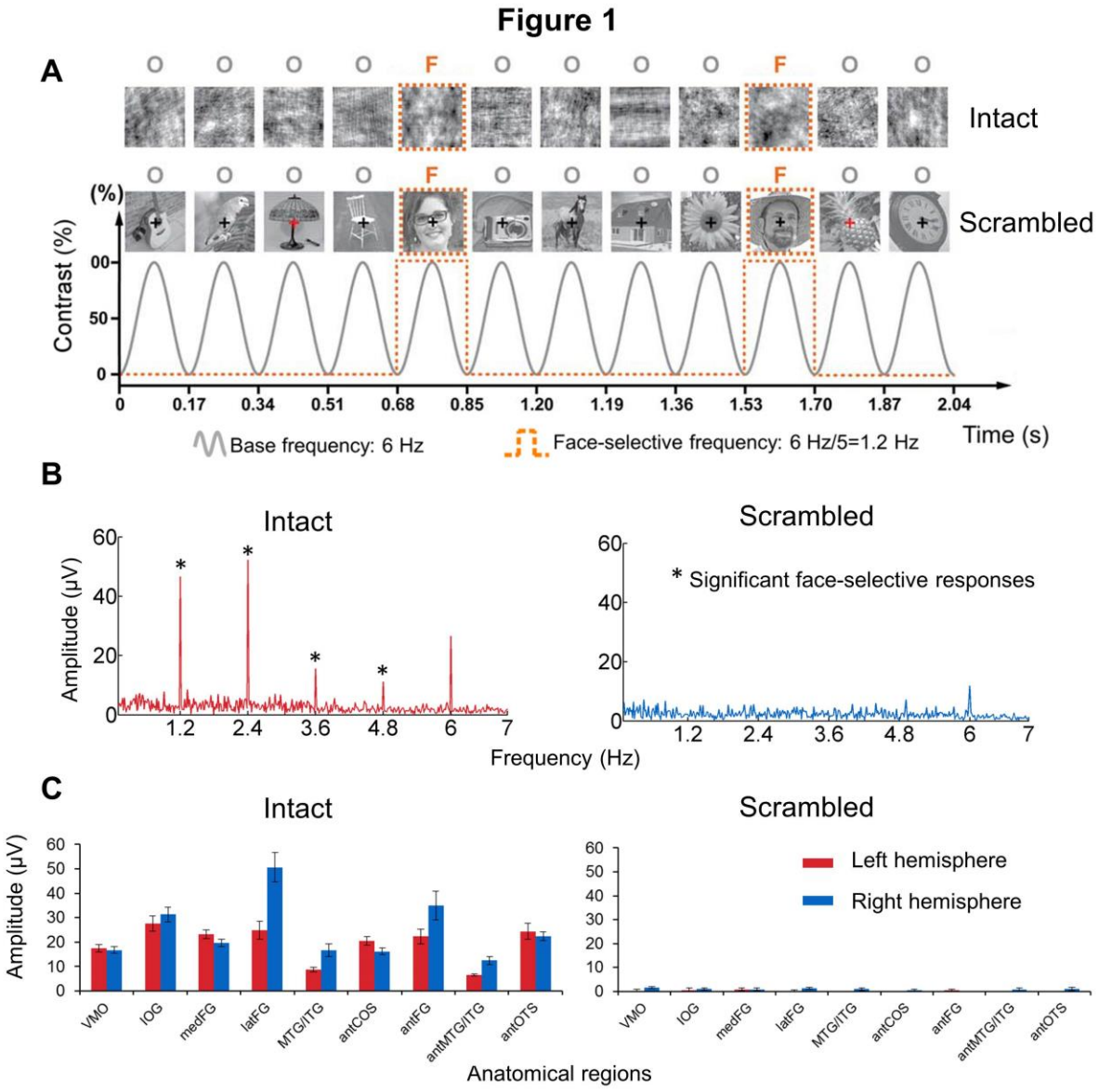
Topic: D.07. Vision

Support: ERC facessvep 284025

Title: Large category-selective responses of populations of neurons in the human ventral occipito-temporal cortex emerge independently of low-level statistical image properties

Authors: *J. JONAS[1,2], C. JACQUES[3], L. KOESSLER[1,2], L. MAILLARD[1,2], B. ROSSION[1,2]
[1]CHRU Nancy, Nancy, France; [2]Univ. de Lorraine-CNRS, Nancy, France; [3]Univ. Catholique de Louvain, Louvain La Neuve, Belgium

Abstract: Perceptual categorization, a critical brain function, is thought to be supported by high-level visual regions of the human ventral occipito-temporal cortex (VOTC). While the factors driving VOTC category-selectivity remain unknown, recent neuroimaging studies using within-category visually homogenous image sets have emphasized the contribution of low-level visual properties. Here we recorded direct (electrophysiological) neural activity from 3525 recording contacts implanted in the VOTC of 61 epileptic patients viewing highly variable images of objects presented at a periodic rate (6 Hz), with variable face images interleaved as every 5th image (1.2 Hz). Images were presented either in their intact or phase-scrambled versions in separate sequences (Fig.1A). Face-selective responses were objectively quantified at the face stimulation frequency (1.2 Hz) and harmonics (2.4 Hz, etc.). In the intact condition, 853 face-selective contacts were identified throughout the whole VOTC, with a peak of activity in the right lateral fusiform gyrus (latFG). The contribution of low-level properties in generating these face-selective responses was assessed by measuring responses in the scrambled condition at these 853 contacts. Strikingly, only two face-selective contacts (2/853, 0.002%) showed a significant response in the scrambled condition (see Fig.2B for typical responses in the frequency domain recorded in a single contact in the right fusiform gyrus). Moreover, response amplitudes in the scrambled condition were negligible compared to the intact condition (Fig.1C). Finally, across all face-selective contacts, the amplitude of face-selective response in the scrambled condition did not predict the response in the intact condition (Pearson correlation r=0.067). These observations show that large category-selective responses of populations of neurons in the human VOTC emerge independently of low-level statistical image properties.



Disclosures: J. Jonas: None. **C. Jacques:** None. **L. Koessler:** None. **L. Maillard:** None. **B. Rossion:** None.

Nanosymposium

106. Vision: Representation of Faces and Bodies

Location: SDCC 24

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 106.02

Topic: D.07. Vision

Support: National Eye Institute Grant NEI EY 16187
NSF STC award CCF-1231216
National Eye Institute Grant NEI EY 011379
Core Grant for Vision Research NEI EY12196

Title: Defining representations by visually responsive neurons using feature maps

Authors: *C. R. PONCE[1], T. S. HARTMANN[2], M. S. LIVINGSTONE[3]
[1]Neurosci., Washington Univ. At St. Louis, Saint Louis, MO; [2]Neurobio., [3]Harvard Med. Sch., Boston, MA

Abstract: In the non-human primate, inferotemporal cortex neurons emit action potentials when complex objects appear in their receptive fields. These neurons are a focus in the search to understand visual recognition. The problem is that the space of complex visual objects is large, so the identification of a given neuron's preferred objects frequently requires pre-selecting semantically defined objects such as faces, body parts or places, which can limit subsequent interpretation. In this study, we used the machine-learning concept of "attribution" to identify visual patterns in natural scenes without this pre-selection constraint. We convolved large natural images with V1 and IT neurons' receptive fields in five monkeys to create feature maps, which highlighted locations within each image that best stimulated the cells. We interpreted these feature maps using prediction feature maps obtained from algorithms in classical computer vision, convolutional neural networks (CNNs), semantic hypotheses and gaze-predicting saliency algorithms. We found that for IT neurons predictions from semantics and saliency algorithms were generally as effective (or more so) than predictions from deep layers in convolutional neural networks, especially if neurons were highly selective to categories like "faces." This was surprising because 99.9% of all of our predictions came from CNNs. V1 feature maps, in contrast, matched well with early convolutional layers of neural networks. We also found that feature maps in V1 shifted to match predictions from deep CNN layers over tens of milliseconds and thus to also resemble IT feature maps, especially during post-stimulus intervals (when the screen was blank). We conclude that future CNN models of the visual brain should be trained to reflect the neuro-ethological profiles of the primate visual recognition cortex and that V1 neurons may encode feedback from IT.

Disclosures: C.R. Ponce: None. **T.S. Hartmann:** None. **M.S. Livingstone:** None.

Nanosymposium

106. Vision: Representation of Faces and Bodies

Location: SDCC 24

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 106.03

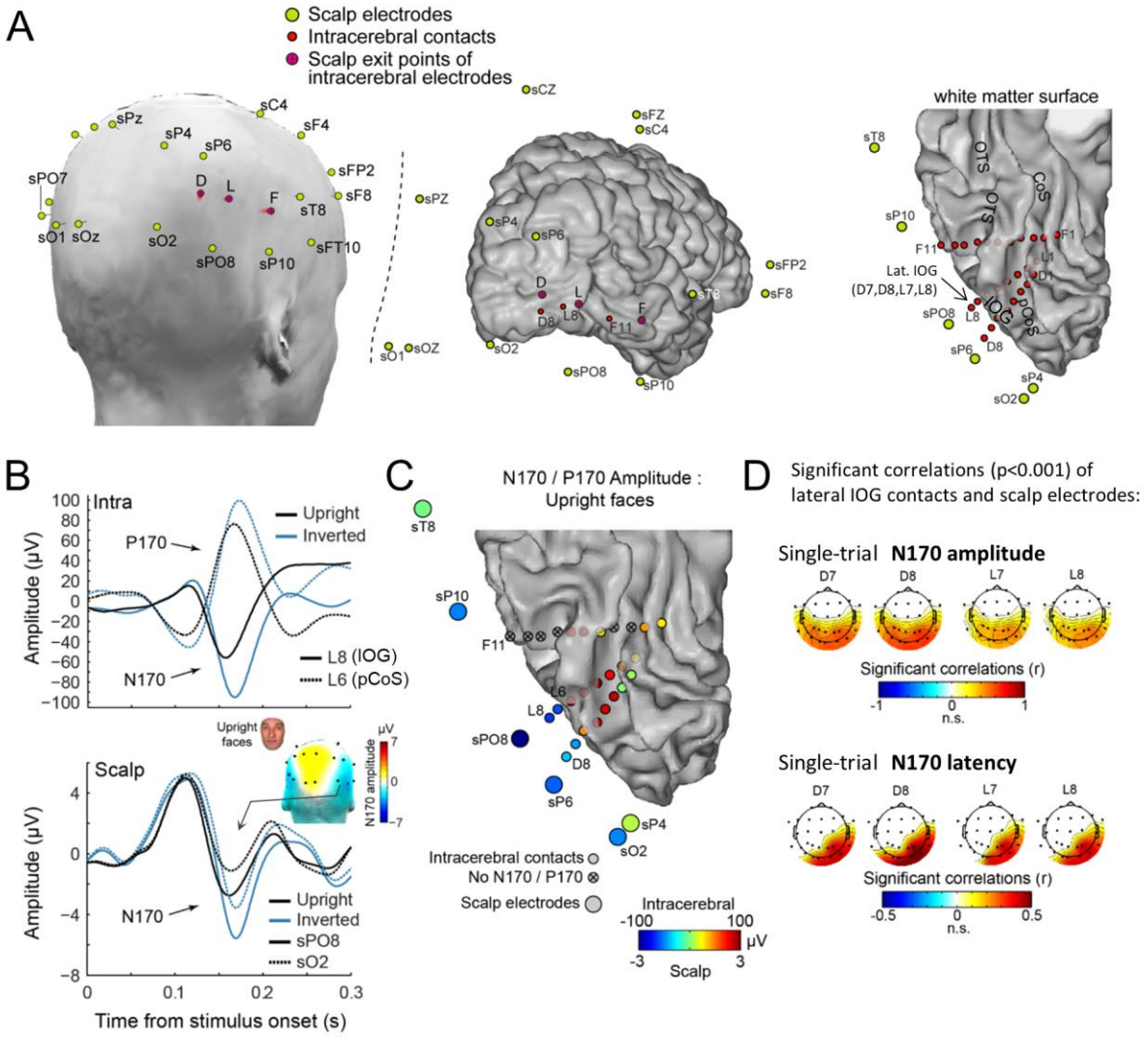
Topic: D.07. Vision

Support: European Research Council Grant, facessvep 284025

Title: The lateral inferior occipital gyrus as a major cortical source of the face-evoked N170: Evidence from simultaneous scalp and intracerebral human recordings

Authors: *C. JACQUES[1,2], J. JONAS[3,4], L. MAILLARD[3,4], L. KOESSLER[3,4], B. ROSSION[1,3,4]
[1]Psychological Sci. Res. Inst. (IPSY), Univ. Catholique de Louvain, Louvain-la-Neuve, Belgium; [2]Res. Group Psychiatry, Univ. of Leuven, Leuven, Belgium; [3]Univ. de Lorraine, CNRS, CRAN, Nancy, France; [4]Univ. de Lorraine, CHRU-Nancy, Service de Neurologie, Nancy, France

Abstract: The sudden onset of a face image leads to a prominent face-selective response in human scalp electroencephalographic (EEG) recordings, peaking 170 ms after stimulus onset at occipital-temporal (OT) scalp sites: the N170 (or M170 in Magnetoencephalography). According to a widely held view, the main cortical source generating the N170 lies in the fusiform gyrus (FG), whereas the posteriorly located face-selective region in the inferior occipital gyrus (IOG) would rather generate substantially earlier face-selective responses. Here we report neural responses to upright and inverted faces in a unique epileptic patient where neural signals were recorded simultaneously from 27 electrodes on the scalp and from intracerebral electrode arrays implanted in the right IOG and in the occipito-temporal sulcus (OTS), above the right lateral FG (Figure 1A). We made 4 key observations. First, a large N170 was measured at intracerebral contacts in the right IOG (Figure 1: contacts D7,D8,L7,L8), about 3 cm away from scalp electrodes over the OT regions where the largest N170 was recorded in the patient as well as in typical healthy individuals (Figure 1B). Second, the N170 measured on the scalp and in the IOG were strikingly similar in terms of polarity, mean peak latency and sensitivity to face inversion (i.e. increased and delayed N170 to inverted faces, Figure 1B,C). Third, thanks to the original simultaneous scalp-intracerebral recordings, we found that the latency and amplitude of the N170 measured in the IOG and on the scalp OT lateral surface were correlated at the single-trial level (Figure 1D). Last, a P170 component was also prominent above the FG, suggesting the presence of a vertically oriented equivalent dipole generating a positivity (i.e. P170) on the scalp and a N170 (or “N200”) on the ventral surface of the FG, likely invisible over the lateral OT scalp region. Altogether, these observations provide direct evidence for the IOG rather than the FG as a major cortical generator of the face-selective scalp N170, questioning a serial spatio-temporal organization of the human cortical face network.



Disclosures: C. Jacques: None. **J. Jonas:** None. **L. Maillard:** None. **L. Koessler:** None. **B. Rossion:** None.

Nanosymposium

106. Vision: Representation of Faces and Bodies

Location: SDCC 24

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 106.04

Topic: D.07. Vision

Support: NIH Intramural Grant ZIAMH002920

Title: Face memory performance is predicted by the strength of resting state functional connectivity between task-defined face patches and medial temporal lobe structures

Authors: *M. RAMOT[1], C. WALSH[2], A. MARTIN[3]
[1]NIH/NIMH, Bethesda, MD; [2]Natl. Inst. of Mental Hlth., Bethesda, MD; [3]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: There is great degree of variance in the population in face memory capabilities, ranging from congenital prosopagnosia at one end, to "super-recognizers" on the other. In this study, we sought to characterize the neural networks underlying face memory, as measured by the Cambridge Face Memory Test. To evaluate the specificity of our face memory findings, we also administered the Cambridge Car Memory Test. Healthy volunteers completed the memory tasks outside the scanner, and then underwent a 3T fMRI scan, comprised of two rest scans and a face localizer. We found that performance on the face memory task, but not the car memory task, was predicted by the correlations, measured at rest, between the localizer-defined ventral face patches and memory related regions, specifically the hippocampus and surrounding parahippocampal tissue, as well as medial parietal regions ($r>0.5$ for all). Face memory, but not car memory, was also predicted by correlations at rest between the task-defined ventral face patches and face-responsive regions of somatosensory cortex ($r=0.52$). Connectivity between the medial temporal lobe structures, medial parietal regions, and somatosensory cortex was equally and selectively predictive of face memory abilities, with only a small subset of these connections also predictive of car memory. In contrast, car memory performance was predicted by the correlations between a few of these same medial temporal regions and regions commonly associated with non-face object processing (area LO) ($r=0.4$). These results suggest that performance on face memory tasks is underpinned by the strength of intrinsic functional connectivity between and within face selective memory related regions (medial temporal lobe structures), and face selective visual processing regions.

Disclosures: M. Ramot: None. **C. Walsh:** None. **A. Martin:** None.

Nanosymposium

106. Vision: Representation of Faces and Bodies

Location: SDCC 24

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 106.05

Topic: D.07. Vision

Support: NIMH Intramural Research Program

Title: Amygdala lesions in rhesus monkeys eliminate the spontaneous advantage of face stimuli in a free-viewing task

Authors: *J. TAUBERT[1], M. FLESSERT[2], S. G. WARDLE[3], B. M. BASILE[4], A. P. MURPHY[5], E. A. MURRAY[6], L. G. UNGERLEIDER[7]
[1]The Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Lab. of Brain and Cognition, NIMH/NIH/DHHS, Bethesda, MD; [3]Lab. of Brain & Cognition, NIH, Bethesda, MD; [4]Lab. of Neuropsychology, Natl. Inst. of Mental Health, NIH, Bethesda, MD; [5]Section on Cognitive Neurophysiol. and Imaging, Lab. of Neuropsychology, Natl. Inst. of Mental Hlth., Bethesda, MD; [6]Lab. of Neuropsychology, NIMH, NIH, Bethesda, MD; [7]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Rhesus monkeys, like human infants, look longer at images of faces than at non-face objects. This shared involuntary response underscores the importance of faces in the earliest stages of cognitive development, yet its neural basis is poorly understood. Because the amygdala is thought to detect socially-salient objects in the visual environment, we hypothesized that the amygdala is essential for guiding eye movements towards faces, as well as to socially-informative features within faces. We tested this hypothesis by assessing the viewing preferences for faces, illusory faces, and non-face objects in adult rhesus monkeys (*Macaca mulatta*) with selective bilateral excitotoxic amygdala lesions. We presented each subject with all possible pairs of 45 images for four seconds per pair. We collected two dependent measures: how long a subject looked at each of the images in a given pair and where they fixated within each image. Unlike intact monkeys, who show robust preferences for both real and illusory faces, monkeys with selective amygdala damage showed no preference for either real or illusory faces over non-face objects. Further, whereas intact monkeys show classic face viewing patterns prioritizing discrete facial features, such as the eyes and mouth, monkeys with amygdala damage showed disorganized viewing patterns better described by neurally-derived models of perceptual salience. These results identify the amygdala as critical for our earliest specialized response to faces from a developmental perspective; a behavior thought to be a precursor for efficient social communication and essential for the development of face-selective cortex.

Disclosures: J. Taubert: None. **M. Flessert:** None. **S.G. Wardle:** None. **B.M. Basile:** None. **A.P. Murphy:** None. **E.A. Murray:** None. **L.G. Ungerleider:** None.

Nanosymposium

106. Vision: Representation of Faces and Bodies

Location: SDCC 24

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 106.06

Topic: D.07. Vision

Support: Australian NHMRC Early Career Fellowship (APP1072245)
Macquarie University Research Development Grant

Title: Uncovering the temporal dynamics of illusory face perception in the human brain

Authors: *S. G. WARDLE[1,2], J. TAUBERT[1], L. TEICHMANN[3,2], C. I. BAKER[1]
[1]Lab. of Brain & Cognition, NIH, Bethesda, MD; [2]ARC Ctr. of Excellence in Cognition and its Disorders, Sydney, Australia; [3]Cognitive Sci., Macquarie Univ., Sydney, Australia

Abstract: Illusory faces are commonly perceived in inanimate objects such as fruit, trees, and the face of the "Man in the Moon". Examination of the neural response to these natural errors of face detection (face pareidolia) has the potential to reveal new insight into the mechanisms underlying object recognition. Previously we demonstrated with fMRI that face and object-selective regions in the human brain respond to illusory faces in everyday objects (Wardle et al., SfN 2017). It is not yet known how the temporal dynamics of processing for face pareidolia compares to that for real faces. We used magnetoencephalography (MEG) to measure the brain activation patterns of 22 human participants in response to 96 photographs including 32 illusory faces in inanimate objects, 32 similar non-face objects, and 32 human faces. Stimuli were shown for 200ms, with variable ISI 1-1.5s. To maintain attention, participants judged the tilt direction of each image (+/- 3 deg). We applied multivariate pattern analysis to the whole-brain response across all 160 MEG sensors. At ~160-170ms post-stimulus onset, classification performance peaked for distinguishing both illusory and human faces from ordinary objects, and for distinguishing human faces from illusory faces. A second peak in decoding performance was evident around 260ms for discriminating human faces from objects both with and without illusory faces. However, this second peak was not evident in the time course for decoding illusory faces from similar non-face objects. Representational similarity analysis revealed differences in the representation of individual illusory face exemplars such that by ~150ms after stimulus onset, some examples elicited MEG activation patterns that were more similar to non-face objects and others were more similar to human faces. Less than ~100ms later, this organization evolved into one in which all objects were represented similarly regardless of whether they contained an illusory face, and all objects were distinct from human faces. Together the results indicate that illusory faces are processed rapidly by the human brain, however, the representational structure quickly stabilizes into one organized by object content rather than by face perception.

Disclosures: S.G. Wardle: None. **J. Taubert:** None. **L. Teichmann:** None. **C.I. Baker:** None.

Nanosymposium

106. Vision: Representation of Faces and Bodies

Location: SDCC 24

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 106.07

Topic: D.07. Vision

Support: ERC Parietalaction

Title: Natural observed action classes in the human brain

Authors: *B. A. URGEN, S. FERRI, G. A. ORBAN
Univ. of Parma, Parma, Italy

Abstract: Visual processing of actions is supported by a three level network consisting of occipito-temporal, posterior parietal (PPC) and premotor cortex (PMC). Recent fMRI evidence shows that PPC exhibits a functional organization that reflects observed action classes (Abdollahi et al 2013, Ferri et al 2015, Corbo and Orban 2017). However, this evidence was provided by a priori defined action classes and small number of action exemplars. To investigate the natural action classes in the human brain and the differences between the levels of the network, we scanned 6 human subjects with fMRI as they watched 3 sec video clips of 100 action exemplars, performed by 3 actors (300 videos). First, we ran a general linear model by including each action exemplar as a regressor and 10 variables of no interest (6 head motion, luminance, speed of motion, low-level form, run), and generated parameter estimates (betas). We defined selective voxels using a cross-validated ranking procedure based on their responses to the 100 actions in PPC and PMC, and projected them to cortical surface using Caret software. Next, we ran principal component analysis on the [cortical surface nodes X actions] beta matrix to reduce the dimensionality, and chose the principal components (PCs) that explained 96% of the total variance. We then ran k-means clustering on the [PCs X actions] matrix, and selected the solution with optimal number of clusters based on the maximum average silhouette. For each cluster, we computed a classification score (CS) defined as the ratio of the correctly attributed actions to the total number of actions in the cluster. Our results show that PPC hosts at least 7 action clusters that are consistent across subjects, including manipulation(CS:86%), hand onto body(CS:82%), acting in a certain direction in space(CS:100%), vocal and hand communication(82%), locomotion with upright body(CS:84%), upper limbs assisting lower limbs to move in space(CS:68%), interacting with another person physically or emotionally(CS:44%). On the other hand, PMC showed a different clustering pattern emphasizing an effector-based organization. In sum, our results reveal the natural classes of observed actions in the human brain and show the difference in functional organizations between PPC and PMC.

Disclosures: B.A. Urgen: None. **S. Ferri:** None. **G.A. Orban:** None.

Nanosymposium

106. Vision: Representation of Faces and Bodies

Location: SDCC 24

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 106.08

Topic: D.07. Vision

Support: NSF Grant: 1634098 to BD
Israel Science Foundation ISF 1140/13

BSF grant 2013028

Title: Impairment in facial expression perception with normal biological motion perception

Authors: *S. GILAIE-DOTAN[1], S. B. HERALD[2], N. YITZHAK[3], H. AVIEZER[3], B. C. DUCHAINE[2]
[1]Bar Ilan Univ., Ramat Gan, Israel; [2]Dartmouth Col., Hanover, NH; [3]Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Although we view and experience dynamic signals from faces and bodies in tandem (facial expressions and biological motion), it is unclear whether these are processed by joint or separate neural mechanisms. Support for joint mechanisms comes from recent studies showing that brain regions in pSTS processing facial dynamics adjoin or somewhat overlap those processing biological motion. However, in a developmental agnosic individual (LG) we recently showed that his biological motion perception was normal, while he was impaired in perceiving dynamic face expressions. Here we investigate Faith, an individual with acquired prosopagnosia, who reports problems deciphering facial expressions but not body language. We tested Faith's ability to perceive facial expressions from dynamic subtle or intense cues, and her biological motion perceptual threshold from point light displays. In line with Faith's subjective reports, we found that (i) her biological motion perceptual thresholds were in the normal range compared to age-matched neurotypical controls, and that (ii) her perception of subtle dynamic facial expressions was significantly impaired. Since Faith’s lesion is extensive, we are cautious with respect to concluding about the specific brain regions involved, but her dissociation provides further evidence that the perception of dynamic body cues and the perception of dynamic facial cues depend on different processing routes.

Disclosures: S. Gilaie-Dotan: None. **S.B. Herald:** None. **N. Yitzhak:** None. **H. Aviezer:** None. **B.C. Duchaine:** None.

Nanosymposium

106. Vision: Representation of Faces and Bodies

Location: SDCC 24

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 106.09

Topic: D.07. Vision

Title: Prestimulus alpha phase predicts serial dependence of face perception

Authors: *Y. MURAI[1,2], M. MANASSI[1], B. PRINZMETAL[1], K. AMANO[3,4], D. WHITNEY[1]
[1]Dept. of Psychology, Univ. of California, Berkeley, Berkeley, CA; [2]Japan Society for the Promotion of Sci., Tokyo, Japan; [3]Ctr. for Information and Neural Networks (CiNet), Osaka, Japan; [4]Grad. Sch. of Frontier Biosci., Osaka Univ., Osaka, Japan

Abstract: Rhythms in the brain drive perception. Recent EEG studies have demonstrated that prestimulus alpha phase predicts the perception of incoming stimuli (van Rullen, 2016). The perception of a stimulus depends not only on the incoming sensory evidence but also on the history of previous sensory inputs. Serial dependence is a representative example of how the past influences the current percept: the perception of a stimulus is biased towards previously seen stimuli (Fischer & Whitney, 2014; Cicchini et al., 2014). The present study investigates whether prestimulus brain oscillations affect the current perception contingent on previous stimuli. In an experiment, a test face drawn from a continuous array of morphed facial identities was briefly presented, and then subjects adjusted a response face to match the test face identity. EEG signals were recorded throughout the trial. In the analysis, we sorted trials based on the phase of various oscillation frequencies (3-40 Hz) at various timings relative to the stimulus onset, and calculated the magnitude of serial dependence (i.e., how much the current face was reported as pulled toward the faces seen in previous trials) separately for trials with different oscillation phases. We found the serial dependence fluctuated periodically, depending on the theta-to-alpha phase around the time of the stimulus onset in frontal and occipital sites and the alpha-to-beta phase about 300-400 ms before the stimulus onset in bilateral occipito-temporal sites. We further analyzed event-related potentials (ERPs) separately for trials with different phases, and found that the amplitude of an ERP component elicited strongly for face stimuli, the N170, was modulated systematically with prestimulus alpha phase, and the amplitude of N170 and the serial dependence showed a clear inverse correlation. These results suggest that prestimulus alpha oscillations predict the encoding of face information and modulate positive serial dependence in face perception. Serial dependence may result from the perceptual ambiguity of the incoming stimulus, which depends on the phase of the prestimulus alpha oscillations.

Disclosures: Y. Murai: None. **M. Manassi:** None. **B. Prinzmetal:** None. **K. Amano:** None. **D. Whitney:** None.

Nanosymposium

106. Vision: Representation of Faces and Bodies

Location: SDCC 24

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 106.10

Topic: D.07. Vision

Support: NIH R01 NS099061
NIH R21 NS076176
NIH R01 NSO89069
NIH 5T32EY007125-24
NIH 5T32HD071844-05
NSF BCS-1349042
NIH P30 EY001319

Title: Object-directed action modulates object perception: Insights from voxelwise lesion-activity mapping and task-based functional connectivity

Authors: *F. GARCEA[1], B. Z. MAHON[2,3], L. J. BUXBAUM[1,4]
[1]Moss Rehabil. Res. Inst., Elkins Park, PA; [2]Carnegie Mellon Univ., Pittsburgh, PA; [3]Neurosurg., Univ. of Rochester, Rochester, NY; [4]Dept. of Rehabil. Med., Thomas Jefferson Univ., Philadelphia, PA

Abstract: The ability to identify, grasp, and manipulate an object according to its function requires the integration of computations supported by anatomically remote regions in the brain. A critical issue is understanding interactions between action systems in left parietal cortex and object perception systems in ventral temporal cortex (VTC). Here we present two studies using functional magnetic resonance imaging (fMRI) in 98 adults that test whether disruption or modulation of responses in the anterior intraparietal sulcus (aIPS) in turn modulates responses in VTC. In the first study, we used a novel analytic tool, voxelwise lesion-activity mapping (VLAM), to test how lesions to anatomically remote regions would modulate neural responses for tools. Thirty-five brain tumor patients took part in an fMRI experiment designed to identify neural preferences for tools in VTC. We found that lesions to the left aIPS, a region that supports hand-shaping during object grasping and manipulation, disrupted tool responses in left VTC. Control analyses demonstrated that neural responses to place stimuli in left VTC were unaffected by lesions to the left aIPS, suggesting domain-specific parietal modulations of tool responses in left VTC. Using a separate dataset from 38 healthy adults who participated in the same fMRI experiment, we confirmed that responses for tool stimuli were maximal in a portion of the left aIPS identified in the VLAM analysis of neurosurgery participants. In a second study, 22 healthy adults took part in an fMRI experiment designed to test the prediction that functional connectivity between the left aIPS and VTC would be modulated by task instructions to plan and generate tool-directed use or move actions. Participants were presented with images of tools and were instructed to passively fixate on the object, internally plan a tool-directed grasping action, and to then pantomime either using or moving the object. Using a sparse event-related design, we modeled functional connectivity separately for tool use and tool move actions. Planning and generating tool use actions elicited increased functional connectivity among the left supramarginal gyrus, left aIPS, left VTC, and left posterior middle temporal gyrus. In contrast, planning and generating tool move actions elicited increased functional connectivity among the left aIPS, left somatosensory cortex, and left dorsolateral prefrontal cortex.
These findings provide causal evidence that neural representations of tools in left VTC are selectively modulated by processing in left aIPS, and that functional connectivity among those regions is selectively driven by planning and generating tool use actions.

Disclosures: F. Garcea: None. **B.Z. Mahon:** None. **L.J. Buxbaum:** None.

Nanosymposium

106. Vision: Representation of Faces and Bodies

Location: SDCC 24

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 106.11

Topic: D.07. Vision

Support: ERC Parietalaction

Title: Fast, selective processing of person identity in human anterior temporal lobe

Authors: *A. PLATONOV[1], P. AVANZINI[2], V. PELLICCIA[3], M. RIZZI[3], G. LO RUSSO[3], I. SARTORI[3], G. A. ORBAN[1]
[1]Parietalaction lab, Univ. of Parma, Dept. of Med. and Surgery, [2]Univ. of Parma, Parma, Italy; [3]Dept. of Neurosci., Epilepsy Surgery Ctr. "Claudio Munari" Niguarda Ca' Granda Hosp., Milano, Italy

Abstract: Neuropsychological and functional imaging evidence suggests the involvement of human anterior temporal lobe (ATL) in processing person-specific knowledge (e.g. Wang et al 2015). Whether the ATL is also involved in person identity perception is unknown, as is its timing. Therefore, we recorded in the current study intracranial stereo-EEG from epilepsy patients performing a discrimination task.
Patients (n=15) fixated the center of a screen on which videos were shown, depicting one of two actors (male, female), seen from the side, with their face in left or right visual field, performing one of two hand actions (grasp, drag an object). The first movie frame was presented for a 200 to 800 ms period, before video onset. In half of the trials, patients had to discriminate actions, in the other half actors. Subjects fixated well (eye tracking) and used only the static phase for gender discrimination (reaction time analysis). We analyzed the gamma band power (50-150 Hz) during the trial using a two-way ANOVA (FDR-correction) to select leads with a main effect of the task or an interaction of task with the movie epoch (baseline, static, dynamic stimulus and response phases) and submitting those to a post-hoc analysis (Tukey HSD) to isolate leads specific for the static presentation.
One group of leads (n=41) displayed a sharp transient activation in response to the static onset only in actor identity and not action discrimination. 29 of these leads were located in the right (5 patients) and left (2 patients) ATL, ranging from the vicinity of ATFP, at the end of the collateral sulcus, to the tip of temporal lobe. The remaining leads were located predominantly (9/12) in the orbito-frontal cortex. A second group of leads (n= 24), also specific for the static phase, but not task dependent, were located more posteriorly in occipito-temporal and parietal regions.
The latency of the ATL activation varied between the patients (145 to 215ms) and was correlated ($r= 0.80$, $p<0.02$) with the individual reaction times in gender discrimination. The duration of the ATL activation was brief (130 ms) and did not depend on the duration of the static stimulus.

ATL leads were more activated by movies in which the actor's face was present in the ipsilateral visual field. Analyzing the position of the hand in the video indicated that the activation reflected the presence of the hand in the contralateral field.
Our data support the notion that ATL is intrinsically involved in the processing person's identity, including for perception, and using body parts in addition to faces. This involvement occurs on a surprisingly short time scale, freeing the limited ATL resources for the next behavioral task.

Disclosures: A. Platonov: None. **P. Avanzini:** None. **V. Pelliccia:** None. **M. Rizzi:** None. **G. Lo Russo:** None. **I. Sartori:** None. **G.A. Orban:** None.

Nanosymposium

107. Voluntary Movements

Location: SDCC 25

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 107.01

Topic: E.04. Voluntary Movements

Support: NSERC
University of Toronto Scarborough
University of Toronto

Title: Decoding the timecourse of visual-to-motor transformations during grasp planning and execution from the dynamics of electrophysiological signals

Authors: *L. GUO, A. NESTOR, D. NEMRODOV, M. NIEMEIER
Univ. of Toronto, Scarborough, ON, Canada

Abstract: The time course of visuomotor transformations of human grasp actions remains largely unclear. For instance, the informativeness of electroencephalography (EEG) data is limited both because of the anatomy of the visuomotor cortex and because of the traditional emphasis on univariate effects in EEG investigations. Here, we applied classification techniques to spatiotemporal EEG patterns to characterize the electrophysiological dynamics of visuomotor processes during grasp planning and execution. To this end, we recorded from 64 channels while participants used their right dominant hand to grasp 3D objects with two kinds of shapes and textures, using two different grasp orientations. Each trial encompassed three relevant events; a 200ms Preview of the object followed by a variable delay in darkness, a Go period during which the object re-appeared indicating that participants should move to grasp it, and a Movement onset period. After aligning event-related potentials (ERPs) with each event we attempted to classify visual object features (i.e., different object shapes or different textures) and grasp orientations based on all channels across ~10ms temporal windows. Our results show that shape classification was robust, peaking at ~100ms after Preview onset and slowly declining during darkness. The Go period showed a similar shape classification curve, but around Movement

onset the curve remained close to chance level. Grasp orientation regardless of object features was successfully decoded during Preview, yet it ramped up to higher levels during the Go period, and prior to Movement onset. Texture classification was poor throughout, even when it cued participants as to how to grasp the objects. Finally, decoding with temporal generalization showed that shape classification during ~100 - 200ms after Preview onset generalized across the entire Preview event. More so, shape classification during ~100 - 200 ms after Go onset generalized across Go, Preview as well as Movement Onset. Together, these results reveal the progression of visual to visuomotor and motor representations over the course of planning and executing grasp movements as reflected in the dynamics of electrophysiological signals.

Disclosures: L. Guo: None. **A. Nestor:** None. **D. Nemrodov:** None. **M. Niemeier:** None.

Nanosymposium

107. Voluntary Movements

Location: SDCC 25

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 107.02

Topic: E.04. Voluntary Movements

Support: NIH Grant R01AG050523

Title: Sensorimotor network segregation declines with age, is linked to neural distinctiveness, and predicts sensorimotor performance

Authors: *K. E. CASSADY[1], H. C. GAGNON, 48103[2], P. S. LALWANI[3], M. SIMMONITE[3], B. C. FOERSTER, 48103[2], M. PETROU[2], S. F. TAYLOR[4], D. C. WEISSMAN, 48103[2], R. D. SEIDLER[2], T. A. POLK[5]
[1]Univ. of Michigan - Ann Arbor, Ann Arbor, MI; [3]Dept. of Psychology, [2]Univ. of Michigan, Ann Arbor, MI; [4]Psychiatry, Univ. of Michigan Dept. of Psychiatry, Ann Arbor, MI; [5]Psychology, Univ. of Michigan Dept. of Psychology, Ann Arbor, MI

Abstract: Normal aging is associated with declines in sensorimotor control and functioning. Previous studies have linked some age-related declines in behavior to decreases in network segregation: Compared to young adults, older adults typically demonstrate weaker connectivity within functional brain networks but stronger connectivity between networks. Likewise, our group has shown that neural activation patterns in response to different visual stimuli or motor actions are less distinctive in older compared to younger adults and that less distinct neural representations predict worse behavioral performance. However, no studies to date have explored the relationship between these two measures of what is sometimes called age-related neural dedifferentiation, and whether they explain the same aspects of age-related declines in behavior. In the present study, we employed multi-voxel pattern analysis on fMRI data to measure age differences in the distinctiveness of neural representations in motor cortex. We also

performed graph theoretical analysis on resting state fMRI data to measure network segregation and collected a battery of sensorimotor behavioral measures. Preliminary results from 21 younger adults (ages 19-29) and 22 older adults (ages 65-81) revealed that motor representations were less distinct, and that resting state networks were less segregated in older compared to younger adults. Participants with the most distinctive motor representations also exhibited the most segregated networks. Furthermore, network segregation predicted individual differences in sensorimotor performance whereas neural distinctiveness did not. These findings link, for the first time, network segregation to neural distinctiveness, but suggest that segregation may be a more sensitive predictor of sensorimotor behavior.

Disclosures: K.E. Cassady: None. **H.C. Gagnon:** None. **P.S. Lalwani:** None. **M. Simmonite:** None. **B.C. Foerster:** None. **M. Petrou:** None. **S.F. Taylor:** None. **D.C. Weissman:** None. **R.D. Seidler:** None. **T.A. Polk:** None.

Nanosymposium

107. Voluntary Movements

Location: SDCC 25

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 107.03

Topic: E.04. Voluntary Movements

Support: Monash University Platform access grant
HDSA Postdoctoral Fellowship to SA

Title: Effect of exercise intensity on synaptic plasticity following theta-burst stimulation

Authors: *J. P. COXON, D. CURTIN, J. STOUT, S. ANDREWS
Sch. of Psychological Sci., Monash Univ., Melbourne, Australia

Abstract: Regular physical exercise has widespread benefits for the human body, and is known to enhance brain structure and function. Recently, it has been shown that even a single bout of cardiovascular exercise can enhance synaptic plasticity in the human cortex; however, the intensity required for optimal enhancement is currently debated. Understanding the optimal intensity is important for designing exercise-based interventions that provide consistent and effective outcomes for brain health. Here, we investigated the effect of exercise intensity on motor cortex synaptic plasticity following intermittent theta-burst stimulation (iTBS) using a repeated measures design. We hypothesised that high-intensity interval training (HIIT) exercise would have the greatest effect on the response to iTBS. We reasoned that HIIT causes the greatest increases in lactate and brain-derived neurotrophic factor, both of which are known synaptic plasticity signalling molecules. Twenty healthy adults (M_{age} = 35.10 ± 13.25 years) completed three sessions in which measures of cortical excitability and inhibition were obtained before and after a 20-minute bout of either HIIT, moderate-intensity continuous training, or rest,

and then again after iTBS. Results showed that HIIT enhanced iTBS plasticity more than rest, manifest as increased cortico-motor excitability (p = .003) and intracortical facilitation (p = .03), and reduced intracortical inhibition (p = .008). In comparison, moderate-intensity exercise tended to show an effect that was intermediate relative to high-intensity exercise and rest. Analysis of each individual's plasticity response profile indicated that high-intensity exercise increased the likelihood of a facilitatory response to iTBS (from 15% in the rest session to 65% in the HIIT session). Our results suggest that when planning exercise interventions designed to enhance neuroplasticity, HIIT exercise should be considered. Priming with high-intensity exercise could be utilised in neurorehabilitation settings, when feasible, to maximise the therapeutic potential of non-invasive brain stimulation.

Disclosures: J.P. Coxon: None. **D. Curtin:** None. **J. Stout:** None. **S. Andrews:** None.

Nanosymposium

107. Voluntary Movements

Location: SDCC 25

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 107.04

Topic: E.04. Voluntary Movements

Support: ONR Global (N62909-15-1-2002)
Fondazione Roma (NCDS-2013-00000349)
D1 Funds Università Cattolica

Title: Transcranial direct current stimulation (tDCS) modulates mouse motor cortex activity and plasticity, and improves motor recovery after stroke

Authors: *M. V. PODDA[1], S. A. BARBATI[1], S. COCCO[1], V. LONGO[1], K. GIRONI[1], A. MATTERA[1], M. SPINELLI[1], F. VECCHIO[2], F. MIRAGLIA[2], P. M. ROSSINI[3], C. GRASSI[1]
[1]Inst. of Human Physiol., Univ. Cattolica del Sacro Cuore, Rome, Italy; [2]Brain Connectivity Lab., IRCCS San Raffaele Pisana, Rome, Italy; [3]Inst. of Neurology, Area of Neuroscience, Dept. of Geriatrics, Neurosciences, Orthopaedics, IRCCS Fondazione Policlinico Universitario A. Gemelli, Rome, Italy

Abstract: The knowledge of mechanisms subtending the beneficial effects of transcranial direct current stimulation (tDCS) on motor and cognitive functions is important for a more rationale use of this technique in clinical settings. Here we specifically investigated tDCS effects on motor cortex (M1) activity and plasticity in healthy mice and in mice subjected to M1 ischemia by photothrombosis. Electrophysiological, behavioral and molecular analyses were performed on C57BL/6 mice subjected to 3 daily sessions of anodal tDCS (20 min, 40 $\mu A/mm^2$) or sham stimulation. Few hours after tDCS, mice displayed increased long-term potentiation at M1 layer II/III synapses (66.5 ± 11.4% [n=9 slices from 6 tDCS mice] *vs.* 38.5 ± 5.8% [n=13 slices from 6

control mice]. These effects persisted 1 week after stimulation. AMPA/NMDA current ratio was also significantly enhanced by tDCS (1.20 ± 0.17 [n=20 slices from 7 tDCS mice] *vs.* 0.78 ± 0.11 [n=20 slices from 7 control mice], P<0.05). M1 extracts from tDCS mice showed increased pCREBSer133 and pCaMKIIThr286 levels and enhanced mRNA levels of the transcription factor Mef2c, Bdnf and GluA1. Analysis of motor behavior, assessed by the single pellet reaching task, revealed that success rate and success speed in pellet retrieval were significantly increased by tDCS 1 week after stimulation (success rate 38.0 ± 4.0% [n=8 tDCS mice] *vs.* 28.0 ± 2.0% [n=7 control mice], P<0.05; speed of success: 2.2 ± 0.2 *vs.* 1.5 ± 0.2, P<0.05). These data indicate that tDCS enhanced motor cortex plasticity in healthy mice. Of note, tDCS also ameliorated motor performance of the paretic limb in stroked mice (success rate 1 week after stroke: 11.3 ± 1.9 in 5 tDCS mice *vs.* 4.6 ± 2.3% in 4 sham stimulated mice, P<0.05; speed of success 1 week after stroke: 0.7 ± 0.1 in tDCS mice *vs.* 0.3 ± 0.2 in sham-stimulated mice, P<0.05). Neuromuscular strength 1 week after stroke was also enhanced by tDCS (3.2 ± 0.2 *vs.* 2.5 ± 0.2 g/body weight; P<0.05). EEG recordings were also performed in healthy and stroked mice by means of epidurally implanted electrodes over the left and right motor and somatosensory cortices. Stroked mice showed a time-dependent increase in alpha frequency power. Connectivity analysis showed a frequency-dependent network modulation as revealed by graph theory parameters such as Small-Word index. Additionally, stroked mice subjected tDCS showed different pattern of brain activity compared to sham-stimulated stroked mice, which might correlate to increased functional recovery. Altogether these data show that tDCS increased motor cortex plasticity and this mechanism might be responsible for improved motor functions under physiological conditions and after stroke.

Disclosures: M.V. Podda: None. **S.A. Barbati:** None. **S. Cocco:** None. **V. Longo:** None. **K. Gironi:** None. **A. Mattera:** None. **M. Spinelli:** None. **F. Vecchio:** None. **F. Miraglia:** None. **P.M. Rossini:** None. **C. Grassi:** None.

Nanosymposium

107. Voluntary Movements

Location: SDCC 25

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 107.05

Topic: E.04. Voluntary Movements

Support: ERC “All-optical brain-to- brain behaviour and information transfer” (BrainBit)
HBP Co-Design Project “Development of Whole Mouse Brain Model and related Mouse Brain Atlas”

Title: Simultaneous all-optical stimulation and readout of neuronal activity during optogenetically-evoked motor task

Authors: *F. RESTA, E. CONTI, E. MONTAGNI, G. DE VITO, A. SCAGLIONE, L. SACCONI, A. ALLEGRA MASCARO, F. PAVONE
?LENS - European Lab. for Non-Linear Spectroscopy, Univ. of Florence, Sesto Fiorentino, Italy

Abstract: The use of light to study neuronal networks has several advantages, such as the noninvasiveness and the possibility to target with high precision specific population of cells. In the past decade, there was a revolution in the use of light for both recording and stimulation of neuronal activity. The development of genetically encoded activity sensors brought us close to single-action-potential sensitivity and, on the other side, optogenetic allows to stimulate or inactivate defined populations of neurons with single-cell precision on millisecond time-scale. However, achieving an all-optical interrogation of neural circuits by combining these tools is still arduous, mainly due to the spectral overlap between actuators and indicators. To this aim we developed a new all-optical system based on a red-shifted GECI (RCaMP1a) combined with channelrhodopsin II (ChR2). Our preliminary results shows that we could induce the expression of RCaMP1a on most of the targeted hemisphere, including motor-associated areas. The coupling of RCaMP1a and ChR2 allowed simultaneous stimulation and readout from the same functional areas. By performing single pulse irradiation we observed that evoked calcium signals rise at increasing laser power, reaching a plateau around 5 mW laser power. We also observed that the stimulated calcium response did not change 3 or 4 weeks after the transfection, indicating the stability of the all-optical system in time and allowing longitudinal experiments. In order to study the cortical activation underlying a specific motor behavior we performed optical stimulation of the Rostral Forelimb Area (RFA) in awake mice. By using a stimulus train we could activate selective movements, like licking and grasping with the contralateral forelimb. Cortical dynamic recorded during the optogenetically-evoked motor task showed correlated activity in the RFA and nearby motor areas. The all-optical system developed here will allow full integration of stimulation and readout of cortical activity of the sensorimotor circuit and the correlated animal behavior, thus shedding light on the neuronal patterns responsible for selected behaviors. Finally, the development of an entirely optical device for interrogation and modulation of motor cortex activity would be a key point in the study of optogenetic-guided rehabilitation after stroke.

Disclosures: F. Resta: None. **E. Conti:** None. **E. Montagni:** None. **G. De Vito:** None. **A. Scaglione:** None. **L. Sacconi:** None. **A. Allegra Mascaro:** None. **F. Pavone:** None.

Nanosymposium

107. Voluntary Movements

Location: SDCC 25

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 107.06

Topic: E.04. Voluntary Movements

Support: NIH Grant R01MH111417
EU ERC-Advanced, 320708

Title: Population Receptive Fields revealed in sensorimotor hand region with 7 Tesla fMRI and high-density ECoG recordings

Authors: *W. SCHELLEKENS[1], G. PIANTONI[2], M. PEDROSO[1], J. WINAWER[3], N. PETRIDOU[1], N. F. RAMSEY[4]
[2]Dept Neurol., [1]UMC Utrecht, Utrecht, Netherlands; [3]Psychology, New York Univ., New York, NY; [4]Brain Ctr. Rudolf Magnus, Univ. of Utrecht, Utrecht, Netherlands

Abstract: A goal in sensory neuroscience is to be able to predict responses to arbitrary sensory inputs. Population receptive field (pRF) modeling has been an important step toward this goal. PRFs generalize the concept of receptive fields from single neurons to neuronal populations measured with fMRI or electrocorticography (ECoG), providing a computational framework to link sensory inputs to neuronal outputs. In the current study, a pRF model is applied to sensorimotor cortex activity following a finger digit motor task. Receptive field properties of finger digit representations are compared between high-field 7 Tesla (7T) fMRI and high-density ECoG recordings.
An epilepsy patient carried out a finger digit motor task during both a 7T fMRI session and subsequent high-density 64-channel ECoG recordings. The task required the sequential flexion and extension of each digit of the left hand. We modeled each cortical location with a Gaussian population receptive field centered on one of the 5 digits with a standard deviation specified in digits, representing a neuronal population's receptive field.
A clear somatotopy was observed on the crown of the postcentral gyrus for both modalities. The pRF maps agreed considerably for both flexion (spatial correlation R=.49) and extension (R=.32). Receptive field sizes were on average slightly smaller for ECoG (σ = .94) versus fMRI measurements (σ = 1.20). Additionally, through both measurements it was established that receptive field sizes consistently increased with finger representation: smallest pRF sizes were obtained for thumb representations, which gradually increased for remaining finger and were largest for little finger representations.
In the current study, we extended the pRF modeling approach from visual to sensorimotor function. This model applies to both ECoG and fMRI and provides a framework for in-depth investigation of cortical motor representation and sensorimotor integration. Results from one patient reveal highly similar somatotopies and pRF properties accompanied by several interesting differences. The current pRF model applied to multiple modalities provides a framework for in-depth investigation of the source of fMRI signal in sensorimotor cortex.

Disclosures: W. Schellekens: None. **G. Piantoni:** None. **M. Pedroso:** None. **J. Winawer:** None. **N. Petridou:** None. **N.F. Ramsey:** None.

Nanosymposium

107. Voluntary Movements

Location: SDCC 25

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 107.07

Topic: E.04. Voluntary Movements

Support: CIHR Doctoral award
CIHR Fellowship

Title: Acute exercise modulates excitability of M1 interneurons indexed by anterior-to-posterior current

Authors: *S. PETERS, J. L. NEVA, K. E. BROWN, M. BOISGONTIER, L. A. BOYD
Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Recent work suggests that aerobic exercise has potential to modulate cortical excitability measured by transcranial magnetic stimulation (TMS) [1]. Accumulating evidence demonstrates intracortical inhibition, reflective of $GABA_A$-related activity, is modulated after acute cycling exercise, without concurrent changes in corticospinal excitability [1-3]. Critically, we do not know whether exercise modulates intraneuronal circuitry that can be preferentially activated by an anterior-to-posterior (AP) induced current in the brain. These interneurons demonstrate unique neurophysiologic characteristics compared with traditional posterior-to-anterior (PA) current direction [4-6]. Previous work suggests $GABA_A$-related activity interacts with neurons preferentially activated via AP current. As they likely reflect activity in different interneuron populations, it is important to understand the exercise-induced modulation of intracortical circuitry as measured with AP versus PA induced currents [4-5]. Thus, the purpose of this study was to investigate the effects of acute exercise on this specific interneuronal circuitry within M1. Single and paired pulse TMS measured corticospinal and intracortical excitability over M1 representation of the non-exercised abductor pollicis brevis (APB) in both the AP and PA current directions. TMS measurement occurred at two time points before and after acute cycling exercise. Motor evoked potentials (MEPs) were measured at 110%, 130% and 150% of resting motor threshold (RMT). Short-intracortical inhibition (SICI) measured intracortical inhibition. Moderate intensity exercise was performed for 20 min at 65-70% of age-predicated maximum heart rate on a stationary cycle ergometer. Preliminary results suggest AP MEPs at 110% and 130% RMT were modulated by exercise, whereas no change was observed at 150% or at any intensity of PA MEPs. Specifically, AP MEPs at 110% RMT showed a decrease in amplitude, whereas 130% RMT showed an increase in amplitude immediately following exercise. For PA SICI, there appears to be decreased inhibition at both time points post exercise. This is the first study to suggest that intraneuronal circuitry preferentially activated by AP-induced current plays an important role in the exercise-induced modulation of cortical

excitability. [1] Singh et al. (2014) *BMC Sports Sci Med Rehabil*, 6:23. [2] Smith et al. (2014) *Exp Brain Res*, 6:1875-1882. [3] Lulic et al. (2017) *PLoS One*, 12:e0173672. [4] Di Lazzaro et al. (2017) *Neurosci*. 1-15. [5] Di Lazzaro et al. (2014) *J Physiol*, 19:4115-4128. [6] Mirdamadi et al. (2017) *Neurosci*, 359:151-158.

Disclosures: S. Peters: None. **J.L. Neva:** None. **K.E. Brown:** None. **M. Boisgontier:** None. **L.A. Boyd:** None.

Nanosymposium

107. Voluntary Movements

Location: SDCC 25

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 107.08

Topic: E.04. Voluntary Movements

Support: NSERC Discovery Grants Program - Individual RGPIN-2017-04154

Title: Modulation of interneuron excitability after motor sequence skill acquisition and learning

Authors: *J. L. NEVA[1], S. J. FELDMAN[2], K. E. BROWN[3], L. A. BOYD[4]
[1]Dept. of Physical Therapy, [2]Neurosci., [3]Physical Therapy, [4]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Motor skill practice can enhance corticospinal excitability [1, 2] and decrease intracortical inhibition [1], measured by transcranial magnetic stimulation (TMS). However, no studies have investigated neurophysiologic changes in primary motor cortex (M1) associated with sequence-specific motor learning to those following non-sequence specific motor control. Also, the specific neurophysiologic circuitry altered following skill acquisition and at a 24-hr retention test is not known. Critically, the impact of skilled motor practice on specific motor interneurons is not well understood, particularly when TMS is applied with an anterior-posterior (AP) directed current [3]. This motor circuitry has shown unique neurophysiologic characteristics, including association with unique forms of motor skill practice [3] and greater modulation during attention demanding tasks [4], compared to that measured with a posterior-anterior (PA) current [3, 4]. Therefore, it is possible that these specific interneurons are uniquely impacted by skill acquisition and learning. Here, we aimed to discover which interneuron circuitry are modulated by sequence-specific motor practice and whether these persist at a 24-hr retention test. Two separate experimental sessions were performed in a pseudo-random order, within-subjects design to test the modulation of interneuron circuitry following sequence-specific and non-sequence specific motor practice. Motor evoked potentials (MEPs) and short-intracortical inhibition (SICI) were measured in the PA and AP current directions over the trained abductor pollicis brevis (APB) muscle M1 representation. TMS measures occurred at two time-points prior to, after initial motor skill (early) practice and after further skill (late) practice.

Participants returned 24-hrs later where MEPs and SICI were measured before and after a retention test. Preliminary results suggest a decrease in PA MEPs noted for early non-sequence specific compared to sequence-specific motor skill practice. Conversely, AP SICI demonstrated a greater decrease than PA SICI in the sequence-specific motor acquisition, with little change during non-sequence specific practice. At retention, preliminary results suggest that PA MEPs are greater for the sequence-specific motor task. The results suggest unique modulation of interneuron circuitry induced by AP versus PA directed currents following sequence-specific motor acquisition and learning.
[1] Cirillo et al., 2011 *Eur J Neurosci* 34:1847-1856. [2] Christiansen et al., 2018 *Brain Stimul* 11:346-357. [3] Hamada et al., 2014 *J Neurosci* 34:12837-49. [4] Mirdamadi et al., 2017 *Neurosci*, 359:151-158

Disclosures: J.L. Neva: None. **S.J. Feldman:** None. **K.E. Brown:** None. **L.A. Boyd:** None.

Nanosymposium

107. Voluntary Movements

Location: SDCC 25

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 107.09

Topic: E.04. Voluntary Movements

Support: NIH Grant R01MH106174
NIH Grant P41RR14075

Title: Brain-state changes related to visuomotor adaptation

Authors: *J. AHVENINEN[1], P. SUNDARAM[1], S. LEE[2], J. A. GUERIN[2], E. PIRONDINI[5], W. F. ASAAD[3], M. HAMALAINEN[6], S. R. JONES[4]
[1]Athinoula A. Martinos Ctr., MGH/Harvard Med. Sch., Charlestown, MA; [2]Neurosci., [4]Dept. of Neurosci., [3]Brown Univ., Providence, RI; [5]EPFL, Geneve, Switzerland; [6]Massachusetts Gen. Hosp., Harvard Med. Sch., Charlestown, MA

Abstract: Visuomotor adaptation (VMA) is a process that helps recalibrate motor actions based on their differing sensory consequences. Here, we examine the neuronal basis of VMA during a visuomotor remapping task using magnetoencephalography and electroencephalography (MEG/EEG). In the visuomotor task, subjects use a joystick in their dominant hand to move a computer cursor to a cued direction. In different task blocks, the resulting cursor motion either matches the joystick motion or is rotated by a fixed angle. Behaviorally, VMA was evidenced as (a) the gradual reduction of direction errors caused by the mismatch between the actual and desired cursor movements in the rotated blocks and (b) the transient re-emergence of these direction errors in the subsequent non-rotated blocks. To pursue brain activity changes related to VMA, we used a linear mixed effects model of correlations between the trial to trial variability

of neuronal oscillations at 6-100 Hz (4 Hz intervals) and the initial direction error of the cursor trajectory (Initial Angle of Deviation, IAD). IAD was negatively correlated with increased power at 30-35 Hz (i.e., high beta / low gamma range) in or near sensorimotor and posterior parietal cortices contralateral to the active hand. Our working hypothesis for future studies is that correlates of VMA could be identified in minute changes in the oscillatory brain states of motor and visuomotor networks.

Disclosures: J. Ahveninen: None. **P. Sundaram:** None. **S. Lee:** None. **J.A. Guerin:** None. **E. Pirondini:** None. **W.F. Asaad:** None. **M. Hamalainen:** None. **S.R. Jones:** None.

Nanosymposium

107. Voluntary Movements

Location: SDCC 25

Time: Sunday, November 4, 2018, 8:00 AM - 10:30 AM

Presentation Number: 107.10

Topic: E.04. Voluntary Movements

Title: Motor cortex inhibition with somatosensory and transcranial direct current stimulation: A metaplasticity study

Authors: *W. D. BYBLOW[1,2], A. M. TRUDGEN[1], J. CIRILLO[1,2]
[1]Dept. of Exercise Sci., [2]Ctr. for Brain Res., Univ. of Auckland, Auckland, New Zealand

Abstract: Priming the brain may provide potential treatment strategies for neurological disorders and stroke. Mesh glove stimulation (MGS) provides a non-motor target for rehabilitation. Following thirty minutes of suprasensory threshold MGS there is an increase in corticomotor excitability that is likely mediated by long-term potentiation. Transcranial direct current stimulation (tDCS) of primary motor cortex can induce global changes in corticomotor excitability. Nine minutes of cathodal tDCS (c-tDCS) produces a lasting decrease in corticomotor excitability mediated by long-term depression. Whether priming MGS with c-tDCS further enhances corticomotor excitability through homeostatic metaplasticity mechanisms is unknown. Sixteen right-handed neurologically healthy individuals (9 female, 19-36 years) participated in a repeated measures cross-over study, nine minutes of sham- or c-tDCS followed by 30 minutes of suprasensory threshold MGS. Single-pulse transcranial magnetic stimulation (rest motor threshold and motor evoked potential amplitude), paired-pulse transcranial magnetic stimulation (intracortical facilitation, short afferent inhibition (SAI), short interval intracortical inhibition (SICI), and SAI with SICI (SAIxSICI)), and motor performance (grooved pegboard test) of the left hand were obtained at baseline, post-tDCS, and immediately, 30 and 60 minutes post-MGS. There was more disinhibition of SAI, and an increase in rest motor threshold and SAIxSICI after MGS was primed with c-tDCS compared with sham-tDCS. There was also a greater improvement in the grooved pegboard task after c-tDCS primed MGS than sham. Our results indicate a non-homeostatic metaplastic modulation of corticomotor excitability with c-

tDCS primed MGS. Consequently, c-tDCS did not modulate corticomotor excitability after MGS, but did improve motor performance. Therefore, c-tDCS may be an effective priming modality to induce non-homeostatic metaplasticity.

Disclosures: W.D. Byblow: None. **A.M. Trudgen:** None. **J. Cirillo:** None.

Nanosymposium

108. Behavioral Neuroendocrinology: Hormones and Cognition

Location: SDCC 5

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 108.02

Topic: F.02. Behavioral Neuroendocrinology

Support: CIHR PJT Grant 156414 to IBZ
NSERC DG Grant 312458 to DAM
NSERC PGSD Grant 424569 to FR

Title: Androgen receptors and Histone Variant H2A.Z interact to affect memory through changes on memory-related genes

Authors: *F. RAMZAN[1], C. T. TAO[2], A. B. AZAM[3], K. NARKAJ[3], G. STEFANELLI[4], D. A. MONKS[4], I. B. ZOVKIC[4]
[1]Univ. of Toronto, Mississauga, ON, Canada; [2]Psychology, Univ. of Toronto, Toronto, ON, Canada; [3]Cell and Systems Biol., Univ. of Toronto, Mississauga, ON, Canada; [4]Psychology, Univ. of Toronto Mississauga, Mississauga, ON, Canada

Abstract: Hormones have a significant effect on fear memory. While much is known about ovarian steroid hormones (e.g. estrogen) facilitating contextual fear conditioning in mice, much less is known about the role of androgens (e.g. testosterone) and the androgen receptor (AR) in memory formation. Previous literature shows mixed results, with testosterone leading to either a reduced or an enhanced contextual fear response. Using transgenic mice overexpressing AR, we showed that AR overexpression impairs fear memory. Gonadectomy eliminated group differences between AR-overexpressing and WT males, implicating testosterone as a negative regulator of fear memory through actions on AR. Further, treatment with the AR-blocker flutamide increased fear memory, suggesting that AR negatively regulates fear memory. In addition, we showed that expression of H2A.Z, a memory suppressor identified in our lab, is increased in AR overexpressing mice, prompting us to investigate AR regulation in H2A.Z conditional knockout mice. In contrast to AR overexpression, H2A.Z depletion results in increased fear memory and decreased AR expression in area CA1 of the hippocampus. Castration with DHT (dihydrotestosterone) replacement resulted in genotype-specific effects on fear memory, pointing to an interaction between H2A.z and AR. We also find corresponding changes in gene expression of genes encoding for synaptic proteins and memory-related genes.

These results suggest a role of AR in modulating fear memory through interactions with nuclear histone proteins. This is a novel finding that we plan to expand on further to understand the neuronal mechanisms through which this occurs.

Disclosures: F. Ramzan: None. **C.T. Tao:** None. **A.B. Azam:** None. **K. Narkaj:** None. **G. Stefanelli:** None. **D.A. Monks:** None. **I.B. Zovkic:** None.

Nanosymposium

108. Behavioral Neuroendocrinology: Hormones and Cognition

Location: SDCC 5

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 108.03

Topic: F.02. Behavioral Neuroendocrinology

Support: NSF Award #1649717

Title: Sleep deprivation between genders and age in *Drosophila melanogaster*: Determining whether prolactin levels affect sleep deprivation

Authors: C. TURNER[1], *F. JEFFERSON[2]
[1]Biol., [2]Fort Valley State Univ., Fort Valley, GA

Abstract: Prolactin is a complex protein hormone of the anterior pituitary gland that was originally named for its ability to promote lactation. Prolactin is synthesized in the pituitary gland, where sleep hormones are secreted, and within the central nervous system, immune system, the uterus, tissues of conception, and the mammary gland. Prolactin controls a variety of behaviors and plays a role in homeostasis. During sleep, prolactin is secreted into Non-REM and REM sleep cycles. Concentrations of prolactin remain high during later cycles that occur more towards the morning hours. This shows that high prolactin regularly occurs during sleep cycles with small amounts of slow-wave sleep. Maximal prolactin concentrations during sleep are affected neither by preceding daytime physical exercise nor by selective deprivation of slow sleep stages 3 and 4. This is further evidence that slow-wave sleep stages are not necessary for the development of high plasma prolactin concentrations. Long-term total sleep deprivation can result in death. During sleep deprivation, the body shuts down certain organs to overcompensate elsewhere and utilize other organs. In this study, a scientific method approach was used to test whether prolactin acting with an external stimulant would cause severe sleep deprivation in more mature female flies. Control tubes of larvae and young flies and full maturation of male and female flies were used, along with tubes with caffeine and tubes with a light stimulant. Sleep deprivation in young *Drosophila* resulted in a deficit in behavior and performance requiring memory. This research will provide a method to reliably extract quantitative information from the *Drosophila* to better understand sleep deprivation in humans and its effects on the brain and the body with increasing age. This research also has potential to improve patient outcomes by

focusing on the physiological issues that cause sleep deprivation. Sleep deprivation studies have helped healthcare providers such as endocrinologist and those who use polysomnography. Further investigation into physiological effects on sleep deprivation is expected.

Disclosures: C. Turner: None. **F. Jefferson:** None.

Nanosymposium

108. Behavioral Neuroendocrinology: Hormones and Cognition

Location: SDCC 5

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 108.04

Topic: F.02. Behavioral Neuroendocrinology

Support: CONACyT Grant FCB576165

Title: Effect of lithium-pilocarpine-induced status epilepticus during infancy on adult female rat sexual behavior

Authors: *F. CHENA BECERRA[1], G. A. CORIA-AVILA[2], L. BELTRAN-PARRAZAL[2], J. MANZO[2], L. LOPEZ-MERAZ[2]
[1]Doctorado En Investigaciones Cerebrales, [2]Ctr. De Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Mexico

Abstract: Epilepsy is frequently associated to sexual disorders, however, how epilepsy affects this behavior is poorly understood. Previous studies have shown that *status epilepticus* (SE) can modify sexual performance in adult rats. Nevertheless, SE incidence is higher during infancy. Hence, the aim of our study was to evaluate sexual performance on female adult rats with previous SE during childhood. To that end, thirteen-days-old (P13) female rat pups received an intraperitoneal injection of lithium chloride (3mEq/kg, i.p.). Twenty hours later, rats were injected subcutaneously with pilocarpine hydrochloride (100mg/kg, s.c.); control (CTRL) rats received the same volume of saline (0.9%). At P21, the rats were weaned and at P80 they were ovariectomized (OVX) to control their sexual cycle. Receptivity was induced before each trial with hormone replacement of subcutaneous injections of estradiol benzoate (10 μg) and progesterone (500 μg), 48h and 4h, respectively. Sexual behavior was evaluated in the course of five sessions (every four days) of 30 minutes each with a sexually experienced adult male. Latency and frequency of solicitations, hops and darts and lordosis were assessed. Additionally, male mounts, intromissions and ejaculations were quantified. An open-field test occurred five minutes before the first mating trial to measure locomotor activity. After the fifth session, serum corticosterone levels were quantified with an ELISA kit. Results showed significant differences between groups in latency to solicitations at first and second trial and frequency to the same parameter at second trial. No differences were found between SE or CTRL rats in locomotor activity (measured as number of squares crossed) and corticosterone levels. Also male sexual

behavior showed no differences among groups. Hence, we argue that SE affects females' proceptivity but not attractivity or receptivity. Given that such results are not observed from trial three, it is possible that sexual behavior is normalized after experience. Accordingly, SE during infancy would mainly affect mechanisms of sexual desire but not performance.

Disclosures: F. Chena becerra: None. **G.A. Coria-Avila:** None. **L. Beltran-Parrazal:** None. **J. Manzo:** None. **L. Lopez-Meraz:** None.

Nanosymposium

108. Behavioral Neuroendocrinology: Hormones and Cognition

Location: SDCC 5

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 108.05

Topic: F.02. Behavioral Neuroendocrinology

Support: R21AG048463

Title: Frontoparietal network activation during an auditory oddball task differs across the hormonal contraceptive cycle

Authors: *A. Y. HERRERA[1], K. GILLETTE[2], D. V. CLEWETT[3], R. VELASCO[2], S. FAUDE[2], J. WHITE[2], M. MATHER[1]
[1]Davis Sch. of Gerontology, [2]USC, Los Angeles, CA; [3]Psychology, New York Univ., New York, NY

Abstract: Emerging research indicates that hormonal contraception (HC) influences cognition. However, the effects may depend on cycle phase, as oral hormonal contraception and vaginal rings typically deliver synthetic estradiol and progestins for a specific time window followed by a period of no synthetic sex hormones. Using functional magnetic resonance imaging, we examined the effects of HC phase on brain activation patterns during an auditory oddball task. Twenty healthy young women using monophasic 28-day HC containing 7 no-hormone days were scanned twice across the HC cycle, once during days 8 to 21 (hormone phase) and once during days 24 to 28 (no-hormone phase). In the scanner, women performed an auditory oddball task to examine how HC phase influenced brain activity in regions and networks associated with arousal and task-relevant processing. During the task, women heard a series 120 sounds, each presented for 200ms. Ninety-six stimuli were low-frequency tones (500Hz; standard tone), twelve were natural sounds (novel tones), and twelve were high-frequency tones (1000Hz; oddball tone). Women were told to press a button as quickly as possible whenever they heard the oddball tone. Oddball detection speed and accuracy did not differ across HC phase nor did task-related differences in whole-brain activation patterns. However, a tensor independent component analysis revealed differences in functional brain network activation across the task depending on HC phase. Specifically, right frontoparietal network activation was greater when women heard a

novel versus a standard or oddball tone, with the most robust frontoparietal network activation to the novel tone observed during the no-hormone phase.
Greater frontoparietal network activation during the novel tone may be related to inhibition of task-irrelevant and/or bottom-up arousal responses, because, although heard as infrequently as the oddball tone, the novel tone required suppressing a behavioral response. This activation pattern was greater during the no-hormone phase, suggesting that women may differ in their ability to inhibit unwanted emotional or behavioral responses according to hormone status, which has important implications for women's mental health and wellbeing across both early and late adulthood.

Disclosures: A.Y. Herrera: None. **K. Gillette:** None. **D.V. Clewett:** None. **R. Velasco:** None. **S. Faude:** None. **J. White:** None. **M. Mather:** None.

Nanosymposium

108. Behavioral Neuroendocrinology: Hormones and Cognition

Location: SDCC 5

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 108.06

Topic: F.02. Behavioral Neuroendocrinology

Support: Rhodes College Internal Funding
NSF Graduate Fellowship to CAW
NSF IOS-1501704 to HAH
NSF IOS-1601734 to CAW and HAH

Title: Neural activity in the social decision-making network of the brown anole during reproductive and agonistic encounters

Authors: *D. KABELIK[1], C. A. WEITEKAMP[2], S. C. CHOUDHURY[1], J. T. HARTLINE[1], A. N. SMITH[1], H. A. HOFMANN[2]
[1]Dept. of Biology, Program in Neurosci., Rhodes Col., Memphis, TN; [2]Univ. of Texas at Austin, Austin, TX

Abstract: It has been debated whether an intact social decision-making network (SDMN), consisting of interconnected social behavior and mesolimbic reward networks, exists across all vertebrate groups. We therefore examined neural activation across the SDMN and associated regions in 57 male brown anoles (*Anolis sagrei*), within reproductive, agonistic, and non-social control contexts. We examined neural activation within the SDMN by quantifying immunoreactive (ir) expression of the immediate early gene product Fos. We then related Fos-ir density to social context, behavioral expression, and activity (colocalization with Fos-ir) within different phenotypes of 'source' nodes that release neurotransmitters (catecholamines and serotonin) and neuropeptides (vasopressin and oxytocin), which can modulate SDMN 'target'

node activity. Our results demonstrate that (1) neural activity of a core network of SDMN nodes varies across social conditions; (2) functional connectivity within the SDMN varies across social encounters (the greatest mean connectivity is present during reproductive encounters, although a larger significantly correlated (though more weakly connected) cluster of nodes is present in the agonistic encounter treatment); (3) functional connectivity of source nodes to SDMN target nodes varies across type of signaling molecule and social condition - in general, vasopressin, catecholamines, and serotonin are negatively connected and oxytocin positively connected to SDMN activity; (4) measures of social behavior are not associated with activity of the core SDMN network; and (5) the intensity of aggressive behavior is correlated with catecholaminergic activity in the periventricular nucleus of the anterior hypothalamus and the raphe, whereas the frequency and intensity of courtship displays is strongly correlated with co-activation of hypothalamic and midbrain catecholamine neurons. Our findings therefore present evidence for a functional SDMN in reptiles, and detail its regulation across social contexts.

Disclosures: D. Kabelik: None. **C.A. Weitekamp:** None. **S.C. Choudhury:** None. **J.T. Hartline:** None. **A.N. Smith:** None. **H.A. Hofmann:** None.

Nanosymposium

108. Behavioral Neuroendocrinology: Hormones and Cognition

Location: SDCC 5

Time: Sunday, November 4, 2018, 8:00 AM - 10:00 AM

Presentation Number: 108.08

Topic: F.02. Behavioral Neuroendocrinology

Support: HRC

Title: Identifying prolactin-responsive neurons important for the transition to paternal care

Authors: *K. O. SMILEY[1], R. S. E. BROWN[2], D. R. GRATTAN[2]
[2]Ctr. for Neuroendocrinology, Dept. of Anat., [1]Univ. of Otago, Dunedin, New Zealand

Abstract: Paternal care is important for healthy offspring development. However, the neuroendocrine regulation of paternal care remains poorly understood, in comparison to maternal care. There is a well-established role for the hormone prolactin (PRL) in mediating maternal behavior through its actions on central prolactin receptors (PRLR). Male mice have a similar central PRLR distribution as females, however, it is unknown whether PRL actions in the brain are critical for paternal behavior expression as it is for females. In sharp contrast to virgin female mice, virgin male mice are infanticidal towards pups, but approximately 2 weeks after mating, infanticidal behavior is suppressed and the emergence of paternal care coincides with the birth of pups. Therefore, the transition to paternal care involves both the promotion of pup-directed behaviors and the suppression of aggressive tendencies towards the pups, which is induced from the act of mating. To begin testing whether PRL is involved in the mating-induced transition to

paternal care we performed two experiments to identify specific groups of PRL-responsive neurons that are activated after mating and during pup care. The first experiment collected brains from virgin males that were allowed to either mate with a receptive female or control (no female). The second experiment used males who were allowed to mate and sire pups before being separated from the litter on postpartum day 3. The following day males were either exposed to pups or no pups and brains were collected. Brains were processed for c-fos using immunohistochemistry in our novel Prlr-Cre/td-tomato mouse line, which are genetically modified such that PRL-responsive neurons are labeled with a fluorescent tag (td-tomato) so that they can be visualized. We predict that mated males will show more c-fos overlap with PRL-responsive cells then non-mated males, particularly in the bed nucleus of the stria terminalis and medial amygdala, two brain areas which have been previously identified to be active after mating in male mice and express PRL receptors. We expect that fathers with pups will show increased c-fos activation in PRLR neurons in the medial preoptic area, which is critical area for both maternal and paternal care. This work will inform future hypotheses and predictions which causally test for a role of neural PRL signaling in paternal care and will inform us whether paternal care is regulated in a similar manner as maternal care.

Disclosures: K.O. Smiley: None. **R.S.E. Brown:** None. **D.R. Grattan:** None.

Nanosymposium

109. Basal Ganglia Circuitry for Motivation and Reward

Location: SDCC 2

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 109.01

Topic: G.02. Motivation

Support: UL1TR001427
KL2TR001429
TL1TR001428

Title: Pallidal neural correlates of reward in Parkinson's disease

Authors: *R. S. EISINGER[1], E. OPRI[2], J. ALCANTARA[3], M. E. VAZQUEZ[3], K. D. FOOTE[4], M. S. OKUN[5], A. GUNDUZ[3]
[1]Neurosci., [3]Biomed. Engin., [4]Neurosurg., [5]Neurol., [2]Univ. of Florida, Gainesville, FL

Abstract: Background: Reward processing dysfunction in Parkinson's disease (PD) is common and can occur with deep brain stimulation (DBS) of the globus pallidus internus (GPi). Numerous primate studies and a limited number of human studies have identified reward-related single-units in the pallidum, but local field potential studies are lacking.
Methods: 10 PD participants undergoing DBS played a modified Go/No-Go reward processing task during surgery after implantation of the macroelectrode into the GPi. In each trial,

participants viewed a colored stimulus and either responded (Go) or not (No-Go) based on the prospect for reward (+100 points) or loss avoidance (no-reward: +0 points; loss:-100 points). Participants learned to associate stimuli with outcomes during preoperative training. During intraoperative game play, monopolar recordings were acquired at each contact of a Medtronic 3387 DBS lead. We searched for neural correlates of reward using spectral decomposition and event related potential (ERPs) techniques. Go and No-Go trials were compared to study neural correlates of movement, and reward and no-reward trials were compared to study neural correlates of reward processing. We examined reward anticipation, action for reward, and reward feedback separately.
Results: We observed prominent decreases in GPi beta band (11-30 Hz) power during movement compared to rest. ERPs were seen in response to stimulus and feedback onset across all trial conditions. There were no differences in ERP or spectral content of signals during stimulus onset between reward and no-reward trials. However, the GPi exhibited significantly higher ERP amplitudes and increased theta (4-8 Hz) power in response to reward feedback. Relative to no-reward trials, we also observed increased beta power in response to reward feedback during No-Go trials.
Conclusions: Our results indicate that the GPi participates in reward-processing through measurable changes in field potentials (neural population). This is the first report of low-frequency changes in the GPi during reward feedback. In the future we aim to relate basal ganglia neural correlates of reward to clinically diagnosed impulsivity and apathy.

Disclosures: R.S. Eisinger: None. **E. Opri:** None. **J. Alcantara:** None. **M.E. Vazquez:** None. **K.D. Foote:** None. **M.S. Okun:** None. **A. Gunduz:** None.

Nanosymposium

109. Basal Ganglia Circuitry for Motivation and Reward

Location: SDCC 2

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 109.02

Topic: G.02. Motivation

Support: NIH grant MH108924
NIH grant MH101214
NIH grant MH113316
NARSAD Independent Investigator Grant

Title: Genetically-distinct ventral pallidal neurons drive the motivation for reward approach and punishment avoidance through projections to the lateral habenula

Authors: *C. BRAVO-RIVERA[1], M. STEPHENSON-JONES[2], A. FURLAN[1], C. FERNANDES-HENRIQUES[1], X. ZHANG[1], X. XIAO[1], T. YANG[1], B. LI[1]

[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Sainsbury Wellcome Ctr. for Neural Circuits and Behaviour, Univ. Col. London, London, United Kingdom

Abstract: Motivated behaviors can be driven by two opposing processes; reward seeking and punishment avoidance. The ventral pallidum (VP) is critical for attributing motivation salience to cues that predict reward and for invigorating reward-seeking behavior. Furthermore, the VP also regulates motivation for punishment avoidance. However, it remains to be determined whether different cell types in VP control different motivational drives. Additionally, it remains unclear which is the target of VP neurons that control motivation. Here we probe the role of GABAergic and glutamatergic VP projections to the lateral habenula (VP-LHb), a structure implicated in motivation regulation, in the control of reward approach and punishment avoidance. We developed a task in which different auditory tones predict different levels of reward (water) in head-fixed, water-deprived mice. To obtain the water reward, mice needed to lick the water spout within a time frame after the cue presentation. We found that optogenetic activation of GABAergic VP-LHb projections increased licking responses whereas activation of glutamatergic VP-LHb projections reduced licking responses. Conversely, optogenetic silencing of GABAergic VP-LHb projections decreased licking responses whereas silencing of glutamatergic VP-LHb projections had no effect. This suggests that GABAergic VP-LHb projections mediate the motivational drive to pursue reward attainment. Incorporating a punishment (air-puff) with reward delivery in this task decreased licking responses, but silencing of glutamatergic VP-LHb projections prevented this decrease. This suggests that this glutamatergic VP-LHb projection encodes the punishing cost in a reward/punishment conflict scenario. We subsequently trained head-fixed mice to run on a wheel during cue presentations for water reward or punishment avoidance. We found that optogenetic silencing of GABAergic VP-LHb projections decreased running responses for reward attainment, but not for punishment avoidance. Conversely, optogenetic silencing of glutamatergic VP-LHb projections had no effect on running responses for reward attainment, but decreased running for punishment avoidance. Together, these results suggest that GABAergic VP-LHb projections are necessary for reward approach, whereas glutamatergic VP-LHb projections are necessary for punishment avoidance. Characterization of this VP circuit will broaden our understanding of how motivation is encoded in the basal ganglia.

Disclosures: C. Bravo-Rivera: None. **M. Stephenson-Jones:** None. **A. Furlan:** None. **C. Fernandes-Henriques:** None. **X. Zhang:** None. **X. Xiao:** None. **T. Yang:** None. **B. Li:** None.

Nanosymposium

109. Basal Ganglia Circuitry for Motivation and Reward

Location: SDCC 2

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 109.03

Topic: G.02. Motivation

Title: Impairment of motivational behavior associated with chronic pain: The role of communication between medial prefrontal cortex and nucleus accumbens

Authors: *C. BAO, Y. CHEN, Y. XIN, Z. X. DONG
East China Normal Univ., Shanghai, China

Abstract: Chronic pain-induced depression and fatigue were found to be closely associated with the decline in motivation in patients. However, the neural basis for the impairment remains unclear. In the present study, we explored the neuronal mechanism underlying motivational impairment induced by chronic pain in neuropathic rats with sural-spared sciatic nerve injury (SNI). We used an operant effort-based decision-making paradigm, in which animals could choose either to obtain a large reward by climbing a barrier or to select another option with small reward. The SNI rats showed a reduced rate of choosing the high effort/high reward arm, suggesting declined motivation in the condition of chronic pain. We simultaneously recorded neural activity in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) when the rats were performing the effort-based decision-making task. We found that 1) the theta-band power of the local field potential (LFP) in the mPFC was positively correlated with the number of high effort/high reward choices; 2) the SNI rats showed significantly lower theta-band power of the LFP in the mPFC and lower gamma-band power in the NAc during the decision-making task; and 3) both the coherence of theta-band oscillation between the mPFC and the NAc, and the coupling of mPFC theta phase-NAc gamma amplitude decreased in the SNI rats. These results suggested that the alteration of neural activities in the mPFC and NAc and the attenuation of communication between these two areas may serve as the neural mechanism for the impaired performance in motivational decision making in chronic pain conditions. In line with this postulation, further optogenetical experiments demonstrated that deactivation of terminals projected from the mPFC to the NAc also caused a decrease of the high effort/high reward choices in the sham rats. Our findings provide important information for the understanding of the neural basis for the association between the declined motivation and chronic pain.

Disclosures: Y. Chen: None. **Y. Xin:** None. **Z.X. Dong:** None.

Nanosymposium

109. Basal Ganglia Circuitry for Motivation and Reward

Location: SDCC 2

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 109.04

Topic: G.02. Motivation

Support: 8319-2013-RGPIN

Title: Expression of connexin-36 in the ventral tegmental area is necessary for the development of opiate-dependent motivation

Authors: *G. MAAL-BARED[1], M. BERGAMINI[1], M. YEE[1], M. GHEBRESELASSIE[1], E. KIM[1], R. CHOY[1], M. PATEL[1], D. J. VAN DER KOOY[2]
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Dept Med. Genet, Univ. Toronto, Toronto, ON, Canada

Abstract: The ventral tegmental area (VTA) is crucial for adaptive and maladaptive motivated behaviours such as eating and chronic drug-seeking. VTA GABA neurons 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. Here, we report that VTA connexin-36, a gap junction-expressing protein, 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. Moreover, knocking out Cx36 in GABA neurons produces perpetually drug-naïve mice such that mCPP are always mediated by the TPP and withdrawal aversions never manifest. These results demonstrate that Cx36 in VTA GABA neurons is *necessary* for the development of drug-dependent motivation. We currently are investigating whether Cx36 in VTA GABA neurons is *sufficient* to restore susceptibility to drug dependence. Given the functional importance of this subpopulation of VTA GABA neurons, we also are performing retrograde tracing experiments to identify the pathways to which they contribute.

Disclosures: G. Maal-Bared: None. **M. Bergamini:** None. **M. Yee:** None. **M. Ghebreselassie:** None. **E. Kim:** None. **R. Choy:** None. **M. Patel:** None. **D.J. Van Der Kooy:** None.

Nanosymposium

109. Basal Ganglia Circuitry for Motivation and Reward

Location: SDCC 2

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 109.05

Topic: G.02. Motivation

Support: NIDA grant DA041781

Title: Dissecting dopamine pathways altered by pain-induced dysfunction in opioid signaling

Authors: *T. MARKOVIC[1], N. MASSALY[1], L. HIPOLITO[3], C. PEDERSEN[2], S. LIU[4], C. M. CAHILL[4], M. BRUCHAS[1], J. MORON-CONCEPCION[1]
[1]Anesthesiol., [2]Washington Univ. Sch. of Med., Saint Louis, MO; [3]Univ. of Valencia, Valencia,

Spain; [4]Dept. of Psychiatry & Biobehavioral Sci., Semel Inst. of Neurosci. and Human Behavior, UCLA, Los Angeles, CA

Abstract: Pain is a complex phenomenon composed of sensory and affective components. In addition to sensory disturbances, patients experiencing pain report the presence of other negative symptoms such as dysphoria, anhedonia, and anxiety. These co-morbid disturbances can lead to depression and opioid misuse, consequently escalating into life threatening events such as suicide attempts or accidental opioid overdoses. Clinical studies have correlated these pain-induced pathological states with a decrease in dopamine (DA) neurotransmission and maladaptive changes in the nucleus accumbens (NAc). In the same line, using an animal model of inflammatory pain it has been reported that opioid evoked DA release in the NAc is attenuated in pain. This pain-induced suppression of DA transmission is likely due to downregulation of mu opioid receptor function in the ventral tegmental area (VTA) GABA neurons. Moreover, animals experiencing inflammatory pain show impaired motivated responses to natural and opioid rewards which are sustained, at least in part, by a decrease in midbrain DA signaling. All together these findings link pain-induced loss of motivation and co-morbidities with a general allostatic impairment of DA neurotransmission. The most dense DA pathway arising from the VTA is the mesolimbic reward pathway (VTA-NAc). Considering the role of this pathway in the integration of rewarding and aversive stimuli, it represents an ideal circuit for studying the co-morbidity of pain and loss of motivation. Using chemogenetics we demonstrate that stimulating DA neurons in the VTA is sufficient to prevent pain-induced decrease in motivation. Furthermore, we validate that the recovery of motivation is not due to the analgesic effect of the treatment, as activation of DA neurons did not reverse pain induced thermal hyperalgesia. While global activation of VTA DA neurons fully prevented pain-induced motivational deficit, the activation of VTA-NAc pathway using intersectional chemogenetics partially restored motivation in animals in pain. Interestingly, by activating the VTA-NAc pathway a significant positive correlation in between the number of DREADD-infected DA neurons in the VTA and the amount of prevention of pain-induced decrease in motivation was drawn. Lastly, using fiber photometry we demonstrate a robust DA activity correlated with the delivery of reward during the sucrose self-administration, furthermore allowing us to assess pain induced changes in DA activity during the motivational task within the same animal. In conclusion, our findings provide a mechanistic evidence for the involvement of DA pathways in pain-induced negative emotional states.

Disclosures: T. Markovic: None. **N. Massaly:** None. **L. Hipolito:** None. **C. Pedersen:** None. **S. Liu:** None. **C.M. Cahill:** None. **M. Bruchas:** None. **J. Moron-Concepcion:** None.

Nanosymposium

109. Basal Ganglia Circuitry for Motivation and Reward

Location: SDCC 2

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 109.06

Topic: G.02. Motivation

Support: NIDDK Intramural Program
NIH Center for Compulsive Behavior Training Fellowship

Title: Exploring a role for dopamine in dieting using a mouse model

Authors: *W. FOBBS[1], A. KRAVITZ[1,2]
[1]NIDDK, NIH, Bethesda, MD; [2]Nida, NIH, Baltimore, MD

Abstract: Because our modern food environment is rich in highly palatable, calorie-dense foods, it is very easy to overeat, or consume excess calories. While most individuals remain in a state of caloric surplus, a growing number of individuals overeat to the point of developing obesity and associated health consequences. Despite the growing awareness of the detrimental effects of overeating, individuals with and without obesity find it very difficult to diet, or to reduce overeating by switching to less- palatable, lower calorie alternatives. To explore the behavioral and neural basis of dieting difficulties, we developed a short-term mouse model of overeating and dieting. In our model, mice are given *ad libitum* access to high-fat diet (60% fat) for 3 days before being switched back to chow. They robustly overeat during high-fat diet access and then dramatically reduce their chow intake on the switch day (diet day) relative to their intake before high-fat diet. We have now shown that the chow undereating effect is sensitive to the magnitude of overeating but is not attributable to a single fat source, a lack of food choice, nor palatability alone. Many have hypothesized that increased preference/craving for palatable foods plays a critical role in derailing diets, and we believe that the undereating effect reflects another important driver of dieting difficulty- reduced preference/motivation for less-palatable alternatives. Thus, given that dopamine signaling is implicated in conveying reward and motivation information and altered dopamine signaling has been linked to enhanced cravings for and overconsumption of palatable foods, we are currently assessing whether and how the reinforcing efficacy of dopamine self-stimulation and the calcium activity of VTA dopamine cells are changed during our model by using optogenetics and fiber photometry, respectively.

Disclosures: W. Fobbs: None. **A. Kravitz:** None.

Nanosymposium

109. Basal Ganglia Circuitry for Motivation and Reward

Location: SDCC 2

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 109.07

Topic: F.10. Food Intake and Energy Balance

Support: JSPS Grant 15K09426

Title: $GABA_B$ receptor signaling in dopaminergic or striatal neurons suppresses food intake during intermittent access to a high fat diet in mice

Authors: *T. TSUNEKAWA[1], R. BANNO[1,2], H. YAGINUMA[3], K. TAKI[3], A. MIZOGUCHI[3], M. SUGIYAMA[1], H. TAKAGI[1], Y. ITO[1], H. ARIMA[3]
[1]Dept. of Endocrinol. and Diabetes, Nagoya Univ. Hosp., Nagoya-shi, Japan; [2]Res. Ctr. of Health, Physical Fitness and Sports, Nagoya Univ., Nagoya-shi, Japan; [3]Dept. of Endocrinol. and Diabetes, Nagoya Univ. Grad. Sch. of Med., Nagoya-shi, Japan

Abstract: The feeding behavior is regulated not only by the hypothalamus but also the limbic system, which is related to addiction. In the limbic system, dopaminergic neurons in the ventral tegmental area (VTA) project to the nucleus accumbens (NAc) in the striatum (Stri). Recent studies suggest that there are several similarities in the pathological mechanisms of addiction among alcohol, drugs and a high fat (HFD). Baclofen, a gamma aminobutyric acid type B receptor ($GABA_B$-R) agonist, has been shown to be effective for the treatment of alcohol and drug addiction. We previously reported that baclofen reduced appetite and the desire for snacking in human, although the neurons which mediate baclofen action have not been clarified yet. To elucidate the role of $GABA_B$-R for feeding behavior in the limbic system, we generated dopaminergic or striatal neuron specific $GABA_B$-R deficient mice (D-KO or S-KO, respectively) by Cre-loxP system. We placed wild-type mice (WT), D-KO and S-KO on HFD for 16 weeks, and measured body weight changes and food intake. We also performed intraperitoneal (ip) injection of baclofen every 6 hours into WT, D-KO and S-KO that had fed HFD for 6 weeks, and measured body weights and food intake of HFD for 2 days. Next, to evaluate the addiction to HFD, we placed WT, DKO and SKO on ad libitum access to a chow diet for 24h and intermittent access to HFD for 2h per day. We also performed ip injection of baclofen or vehicle 30 minutes before intermittent access to HFD, and measured food intake of HFD for 2h. There were no significant differences in body weight and food intake between WT and either D-KO or S-KO on HFD. While baclofen administration reduced body weight and intake in WT, D-KO and S-KO, there were no significant differences between genotypes. During intermittent access to HFD, the food intake in S-KO but not in D-KO was significantly increased compared to WT. Whereas baclofen administration significantly decreased food intake compared to vehicle in WT during intermittent access to HFD, these effects seen in WT were canceled in both D-KO and S-KO. These results suggest that $GABA_B$ receptor signaling in dopaminergic neurons or striatal neurons suppresses food intake during intermittent access to HFD, and the effect is dominant in striatal neurons.

Disclosures: T. Tsunekawa: None. **R. Banno:** None. **H. Yaginuma:** None. **K. Taki:** None. **A. Mizoguchi:** None. **M. Sugiyama:** None. **H. Takagi:** None. **Y. Ito:** None. **H. Arima:** None.

Nanosymposium

109. Basal Ganglia Circuitry for Motivation and Reward

Location: SDCC 2

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 109.08

Topic: G.02. Motivation

Title: Reward synchronizes dopamine axons into directional waves

Authors: *A. HAMID[1], M. J. FRANK[3], C. I. MOORE[2]
[1]Dept. of Neurosci., [2]Neurosci., Brown Univ., Providence, RI; [3]Brown Univ., Brown Inst. for Brain Sci., Providence, RI

Abstract: Dopamine (DA) activity is critical for learning and motivational functions, but details of how DA mediates flexible behaviors continues to be refined. The most intensely debated aspect of DA function involve *what* decision signals are relayed, and *how* these messages are communicated to post synaptic cells. One dominant theory asserts that DA encodes reward prediction error (RPE) signals that are uniformly broadcast to recipient regions. Indeed, the anatomy of DA axon arbors and spiking of midbrain DA cells are extensively reported to support this theory. Contrary to this notion, however, many studies demonstrate mismatches in the temporal pattern of DA release across striatal sub-regions. It is now increasingly evident that DA signaling is spatially and temporally heterogeneous, yet we do not understand the organizational principles or computational functions of heterogeneous DA decision signals.
We performed functional imaging of VTA axons in the dorsal striatum. DAT-cre mice received midbrain infusion of GCAMP6f, and implanted with imaging cannula or GRIN lenses for optical access into the striatum. After recovery from surgery, we imaged large-scale (~8-9 mm^2 area, using 1-photon microscopy) or fine scale (~10s of μms, using 2-photon microscopy) activity of DA terminals in the striatum during performance of tone- guided reward expectation tasks.
We report a novel set of spatio-temporal trajectories of DA axons across the dorsal striatum (DS). The spontaneous activity of DA axons is organized into irregular, but spatially and temporally continuous waves that extend across 8-9 mm^2 of mouse striatum. Further, reward immediately resynchronized activity into directional waves. Specifically, in pavlovian tone-reward association task, DA waves initiate in lateral DS and propagate medially, terminating in the anatomical equivalent of head of the caudate. By contrast, reward delivery in instrumental tasks that require mice to walk for distant rewards produce waves that initiated in the medial DS and propagate laterally. These results indicating that opponent trajectories of DA reward responses communicate decision signals for flexible behaviors. We consider different formulations of possible computational functions of pre-reward ramps in DA and subsequent waves.

Disclosures: A. Hamid: None. **M.J. Frank:** None. **C.I. Moore:** None.

Nanosymposium

109. Basal Ganglia Circuitry for Motivation and Reward

Location: SDCC 2

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 109.09

Topic: G.02. Motivation

Support: NIH Grant R01MH095953

Title: A derivative-like computations underlie dopamine prediction error coding based on dynamic sensory stimuli

Authors: *H. R. KIM[1], N. UCHIDA[2]
[1]Mol. and Cell Biol., Harvard Univ., Cambridge, MA; [2]Dept Mol. & Cell. Biol, Harvard Univ. Dept. of Mol. and Cell. Biol., Cambridge, MA

Abstract: It has been postulated that midbrain dopamine (DA) neurons signal reward prediction errors (RPEs), or the discrepancy between actual and predicted reward. The response of DA neurons has been characterized in relatively simple tasks such as classical conditioning paradigms in which a discrete cue predicts a future reward. Humans and animals move in space in the pursuit of reward. In these situations, dynamic sensory inputs, instead of discrete cues, may signal a gradual change in the proximity to a reward. How DA neurons respond in these situations remain unclear. Recent studies have shown that the DA concentration in the ventral striatum gradually ramps up as the animal approaches to a reward location. Such DA ramps have been proposed to encode a gradually increasing value of location as defined by an estimate of temporally discounted future reward, or 'state value'. However, the notion that DA activity represents 'value' contradicts the canonical view that DA activity represents RPE or temporal difference (TD) error, which is approximately the derivative of the value function. Gershman (2013) showed theoretically that if the value function conforms a particular shape (a convex function), DA ramps may result from a derivative-like RPE computation (i.e. TD error).
To distinguish these possibilities -- state value versus RPE, we devised a set of experimental tests using visual virtual reality in mice. We monitored dopamine axon activity from the ventral striatum using fiber photometry while mice ran on a 1-dimensional virtual corridor to obtain reward. We first show that DA ramped as the animal approached a reward location ($n = 6$, all $P < 0.01$). When a scene movement was decoupled from the animal's locomotion, a DA ramp occurred regardless of whether the animal ran or not during a scene movement. In some trials, the animal was teleported from an intermediate location to a location closer to the reward. The state value hypothesis predicts a step-wise change in DA activity, whereas the RPE hypothesis predicts a phasic excitation at the time of teleport. Our results showed a phasic activation of DA axons. Furthermore, the magnitude of these DA transients was larger when a teleportation of the same distance occurred closer to a reward location, consistent with a convex value function

(mean R = 0.26, n = 4, P < 0.05 for 3 animals, correlation between teleport position and magnitude of DA activity). These results indicate that DA ramp occurs due to dynamic sensory inputs that indicate the proximity to reward, and DA ramps are consistent with TD error, i.e. a derivative-like computation over a convex value function across space.

Disclosures: H.R. Kim: None. **N. Uchida:** None.

Nanosymposium

109. Basal Ganglia Circuitry for Motivation and Reward

Location: SDCC 2

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 109.10

Topic: G.02. Motivation

Support: NIDA ZIA-DA000587
NHMRC CJ Martin RG160338

Title: Dopamine transients contribute to model-based learning without endowing antecedent cues with value

Authors: *M. SHARPE[1,2], H. BATCHELOR[1], L. MUELLER[1], Y. NIV[3,2], G. SCHOENBAUM[1,4,5]
[1]Natl. Inst. on Drug Abuse, Baltimore, MD; [2]Princeton Neurosci. Inst., Princeton, NJ; [3]Dept. of Psychology, Princeton Univ., Princeton, NJ; [4]Departments of Anat. & Neurobio. and Psychiatry, Univ. of Maryland, Baltimore, MD; [5]Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: When something unexpected occurs in our environment, dopamine neurons in the midbrain exhibit a very brief increase in activity, referred to as a prediction error. Current theory restricts the dopamine prediction error to a signal reflecting errors in the prediction of future (or current) reward value, which is used to learn such value predictions. This learning is referred to as “model-free” because it drives simple increases or decreases in scalar value attributed to predictive cues but does not contain more detailed information about what exactly is expected to occur. This is in contrast to “model-based learning” which incorporates a detailed cognitive model of the relationships between events in the environment to predict upcoming rewards.
We have previously shown that the dopamine prediction error is capable of contributing to associations that facilitate model-based learning. To do this, we used a modified version of the sensory preconditioning procedure in rats. Sensory preconditioning involves first presenting two neutral cues in close succession such that a predictive association forms between them (e.g. A-B; termed a “preconditioning phase”). This association can then be revealed if cue B is paired with food reward (B-US), in that subsequently, rats will show an appetitive response towards cue A, showing that they inferred that cue A is likely to lead to reward by virtue of its prior association

with reward-predictive cue B. In a "blocking" procedure designed to reduce the likelihood that rats would form an association between A and B in the preconditioning phase, we found that introduction of a dopamine transient at the beginning of cue B facilitated the development of the learned association between cues A and B. This showed that the dopamine prediction error can facilitate learning that is not dependent on rewards or value predictions (Sharpe et al., 2017; *Nature Neuroscience*).
Here we extend these findings and show that the introduction of the dopamine transient facilitates the development of an association between A and B without endowing cue A with value. Specifically, while rats showed an enhanced appetitive response for cue A, they would not press a lever to receive presentations of cue A. This shows that cue A did not acquire value, which would have allowed it to support the acquisition of a novel instrumental response. Together, these data show that the dopamine prediction error acts as a model-based signal to drive associations between events without endowing cues with model-free value. These data challenge current conceptions of dopamine function and call for deeper investigation into how this signal is utilized at the circuit level.

Disclosures: M. Sharpe: None. **H. Batchelor:** None. **L. Mueller:** None. **Y. Niv:** None. **G. Schoenbaum:** None.

Nanosymposium

109. Basal Ganglia Circuitry for Motivation and Reward

Location: SDCC 2

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 109.11

Topic: G.02. Motivation

Support: NIH T32 DA024635-07
NIDA R01DA035443
NINDS R01NS08749
NIMH R01MH106972

Title: Nucleus accumbens acetylcholine modulates cue-evoked dopamine to regulate cue-motivated reward seeking

Authors: *A. L. COLLINS[1], T. AITKEN[3], V. GREENFIELD[3], S. B. OSTLUND[4], K. M. WASSUM[2]
[2]Psychology, [1]UCLA, Los Angeles, CA; [3]Univ. California, Los Angeles, Los angeles, CA; [4]Dept. of Anesthesiol. and Perioperative Care, UCI Sch. of Med., Irvine, CA

Abstract: Reward-predictive stimuli provide a major source of motivation for reward-seeking actions. Considerable evidence has implicated the nucleus accumbens core (NAc), and dopamine signaling therein, in the expression of a cue's motivational value, but less is known about the

contribution of the striatal cholinergic system to this behavior. Cholinergic interneurons (CINs) provide the main source of acetylcholine to the striatum, and their activity has been shown to be elevated in situations that discourage vigorous reward seeking and depressed in response to reward-predictive cues that encourage reward seeking. These data suggest that NAc CIN activity may gate the expression of cue-motivated behavior, having a suppressive effect when elevated and a permissive effect when depressed. We tested this with bidirectional optogenetic and chemogenetic manipulations of NAc CINs during a Pavlovian-to-instrumental transfer (PIT) test. CIN stimulation during CS^+ presentation was found to blunt the ability of a reward-predictive cue to invigorate reward seeking, whereas CIN suppression augmented such cue-motivated behavior. The effect of CIN stimulation was found to depend on the nicotinic acetylcholine receptors located on dopamine terminals, suggesting a potential mechanism of CIN regulation of cue-motivated behavior is via terminal regulation of dopamine release. In support of this, we found that that local blockade of NAc nicotinic receptors augmented cue-evoked dopamine release, measured with fast-scan cyclic voltammetry, during PIT. These data indicate that NAc CINs act as a gate over cue-motivated behavior by terminally regulating the degree to which reward-predictive cues can evoke dopamine release.

Disclosures: A.L. Collins: None. **T. Aitken:** None. **V. Greenfield:** None. **S.B. Ostlund:** None. **K.M. Wassum:** None.

Nanosymposium

109. Basal Ganglia Circuitry for Motivation and Reward

Location: SDCC 2

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 109.12

Topic: G.02. Motivation

Support: POCI-01-0145-FEDER-016428
NORTE-01-0145-FEDER-000013
POCI-01-0145-FEDER-007038

Title: Nucleus accumbens microcircuit underlying D2-MSN-driven increase in motivation

Authors: *C. SOARES-CUNHA[1], B. COIMBRA[1], A. DOMINGUES[1], N. VASCONCELOS[1,2], N. SOUSA[1], A. RODRIGUES[1]
[1]Life and Hlth. Sci. Res. Inst. (ICVS), Braga, Portugal; [2]Dept. de Física, Univ. Federal de Pernambuco, Recife, Pernambuco, Brazil

Abstract: The nucleus accumbens (NAc) plays a central role in reinforcement and motivation. Around 95% of the NAc neurons are medium spiny neurons (MSNs), divided into those expressing dopamine receptor D1 (D1R, D1-MSNs) and dopamine receptor D2 (D2R, D2-MSNs). Previous results showed that optogenetic activation of D2-MSNs increased motivation,

whereas inhibition of these neurons produced the opposite effect. Yet, it was unclear how activation of D2-MSNs affected other local neurons/interneurons or input terminals, and how this contributed for motivation. So, we combined optogenetic modulation of D2-MSNs with *in loco* pharmacological delivery of specific neurotransmitter antagonists to answer this remaining question. Optogenetic activation of D2-MSNs increases motivation in a progressive ratio task, and this effect relies on cholinergic-dependent modulation of dopaminergic signaling of VTA terminals, which requires D1R and D2R signaling in the NAc. *In vivo* electrophysiological studies showed that D2-MSN activation decreased ventral pallidum (VP) inhibitory tone over the VTA, increasing VTA dopaminergic activity. Importantly, we further found that optogenetic activation of D2-MSN-to-VP terminals was sufficient to recapitulate the motivation enhancement. In summary, our data suggests that optogenetic stimulation of NAc D2-MSNs indirectly modulates VTA dopaminergic activity, contributing for increased motivation. Moreover, both types of dopamine receptors' signaling in the NAc are required in order to produce the positive behavioral effects.

Disclosures: C. Soares-Cunha: None. **B. Coimbra:** None. **A. Domingues:** None. **N. Vasconcelos:** None. **N. Sousa:** None. **A. Rodrigues:** None.

Nanosymposium

110. Social Communication and Behavior

Location: SDCC 1

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 110.01

Topic: G.02. Motivation

Support: Autism Science Foundation
NIH Grant 1R01MH112846
NIH Grant 1R01NS091390

Title: Neuronal substrates of group competitive foraging in male mice

Authors: *S. W. LI, L. M. JOHNSON, Z. WILLIAMS
Massachusetts Gen. Hosp., Boston, MA

Abstract: Group social interactions play a prominent role in both human and animal behavior, and competitive foraging among conspecifics is an especially significant form of social interaction due to its prevalence in nature and its importance in determining survival and reproductive outcomes. Previous studies have revealed features of competitive foraging behavior that are common to most species, as motivated individuals pursue limited resources from the same food source area with simultaneous access. However, despite the importance of interactive social behavior and its dysfunction, its neuronal underpinnings are poorly understood. In this study, we developed a novel behavioral assay to observe the influences of social dominance

hierarchies on the competitive foraging behavior, which offers a versatile method to ordinally quantify competitive success among larger groups of animals. We also recorded single-unit neuronal activity within the dorsal medial prefrontal cortex (dmPFC) in male wild-type mice while they performed the task. Consistent with prior studies that characterized the tendency of dominant animals to tend to monopolize food more effectively than submissive counterparts, our behavioral data revealed that greater social dominance directly correlated with greater competitive success. Thus, these results demonstrated a relationship between dominance and competitive success that extends across a social group of familiar mice in a higher-order group setting. Neuronally, we found a subset of neurons in the dmPFC that selectively encoded the animals' hierarchical rank, the order in which they accessed the reward zone, and the reward amount. It is notable that individual dmPFC neurons differed in activity based on the subject's relative rank regardless of others' identity, while other neurons responded selectively to competitive success only before the recorded animal entered the reward zone - suggesting that dmPFC neurons may predict competitive outcomes based on information about competitors. This research provides insight into the social and neurobiological mechanics of dominance, competition, and success, allowing us to better understand group competitive behavior.

Disclosures: S.W. Li: None. **L.M. Johnson:** None. **Z. Williams:** None.

Nanosymposium

110. Social Communication and Behavior

Location: SDCC 1

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 110.02

Topic: G.02. Motivation

Title: *In vivo* responses to infant vocalizations in mouse paraventricular hypothalamus

Authors: *S. VALTCHEVA[1], R. C. FROEMKE[2]
[1]Skirball Inst., [2]Departments of Otolaryngology, Neurosci. and Physiol., NYU Sch. of Med., New York, NY

Abstract: Maternal care is critical for child survival and health (Dulac et al., 2014; Rilling and Young, 2014). Healthy maternal sensitivity is characterized by the ability to reliably recognize and respond to infant signals, initiating appropriate caregiving responses. Although motherhood is a dramatic natural experience, little is known about mechanisms and neural circuits supporting experience-driven plasticity in the maternal brain that enable recognition of infant cues and parental responses for childcare. Recent studies from our lab (Marlin et al., 2015; Mitre et al., 2016) showed that the neuropeptide oxytocin promotes long-term plasticity in mouse auditory cortex in vivo and in vitro, enhancing maternal behavior and leading to long-lasting changes in neural responses to infant sounds. Physiological release of oxytocin from the paraventricular nucleus (PVN) of the hypothalamus in response to infant vocalizations and other stimuli might

help induce recognition of different infant cues. However, it remains unknown which sensory stimuli activate PVN neurons under different contexts to trigger oxytocin release and enable appropriate maternal behaviors. Here we performed in vivo cell-attached and whole-cell recordings from PVN neurons in awake head-fixed mice. We used channelrhodopsin-assisted patching (Munoz et al. 2014) to record from optically-identified PVN oxytocin neurons in newly-maternal and virgin mice. We found that PVN neurons in dams show reliable responses to pup calls, but responses in PVN neurons of virgins were weak and less coherent. Our data suggest that PVN neurons are prewired to specifically respond to natural auditory stimuli with behavioral significance and these responses get selectively strengthened with the transition to motherhood to enable maternal care. Furthermore, we used cell-type specific retrograde labelling with rabies virus to identify inputs driving auditory responses in PVN oxytocin neurons. Finally, we mapped which populations of PVN neurons are activated by pup calls or suckling via the activity-dependent immediate early gene c-fos and if these neurons were magno- or parvocellular. Our results delineate a complex circuit refined by maternal experience for stimulating oxytocin release.

Disclosures: S. Valtcheva: None. **R.C. Froemke:** None.

Nanosymposium

110. Social Communication and Behavior

Location: SDCC 1

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 110.03

Topic: G.02. Motivation

Support: HD088411
MH106744
NARSAD

Title: Social transmission of maternal behavior by oxytocin

Authors: *I. CARCEA[1], N. LOPEZ-CARABALLO[2], R. OYAMA[2], J. M. MENDOZA-NAVARRO[3], D. RAMOS[2], M. OPENDAK[4], K. MOGI[7], T. KIKUSUI[7], A. C. MAR[5], R. SULLIVAN[6], R. C. FROEMKE[8]
[1]Skirball Inst., NYU Med. Ctr., New York, NY; [2]Neurosci., [3]Mol. Neurobio., [4]Child and Adolescent Psychiatry, [5]Neurosci. and Physiol., [6]Child and Adolescent Psych, New York Univ., New York, NY; [7]Azabu Univ., Sagamihara, Japan; [8]Otolaryngology, NYU Med., New York, NY

Abstract: Maternal care is profoundly important for mammalian survival, and maternal behaviors can also be expressed by non-biological parents after experience with infants. One critical molecular signal for maternal behavior is oxytocin, released by hypothalamic paraventricular nucleus (PVN) and enabling plasticity within maternal auditory cortex for

recognizing infant cues. To determine how these changes occur during natural experience, we continuously monitored homecage behavior of female virgin mice co-housed for days with an experienced mother and litter, synchronized with in vivo recordings from virgin PVN/oxytocin neurons. Mothers engaged virgins in maternal care, by ensuring that virgins were in the nest and self-generating episodes of isolated pup retrievals. These behaviors activated virgin PVN and gated behaviorally-relevant plasticity to improve behavior and cortical responses to pup distress calls. Thus maternal behavior can be learned by social transmission, and our results describe a mechanism for adapting the newly-maternal brain to infant needs via endogenous oxytocin.

Disclosures: I. Carcea: None. **N. Lopez-Caraballo:** None. **R. Oyama:** None. **J.M. Mendoza-Navarro:** None. **D. Ramos:** None. **M. Opendak:** None. **K. Mogi:** None. **T. Kikusui:** None. **A.C. Mar:** None. **R. Sullivan:** None. **R.C. Froemke:** None.

Nanosymposium

110. Social Communication and Behavior

Location: SDCC 1

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 110.04

Topic: G.02. Motivation

Support: SYNAPSIS FOUNDATION

Title: Oxytocin mediates the switch from passive to active defensive reactions in the central amygdala

Authors: *R. TRIANA-DEL RIO, D. SCHEGGIA, A. CIOBANU, C. HEGOBURU, E. VAN DEN BURG, R. STOOP
Ctr. De Neurosciences Psychiatriques-unil-Chuv, Prilly, Switzerland

Abstract: In rodents, different defensive behaviors can be expressed when facing dangerous situations: passive reactions (freezing), or active actions to escape from the threat (active avoidance). In addition, translational studies have shown that the basolateral amygdala (BLA) is necessary for the induction of escape behavior from imminent, but not distant threats, by inhibiting central amygdala (CeA) output. In the current project, we show that avoidance behaviors are modulated by excitatory projections from BLA to a specific population in the CeA that expresses the oxytocin receptor (OTR) and inhibit CeA output to the brainstem. By using the threat escaping test (TET), we categorized two populations of rats depending on their successful escape responses to imminent threats: high escapers (HE) and low escapers (LE). Then, we measured synaptic plasticity in BLA-induced excitatory transmission ex vivo onto different types of CeL neurons after TET training. By whole-cell patch-clamp recordings, we assessed the AMPA/NMDA ratios of pharmacologically and functionally identified OTR+ and OTR-neurons in CeA. The AMPA/NMDA ratio of OTR+ neurons in HE was higher than the one expressed by

OTR+ neurons in LE or unconditioned animals, demonstrating that postsynaptic plasticity in OTR+ cells is specifically induced in HE rats. Behaviorally, acute pharmacological modulation of OTR+ neurons in CeA mediated the switch from passive (freezing) to active (avoidance) responses to imminent threat in a shuttle box test, but did not induce avoidance memory. Importantly, OTR activation in CeA rescued avoidance behavior in animals whose BLA was down-regulated chemogenetically, reflecting the relevance of OTR signaling for switching between freezing and escape behavior. We are now running experiments to elucidate the underlying functional mechanism of OTR in CeA in avoidance learning. Furthermore, to assess the role of endogenous oxytocin in the different groups (HE, LE, unconditioned animals), we are measuring oxytocin by mass spectrometry in cerebrospinal fluid and blood. Current data support the necessity of oxytocin signaling in the CeA to modulate the plasticity of a circuit that switches fear behavior from passive to active responses.

Disclosures: R. Triana-Del Rio: None. **D. Scheggia:** None. **A. Ciobanu:** None. **C. Hegoburu:** None. **E. Van den Burg:** None. **R. Stoop:** None.

Nanosymposium

110. Social Communication and Behavior

Location: SDCC 1

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 110.05

Topic: G.02. Motivation

Support: Generalitat de Catalunya
Spanish Ministry of Economy and Competitiveness (grant FFI2016-78034-C2-1-P)
Marie Curie International Reintegration grant (PIRG-GA-2009-256413)
Fundació Bosch i Gimpera
Generalitat de Catalunya (2014-SGR-200)
Howard Hughes Medical Institute
Rockefeller University

Title: The effect of social reward in vocal learning: Testing an oxytocin-dependent mechanism

Authors: *C. THEOFANOPOULOU[1,2], D. LIPKIND[3], O. TCHERNICHOVSKI[4], C. BOECKX[5], E. D. JARVIS[6]
[1]Univ. De Barcelona, Barcelona, Spain; [2]Rockefeller Univ., New York, NY; [3]Dept Psychology, [4]Dept. of Psychology, Hunter Col., New York, NY; [5]Univ. de Barcelona, ICREA, Barcelona, Spain; [6]The Rockefeller Univ., New York, NY

Abstract: Social reward has been traditionally thought to enhance learning, with most experiments testing whether it makes learning faster or better. It remains unclear how social reward affects speech learning. We hypothesized that social reward affects a specialized

component of speech learning, vocal learning. We tested this hypothesis using the zebra finch, a vocal learning songbird species commonly used as a model for human spoken-language development. To do so, we developed a rapid vocal learning behavioral paradigm that attempted to dissociate social reward from vocal learning. Juvenile male zebra finches were first operantly taught to imitate a two-syllable song for 20 days. Then for the next 30 days they were exposed to two different contexts, switched every other day: an isolation context and a social reward context with an animal model of a bird they treated as their father, and a non-singing but live female bird. In these two different contexts, they were exposed to two very similar songs (played from speakers), comprised of two syllables, the same syllables of the song they had learnt, only differing by two semitones in the pitch of the second syllable. Five out of the six birds tested picked up the pitch of the song they heard in the social reward context, suggesting that fine aspects of vocal learning, like pitch, can be gated by social reward. In another experiment, we tested the effects of oxytocin, a neurotransmitter implicated in social reward, in their singing behavior. We administered oxytocin antagonist intranasally in males, singing in two social contexts: singing alone (undirected singing) or co-housed with a female and singing to attract her (directed-singing). We found that oxytocin-antagonist-treated males show a significant drop in the number of introductory notes in their directed love song. To test whether the oxytocin-antagonist crossed the blood-brain barrier, we delivered an oxytocin antagonist-SAP conjugate by intranasal, intracranial, or intramuscular routes, and found via immunocytochemistry (with a SAP-antibody) that the product crosses the blood-brain barrier only with intranasal and intracranial delivery, but not intramuscular delivery. Given the convergent behaviors and neural pathways for learned vocal communication in zebra finches and humans, our results imply that social reward could help gate learning of speech sounds and that oxytocin may modulate what is vocally produced. This finding also has implications for intranasal administration of oxytocin that is currently used in patients of autism, albeit so far to study other aspects of cognition.

Disclosures: C. Theofanopoulou: None. **D. Lipkind:** None. **O. Tchernichovski:** None. **C. Boeckx:** None. **E.D. Jarvis:** None.

Nanosymposium

110. Social Communication and Behavior

Location: SDCC 1

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 110.06

Topic: G.02. Motivation

Support: Ministry for Science and Education of Lower Saxony and the Volkswagen Foundation "Niedersächsisches Vorab"
Leibniz Association: Leibniz ScienceCampus Primate Cognition

Title: Transparent games: Investigating the influence of action visibility on social and economic decisions in human and macaque pairs

Authors: *S. MOELLER[1], A. M. UNAKAFOV[2,3,4], A. GAIL[1,4,5,2], S. TREUE[1,4,5,2], I. KAGAN[1,4]
[1]Cognitive Neurosci. Lab., German Primate Ctr., Goettingen, Germany; [2]Fac. of Biol. and Psychology, Georg-August-University, Göttingen, Germany; [3]Max Planck Inst. for Dynamics and Self-Organization, Göttingen, Germany; [4]Leibniz ScienceCampus Primate Cognition, Göttingen, Germany; [5]Bernstein Ctr. for Computat. Neurosci., Göttingen, Germany

Abstract: In classical game theory agents act simultaneously or sequentially. This approach has been utilized in recent social neuroscience studies. In many real-world scenarios, however, decisions are made in real-time, often with visibility of others' actions. This visibility has direct consequences for information availability about other's decisions: acting faster means foregoing this information while acting slower allows taking the other's choice into account. To investigate social decision-making under conditions of action visibility, termed 'transparent games', we created a setup in which two agents sit vis-à-vis separated by a transparent display sandwiched between two touchscreens. This allows agents to see each other and to interact with the same visual objects by reaching to them in the shared workspace. Here we compare behavior of human and macaque pairs in the classical coordination game 'Bach or Stravinsky'. In this game, each agent has a preferred target associated with larger monetary or liquid reward; one agent's high-value target is the other's low-value target. Importantly, selecting the same target adds equal bonus to the target value for both agents. Thus, joint selection increases reward for both agents, but the agent whose preferred target is selected earns more. This game has two Nash equilibria: the joint selection of either target; but selecting only one of these leads to unequal payoffs. Several human pairs converged to a Nash equilibrium, coordinating to select the same target. Most also adopted turn-taking strategies to equalize the payoffs: alternating between the two targets on a trial-by-trial basis, or switching between the targets in longer blocks. Macaques also tended to converge to a Nash equilibrium, after multiple sessions. But unlike humans, the leading monkey mainly insisted on his preference and the second monkey followed to gain the coordination bonus. Two monkeys also underwent training with a human confederate, who adhered to "turn-taking" by switching between own or monkey's preferred target in blocks. After several sessions, monkeys adopted largely optimal behavior, by coordinating their choices with the human counterpart. Blocking the view of the human's hand resulted in a coordination loss, implying that monkeys actively observed the human. After this training, when playing together, when both monkeys displayed similar reaction times, a turn-taking pattern emerged: each monkey led and followed in blocks. So far, this behavior occurred transiently and they mostly reverted to a leader-follower strategy. These findings demonstrate the importance of action visibility in emergence and maintenance of coordination.

Disclosures: A.M. Unakafov: None. **A. Gail:** None. **S. Treue:** None. **I. Kagan:** None.

Nanosymposium

110. Social Communication and Behavior

Location: SDCC 1

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 110.07

Topic: G.02. Motivation

Support: Stanford Neurosciences Institute NeuroChoice (RCM)
P50 DA042012 (RCM)
K08 MH110610 (BDH)

Title: MDMA's prosocial and rewarding effects require distinct neural mechanisms

Authors: *B. D. HEIFETS[1], J. S. SALGADO[2], M. D. TAYLOR[3], P. HOERBELT[3], J. J. WALSH[3], E. E. STEINBERG[3], J. SZE[4], R. C. MALENKA[3]
[1]Stanford Univ., Stanford, CA; [2]Anesthesiology, Perioperative & Pain Med., [3]Psychiatry & Behavioral Sci., Stanford Univ. Sch. of Med., Stanford, CA; [4]Dept. of Mol. Pharmacol., Albert Einstein Col. of Med., Bronx, NY

Abstract: The recreational drug ± 3,4-methylenedioxymethamphetamine (MDMA), also known as “ecstasy”, is well-known for generating feelings of empathy and closeness in human users, as well as feelings of euphoria and intoxication. MDMA’s prosocial effects and demonstrated ability to facilitate positive social interactions are believed to underlie its potential therapeutic efficacy in clinical trials where it has been used as an adjunct to psychotherapy for Post-Traumatic Stress Disorder. However, it is unknown whether MDMA’s prosocial effect and abuse liability have separable neural mechanisms. MDMA has a high affinity interaction with the serotonin transporter (SERT), leading to efflux of serotonin (5-HT) through a reverse-transport mechanism. Recent work in our laboratory suggests that 5-HT release in the nucleus accumbens (NAc) is important for social reward and social preference. We hypothesized that this mechanism could account for MDMA’s prosocial effect, but not its rewarding properties, in a mouse model recapitulating some of the major aspects of MDMA’s human effects. Using male and female adult C57/Bl6 mice, we identified a low dose of MDMA that elicited social preference in a 3-chamber assay, but not conditioned place preference or locomotor sensitization. A higher dose of MDMA produced all three behaviors. Using intracerebral drug microinjection into the NAc, and a conditional knockout of SERT, we find that MDMA’s interaction with SERT in the NAc is necessary to account for its prosocial effect, but does not alter its rewarding properties. MDMA-induced prosocial behavior was unaffected by disruption of oxytocinergic transmission in the NAc. We further found that MDMA’s prosocial effect, and its acute effect on excitatory synaptic transmission onto D1 and D2 medium spiny neurons (MSNs) of the NAc, require 5HTR1b activation. Ongoing experiments are detailing how MDMA modulates natural neural dynamics of D1 and D2 MSNs during social behavior. Our data suggest that the prosocial,

therapeutic effects of MDMA could potentially be recreated through a neural circuit-based mechanism that minimizes this drug's abuse potential.

Disclosures: B.D. Heifets: None. **J.S. Salgado:** None. **M.D. Taylor:** None. **P. Hoerbelt:** None. **J.J. Walsh:** None. **E.E. Steinberg:** None. **J. Sze:** None. **R.C. Malenka:** None.

Nanosymposium

110. Social Communication and Behavior

Location: SDCC 1

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 110.08

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Validation of a psychosocial chronic stress model in pigs

Authors: *S. MENNESON[1,2], S. MENICOT[1], A. FAU[1], V. NOIROT[2], P. ETIENNE[2], N. COQUERY[1], D. VAL-LAILLET[1]
[1]Inra Umr 1341 Numecan, Saint Gilles, France; [2]Laboratoires Phode, Albi Terssac, France

Abstract: Chronic stress is a major disorder and its repercussions on health are numerous (anxiety, depression, metabolic and gastrointestinal diseases, *etc.*). Its physiology and impacts have been widely studied in different rodent models, but models with a better face validity are still required. We attempted to describe and validate a chronic stress model associated with the onset of anxiety-depressive-like symptoms in pigs.
Thirty-six 11-weeks-old pigs have been exposed to a psychosocial stress consisting in social isolation as well as environment impoverishment and unpredictability for 7 weeks. Three groups have been studied: non-stressed, housed by pairs with environmental enrichments (S-), stressed (S+), and stressed treated with the antidepressant fluoxetine (S+F; 60mg per day, p.o). A contention test evaluating resignation was performed and salivary cortisol, glycaemia and the activity of intestinal microbiota were measured. Molecular biology and fMRI were also performed respectively to assess the modulation of monoaminergic systems and the cerebral responses to unknown olfactory stimulations in brain areas associated with cognition and depression.
After a month, non-stressed animals were significantly heavier than the stressed ones (S- = 52.0 ± 1.3 kg compared to S+ = 49.1 ± 0.6 kg, $p = 0.054$, and S+F = 48.0 ± 0.7 kg, $p = 0.008$). During contention, S+ animals tended to be more resigned than the others (average duration of an attempt to escape: S- = 3.34 ± 0.38 s and S+ = 2.25 ± 0.26 s, $p = 0.077$). They also had a higher level of salivary cortisol (S+ = 5.14 ± 1.58 ng/ml, S+F = 1.61 ± 0,23 ng/ml, S- = 2,04 ± 0.21 ng/ml; S-/S+: $p = 0.075$, S+F/S+: $p = 0.035$). Glycaemia was higher for stressed animals (S- = 4.76 ± 0.16 mmol/l compared to S+ = 5.33 ± 0.21 mmol/l, $p = 0.049$, and S+F = 5.43 ± 0.10 mmol/l, $p = 0.018$) while the microbiota activity was reduced (fecal short chain fatty acids: S-/S+, $p = 0.022$). fMRI study showed that stressed, compared to non-stressed animals, had a

significantly lower brain activity in the hippocampus during stimulation with new odors, which was also linked with a deregulation of the serotoninergic system in this zone (decreased level of 5HT1AR).
We have validated our psychosocial chronic stress model in pigs *via* a large panel of measurements usually used in preclinical studies for evaluating chronic stress and depression. As the pig is a privileged model to study nutrition and brain responses in health and neuro-digestive disorders, this model might be useful to explore therapeutic solutions particularly through nutrition.

Disclosures: S. Menneson: None. **S. Menicot:** None. **A. Fau:** None. **V. Noirot:** None. **P. Etienne:** None. **N. Coquery:** None. **D. Val-Laillet:** None.

Nanosymposium

110. Social Communication and Behavior

Location: SDCC 1

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 110.09

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CIHR Grant
Canada Research Chair Grant

Title: Sex-specific effects of social isolation on dorsal raphe serotonin neurons and behaviour

Authors: *K. INTSON[1], D. K. OLIVER[2], S. SIVAKUMARAN[2], S. K. POWER[2], D. SARGIN[5,6], E. K. LAMBE[2,3,4]
[2]Physiol., [3]Dept. of Obstetrics and Gynaecology, [4]Dept. of Psychiatry, [1]Univ. of Toronto, Toronto, ON, Canada; [5]Physiol. & Pharmacol., Univ. of Calgary, Calgary, AB, Canada; [6]Hotchkiss Brain Inst., Calgary, AB, Canada

Abstract: Early social isolation is a well-validated stressor linked to the induction of depression and anxiety in adulthood. In biomedical research, isolation following weaning in animals has persisted as an environmental model of those mood disorders. Previously, we characterized the behavioural profile of male mice socially isolated at weaning, and reported electrophysiological findings that their raphe neuron excitability is decreased (Sargin et al., Elife, 2016). Here, we investigated whether these findings were also true in female mice. In male socially-isolated mice, we found behavioural changes on tests relevant to a depressive-like state. By contrast, we observed either no change or opposite change in the female groups. We also found that dorsal raphe serotonin neurons in the socially-isolated females are more excitable than those in group-housed females, contrasting with our previous findings in male animals. Of note, dorsal raphe neurons from group-housed female mice had an increased propensity to enter depolarization block upon stronger stimulation. Ongoing experiments are examining a number of cell and

circuit factors that may contribute to these observations, i.e., membrane and action potential properties, regulation by 5-HT1A autoreceptors, and synaptic input. Based on our previous findings, we are particularly interested in the functional role of SK2 and SK3 channels by sex in the different housing conditions. These results highlight likely sex-specificity in the effects of chronic isolation on behaviour, and within the serotonergic system. They also highlight the importance of correcting the longstanding bias of only using male subjects in preclinical research.

Disclosures: K. Intson: None. **D.K. Oliver:** None. **S. Sivakumaran:** None. **S.K. Power:** None. **D. Sargin:** None. **E.K. Lambe:** None.

Nanosymposium

110. Social Communication and Behavior

Location: SDCC 1

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 110.10

Topic: G.02. Motivation

Support: Financial support from Hitachi, Ltd.

Title: An fMRI investigation on the positive consequences of being imitated by a virtual non-human agent

Authors: *H. SATO[1], T. NUMATA[2], Y. ASA[2], T. KOIKE[3], K. MIYATA[3], E. NAKAGAWA[3], M. SUMIYA[3], N. SADATO[3]
[1]Dept. of Biosci. and Engin., Shibaura Inst. of Technol., Saitama-shi, Japan; [2]Hitachi, Ltd., Ctr. for Exploratory Res., Hatoyama, Japan; [3]Natl. Inst. for Physiological Sci., Okazaki, Japan

Abstract: With advances in artificial intelligence, developing affective communication between humans and virtual agents is important. To this end, we are exploring various ways of applying human mimicry behavior, which may lead to successful interactions between humans and virtual agents. Specifically, does mimicry produce positive feelings in humans when interacting with a non-human agent that has a different appearance? A previous study on gaze-following by human-like and robot-like agents showed that agent behavior but not appearance affected participants' performance (Abubshait et al., 2017). While three systems are believed to be involved in being mimicked: (1) a perception-action matching system, (2) a self-other system, and (3) a reward system (Hale & Hamilton, 2017), we explored the underlying neural substrates to determine the dominant system when humans are being mimicked by virtual agents. We conducted an fMRI study where 39 participants performed a facial interaction task with a non-human virtual agent in the form of a chick. In the task, participants were instructed either to smile or to just look at the chick; immediately after, the chick displayed three kinds of expressions (happy, sad, or no expression). The timing and strength of the chick's expressions

were modulated by the degree of a participant's smile in the smile conditions. Each task was followed by a subjective rating of participants' current feelings on a 9-point scale (-4 = negative, 4 = positive). As expected, participants reported positive feelings only when they were imitated in the smile condition (Smile_Happy), indicating that the positive or congruent response by the chick is important in inducing positive feelings in participants. The fMRI results showed that being imitated in the smile condition, compared to other conditions (Smile_Happy - Smile_Sad&No > JustLook_Happy - JustLook_Sad&No), activated the rostral anterior cingulate cortex (ACC), precuneus/posterior cingulate cortex (PCC), superior occipital gyrus, lingual gyrus, and middle frontal gyrus. ACC and precuneus/PCC are suggested to be important in integrating social signals during affective mentalizing (Takahashi et al., 2015). Since mentalizing is closely related to self-other processing, involvement of the self-other system is implied. In summary, imitation of positive facial expressions by a non-human virtual agent with no morphological similarity to human faces can produce positive feelings in humans. In addition, this interaction involves a part of the affective mentalizing network. These results suggest the feasibility of using virtual agents with divergent appearances in interactions with humans.

Disclosures: H. Sato: 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.; Hitachi, Ltd. **T. Numata:** A. Employment/Salary (full or part-time):; Hitachi, Ltd. **Y. Asa:** A. Employment/Salary (full or part-time):; Hitachi, Ltd.. **T. Koike:** None. **K. Miyata:** None. **E. Nakagawa:** None. **M. Sumiya:** None. **N. Sadato:** None.

Nanosymposium

110. Social Communication and Behavior

Location: SDCC 1

Time: Sunday, November 4, 2018, 8:00 AM - 10:45 AM

Presentation Number: 110.11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NSERC Discovery Grant
Canada Research Chair in Developmental Cortical Physiology
NSERC USRA
CIHR

Title: Sex-specific behavioral consequences of chronic social isolation

Authors: *D. K. OLIVER[1], K. INTSON[2], S. SIVAKUMARAN[1], S. K. POWER[1], D. SARGIN[1], E. K. LAMBE[3]
[1]Physiol., [2]Pharmacol. Toxicology, [3]Dept Physiology, Dept Psychiatry, Dept OBGYN, Univ. of Toronto, Toronto, ON, Canada

Abstract: Mood disorders can be severe and debilitating and cost billions of dollars annually. Interestingly, mood disorders are diagnosed at a much higher rate in women compared to men, but the etiology of this sex-difference remains unknown. Early life social isolation is a recognized risk factor in the development of depression and anxiety. Chronic social isolation through single-housing is an emerging mouse model for these disorders. Previous work from our lab has demonstrated that post-weaning chronic social isolation induces a depressive-like phenotype that can be normalized through systemic blockade of SK channels (Sargin et al., Elife, 2016). Here, we investigate the behavioral effects of chronic social isolation on both male and female mice. We performed a battery of characterizations including measures of weight, activity level, and performance on tests of depressive-like and anxiety-like behaviour, observing a number of interactions between sex and social isolation. In both sexes, we found that social isolation had a greater impact on tests thought to measure depressive-like compared to anxiety-like behavior. Yet, we were surprised to see a number of baseline differences between group-housed males and females, with group-housed females more closely resembling single-housed males. Intriguingly, single-housing appeared to exert opposite behavioral consequences for male and female mice on several tests, raising some questions of interpretation. Ongoing work is examining the regulation and functional role of SK channels by sex in the different housing conditions. Our results show a baseline sex-difference, a sex-specific behavioral response to chronic social isolation and highlight the importance of sex-differences in animal models of mood disorders.

Disclosures: D.K. Oliver: None. **K. Intson:** None. **S. Sivakumaran:** None. **S.K. Power:** None. **D. Sargin:** None. **E.K. Lambe:** None.

Nanosymposium

111. Decision Making: Circuits and Computations

Location: SDCC 7

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 111.01

Topic: H.02. Human Cognition and Behavior

Support: University of Pennsylvania Translational Neuroscience Initiative
NIH Training Grant - BCN: T32-MH017168
NIH Training Grant - SIB: 5 T32 GM007517
NIH Grant 1-R37-MH-109728-01
University of Pennsylvania Wharton Behavioral Labs

Title: Exploring the mechanisms of adaptation to a changing reward task

Authors: *A. C. DALLSTREAM[1], M. L. PLATT[2], J. I. GOLD[3]
[2]Neurosci. Wharton Psychology, [1]Univ. of Pennsylvania, Philadelphia, PA; [3]Dept Neurosci, Univ. Pennsylvania, Philadelphia, PA

Abstract: The ability to make flexible decisions is crucial to everyday life but can differ considerably across individuals. This individual variability partly reflects certain clinical conditions, like depression, that can dramatically affect decision flexibility. Across a broad range of studies and tasks, people with depression have been shown to inadequately adjust to task-relevant changes, especially in response to negative events. Understanding this kind of maladaptive decision-making first requires a better understanding of how healthy individuals make flexible decisions in response to positive and negative events. To that end, this study uses a novel changing reward task to measure how healthy human participants adapt their decision-making to changing conditions.
For this task, participants are asked to pick one of two options on a screen with the objective of gaining reward tokens. One option is associated with a higher reward payout than the other. Outcomes can be gain or loss. Importantly, the location of the reward distributions changes based on experimenter-set hazard, or switch, rates. Previous work in our lab using inference tasks with this kind of change-point structure showed that human participants can adaptively adjust to different objective hazard rates, albeit with substantial individual variability and an overall bias towards assuming a more random, history-independent hazard rate environment. Here we focus on how these learning processes are affected by the relative gains and losses associated with the switching alternatives. We also ask participants to take depression and anxiety inventories to test the hypotheses that: 1) those with higher anxiety scores will tend to be overly adaptive, and 2) those with higher depression scores without high anxiety scores will tend to be insufficiently adaptive to changes in hazard rate, particularly for small reward differences, but will tend to be overly adaptive to larger negative reward outcomes. We also measure pupil diameter to test the hypothesis that changes in pupil-linked physiological arousal are associated with both change detection and the subjective value of the outcome. This study is designed to establish a rigorous psychophysical foundation for future work to more directly probe adaptive decision-making in people with depression and the underlying neural mechanisms in non-human primates.

Disclosures: A.C. Dallstream: None. **M.L. Platt:** None. **J.I. Gold:** None.

Nanosymposium

111. Decision Making: Circuits and Computations

Location: SDCC 7

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 111.02

Topic: H.02. Human Cognition and Behavior

Support: F30MH110084
Klingenstein-Simons
MQ
NARSAD
Whitehall

R01DA042038
R01NS104834

Title: Prefrontal projections to striatum persistently encode decision variables

Authors: *B. A. BARI[1], C. D. GROSSMAN[2], E. E. LUBIN[2], A. E. RAJAGOPALAN[2], J. I. CRESSY[2], J. Y. COHEN[3]
[2]Neurosci., [1]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: In dynamic environments, the brain relies on recent experience to make adaptive decisions. Despite the ubiquity of this phenomenon, the neural mechanisms of flexible decision making are poorly understood. Here, we identified how the medial prefrontal cortex (mPFC) persistently encodes value-based decision variables to generate flexible behavior. We developed a dynamic foraging task in head-restrained mice, adapted from one in monkeys (Sugrue, Corrado, Newsome, 2004; Lau, Glimcher, 2005; Tsutsui, Grabenhorst, Kobayashi, Schultz, 2016). Mice chose between two lick ports, each of which delivered reward with probabilities that changed over time. To obtain a generative understanding of behavior, we developed a simple action-value reinforcement-learning model which predicts that animals produce dynamic values for each action. We demonstrate that the relative value (difference between the two action values) predicted choice behavior and that the total value (sum of the two action values) predicted choice reaction time.
To determine how mPFC contributes to behavior, we reversibly inactivated it. This prevented mice from updating actions adaptively and increased reaction times, demonstrating the necessity of mPFC for flexible decision making. Experiments using other behavioral tasks revealed this effect was not due to a deficit in mapping decisions onto motor outputs (i.e., licking appropriately in either direction), nor was it due to slowing of movements. We next recorded action potentials from more than 3,000 neurons in ten mice performing the foraging task. We discovered highly dynamic persistent firing rates in the majority of neurons (more than 80%) that lasted for tens of seconds or longer. One population of these neurons dynamically encoded relative value, a control signal necessary for decision making. Another population of neurons encoded total value, predicting reaction times. Many neurons jointly encoded relative and total value. To test whether these persistent representations may inform action selection, we recorded action potentials from mPFC neurons projecting to dorsomedial striatum. We discovered that mPFC projections to striatum persistently represented relative value and total value. Thus, we define a specific mechanism for mPFC to drive flexible decision making.

Disclosures: B.A. Bari: None. **C.D. Grossman:** None. **E.E. Lubin:** None. **A.E. Rajagopalan:** None. **J.I. Cressy:** None. **J.Y. Cohen:** None.

Nanosymposium

111. Decision Making: Circuits and Computations

Location: SDCC 7

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 111.03

Topic: H.02. Human Cognition and Behavior

Support: CIHR
NSERC

Title: Ensemble mechanisms of conditional associative learning in primate prefrontal cortex

Authors: *M. L. LEAVITT[1], C. BOULAY[3], R. A. GULLI[4], L. DUONG[5], A. J. SACHS[6], J. C. MARTINEZ-TRUJILLO[2]
[2]Physiol. and Pharmacol., [1]Univ. of Western Ontario, London, ON, Canada; [3]Neurosciences, Ottawa Hosp. Res. Inst., Ottawa, ON, Canada; [4]Dept. of Pharmacol. and Physiol., Western Univ., London, ON, Canada; [5]Robarts Res. Inst., London Ontario, ON, Canada; [6]Neurosciences, Neurosurg., Ottawa Hosp. Res. Institute, Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Lateral prefrontal cortex (LPFC) is necessary for learning associations between arbitrary sets of stimuli and responses. Lesions to LPFC area 8a impair the ability of macaques to learn associations between more than one stimulus-response pair simultaneously (Petrides, 1986), and saccade direction selectivity in single neurons emerges more rapidly as macaques learn visuomotor associations (Asaad et al., 1998). However averaging across multiple instances of learning in single neuron recordings can mask underlying behavioral (Gallistel et al., 2004) and neuronal dynamics (Durstewitz et al., 2010). Thus the ensemble-level mechanisms of rule learning in macaques remain poorly understood. We investigated this issue by recording from microelectrode arrays implanted in macaque area 8a while subjects performed a visuomotor rule-learning task. At the beginning of each session a rule was generated by randomly selecting two of three possible color cues and one of four possible pairs of target locations. Each color cue was associated with one of the targets, for example blue = top, green = bottom. On each trial the animal was presented with one of the two color cues and both saccade targets, and learned the associations via operant conditioning. After reaching criterion (≥ 50 trials with ≥ 80% success) a new rule randomly generated from the pool of cue colors and target locations. Single neurons were selective for a diversity of task features, including previous trial outcome, cue color, saccade location, and interactions between these features. Importantly, selectivity for these features was strongly modulated by the animal's learning state. A logistic regression model predicting the subject's choice from ensemble firing rates showed that the log-odds of a correct prediction were positively correlated with the animal's success rate in 22 of 31 instances. This learning-related enhancement of choice coding gradually emerges within a trial and remains pronounced until saccade initiation. Learning also increased the temporal stability of choice

coding, as assessed using a cross-temporal decoding analysis. Our results demonstrate that the robustness of choice representation in LPFC neuronal ensembles correlates with learning-related fluctuations in behavioral performance.

Disclosures: M.L. Leavitt: None. **C. Boulay:** None. **R.A. Gulli:** None. **L. Duong:** None. **A.J. Sachs:** None. **J.C. Martinez-Trujillo:** None.

Nanosymposium

111. Decision Making: Circuits and Computations

Location: SDCC 7

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 111.04

Topic: H.02. Human Cognition and Behavior

Support: NIMH DIRP

Title: Neural coding of explore-exploit decisions in macaque prefrontal cortex

Authors: *V. D. COSTA[1], R. BARTOLO[2], A. R. MITZ[3], R. C. SAUNDERS[4], B. B. AVERBECK[2]
[1]Lab. of Neuropsychology, [2]NIMH/NIH, Bethesda, MD; [3]Lab. of Neuropsychology, NIH, Bethesda, MD; [4]Lab. Neuropsychol, NIMH, Bethesda, MD

Abstract: The explore-exploit dilemma describes agents decisions to forego immediate rewards and explore an unknown option, to learn if it is better than something they already experienced. Previous studies find that cortical regions encode exploratory choices when primates deviate from specified decision policies. However, without explicit task constraints it is difficult to tell if off policy-choices reflect exploration, decision noise, or poor learning. Novelty seeking is an evolved solution to the explore-exploit dilemma and of interest because it is computationally tractable. In the present study we combined high channel count single-unit recordings (768 electrodes; > 3000 neurons) from macaque prefrontal cortex (Area 9/46) with computational modeling of two monkeys' behavior on a multi-arm bandit task. The monkeys learned to choose between three, probabilistically rewarded images. Periodically one of the choices was replaced with a novel image the monkey had not yet associated with reward. This induced an explore-exploit tradeoff, forcing the monkeys to either explore the novel option or exploit their existing knowledge about the two remaining familiar options. We used a Partially Observable Markov Decision Process (POMDP) model to quantify the value of choosing each option based on the likelihood that choice would be rewarded on the current trial (immediate expected value) the overall richness of the reward environment (future expected value), and the relative difference in the total number of future rewards to be gained by choosing to explore or exploit novel versus familiar options (exploration bonus). Prefrontal neurons encoded each of these value computations, however, there were key differences in when these value signals were encoded.

We observed both tonic encoding of the immediate and future expected value of choices during the inter-trial interval, as well as phasic encoding of these values at the time of choice. Whereas, the exploration bonus tied to novelty seeking was only encoded after the monkeys chose to explore or exploit particular options. Prefrontal neurons also encoded the identity of the chosen stimulus and choice outcomes. This is important because the immediate expected value, stimulus identity, and outcome of choices defines the state and the state transition in the POMDP algorithm we used to derive choice values. Interestingly, choice location which was task irrelevant but important for action selection, was also strongly encoded. Overall, these results suggest that prefrontal cortex is important in resolving uncertainty about the value of unexplored, novel options to efficiently manage the explore-exploit dilemma.

Disclosures: V.D. Costa: None. **R. Bartolo:** None. **A.R. Mitz:** None. **R.C. Saunders:** None. **B.B. Averbeck:** None.

Nanosymposium

111. Decision Making: Circuits and Computations

Location: SDCC 7

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 111.05

Topic: H.02. Human Cognition and Behavior

Support: Google employment
NSF Collaborative Research in Computational Neuroscience (CRCNS) Program Grant IIS-120 7833
The John Templeton Foundation
Gatsby Charitable Foundation
the Wellcome Trust

Title: Representation learning for exploration and generalization in RL

Authors: *K. L. STACHENFELD[1,2], J. GEERTS[3], N. BURGESS[3], T. E. J. BEHRENS[4], M. M. BOTVINICK[5,3], S. GERSHMAN[6]
[1]Deepmind, London, United Kingdom; [2]Neurosci., Princeton Univ., Princeton, NJ; [3]Univ. Col. London, London, United Kingdom; [4]Oxford Univ., Oxford, United Kingdom; [5]DeepMind, London, United Kingdom; [6]Psychology, Harvard Univ., Cambridge, MA

Abstract: Humans and animals exhibit flexible, adaptive behavior by learning about the underlying structure of the world. An important question is therefore what kind of representational objectives encourage humans and other animals to encode this structure. This can be formalized as ``representation feature learning,'' in which the animal or agent learns to form state representations that preserve information potentially relevant to the downstream reinforcement learning (RL) process. Value and policy can then be approximated in the

simplified space of representation features, which enables faster RL. The representation features have important implications for the downstream RL process, particularly in terms of how this RL process trades off exploration and exploitation. We characterize a conflict between capturing on-policy transition statistics and capturing underlying transition structure absent the current policy. This manifests geometrically in the representation space as a tension between representing the task manifold and representing distance from goal locations. We also explore the relationship between features that comprise a good representation space for RL and features that comprise a good objective functions to motivate exploration. Recent work has shown that protovalue functions, previously suggested as representation features for RL, can also be used to learn options that facilitate exploration (Mahadevan & Maggioni, 2006; Machado et al., 2017). We explore this in the context of spatial representations and patterns of activity in hippocampus and entorhinal cortex. The representation learning formalism also provides a platform for the important distinction between different types of exploration: exploration within the RL process, intended to gain information about reward, and exploration within the representation learning process, intended to gain information about the environment structure. We will discuss how the similarities and differences between these exploration modes make different behavioral predictions within this framework.

Disclosures: **K.L. Stachenfeld:** A. Employment/Salary (full or part-time):; DeepMind, Google. **J. Geerts:** None. **N. Burgess:** None. **T.E.J. Behrens:** None. **M.M. Botvinick:** A. Employment/Salary (full or part-time):; DeepMind, Google, University College London. **S. Gershman:** None.

Nanosymposium

111. Decision Making: Circuits and Computations

Location: SDCC 7

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 111.06

Topic: H.02. Human Cognition and Behavior

Support: NSF-NCS 1533623
R21 11689422

Title: Locus coeruleus modulation of adaptive behavior and neuronal activity in anterior cingulate cortex

Authors: ***S. JOSHI**[1], J. I. GOLD[2]
[1]Dept. of Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [2]Dept Neurosci, Univ. Pennsylvania, Philadelphia, PA

Abstract: The locus coeruleus (LC)-norepinephrine (NE) system modulates physiological arousal via its extensive projections throughout the brain. LC function has also been linked to

adaptive behaviors via its association with pupil diameter. This link is thought to be mediated in part via the strong reciprocal connections between LC and the anterior cingulate cortex (ACC). However, little is known about how the LC-NE system modulates task-relevant patterns of neural activity in the ACC, and how that modulation relates to adaptive behavior. We explored the links between behavior, cortical activity, and arousal by making direct simultaneous measurements of neuronal activity in LC and in ACC while also monitoring pupil size in monkeys performing fixation and change-point/choice tasks.

We monitored pupil size while simultaneously recording from single, well-isolated LC neurons and groups of 2–19 well-isolated ACC neurons. Recordings were made while the monkey performed two tasks. For the first task, the monkey maintained stable fixation for 1–5 s. On a randomly selected subset of trials, a startling sound was played (beep trials). This design allowed us to assess the link between spontaneous and evoked changes in LC activation and ongoing ACC activity. For the second task, the monkey was required to make a saccade to one of two spatially separated but otherwise identical visual targets that were rewarded with a high or low probability, respectively. In a given block (200–400 trials), we fixed the probability ("hazard rate") of switching the identities of high and low probability targets at 0.1, 0.3, 0.5, 0.7 or 0.9. In a separate set of sessions, we delivered electrical microstimulation to LC while the monkey performed the choice task. An extended fixation epoch at the start of each trial allowed us to measure pupil size before the monkey made a choice saccade. The monkey typically performed 3–5 blocks per session.

The monkeys' behavior reflected the dynamic environment, including increased switching behavior for higher hazard rates. Accuracy on change-point and subsequent trials scaled with hazard rate. We identified the first direct link between LC activity and the subjective estimate of hazard rate. We also found evidence for a causal link between LC activation and switching behavior: electrical microstimulation of LC resulted in an increase in the monkeys' switching behavior, particularly at low hazard rates when the tendency to switch is low.

Taken together, these results suggest a role for the LC-NE system in modulating choice behavior in a dynamic environment. Ongoing work will assess the link between ACC neuronal activity and behavior.

Disclosures: S. Joshi: None. **J.I. Gold:** None.

Nanosymposium

111. Decision Making: Circuits and Computations

Location: SDCC 7

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 111.07

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01-EY014924
NIH Grant R01-DA038615

NIH Grant R01-DA037229
NIH Grant F32-MH102049
CV Starr Foundation
Howard Hughes Medical Investigators

Title: Exploration via disrupted sensorimotor control dynamics

Authors: *B. A. EBITZ[1], T. MOORE[3], B. Y. HAYDEN[2]
[1]Neurosci., Univ. of Minnesota, Minneapolis, MN; [2]Univ. of Minnesota, Saint Paul, MN;
[3]Neurobio., Howard Hughes Med. Inst. - Stanford Univ., Stanford, CA

Abstract: In variable and uncertain environments, solely "exploiting" rewarding options is not a sufficient strategy. Instead, intelligent decision-makers also "explore" alternatives to the most rewarding option. By doing so, they gather helpful information about the state of the environment, even if they forgo a few rewards in the gathering. Explore choices cannot be made with the same reward-maximizing computations that are used to make exploit choices because explore choices are orthogonal to reward value by definition. The mechanisms that underlie explore choices are likely to be essential for flexible decision-making and learning more generally, though they remain poorly understood. Therefore, we examined how sensorimotor decision-making differed across exploration and exploitation. To do this, we used a combination of methods, including psychophysics in humans and rhesus macaques, electrophysiology in rhesus macaques, and computational modelling. First, we developed a model of exploration and exploitation based on the dynamics of sequential choice behavior in humans and rhesus macaques. Next, we used this model to decode whether the monkeys were exploring or exploiting on single trials while we recorded from populations of neurons in the frontal eye fields (FEF): a part of the brain involved in directing attention and generating decisions. Although FEF neurons are classically choice-predictive (and were choice-predictive during exploitation), it was impossible to predict the choice before it was made during exploration. These results suggested that exploration coincided with a disruption of prefrontal sensorimotor control. However, if this were true, then it should be easier to perturb behavior during exploration (when control was disrupted) than during exploitation (when control was robust). We tested this hypothesis in two ways. First, we distracted humans and rhesus macaques with irrelevant information while they were exploring and exploiting. We found that both species were more distractible during exploration than exploitation. Second, we measured the behavioral effects of direct cortical stimulation while the monkeys were exploring and exploiting. We found that it was easier to perturb choices with direct cortical stimulation during exploration and that there was less choice-predictive information in evolving motor plans during exploration. Together, the results of these experiments were consistent with our hypothesis that prefrontal sensorimotor control is disrupted during exploration. This disruption would permit exploratory discovery via randomizing choice with respect to the prefrontal cortex's control policies.

Disclosures: B.A. Ebitz: None. **T. Moore:** None. **B.Y. Hayden:** None.

Nanosymposium

111. Decision Making: Circuits and Computations

Location: SDCC 7

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 111.08

Topic: H.02. Human Cognition and Behavior

Title: Deep exploration explains the tradeoff between directed and random exploration

Authors: *R. C. WILSON[1], J. D. COHEN[2]
[1]Univ. of Arizona, Tucson, AZ; [2]Princeton Univ., Princeton, NJ

Abstract: Many decisions involve a choice between exploring options that are unknown exploiting options we know well. Work across a variety of domains, has suggested that animals solve such "explore-exploit dilemmas" with a mixture of at least two exploration strategies - one driven by information seeking (directed exploration) and the other by behavioral variability (random exploration). Here we propose a unifying theory in which these two strategies *emerge* naturally from a kind of stochastic planning, known in the machine learning literature Deep Exploration.

In this model we assume that people make explore-exploit decisions by simulating a small number (as low as 1) random, but plausible, future experiences in order to approximate the expected value of taking different actions. Once these values are computed, the decision is made by picking the action with highest simulated value. Random exploration arises naturally from this model because the simulations are stochastic. More subtly, directed exploration arises from the details of how the simulated choices play out. Crucially, this model predicts a tradeoff between directed and random exploration that is mediated by the number of simulations used to compute values, with more simulations corresponding more directed and less random exploration.

We tested the predictions of Deep Exploration in a simple explore-exploit task known as the Infinite Bandits Task. In this task, subjects play a series of games in which they make repeated choices between two options - a fully known exploit option, corresponding to the best outcome they have seen so far, and an unknown explore option, corresponding to a random draw from a uniform distribution. By fitting a simple logistic model to human behavior in this task, we found a negative correlation between directed and random exploration, suggesting a tradeoff between directed and random exploration across the population.

In a follow up experiment, we found that this directed-random tradeoff could be manipulated within subject by changing reaction time (a proxy for the number of simulations used in each decision). Here subjects played the Infinite Bandits Task in two conditions with fast and slow inter-trial intervals (ITIs). Slowing the ITI caused subjects to respond more slowly, potentially allowing them to generate more simulations before making each choice. In line with them generating more simulations, we found an increase in directed and a decrease in random

exploration in the slow ITI condition.
Taken together, these findings provide strong initial evidence that humans use mental simulations based on Deep Exploration to solve the explore-exploit dilemma.

Disclosures: R.C. Wilson: None. **J.D. Cohen:** None.

Nanosymposium

111. Decision Making: Circuits and Computations

Location: SDCC 7

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 111.09

Topic: H.02. Human Cognition and Behavior

Title: Deep exploration accounts for stopping threshold and behavioral variability in an optimal stopping task

Authors: *S. WANG[1], A. GILLILAND[2,3], M. CALDER[4], R. C. WILSON[1,5]
[1]Psychology, [2]Neurosci. & Cognitive Sci., [3]Computer Sci., [4]James E. Rogers Col. of Law, [5]Cognitive Sci., Univ. of Arizona, Tucson, AZ

Abstract: Imagine you are on a road trip and looking to refuel. The next gas station is slightly overpriced, do you stop here to refuel or keep driving in the hopes of finding a lower price? This type of question is known as a "Stopping Problem", and whether one is trying to find the best price on gas or the best person to fill a
job, such problems occur frequently in daily life. Theoretical strategies for stopping problems have been extensively studied; but how humans solve these problems has received less attention. To investigate how humans solve optimal stopping problems, we designed a simple card game that we refer to as the Card Stopping Task. In this task, participants are presented with a row of 5 or 10 face down cards. Each card can have any number from 1 to 100 (uniformly distributed) which represents the
amount of reward available if that card is chosen. On each trial one of the cards is flipped and participants must decide whether to accept or reject this card. If they accept the card the game stops and they receive a points reward equal to the value of the accepted card. If they reject the card, the next card in the
sequence is flipped and the process repeats.
A key factor in the Card Stopping Task is the 'horizon', the number of face down cards remaining which plays a central role in deciding whether to stop. For example, if there are many gas stations in range, you may be more likely to pass the current gas station that is overpriced. But if your gas light is on, you wouldn't hesitate to stop and refuel.
Behavior in the Card Stopping Task can be quantified with two parameters: the stopping threshold, i.e. the card value above which people were more likely to stop than continue, and the decision noise, i.e. the variability in the stopping threshold. By fitting these parameters to the

behavioral data we found that as the horizon decreases (1) the stopping threshold decreases and (2) the decision noise increases. That is, as the game goes on, they are more likely to accept low valued cards, but are also more random in their choice.
This opposite horizon dependence for threshold and noise can be accounted for by a simple sampling model based on the idea of Deep Exploration (Osband et al., 2016). In this model, we assume that people make the accept/reject decision by simulating a small number (between 1 and 4) possible futures if they were to reject the card. Comparing this simulated outcome with the current card, they would stop if the current card is higher than the simulated outcome and continue otherwise. This model successfully accounts for the simultaneous decrease of threshold and increase of noise with horizon, suggesting a potential mechanism for how humans solve the optimal stopping problem.

Disclosures: S. Wang: None. **A. Gilliland:** None. **M. Calder:** None. **R.C. Wilson:** None.

Nanosymposium

111. Decision Making: Circuits and Computations

Location: SDCC 7

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 111.10

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R21HD088731

Title: Uncertainty-based adjustment of internal model during perceptual sequential decision-making

Authors: *J. FISER[1], A. KOBLINGER[2], J. ARATO[3]
[1]Dept. of Cognitive Sci., [2]Cognitive Sci., Central European Univ., Budapest, Hungary;
[3]Cognitive Sci., Central European Uninversity, Budapest, Hungary

Abstract: Repeated perceptual decision-making is typically investigated under the tacit assumption that each decision is an independent process or, at most, it is influenced by a few decisions made prior to it. We investigated human sequential 2-AFC decision-making under the condition, when more than one aspect of the context could vary during the experiment: both the level of noise added to the stimulus and the cumulative base rate of appearance (how often A vs. B appeared) followed various predefined patterns. In seven experiments, we established that long-term patterns in the context had very significant effects on human decisions. Despite being asked about only the identity of the present stimulus, participants' decisions strongly reflected summary statistics of noise and base rates collected dozens to hundreds of trials before. In addition, these effects could not be described simply as cumulative statistics of earlier trials: for example, a significant step change in base rate (a change point) could induce the same effect as a prolonged shift, while a gradual change did not induce any effect. As standard decision making

models cannot explain these results, we developed a hierarchical Bayesian model that simultaneously represented the priors over the base rates and a potentially non-uniform noise model over the different stimulus identities. Based on simulations with the model, we conducted additional experiments and found that when a change occurred in the context that could be captured equally well by adjusting one or another aspects of the model, humans chose adjusting the variable that was less reliable as defined by variability in the preceding extended set of trials. In general, regardless of the simplicity of a perceptual decision-making task, humans automatically develop a complex internal model, and in the light of a detected change, they adaptively alter the component of this model that is implicitly judged to be the least reliable one.

Disclosures: J. Fiser: None. **A. Koblinger:** None. **J. Arato:** None.

Nanosymposium

111. Decision Making: Circuits and Computations

Location: SDCC 7

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 111.11

Topic: H.02. Human Cognition and Behavior

Support: ONR Grant no. N00014-17-1-2041
NIH/NEI 019041

Title: Categorical perception: Probing top-down signaling and predictive coding

Authors: *B. MIN[1], D. P. BLISS[1], Y. ZHOU[2], D. J. FREEDMAN[3], X.-J. WANG[1]
[1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]The department of neurobiology, The Univ. of Chicago, Chicago, IL; [3]Neurobio. and Computat. Neurosci., Univ. of Chicago, Chicago, IL

Abstract: A fruitful theme of cognitive science is the interplay between analog feature-based perception and discrete categorization. There is early evidence of interactions between the two, called the “categorical perception” effect, in which category learning warps perception such that differences between objects that belong to different categories are accentuated (expansion) while differences within the same category are deemphasized (compression). This suggests a top-down influence from category-selective to feature-selective representations, but the underlying neural mechanisms have not been established. This topic has gained increasing relevance recently because it also provides a possible way to test the idea of predictive coding. To gain insight into this question, we examined data from behavioral categorization experiments in non-human primates, which helped constrain a biological neural circuit model of categorical perception. In the experiments, monkeys performed the same visual motion discrimination task before and after visual motion categorization training. Data analysis shows that, after categorization training, stimuli within the same category were more difficult to discriminate than before categorization

training, while the change for stimuli that belong to different categories was less pronounced, supporting compression without clear expansion. To explain this result, our neural circuit model incorporates key existing experimental findings and makes new predictions, including: (1) learned categories are encoded in the spiking activities of neurons in the lateral intraparietal (LIP) area, (2) neurons in the middle temporal area show graded encoding of stimulus motion directions and (3) neurons in the medial superior temporal (MST) area integrate top-down category and bottom-up motion direction information. This model proposes that it is mainly through the feedback projections from LIP to MST that learned categories induce categorical perception. We find that this prediction is largely consistent with recent single neuron recordings in the MST and LIP areas. Collectively, we show monkey experimental evidence for compression in visual motion and develop a neural circuit model that allows us to make experimentally testable predictions, thereby potentially elucidating the underlying neural mechanisms of categorical perception and its relationship with categorical decision making.

Disclosures: D.P. Bliss: None. **Y. Zhou:** None. **D.J. Freedman:** None. **X. Wang:** None.

Nanosymposium

111. Decision Making: Circuits and Computations

Location: SDCC 7

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 111.12

Topic: H.02. Human Cognition and Behavior

Support: NRF-2016R1C1B2016039
NRF-2016R1E1A2A01939949

Title: Intrinsic timescales of sensory integration during perceptual decision

Authors: *W. CHOI[1,2], S.-B. PAIK[1,2]
[1]Dept. of Bio and Brain Engineering, KAIST, Taejon-City, Korea, Republic of; [2]Program of Brain and Cognitive Engineering, KAIST, Taejon-City, Korea, Republic of

Abstract: Perceptual decision making is an act of choosing an option based on the evaluation of sensory information (Heekeren *et al.*, 2008). Computational models and neurophysiological evidence suggest that perceptual decision making reveals the detailed process by which sensory information is integrated (Ratcliff and McKoon, 2008). An important characteristic of perceptual decision is that there is substantial variation across observers' behavior (e.g. reaction time, accuracy, decision confidence), even when the stimuli presented are identical. Whether this inter-individual variability emerges from the intrinsic, subject-specific neural circuit (Kanai *et al.*, 2010) or from mere stochastic noise remains under debate. Given this, we hypothesized that perceptual decisions reflect the characteristics of each individual's neural circuit, resulting in a subject-specific process of information accumulation. Specifically, we expected that the time

course of sensory integration—the decision kernel—would be consistent within an individual but would vary across between individuals and that this diversity of decision kernel may be the origin of inter-individual variability in perceptual behavior. Thus, we hypothesized that the decision kernel of an individual determines the subject-specific characteristics of perceptual decisions. To validate our hypothesis, we performed a series of psychophysics experiments using a coherence-varying motion discrimination task. We precisely measured the decision kernel of each individual by estimating the response-triggered average of a stimulus. We observed a very consistent profile of the decision kernel in each subject, independent of stimulus dynamics. The observed kernel size varied greatly across subjects and accurately predicted the inter-individual variability in responses. Interestingly, the motion discrimination performance was maximized when the stimulus duration was matched to individuals' kernel size but was degraded when the stimulus duration differed from the kernel size. Furthermore, we found that subjects' characteristics of illusory motion perception were highly correlated with the observed intrinsic decision kernel. Therefore, our results suggest that an intrinsic sensory integration kernel is a critical factor for individuals' perception and that inter-individual variability arises from this subject-specific trait of the decision kernel.

Disclosures: W. Choi: None. **S. Paik:** None.

Nanosymposium

112. Physiological Methods: Optical Methodology

Location: SDCC 30B

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 112.01

Topic: I.04. Physiological Methods

Support: HHMI

Title: All-optical electrophysiology in behaving mice with enhanced near infrared voltage sensors

Authors: *Y. ADAM[1], J. J. KIM[1], S. LOU[1], Y. ZHAO[4], D. BRINKS[1], H. WU[1], M. A. MOSTAJO-RADJI[1], S. KHEIFETS[1], V. J. PAROT[1], S. CHETTIH[5], K. J. WILLIAMS[1], S. L. FARHI[1], L. MADISEN[6], C. D. HARVEY[5], H. ZENG[7], P. ARLOTTA[2], R. E. CAMPBELL[4], A. E. COHEN[3]
[2]Stem Cell and Regenerative Biol., [3]Chem. and Chem. Biol., [1]Harvard Univ., Cambridge, MA; [4]Univ. of Alberta, Edmonton, AB, Canada; [5]Harvard Med. Sch., Boston, MA; [7]Structured Sci., [6]Allen Inst. for Brain Sci., Seattle, WA

Abstract: A technology to record membrane potential from multiple neurons, simultaneously, in behaving animals will have a transformative impact on neuroscience research. Parallel recordings could reveal the subthreshold potentials and intercellular correlations that underlie

network behavior. Paired stimulation and recording can further reveal the input-output properties of individual cells or networks in the context of different brain states. Genetically encoded voltage indicators are a promising tool for these purposes, but were so far limited to single-cell recordings with marginal signal to noise ratio (SNR) *in vivo*. We developed improved near infrared voltage indicators, high speed microscopes and targeted gene expression schemes which enabled recordings of supra- and subthreshold voltage dynamics from up to 7 spiking neurons simultaneously in mouse hippocampus, *in vivo*. The reporters revealed sub-cellular details of back-propagating action potentials, correlations in sub-threshold voltage between multiple cells, and changes in dynamics associated with transitions from resting to locomotion. In combination with optogenetic stimulation, the reporters revealed brain state-dependent changes in neuronal excitability, reflecting the interplay of excitatory and inhibitory synaptic inputs. These tools open the possibility for detailed explorations of network dynamics in the context of behavior.

Disclosures: Y. Adam: None. **J.J. Kim:** None. **S. Lou:** None. **Y. Zhao:** None. **D. Brinks:** None. **H. Wu:** None. **M.A. Mostajo-Radji:** None. **S. Kheifets:** None. **V.J. Parot:** None. **S. Chettih:** None. **K.J. Williams:** None. **S.L. Farhi:** None. **L. Madisen:** None. **C.D. Harvey:** None. **H. Zeng:** None. **P. Arlotta:** None. **R.E. Campbell:** None. **A.E. Cohen:** None.

Nanosymposium

112. Physiological Methods: Optical Methodology

Location: SDCC 30B

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 112.02

Topic: I.04. Physiological Methods

Support: HHMI

Title: All-optical electrophysiology of cortical neurons *in vivo*

Authors: *L. Z. FAN[1], S. KHEIFETS[1], K. D. PIATKEVICH[3], E. S. BOYDEN[4], A. E. TAKESIAN[5], A. E. COHEN[2]
[2]Chem. and Chem. Biol., [1]Harvard Univ., Cambridge, MA; [3]Media Lab., [4]MIT, Cambridge, MA; [5]Otolaryngology, Massachusetts Eye and Ear, Boston, MA

Abstract: *In vivo* all-optical electrophysiology--simultaneous optical manipulation and optical recording of membrane potential of genetically defined neurons--would greatly facilitate studies of neuronal information processing. We developed a high-speed imaging system in which a spatial light modulator targets fluorescence excitation to multiple user-selected neurons to provide high-contrast 1-photon imaging in strongly scattering tissue. We co-expressed a channelrhodopsin actuator and an improved archaerhodopsin-based voltage indicator in superficial cortical neurons. Together, these advances enabled recording of membrane potential of cortical neurons up to 190 micrometers deep in behaving mice and revealed whisker stimulus-

evoked subthreshold events and spikes in layer 1 (L1) cortical neurons. Simultaneous optogenetic activation and voltage imaging of L1 neurons in vivo probed the intrinsic firing patterns of this little-understood neuronal population under several brain states, including anesthesia, quiet wakefulness, and attention. Paired optogenetic and whisker stimuli revealed the presence of near-simultaneous sensory-evoked excitatory and inhibitory synaptic inputs to L1. We will present detailed characterizations of the input-output properties of L1 neurons which suggest roles for these neurons in regulating attention. These tools promise to provide new insights into principles of neuronal information processing.

Disclosures: L.Z. Fan: None. **S. Kheifets:** None. **K.D. Piatkevich:** None. **E.S. Boyden:** None. **A.E. Takesian:** None. **A.E. Cohen:** None.

Nanosymposium

112. Physiological Methods: Optical Methodology

Location: SDCC 30B

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 112.03

Topic: I.04. Physiological Methods

Support: ERC starting grant MultiSense

Title: Whole-brain calcium imaging in zebrafish behaving in a visual-vestibular closed-loop virtual environment

Authors: *V. BORMUTH, G. MIGAULT, T. PANIER, H. TRENTESAUX, R. CANDELIER, G. DEBRÉGEAS
Lab. Jean Perrin, Univ. Pierre et Marie Curie, Paris, France

Abstract: During in vivo functional imaging, animals are head-fixed and thus deprived from vestibular inputs, which severely hampers the design of naturalistic virtual environments. To overcome this limitation, we developed a miniaturized ultra-stable one- and two-photon light-sheet microscope that can be dynamically rotated during imaging along with a head-restrained zebrafish larva. Rotating the microscope rotates the fish and stimulates the vestibular system while keeping imaging condition stable. The two-photon mode of the microscope gives at the same time high control over the visual stimulus by preventing the light-sheet to excite the visual system. We show cell resolved whole-brain activity responses while zebrafish larvae perform multisensory integration tasks in a closed-loop visual-vestibular virtual environment. This development allows now to study multisensory signal processing on the brain-wide circuit level and expands the potential of virtual-reality systems to explore complex multisensory-motor integration in 3D.

Disclosures: V. Bormuth: None. **G. Migault:** None. **T. Panier:** None. **H. Trentesaux:** None. **R. Candelier:** None. **G. Debrégeas:** None.

Nanosymposium

112. Physiological Methods: Optical Methodology

Location: SDCC 30B

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 112.04

Topic: I.04. Physiological Methods

Support: NSF Grant #1512794

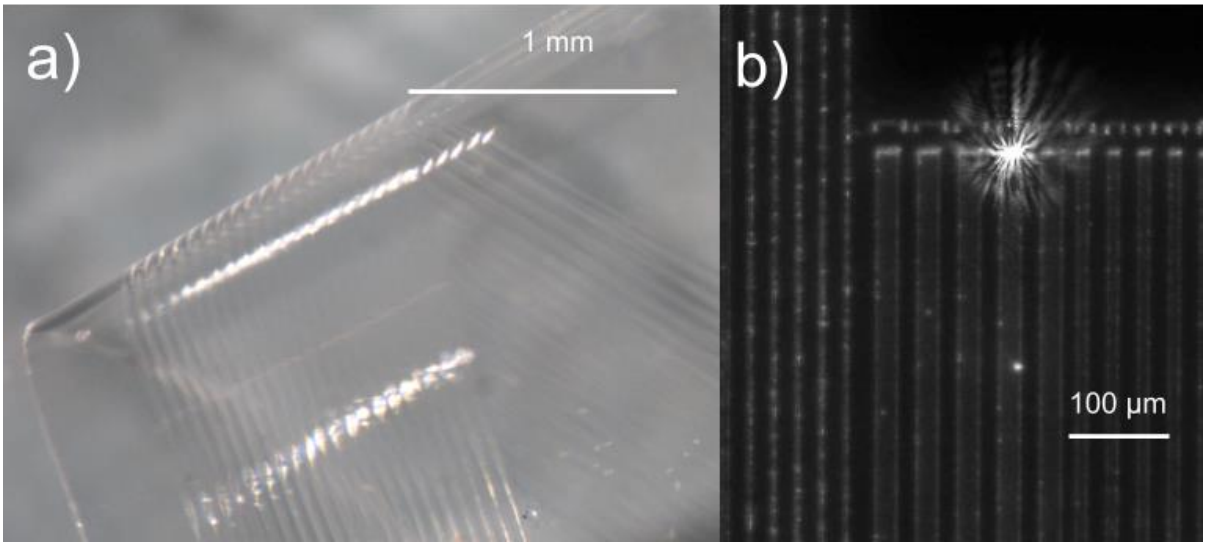
Title: Flexible, polymer waveguide arrays with integrated 90-degree input/output ports for high-resolution light delivery to the brain

Authors: *M. LASSITER, J. REDDY, M. CHAMANZAR
Electrical and Computer Engin., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Modern neuroscience experiments require light delivery deep into the brain. High spatial resolution is needed for optical stimulation and functional or structural imaging. Integrated photonic waveguides can deliver light to target locations within the brain tissue. While most presently available photonic waveguides use rigid dielectrics and semiconductors, flexible, biocompatible, polymer-based optical waveguides are preferred as they minimize tissue damage due to tethering forces and brain micromotions. Here, we demonstrate a flexible, high-density array of optical waveguides made in Parylene C and PDMS ($\Delta n = 0.239$). Both materials are biocompatible polymers, widely used as insulation and substrate layers in neural probes. Our devices utilize integrated micromirrors to achieve 90-degree input/output coupling for illumination volumes normal to the probe surface. We characterize optical loss in a high-density array of compact (5 - 30 μm) Parylene C waveguides at wavelengths of interest for optogenetics (460, 532, 633 nm), showing < 5 dB/cm (at 633 nm) propagation loss. We show a released 5 cm flexible waveguide array with individually addressable light output. A theoretical and experimental study is undertaken to demonstrate low bend losses in such flexible waveguide arrays. We will demonstrate functionality of released, flexible waveguide array neural probes integrated with compact, off-the-shelf laser diodes for stimulation of the opsin Chrimson in transgenic mouse tissue. Applications of this flexible architecture for minimizing tissue damage during chronic implantation and wrapping nerve fibers in the peripheral nervous system will be discussed.

a) Released Parylene C/PDMS waveguide array demonstrating flexibility.

b) Individual waveguide output in array demonstrating 90-degree illumination profile.



Disclosures: M. Lassiter: None. **J. Reddy:** None. **M. Chamanzar:** None.

Nanosymposium

112. Physiological Methods: Optical Methodology

Location: SDCC 30B

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 112.05

Topic: I.04. Physiological Methods

Support: NIH Grant U01NS090596

Title: An implantable neural imaging probe employing single-photon-avalanche-diode arrays

Authors: *J. CHOI[1], A. J. TAAL[2], C. LEE[3], K. KIM[2], L. MOREAUX[4], M. L. ROUKES[4], K. L. SHEPARD[2]
[1]Columbia Univ. in the City of New York, New York, NY; [2]Columbia Univ., New York, NY; [3]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [4]Caltech, Pasadena, CA

Abstract: Optical functional imaging, which employs optical reporters enabling single-cell monitoring of neuronal activity *in vivo*, has revolutionized neuroscience. However, even the most advanced microscopy techniques are fundamentally limited in achievable imaging depth given light scattering and absorption in neural tissue. If the components of an imaging system can instead be implanted into the brain tissue, then imaging at arbitrary depths becomes possible.

To realize this new paradigm, we have developed an implantable, shank-based image sensor array that, when combined with an external pulsed light source, enables recording in brain tissue with cellular resolution. Our neural imaging probes comprise 512 single-photon-avalanche-diode (SPAD) pixels distributed along two 120 μm-wide, 3.2 mm-long shanks. Fabricated in a complementary metal-oxide-semiconductor (CMOS) technology, the shanks are subsequently thinned to 80 μm by a post-processing back-etch of the substrate. By eliminating two constitutive elements of classical fluorescence microscopy, the spectral filter and the focusing lens, we can sufficiently downscale the system size to permit its implantation into brain tissue with minimal tissue displacement. Time-gated pixel circuitry enabling active-quenching during the optical excitation pulses, enables filter-less fluorescence lifetime imaging using time-correlated single-photon counting. In our implementation, lenses are replaced with pixel-level angle-sensitive grating structures, permitting compressive sampling of the tissue volume. This near-field diffraction approach is superior to other lens-less approaches that rely on far-field interactions (*i.e.*, requiring distances of order 200 μm) between a mask and the detector. We show that a sparsity-regulated optimization method enables three-dimensional volumetric image reconstruction and fluorescent lifetime imaging, while simultaneously suppressing correlated noise in highly-scattering tissue.

Disclosures: J. Choi: None. **A.J. Taal:** None. **C. Lee:** None. **K. Kim:** None. **L. Moreaux:** None. **M.L. Roukes:** None. **K.L. Shepard:** None.

Nanosymposium

112. Physiological Methods: Optical Methodology

Location: SDCC 30B

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 112.06

Topic: I.04. Physiological Methods

Support: Carnegie Mellon ProSEED Grant

Title: Flexible, monolithic micro-LED neural probes for optical stimulation and electrical recording

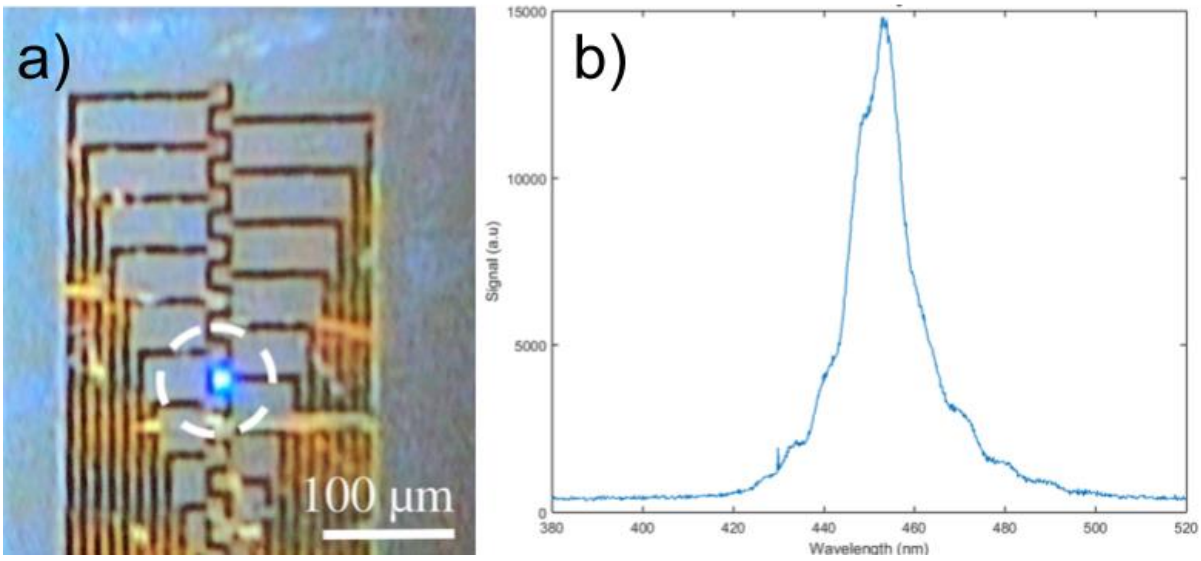
Authors: *J. REDDY, I. KIMUKIN, A. L. BARTH, E. TOWE, M. CHAMANZAR
Carnegie Mellon Univ., Pittsburgh, PA

Abstract: High spatiotemporal resolution patterned light stimulation deep into the brain is highly desired, especially for closed-loop optogenetic experiments. Flexible polymer neural probes allow optical and electrical access to the brain, while reducing tissue damage due to brain micromotions. Although micro-light-emitting diodes (LEDs) have been used for this purpose, the platform has been limited by existing microfabrication techniques requiring either a) integration of separately fabricated LEDs (200 μm x 200 μm) via flip chip bonding, limiting spatial

resolution, or b) monolithic fabrication on a rigid silicon shank. Here, we demonstrate that ultra-compact (22 µm x 22 µm) micro-LEDs can be monolithically co-fabricated with recording electrodes in a flexible, biocompatible Parylene C substrate. Parylene C is a polymer widely used in neural probes as a biocompatible and compliant substrate and insulation layer due to its conformal deposition and impermeability to biological species. Our presented architecture is capable of 1D or 2D individually-addressable array configurations. These micro-LEDs are realized in gallium nitride and designed to emit light at the wavelength of 453 nm, suitable for stimulation of Channelrhodopsin-2 (ChR2). An example is shown in the Figure below, where one LED is selectively turned on in a 1D array, and a bright blue emission is observed. Power density was measured as 12.4 mW/mm^2, significantly higher than the threshold of ChR2. We demonstrate the design and implementation of compact and high-density (400 LEDs per mm^2) 2D micro-LED and recording electrode arrays in a 3.5 cm long implantable neural probe realized on a flexible Parylene C substrate. We will discuss details of the fabrication process, as well as testing and validating the device performance in transgenic mice.

a) Microfabricated 1D micro-LED array consisting of compact (25 micron x 25 micron) GaN LEDs in a Parylene C substrate, with single device illuminated.

b) LED emission spectrum showing 453 nm center wavelength and 14 nm FWHM bandwidth, suitable for stimulation of ChR2.



Disclosures: J. Reddy: None. **I. Kimukin:** None. **A.L. Barth:** None. **E. Towe:** None. **M. Chamanzar:** None.

Nanosymposium

112. Physiological Methods: Optical Methodology

Location: SDCC 30B

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 112.07

Topic: I.04. Physiological Methods

Support: NIH R21DA044010

Title: Near-infrared fluorescent sensor for imaging catecholamine dynamics in the brain extracellular space

Authors: *A. G. BEYENE[1], K. DELEVICH[2], J. T. DEL BONIS-O'DONNELL[4], W. LIN[5], A. W. THOMAS[2], D. PIEKARSKI[7], S. J. YANG[8], L. E. WILBRECHT[3], M. P. LANDRY[6]
[1]Chem. Engin., [2]Psychology, [3]Psychology Dept, UC Berkeley, Berkeley, CA; [4]Chem. Engin., Univ. of California, Berkeley, CA; [5]Psychology, [6]Chem. and Biomolecular Engin., Univ. of California Berkeley, Berkeley, CA; [8]Chem. Engin., [7]Univ. of California, Berkeley, Berkeley, CA

Abstract: Aberrations in neuromodulatory signalling have been implicated in a wide range of neurological and psychiatric disorders. As a result, there is significant need for the development of tools that can image neuromodulator concentrations with high spatial and temporal resolution. Tools that enable the optical report of release, diffusion, and reuptake of modulatory neurotransmitters in extracellular space (ECS) are currently lacking in the neuroscience interrogative toolkit. To this end, we describe the design, characterization, and implementation of a nanoscale turn-on near-infrared (nIR) fluorescent reporter that allows assessment of changes in catecholamine levels in brain tissue. This technology makes use of a single walled carbon nanotube functionalized with single strand DNA (Kruss et al., 2014) that emit in the nIR at 1000-1300 nm. We first show *in vitro* data characterizing the specificity of the nanosensor for catecholamines dopamine and norepinephrine, and demonstrate the nanosensor's relative insensitivity to GABA, glutamate, and acetylcholine. In *ex vivo* brain slices containing the dorsal striatum, the catecholamine sensor is sufficiently sensitive to reflect differences in single pulse electrical stimulation intensity, driving variation in catecholamine release amounts in striatal tissue. Channelrhodopsin stimulation of midbrain dopaminergic vs. cortical glutamatergic terminals in the dorsal striatum (again in *ex vivo* slice preparation) demonstrates the nanosensor responds to dopamine terminal stimulation, but not glutamatergic terminal stimulation. Furthermore, dopaminergic terminal stimulation in the presence of nomifensine yields a prolonged nanosensor signal consistent with reuptake blockade. Together these data suggest nIR nanosensor signals can be driven by an increase in extracellular dopamine and demonstrate feasibility of imaging dopamine release in tissue. We discuss the implementation of all-atom molecular dynamics simulations to elucidate the physical-chemical phenomena underlying the dopamine sensing process, and stochastic simulations to evaluate how optical nanosensors may

capture transitions between phasic and tonic firing of dopaminergic neurons in the living brain. Finally, we describe how nanoparticle exciton engineering may be used to further tune sensor performance and design sensors suited to *in vivo* experimentation. Our experimental and theoretical results show that nIR neurotransmitter nanosensor constructs can relay information about neuronal signaling in the tissue-compatible nIR optical window with spatiotemporal scales relevant to behavioral experimentation.

Disclosures: A.G. Beyene: None. **K. Delevich:** None. **J.T. Del Bonis-O'Donnell:** None. **W. Lin:** None. **A.W. Thomas:** None. **D. Piekarski:** None. **S.J. Yang:** None. **L.E. Wilbrecht:** None. **M.P. Landry:** None.

Nanosymposium

112. Physiological Methods: Optical Methodology

Location: SDCC 30B

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 112.08

Topic: I.04. Physiological Methods

Support: NIH Grant U01MH109146
NIH Grant R01GM027750
Hermann Eye Fund
Endowed Chair AU-0009 Robert A. Welch Foundation

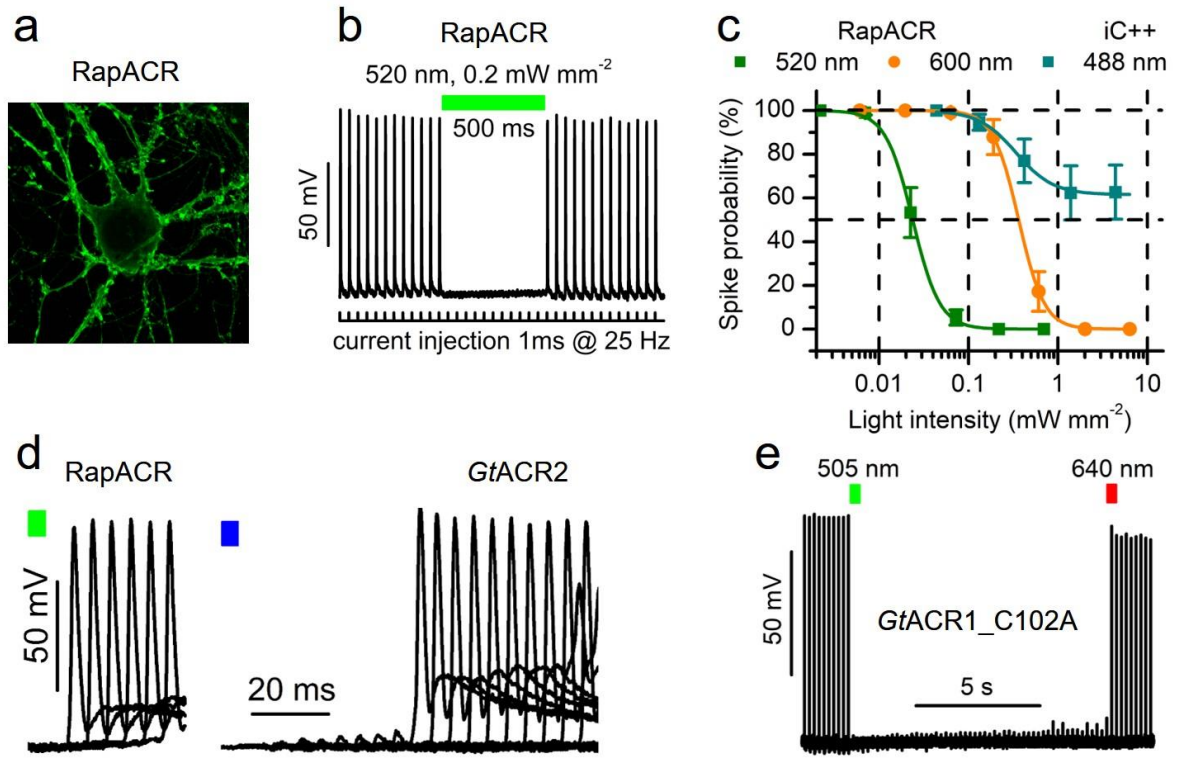
Title: Variant cryptophyte anion channelrhodopsins expand the time domain for neuronal silencing

Authors: *E. G. GOVORUNOVA[1], O. A. SINESHCHEKOV[1], R. HEMMATI[1], R. JANZ[1], O. MORELLE[2], M. MELKONIAN[2], G. K. S. WONG[3], J. L. SPUDICH[1]
[1]Biochem. & Mol. Biol., McGovern Med. Sch. UTHealth, Houston, TX; [2]Univ. of Cologne, Cologne, Germany; [3]Univ. of Alberta, Edmonton, AB, Canada

Abstract: Light control of neuronal function requires both activators and inhibitors (molecular tools that de- and hyperpolarize the membrane, respectively). Neural activation can be achieved by algal light-gated cation channels (cation channelrhodopsins, CCRs), but for inhibition only relatively inefficient tools have been available. Robust light-gated chloride conductance by recently discovered anion channelrhodopsins (ACRs) have opened the way to efficient neural membrane hyperpolarization. Our goal is to develop more powerful and versatile optogenetic inhibitors by algal transcriptome mining and molecular engineering of ACRs. The first two ACRs, found in the alga *Guillardia theta*, generate large photocurrents with a relatively slow decay, which provides potent spike inhibition but limits the time resolution of neuronal silencing. RapACR from *Rhodomonas salina* localized almost exclusively to the plasma membrane when expressed in cultured mouse hippocampal neurons (Fig. 1a). In neurons randomly picked without

inspecting their tag fluorescence, RapACR enabled complete photoinhibition of firing even with 600-nm light (80 nm to the red of its absorption maximum), whereas only ~40% neurons transduced with the second-generation engineered Cl^--conducting channelrhodopsin iC++ were inhibited at the wavelength of its maximal absorption (Fig. 1b & c). RapACR exhibits channel half-closing times below 10 ms and enables temporally precise silencing of neurons firing at frequencies at least up to 100 Hz, whereas the upper limit for the earlier used *Gt*ACR2 is only ~22 Hz (Fig. 1d). The mutation T111C further accelerates RapACR channel kinetics. An ACR mutant with a greatly extended lifetime of the channel open state acts as a bistable photochromic tool in mammalian neurons (Fig. 1e). These molecules extend the time domain of optogenetic neuronal silencing. Also their high conductances enable their use at low expression levels, which minimizes cellular stress and permits low light intensities to avoid tissue overheating in long-term experiments.

Figure 1



Disclosures: **E.G. Govorunova:** A. Employment/Salary (full or part-time):; McGovern Medical School UTHealth. Other; McGovern Medical School UTHealth. **O.A. Sineshchekov:** A. Employment/Salary (full or part-time):; McGovern Medical School UTHealth. Other; McGovern Medical School UTHealth. **R. Hemmati:** A. Employment/Salary (full or part-time):; McGovern Medical School UTHealth. **R. Janz:** A. Employment/Salary (full or part-time):; McGovern Medical School UTHealth. **O. Morelle:** A. Employment/Salary (full or part-time):; University of Cologne. **M. Melkonian:** A. Employment/Salary (full or part-time):; University of Cologne. **G.K.S. Wong:** A. Employment/Salary (full or part-time):; University of Alberta. **J.L. Spudich:**

A. Employment/Salary (full or part-time):; McGovern Medical School UTHealth. Other; McGovern Medical School UTHealth.

Nanosymposium

112. Physiological Methods: Optical Methodology

Location: SDCC 30B

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 112.09

Topic: I.04. Physiological Methods

Support: Health Research Council, New Zealand

Title: Long-term use of a fully implantable optogenetic device in rat studies

Authors: *F. B. CHEN[1], R. A. SMITHER[2], L. PARR-BROWNLIE[2], D. MCCORMICK[1], S. MALPAS[1], D. M. BUDGETT[1]
[1]Auckland Bioengineering Inst., Univ. of Auckland, Auckland, New Zealand; [2]Dept. of Anat., Univ. of Otago, Dunedin, New Zealand

Abstract: The potential of optogenetics becoming an alternative treatment option for neurological disorders is generating a huge amount of research interest. It is now important to understand the long-term therapeutic effects of optogenetic stimulation techniques. It is essential the optogenetic system is fully implantable because it enables long-term use and minimises the risk of infection. This work addresses the long-term performance of an implantable optogenetic device. The key aspect to longevity of operation for a fully implantable optogenetic device is moisture damage of the electronics over time in the body. It is therefore important to protect the device with a package that acts as an effective moisture barrier for at least 3 months, the minimum study period of this project. An optogenetic stimulation system has been designed at the University of Auckland that is fully implantable. The device consists of a light emitting diode light source, optical fibre for light delivery, and supporting electronics. The device produces sufficient light intensity for neural activation (1-32mW/mm^2), allows wireless control of light intensity and stimulation pattern, and uses wireless inductive power transfer technology. The size of the device (7.3 cm^3) is suitable for implantation in rats. For benchtop validation, three optogenetic devices were encapsulated using polyetheretherketone (PEEK) polymer hard case. The devices were being hydrated in saline solution at 38 ^{o}C. A humidity sensor was included in the device to measure the internal relative humidity. For animal studies, three devices were implanted in Wistar rats (300-500 g) expressing channelrhodopsin-2 (ChR2). The main body of the device was implanted in the abdominal cavity of the rats, and the fibre was tunnelled subcutaneously to the dorsal side of the neck so that light could be delivered to the brain. The results from benchtop monitoring the internal humidity of three optogenetic devices show that the PEEK package with desiccant can protect the optogenetic devices from water ingress for more than one year. The longest implantation of a fully functioning optogenetic device in rats

was one year and two months, and ongoing experiments show the polymer package is well-sealed. There is no report of the fibre breaking during or after surgery and the device did not alter behaviours. The remaining devices were implanted for five and eight months. This study has demonstrated the feasibility of a fully implantable optogenetic device that is functional for over 3 months for chronic optogenetic study. The immediate application is to support long-term optogenetic stimulation in animal studies.

Disclosures: F.B. Chen: None. **R.A. Smither:** None. **L. Parr-Brownlie:** None. **D. McCormick:** None. **S. Malpas:** None. **D.M. Budgett:** None.

Nanosymposium

112. Physiological Methods: Optical Methodology

Location: SDCC 30B

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 112.10

Topic: I.04. Physiological Methods

Support: NIH R01MH101218
ARO W911NF-12-1-0594 (MURI)
Kavli Institute of Brain Science

Title: A miniature CMOS multi-clamp amplifier for *in vitro*, *in vivo*, and scanning nanopipette intracellular recordings

Authors: *K. JAYANT[1], S. SHEKAR[2], R. YUSTE[2], K. L. SHEPARD[3]
[1]Electrical Engin. and Biol. Sci., [3]Electrcial Engin., [2]Columbia Univ., New York, NY

Abstract: Intracellular electrophysiological recordings from neurons is a high-fidelity neuroscience technique, required for the fundamental understanding of neuronal computation and function. Benchtop amplifiers perform such recordings in voltage- (VC) and current-clamp (CC) modes with high signal-to-noise ratio (SNR) but use discrete components, long cables, and are bulky and expensive. Furthermore, the size of these amplifiers limits the achievable operational bandwidth and scalability of these systems for many emerging intracellular electrophysiological experiments. Integrated-circuit-(IC-)based solutions can address these problems but have been difficult to realize owing to the large resistance values required in traditional designs and the resultant limits on dynamic range. Non-linear elements used in feedback can be used to overcome these challenges but are susceptible to variations in process parameters and temperature. Here, we present an 8.8 mm^2 multi-clamp amplifier integrated circuit (3.225 mm × 2.725 mm in a 0.18-µm complementary metal-oxide-semiconductor (CMOS) technology) for intracellular electrophysiology, with a power dissipation of only 7 mW (3.3 V supply) but delivering performance comparable to a rackmount instrument. The VC mode has a gain programmable up to 225 MΩ, pipette series resistance compensation programmable

up to 250 MΩ, and achieves 225 fA_{rms} in 5 kHz bandwidth. The CC mode achieves < 20μV_{rms} in 10 kHz bandwidth and has programmable current injection. Both modes have pipette capacitance compensation programmable up to 15 pF. We demonstrate the applicability of the microchip amplifier by performing optimally compensated sharp and whole-cell current-clamp recordings *in vitro* and *in vivo*; demonstrate a unique voltage-clamp circuit operating in negative feedback which achieves 100% compensation up to 20 MΩ; and show how the microchip amplifier can seamlessly switch between CC and VC modes in a scanning-ion-conductance microscope for imaging synapses.
Funding support: Kavli Institute of Brain Science, R01MH101218 and ARO W911NF-12-1-0594 (MURI).

Disclosures: K. Jayant: None. **S. Shekar:** None. **R. Yuste:** None. **K.L. Shepard:** None.

Nanosymposium

112. Physiological Methods: Optical Methodology

Location: SDCC 30B

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 112.11

Topic: I.07. Data Analysis and Statistics

Title: Statistical issues on two-photon imaging in macaques

Authors: *S. KLEIN[1], H. CHAN[1], C. YU[2], N.-S. JU[2]
[1]UC Berkeley, Berkeley, CA; [2]Peking Univ., Beijing, China

Abstract: Our goal was to measure, optimize and model the statistical properties of two-photon imaging in awake behaving macaques. The data had mainly 5 repeats of moving Gabor gratings with a fixed envelope. There were 12 orientations with 30 degree spacing, two sizes and two speeds all randomly intermixed with a variety of color stimuli. A given stimulus was on for 8 frames (one second in total) with a minimum of 14 blank frames between stimuli. The next stimulus was shown when fixation was accurate to within 1 degree. A total of 288 stimuli were presented in 17 minutes. Among the neurons we measured, 264 responded to gratings and 40 to colors. About 50% of those neurons had an average response to certain stimuli that was above twice the standard deviation of the noise. Numerous aspects of the calcium imaging had very different statistical properties than we expected. 1) The standard deviation of the responses to the 5 repeats of each stimulus was quite large with noise that was proportional to the response. For that reason we used the geometric rather than arithmetic mean. 2) It was common to find responses below the noise level even though the other four responses were large. For that reason we found that throwing out the lowest of the 5 responses for all stimuli was much better than the standard average. 3) The background level and its standard deviation differed from neuron to neuron by a factor of 3. This was measured by taking the mean of -5 to +1 frames relative to stimulus onset. This interval was chosen to avoid response to stimuli. 4) We devoted a major

effort into fitting the shape of the response to the onset and offset of the stimuli. We found strong variability across neurons. 4a) The simple aspect is that at stimulus offset there was a clear exponential decay with half-strengths ranging from 0.2 to 0.5 seconds. This speed was due to using calcium indicator GCaMP5. The decay time was relatively independent of stimulus and heavily dependent on neuron. 4b) Even more interesting were the onset properties. Some neurons had exponential looking onset but many also had a Gaussian aspect that we quantified by parameterizing the response with a combination of exponential and Gaussian fit. We also found frequent cases whereby in the final quarter second of stimulation there was a significant decrease in response. Thus we had to add that significant fatigue effect to our fitting program. Luckily when there was that effect it was common to the four different manipulations at each orientation. In summary, we find that 2-photon imaging not only enables one to study the properties of hundreds of neurons to hundreds of stimuli, it also enables one to gather rich data that captures subtle diverse properties of neural response.

Disclosures: S. Klein: None. **H. Chan:** None. **C. Yu:** None. **N. Ju:** None.

Nanosymposium

112. Physiological Methods: Optical Methodology

Location: SDCC 30B

Time: Sunday, November 4, 2018, 8:00 AM - 11:00 AM

Presentation Number: 112.12

Topic: I.07. Data Analysis and Statistics

Title: Fast and scalable calcium imaging data analysis with caiman

Authors: *A. GIOVANNUCCI, J. FRIEDRICH, P. GUNN, D. CHKLOVSKII, E. PNEVMATIKAKIS
Flatiron Institute, Ctr. for Computat. Biol., Simons Fndn., New York, NY

Abstract: Advances in fluorescent microscopy techniques have enabled imaging larger brain areas *in-vivo* with finer time resolution. The increased availability and volume of calcium imaging data calls for formal automated analysis methods and reproducible pipelines to extract the relevant information from the recorded movies, like locations of the imaged neurons in the imaged Field of View (FOV) and their activity in terms of raw fluorescence and/or neural activity (spikes). Typical steps in the processing pipelines are: i) Motion correction, where the FOV at each data frame (image or volume) is registered against a template to correct for motion artifacts due to the finite scanning rate and existing brain motion, ii) source extraction where active and possibly overlapping sources are extracted and their signals are separated from each other and from the background neuropil signals, and iii) activity deconvolution, where the neural activity of each identified source is deconvolved from the dynamics of the calcium indicator. Here we present CaImAn, an open source library for calcium imaging data analysis that provides methods for the standard pre-processing problems of motion correction, source extraction and

neural activity deconvolution. CaIman operates in an optimized and automated way that requires minimal user intervention, and can be run on standard computing infrastructure (i.e. a laptop) or on high performance computing clusters. CaImAn improves upon the state of the art to provide speed, scalability, and automated methods for component quality screening. It is suitable for two-photon and one-photon imaging, enables fast (real-time) online analysis on streaming data, and includes methods for automated component tracking across multiple days. We apply CaImAn to a set of one- and two-photon in-vivo datasets, where we show that analysis can be done with faster than real-time speed on modern systems. To benchmark the performance of CaImAn we collect and make available a corpus of ground truth annotations from multiple labelers on a large set of mouse two-photon datasets. Our results demonstrate that CaImAn reliably achieves near-human performance in detecting locations of active neurons, in an efficient and automated way.

Disclosures: A. Giovannucci: None. **J. Friedrich:** None. **P. Gunn:** None. **D. Chklovskii:** None. **E. Pnevmatikakis:** None.

Nanosymposium

184. Postnatal Neurogenesis: Molecular Mechanisms

Location: SDCC 1

Time: Sunday, November 4, 2018, 1:00 PM - 3:30 PM

Presentation Number: 184.01

Topic: A.02. Postnatal Neurogenesis

Support: This study was supported by the Janet and Edward Gildea Charitable Foundation
This study is the result of work supported with resources and the use of facilities at the Edith Nourse Rogers Memorial Veterans Hospital, Bedford, Massachusetts, United States of America

Title: The impact of age on cell proliferation in hippocampal subgranular zone in adult mouse brain

Authors: *M. SEMENOV[1,2], O. L. BORDIUK[1], K. SMITH[1]
[1]GRECC, Edith Nourse Rogers Mem. Veterans Hosp., Bedford, MA; [2]The Dept. of Pathology and Lab. Med., Boston Univ. Sch. of Med., Boston, MA

Abstract: The mouse brain retains an ability to produce hippocampal granule neurons during the mouse's entire lifespan. It is thought that new neurons are involved in such processes as learning, new memory formation, stress response, and emotion. These neurons are produced in the subgranular zone (SGZ) located on the inner surface of the granule cell layer in the dentate gyrus. In our study, we characterize how the production of neural precursors for new hippocampal neurons changes in the mouse brain relative to age. We detected 4,500 proliferating cells with the average local cell density of 67 in the SGZ of 30 day old mice. These numbers decrease by 40% to about 2,650 and 37 correspondingly in the brain of 60 day old mice. During

the next two months the decrease becomes 20% per month, and during the following 8 months the decrease is 12-15% per month. After 12 months it becomes less than 10% per month. In total, from the age of 30 days to the age of 2.5 years the number of proliferating cells in the SGZ decreases 64 fold from 4,500 to 70, and the local cell density decreases 38 fold from 67 to 1.8. Based on the measurements we calculated that in the SGZ, 1.67 million new precursors are produced during this time period. Given that the SGZ contains presumptive neural stem cells and using the published estimates of the number of such cells in the SGZ, we calculated that each presumptive neural stem cell produces on average only 33 progenies between the age of 2 months and 2.5 years. We propose a model that mechanistically explains changes in neurogenesis relative to age and discuss possible implications of this new model on the development of new therapies based on the induction of neurogenesis in the SGZ.

Disclosures: M. Semenov: None. **O.L. Bordiuk:** None. **K. Smith:** None.

Nanosymposium

184. Postnatal Neurogenesis: Molecular Mechanisms

Location: SDCC 1

Time: Sunday, November 4, 2018, 1:00 PM - 3:30 PM

Presentation Number: 184.02

Topic: A.02. Postnatal Neurogenesis

Support: R01AG033570
R01AG033570-S2

Title: Persistence of adult hippocampal neurogenesis through aging and cognitive dysfunction

Authors: *O. LAZAROV[1], K. MUSARACA[1], A. BHERI[1], N. KIM[2], D. BENNETT[2], M. TOBIN[1]
[1]Dept Anat & Cell Biol, Univ. Illinois, Chicago, Chicago, IL; [2]Rush Med. Ctr., Chicago, IL

Abstract: Adult neurogenesis is a highly regulated process and can be affected by numerous different processes including environmental factors, age, behavior, and hormone levels. Neural stem cells are maintained in discrete regions of the brain, namely the subventricular zone and the subgranular layer of the dentate gyrus in the hippocampus. The process of adult neurogenesis is intricately involved in learning and memory and is often altered in neurological disease. It is well established that adult hippocampal neurogenesis declines with age and has been demonstrated in rodents, non-human primates, and adults. However, it is highly controversial to what extent neurogenesis occurs in adult humans with recent data demonstrating that it is both non-existent beyond adolescence and that it continues well throughout aging into the eighth decade of life. Here we demonstrate that not only is adult hippocampal neurogenesis persistent through the tenth decade of life but we also show that it is detectable even in patients with mild cognitive impairment and Alzheimer’s disease - two disease processes known to have deficits in adult

hippocampal neurogenesis. In a cohort of 18 patients with a mean age of 90.6 years (range 78.7-99.4) neural stem cells (nestin-positive), proliferating cells (PCNA-positive), and immature neurons (DCX-positive) were detected in all 18 patients. Furthermore, there are regional changes in expression of the cells with nestin-expressing cells localizing in the more anterior portions of the hippocampus while PCNA- and DCX-expressing cells are more evenly distributed along the entire anterior/posterior axis of the hippocampus. Thus, our results suggest the detectable existence of hippocampal neurogenesis throughout life in the human brain. Future experiments should determine the physiological function of new neurons in the human brain during adulthood and aging.

Disclosures: O. Lazarov: None. **K. Musaraca:** None. **A. Bheri:** None. **N. Kim:** None. **D. Bennett:** None. **M. Tobin:** None.

Nanosymposium

184. Postnatal Neurogenesis: Molecular Mechanisms

Location: SDCC 1

Time: Sunday, November 4, 2018, 1:00 PM - 3:30 PM

Presentation Number: 184.03

Topic: A.02. Postnatal Neurogenesis

Support: NIH Pre-doctoral Training in Molecular Biology, NIH-T32-GM008730
NIH grant AG 037942
NIH grant NS 076291

Title: Alzheimer amyloid beta peptide as a driver of cell-cycle re-entry and aneuploidy in neurons

Authors: *N. ELDER, A.-J. WANG, H. POTTER
Rocky Mountain Alzheimer's Dis. Ctr., Univ. of Colorado, Anschutz Med. Campus, Denver, CO

Abstract: Although levels of aneuploidy in the normal adult brain are very low, previous studies from our and other labs have shown that in patients with neurodegenerative diseases including frontotemporal dementia, Alzheimer's (AD), and Huntington's disease, neurons are often aneuploid, including for both chromosomes 12 and 21. Our lab has shown that mutant genes causing neurodegenerative disease induce aneuploidy in human and transgenic mouse neurons and in transfected cell models. Specifically, amyloid beta (Aβ), the central molecule in AD pathogenesis, is a driver of aneuploidy through direct inhibition of microtubule dependent motor proteins. The resulting aneuploid cells are prone to apoptosis, which may drive neuronal death in these disorders. Although aneuploidy has been observed in the brain, how it arises remains largely unknown. One possible mechanism for generating aneuploid neurons is cell-cycle re-entry. The majority of mature neurons no longer undergo cell division, but research has shown that Aβ can cause neurons to re-enter the cell cycle. However, only entrance into G1 has been

quantified in Aβ-treated neurons. With this exploratory research we aim to determine whether neurons that have re-entered the cell cycle proceed from G1 phase through mitosis to produce aneuploid daughter cells. In our experiments, we used live confocal imaging of human hippocampal neurons transfected with GFP tagged histone H2B and treated with Aβ. This allowed us to visualize mitosis and the possible production of aneuploid daughter cells. All experiments were repeated at least twice, the scientists interpreting the results were blinded to conditions, and both negative and positive controls were used where appropriate to ensure scientific rigor. We found that after Aβ-mediated cell cycle re-entry, some neurons entered mitosis, and a small percentage divided. This is the first evidence that mature neurons treated with Aβ *in vitro* can re-enter the cell cycle and complete mitosis and supports the idea that cell cycle re-entry may serve as one mechanism by which aneuploidy arises in neurons in Alzheimer's.

Disclosures: N. Elder: None. **A. Wang:** None. **H. Potter:** F. Consulting Fees (e.g., advisory boards); NeuroEM Scientific Advisory Committee, Fortress Biotech Consultant.

Nanosymposium

184. Postnatal Neurogenesis: Molecular Mechanisms

Location: SDCC 1

Time: Sunday, November 4, 2018, 1:00 PM - 3:30 PM

Presentation Number: 184.04

Topic: A.02. Postnatal Neurogenesis

Title: Tau phosphorylation at AT8 pathological site during brain development

Authors: *D. TUERDE[1,2], K. FURUSAWA[2], T. TAKASUGI[2], T. KIMURA[2], S. ISHIGAKI[1], K. ANDO[2], G. SOBUE[1], S.-I. HISANAGA[2]
[1]Grad. Sch. of Med., Nagoya Univ., Aichi, Japan; [2]Dept. of Biol. Sci., Tokyo Metropolitan Univ., Tokyo, Japan

Abstract: Tau is a microtubule (MT) -associated protein (MAP), stabilizing MTs in axon of neurons and then supporting neuronal network in healthy brains. In contrast, in Alzheimer`s disease (AD) brains, tau is abnormally phosphorylated more than 40 sites, and aggregated into neurofibrillary tangles (NFTs) in neurons undergoing degeneration. Among many pathological phosphorylation sites, phosphorylation at the AT8 site has been most frequently used for diagnosis of AD. The AT8 site comprises two phosphorylation sites at Ser202 and Thr205, although some literatures demonstrate it as a consequence of triple phosphorylation at Ser199, Ser202 and Thr205. However, it is not completely understood yet how the AT8 reactivity is generated in AD brain and how it contributes to AD development. Tau hyperphosphorylation at specific residues occurs not only in AD brains but also in fetal and early postnatal brains. We found that AT8 is one of highly phosphorylated sites in fetal and neonatal stages of mouse, and it suddenly disappear during 2 to 3 weeks after birth when neuronal circuit is established.

Moreover, hypothyroidism delayed tau dephosphorylation at the AT8 site specifically about 3 days. These results indicate direct relationship between neuronal development and AT8 site phosphorylation. We think it important to understand the role of AT8 phosphorylation in neuronal maturation at a molecular level. Here, we examined the effect of overexpression of wild-type human tau or AT8 site mutants, both unphosphorylatable Ala and phosphomimetic Asp in developing neurons. Our study would shed light on a physiological role of the AT8 phosphorylation in tau and also provide more efficient approaches to tackle AD.

Disclosures: D. Tuerde: None. **K. Furusawa:** None. **T. Takasugi:** None. **T. Kimura:** None. **S. Ishigaki:** None. **K. Ando:** None. **G. Sobue:** None. **S. Hisanaga:** None.

Nanosymposium

184. Postnatal Neurogenesis: Molecular Mechanisms

Location: SDCC 1

Time: Sunday, November 4, 2018, 1:00 PM - 3:30 PM

Presentation Number: 184.05

Topic: A.02. Postnatal Neurogenesis

Support: University of Notre Dame

Title: A mouse model of Kabuki syndrome to study neurogenesis and hippocampal function

Authors: *M. ALAM[1], M. DURHAM[1], K. HALDAR, 46556[2]
[1]Biol. Sci., Univ. of Notre Dame, Notre Dame, IN; [2]Biol. Sci., Univ. of Notre Dame, NOTRE DAME, IN

Abstract: Neurogenesis is a complex cellular process in brain development. It occurs not only in the embryonic and perinatal stage but continues throughout the life in the subventricular zone and dentate gyrus of the hippocampus in mouse models. Impaired neurogenesis affects multiple brain functions such as cognition, memory and intellectual ability and is associated with many neurodegenerative disorders. Epigenetic pathways that include modifications of histone proteins such as methylation and acetylation are emerging as an important regulator of neurogenesis. However, despite recent progress, a comprehensive understanding of how histone modifications regulate neurogenesis remain elusive. Here, we utilize Kabuki Syndrome (KS) as a model to understand epigenetic mechanisms underlying neurogenesis. KS is caused by heterozygous loss-of-function mutations in one of two genes: lysine-specific methyltransferase 2D (*KMT2D*) or lysine-specific demethylase 6A (*KDM6A*). A mouse model carrying loss of function mutation in *Kmt2d* showed reduced histone H3 lysine 4 (H3K4) trimethylation and decreased levels of neuronal progenitor cells in the hippocampus of diseased mice. The length and branching of dendrites originating from neuronal progenitor cells in dentate gyrus were also affected. Data will be presented on the molecular signatures, transcriptional network and functional pathways associated with impaired hippocampal neurogenesis in KS. The study provides important

insights into understanding the molecular mechanisms by which epigenetic factors control neurogenesis and develops strategies to stimulate neurogenesis and treat intellectual disability in KS as well as more prevalent neurological conditions.

Disclosures: M. Durham: None. **K. Haldar:** None.

Nanosymposium

184. Postnatal Neurogenesis: Molecular Mechanisms

Location: SDCC 1

Time: Sunday, November 4, 2018, 1:00 PM - 3:30 PM

Presentation Number: 184.06

Topic: A.02. Postnatal Neurogenesis

Support: NIH grant NS097887
NIH grant NS094144

Title: Autophagy mediated lipid metabolism sustained mTORC1 activation in TSC1-deficient neural stem cells

Authors: *C. WANG, M. HAAS, S. YEO, F. YANG, J. WEN, S. CHEN, T. OKAMOTO, P. SARMA, D. PLAS, J.-L. GUAN
Univ. of Cincinnati, COM, Cincinnati, OH

Abstract: While mTORC1 negatively regulates autophagy in cellular homeostasis, much less is understood on how autophagy impacts on mTORC1 signaling in vivo. By creating and analyzing a mouse model with double conditional knockout of *Tsc1* and an essential autophagy gene *Fip200* in neural stem/progenitor cells (NSCs), we describe mechanisms by which autophagy controls mTORC1 hyper-activation and the neurodevelopmental lesions of Tuberous Sclerosis Complex (TSC) including defective NSC maintenance, differentiation and tumorigenesis. We show that TSC-deficient cells require autophagy to maintain mTORC1 hyper-activation under energy stress conditions. Autophagy of lipid droplets (i.e. lipophagy) is used as an alternative energy source to fuel mitochondrial OXPHOS, ATP generation, and mTORC1 during energy stress. *In vivo*, targeting lipophagy or its downstream catabolic pathway reverses defective phenotypes caused by Tsc1-null NSCs and blocks their tumorigenesis in mouse models. These results reveal a cooperative function of selective autophagy in coupling energy availability with TSC pathogenesis, providing potential new therapeutic strategies to benefit TSC patients driven by mTORC1 hyper-activation.

Disclosures: C. Wang: None. **M. Haas:** None. **S. Yeo:** None. **F. Yang:** None. **J. Wen:** None. **S. Chen:** None. **T. Okamoto:** None. **P. Sarma:** None. **D. Plas:** None. **J. Guan:** None.

Nanosymposium

184. Postnatal Neurogenesis: Molecular Mechanisms

Location: SDCC 1

Time: Sunday, November 4, 2018, 1:00 PM - 3:30 PM

Presentation Number: 184.07

Topic: A.02. Postnatal Neurogenesis

Support: EU H2020, THYRAGE
ANR collaborative project (French Research Agency) OLGA
DIM-cerveau, Ile-de-France Region,

Title: Tight control of thyroid hormone availability regulates neural stem cell fate in the adult mouse brain

Authors: *S. REMAUD[1], C. LUONGO[2], A. SÉBILLOT[1], J.-D. GOTHIÉ[1], K. LE BLAY[1], L. BUTRUILLE[1], H. HEUER[3], B. DEMENEIX[1]
[1]CNRS MNHN 7221, Paris, France; [2]Univ. of Naples Federico II, Napoli, Italy;
[3]Universitätsklinikum Essen (AöR), Univ. Duisburg-Essen, Essen, Germany

Abstract: T3, the active form of thyroid hormones (THs), regulates adult neural stem cell (NSC) fate in the subventricular zone (SVZ), one of two neurogenic niches in the adult mammalian brain. We previously demonstrated that (i) THs favour NSC commitment toward a neuronal fate and (ii) that, in contrast, a transient lack of THs promotes SVZ-derived oligodendrogenesis, allowing complete myelin repair in a mouse model of demyelination. A crucial question is to determine how control of TH availability regulates adult NSC determination towards a neuronal or a glial fate. First, we characterized expression of multiple TH signalling components in the adult mouse SVZ (two-month-old males) by immunohistochemistry and RTqPCR on NSCs and their progeny purified by flow cytometry. Two TH-transporters, MCT8 and OATP1C1, are highly expressed in NSCs and neuronal progenitors (NPCs), but not in oligodendrocyte progenitors (OPCs). In contrast, OPCs, but not NPCs, express high levels of the TH-inactivating deiodinase, Dio3, thus protecting OPCs from T3-neuralizing effects. Second, we determined the effects of modulating TH availability on NSC commitment using neurosphere assays. T3 increases NPC-genesis at the expense of OPCs while a thyroid receptor antagonist (NH3) counteracts the neuralizing effects of T3. Lastly, we analysed effects on the neuron/glia ratio of a strong reduction in TH availability using the double *Mct8/Oatp1c1* KO mice (DKO). In the adult SVZ of DKO mice, we observed a significant decrease in numbers of both proliferating progenitors and NPCs, without any effect on OPC numbers. Taken together, these *in vivo* and *in vitro* data demonstrate that high intracellular TH availability is favoured in NSCs and NPCs by expression of transporters, receptors and absence of Dio3, thus permitting NSC commitment towards NPCs in the adult mouse SVZ. In contrast, in OPCs, Dio3 expression reduces T3 availability thereby promoting glial determination. The absence of both MCT8 and OATP1C1

induces a strong reduction of SVZ-derived NSCs and NPCs. Our work could have numerous applications in stem cell research for neurodegenerative diseases, by providing a better understanding of the mechanisms underlying TH availability in the control of glia-neuron cell-fate choice.

Disclosures: S. Remaud: None. **C. Luongo:** None. **A. Sébillot:** None. **J. Gothié:** None. **K. Le Blay:** None. **L. Butruille:** None. **H. Heuer:** None. **B. Demeneix:** None.

Nanosymposium

184. Postnatal Neurogenesis: Molecular Mechanisms

Location: SDCC 1

Time: Sunday, November 4, 2018, 1:00 PM - 3:30 PM

Presentation Number: 184.08

Topic: A.02. Postnatal Neurogenesis

Support: MCINN BFU2014-57494
MCINN SAF2017-85717-R
CSC fellowship to L. Li

Title: SoxD genes in the control of adult hippocampal neurogenesis

Authors: *A. V. MORALES[1], L. LI[1], M. CIORRAGA[1], C. CÓRDOBA[1], V. ZINCHUK[1], E. CALLEJA[1], S. NICOLIS[2], V. LEFEBVRE[3]
[1]Inst. Cajal (CSIC), Madrid, Spain; [2]Univ. of Milano–Bicocca, Milano, Italy; [3]Cleveland Clin. Lerner Res. Inst., Cleveland, OH

Abstract: Adult neurogenesis, a process of generating functionally integrated neurons throughout life, constitutes an important strategy to generate plasticity in the mature central nervous system. In the adult subgranular zone (SGZ) of the hippocampus, neural stem cells (NSCs) generate new granule cells via a well characterized cell lineage that includes a succession of intermediate progenitor cells (IPCs). The majority of NSCs in the SGZ niche are in a reversible state of quiescence, a situation that protects the cells from DNA damage and the population from depletion. However, little is known, of how the transition from quiescence to an active mitotic state is regulated.
Genes of the Sox family of transcription factors are essential during neurogenesis. In the developing spinal cord, Sox5 controls cell cycle exit of neural progenitors and dorsal interneurons specification counteracting the Wnt signalling pathway (1,2). More recently, we have characterized that both Sox5 and Sox6 are expressed in the majority of NSCs and in IPCs in the SGZ of adult mouse hippocampus.
Using inducible conditional mutant mice to specifically delete Sox5 and Sox6 expression in the adult neurogenic niches, we have determined that Sox5 and Sox6 are required for radial glial-like NSCs proliferation and for the generation of new neurons in the adult SGZ. In neurospheres

cultures obtained from the hippocampus of those mutant mice, we have established that Sox5 and Sox6 are not required for the proliferation of IPCs. However, in neurosphere experiments in a quiescence state promoted by BMP4, the absence of Sox5 blocked the possibility of transition from the quiescence to the proliferating state induced by removal of BMP4 and addition of FGF2. Moreover, looking for the possible molecular mechanism controlled by Sox5 and Sox6 we have determined that proneural gene Ascl1 (required for the NSCs to transit from quiescence to activation) is severly downregulated in the radial glial-like NSCs of the SGZ in Sox5 or Sox6 adult mutant hippocampus.
In summary, Sox5 and Sox6 are required in NSCs for the transition from the quiescence to the activated mitotic state, an step essential to promote neurogenesis in a tightly regulated manner throughout adulthood.
1.Martínez-Morales, P.L., Quiroga, A.C., Barbas, J.A and Morales, A.V. (2010) Sox5 controls cell cycle progression in neural progenitors by interfering with Wnt/β-catenin pathway. *EMBO reports.* 11(6):466-472.
2. Quiroga, A. C., Stolt, C. C., Diez del Corral, R., Dimitrov, S., Perez-Alcala, S., Sock, E., Morales, A. V. (2015). Sox5 controls dorsal progenitor and interneuron specification in the spinal cord. *Dev Neurobiol, 75*(5), 522-538.

Disclosures: A.V. Morales: None. **L. Li:** None. **M. Ciorraga:** None. **C. Córdoba:** None. **V. Zinchuk:** None. **E. Calleja:** None. **S. Nicolis:** None. **V. Lefebvre:** None.

Nanosymposium

184. Postnatal Neurogenesis: Molecular Mechanisms

Location: SDCC 1

Time: Sunday, November 4, 2018, 1:00 PM - 3:30 PM

Presentation Number: 184.09

Topic: A.02. Postnatal Neurogenesis

Support: The Japan Society for the Promotion of Science
Fellowship from the Paul F. Glenn Center for Biology of Aging Research
The Kanae foundation
The Paul G. Allen Family Trust
The JPB Foundation
The Dolby Foundation
The Helmsley Trust

Title: Roles of nuclear lamin in adult neurogenesis and brain aging

Authors: *T. TODA[1,2], T. A. BEDROSIAN[1], N. NOVARESI[1], L. HU[1], S. GHASSEMZADEH[1], S. G. YOUNG[3], F. H. GAGE[1]
[1]Lab. of Genetics-Gage, Salk Inst. For Biol. Studies, LA Jolla, CA; [2]Paul F. Glenn Ctr. for Biol.

of Aging Res. at the Salk Inst., La Jolla, CA; [3]Mol. Biol. Institute, Dept. of Medicine, and Dept. of Human Genet., UCLA, Los Angeles, CA

Abstract: The adult hippocampus hosts neural stem cells (NSCs) that give rise to new neurons throughout the life span. Long-term maintenance of neurogenic property in the adult hippocampus is crucial for retaining structural and functional plasticity, and this neurogenic capability is declined during aging. However, underlying mechanisms still remain elusive. Here we show that deterioration of nuclear lamina organization in adult NSCs (ANSCs) underlies loss of neurogenic properties in the adult hippocampus during aging. We found that LaminB1, a nuclear lamina component, is highly expressed in ANSCs and immature adult-born neurons, but its levels decline during aging. Precocious reduction of LaminB1 by inducible-knockout of Lmnb1 in ANSCs transiently increases proliferation and neurogenesis, but depletes neurogenic properties at later times, suggesting that depletion of LaminB1 in ANSCs recapitulates reduced neurogenic property during aging. Furthermore, depletion of LaminB1 in ANSCs recapitulates age-related anxiety-like behavior, suggesting that LaminB1-directed nuclear architecture may play a critical role in brain aging. These findings reveal that nuclear lamina organized by LaminB1 plays essential roles for maintaining and balancing neurogenic properties and imply an indispensable contribution of nuclear architecture in ANSC's aging.

Disclosures: T. Toda: None. **T.A. Bedrosian:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BehaviorCloud. **N. Novaresi:** None. **L. Hu:** None. **S. Ghassemzadeh:** None. **S.G. Young:** None. **F.H. Gage:** None.

Nanosymposium

184. Postnatal Neurogenesis: Molecular Mechanisms

Location: SDCC 1

Time: Sunday, November 4, 2018, 1:00 PM - 3:30 PM

Presentation Number: 184.10

Topic: A.02. Postnatal Neurogenesis

Support: NIH MH092535
MH092535-S1
HD086984

Title: Coupling of regional cerebral blood flow and functional connectivity at the default-mode-network hubs during infant development

Authors: *Q. YU[1,2], H. KANG[3], M. OUYANG[1,2], Y. PENG[3], F. FANG[4], H. HUANG[1,2]
[1]Dept. of Radiology, Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Dept. of Radiology, Perelman Sch. of Med., Univ. of Pennsylvania, Philadelphia, PA; [3]Dept. of Radiology, Beijing

Children's Hospital, Capital Med. Univ., Beijing, China; [4]Sch. of Psychological and Cognitive Sci., Peking Univ., Beijing, China

Abstract: Introduction: Human brain functional networks consist of densely linked hubs to support information transfer. Meeting metabolic demands of these hubs plays a vital role for maintaining the brain functional connectivity during resting state. Regional cerebral blood flow (rCBF) from pseudo-continuous arterial-spin-labeling (pCASL) perfusion MRI [1] quantifies essential property of brain metabolism. The default-mode network (DMN) [2], is a critical brain network at the resting-state. Functional connectivity among the DMN hubs can be quantified by functional connectivity strength (FCS) from resting-state fMRI (rs-fMRI). During infant brain development, rapid neuronal growth supported by rCBF increases [3] could result in emergence of the DMN [4]. We hypothesize that rCBF increase in infant development is coupled with FCS increase at the DMN hubs. **Methods:** 44 infants (16 females, age range: 1.4 to 27.7 months) were scanned with rs-fMRI and pCASL perfusion MRI sequences with a 3T Philips Achieva scanner. RCBF was estimated from pCASL data using the model in the literature [1]. After preprocessing, independent component analysis (ICA) in FSL software was applied to preprocessed rs-fMRI data to generate individual DMN hubs in a template space. The DMN hub locations were identified in the template space after averaging DMN hubs of individual infants. All DMN hubs in the template space were used as the region-of-interest (ROI) to calculate functional connectivity strength (FCS) [5] within the DMN and rCBF at these DMN hubs. **Results**: Emerging DMN hubs, including left and right posterior cingulate and medial prefrontal cortex, can be identified with the infant rs-fMRI data. RCBF of the DMN network increases significantly during 0-2 years ($r = 0.823$, $p < 0.01$). FCS within the DMN also increases significantly ($r = 0.408$, $p < 0.01$) from 0 to 2 years. Furthermore, significant correlation was found between the increasing rCBF and increasing FCS within the DMN ($r = 0.36$, $p < 0.05$). **Conclusions:** The present study delineated maturational trajectories of rCBF and FCS of the DMN from 0 to 2 years, filling the gap of knowledge of quantified physiological and functional brain development in this critical period. Coupled increases of rCBF and FCS within the DMN suggest increases of rCBF in the DMN meet the metabolic demand of functional maturation within the DMN and provide physiological underpinning of functional emergence of the DMN during infancy. **References:** [1] Alsop et al., (2015) MRM 73: 102. [2] Raichle et al., (2001) PNAS 98: 676. [3] Ouyang et al. (2017) Neuroimage 147: 233. [4] Gao et al., (2009) PNAS 106: 6790. [5] Cao et al., (2017) Cerebral Cortex 27: 1949.

Disclosures: Q. Yu: None. **H. Kang:** None. **M. Ouyang:** None. **Y. Peng:** None. **F. Fang:** None. **H. Huang:** None.

Nanosymposium

185. Neural Stem Cells: Reprogramming, Regeneration, and Transplantation

Location: SDCC 2

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 185.01

Topic: A.03. Stem Cells and Reprogramming

Support: Ontario Institue of Regenerative Medicine, New Ideas Grant
Medicine by Design, New Ideas Grant
Heart and Stroke Foundation of Canada, Grants-in-Aid

Title: Direct reprogramming of astrocytes to neurons leads to functional recovery after stroke

Authors: *M. FAIZ, T. LEE, C. PHILLIPS, A. KRASSIKOVA, J. LIVINGSTON-THOMAS, B. DONVILLE, N. SACHEWSKY, I. VONDERWALDE, C. MORSHEAD
Dept. of Surgery, Univ. of Toronto, Toronto, ON, Canada

Abstract: Astrocyte reprogramming, or forced conversion, to neurons using transcription factors is a promising strategy for stroke repair. This approach offers benefits over traditional cell replacement strategies by enabling the targeted generation of new cells at the site of injury without the challenges associated with transplantation or mobilization of endogenous precursors. To date, a number of studies have demonstrated successful reprogramming of astrocytes to neurons. However, it remains unknown whether reprogramming impacts functional outcome-arguably the most clinically relevant measure of stroke recovery. Using AAV delivery of transcription factor NeuroD1 and cell tracking approaches, we demonstrate that around 15% of all neurons in the stroke-injured cortex are derived from reprogrammed astrocytes. We further demonstrate the production of regionally appropriate neuron phenotypes that span all 6 cortical layers. Importantly, astrocyte reprogramming results in the improvement of motor function, indicating that reprogramming is a viable strategy for stroke repair. Our study is the first to analyze functional outcome following the reprogramming of astrocytes into neurons in a pre-clinical model of stroke.

Disclosures: M. Faiz: None. **T. Lee:** None. **C. Phillips:** None. **A. Krassikova:** None. **J. Livingston-Thomas:** None. **B. Donville:** None. **N. Sachewsky:** None. **I. Vonderwalde:** None. **C. Morshead:** None.

Nanosymposium

185. Neural Stem Cells: Reprogramming, Regeneration, and Transplantation

Location: SDCC 2

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 185.02

Topic: A.03. Stem Cells and Reprogramming

Support: NIH (AG045656)
Alzheimer's Association (ZEN-15-321972)
Charles H. "Skip" Smith Endowment Fund at Pennsylvania State University to G.C

Title: Chemical conversion of human astrocytes into neurons through modulation of multiple pathways

Authors: *J. YIN[1], L. ZHANG[1], X. HOU[1], Z. LEI[1], N. MA[1], F. ZHANG[1], G. LEE[1], Y. WANG[1], F. DONG[1], G.-Y. WU[2], G. CHEN[1]
[1]Biol., Penn State Univ., University Park, PA; [2]Sch. of Life Science, South China Normal Univ., Guangdong, China

Abstract: We have previously identified a cocktail of nine small molecules, when applied by three steps, were able to convert human astrocytes into neurons, but nine molecule stepwise treatment are difficult for clinical applications. Here, we optimize the formula to only 4 or even 3 small molecules for astrocyte-to-neuron conversion. With the four drugs applied together for 6 days, the reprogramming efficiency is further improved than nine small molecules. By replacing the four drugs by their analogues individually or together, we demonstrate that modulation of 4 or 3 signaling pathways among Notch, GSK-3, TGF-β, and BMP pathways are sufficient to change an astrocyte into a neuron. Importantly, chemically converted human neurons can survive more than 7 months. The chemically converted human neurons are fully functional, as shown by repetitive action potential firing and robust synaptic burst activities. Mechanistically, transcriptional activation of NeuroD1 and neurogenin 2, together with an increase of MeCP2 and a decrease of REST, is involved in chemical reprogramming. Interestingly, the chemically converted neurons are mostly forebrain glutamatergic neurons. When administered *in vivo* through intracranial or intraperitoneal injection, the core drugs significantly increase the adult neurogenesis in the mouse hippocampus. Together, our chemical reprogramming approach using a few small molecules to generate functional new neurons may pave the way for a potential drug therapy for brain repair.

Disclosures: J. Yin: None. **L. Zhang:** None. **X. Hou:** None. **Z. Lei:** None. **N. Ma:** None. **F. Zhang:** None. **G. Lee:** None. **Y. Wang:** None. **F. Dong:** None. **G. Wu:** None. **G. Chen:** None.

Nanosymposium

185. Neural Stem Cells: Reprogramming, Regeneration, and Transplantation

Location: SDCC 2

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 185.03

Topic: A.03. Stem Cells and Reprogramming

Support: NSFC grant 81701260
NSFC grant 81671268

Title: Neural stem cell transplantation improves the ability of learning and memory of tau/tta mice by eliminating neurofibrillary tangles

Authors: H. ZHANG, C. YUAN, *Z. QUAN, H. QING
Sch. of Life Sci., Beijing Inst. of Technol., Beijing City, China

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease which affects at least 47 million people worldwide as per World Alzheimer Report of 2016. Currently, there are no specific drugs or therapies that could cure AD effectively. Previous studies have indicated that neural stem cell (NSC) transplantation could improve the ability of learning and memory in AD model mice. In our study, we initially approved the function of NSC transplantation on learning and memory in AD model mice; we also focus on the molecular mechanisms of NSC transplantation on AD pathology. The primary hippocampal NSCs from C57 mice was extracted and cultivated, further infected with lentiviral vectors containing GFP, and then was stereotactic injected to the bilateral cerebral hippocampal CA1 in 21-week-old tau/tta mice. The behavioral tests showed that NSCs transplantation significantly improved the ability of short-term memory and certainly ameliorated the ability of long-term memory in tau/tta mice compared to sham-operated mice. We did immuno-fluorescence tests and found that the GFP-NeuN, GFP-GFAP and GFP-Ibal were co-localized in hippocampus of tau/tta mice, indicating injected exogenous NSCs can differentiate; meanwhile, we did ThS staining test and found the number of neurofibrillary tangles in CA1 region were much decreased compared to that in CA3 or DG region in tau/tta mice. The above results indicated NSCs transplantation has the potential to improve the ability of learning and memory in AD model mice which is possibly related to the elimination of neurofibrillary tangles. Further work will be continued on exploring whether transplanted NSCs would incorporate into neural circuits to perform its function and studying the proteomic analysis to reveal the molecular mechanisms of NSCs transplantation on AD pathology.

Disclosures: H. Zhang: None. **C. Yuan:** None. **Z. Quan:** None. **H. Qing:** None.

Nanosymposium

185. Neural Stem Cells: Reprogramming, Regeneration, and Transplantation

Location: SDCC 2

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 185.04

Topic: A.03. Stem Cells and Reprogramming

Support: NIBIB/NIH Grant P41EB002520
NINDS/NIH Grant R01NS092847
NIH grant S10 OD021626.

Title: Functional and sustainable 3-dimensional human neural network tissue models from pluripotent stem cells

Authors: W. L. CANTLEY[1], C. DU[5], S. LOMOIO[2], T. DEPALMA[3], E. PEIRENT[3], D. KLEINKNECHT[3], M. HUNTER[3], *T. J. F. NIELAND[4], M.-T. SCHOMER[6], G. TESCO[7], D. L. KAPLAN[3]
[1]Cell, Mol. and Developmental Biol., Tufts Univ., Medford, MA; [2]Neurosci., Tufts Univ., Boston, MA; [3]Biomed. Engin., [4]Tufts Univ., Medford, MA; [5]Biomed. Engin., Tufs Univ., Medford, MA; [6]The Jackson Lab., Farmington, CT; [7]Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Three-dimensional (3D) *in vitro* cell and tissue culture models, particularly for the central nervous system, allow for the exploration of mechanisms of organ development, cellular interactions, and disease progression within defined environments. Here we describe the development and characterization of human 3D tissue models that promote the differentiation and long-term survival of functional neural networks. These tissue cultures show diverse cell populations including neurons and astroglial cells interacting in 3D, and exhibit spontaneous neural activity confirmed through electrophysiological recordings and calcium imaging over at least 9 months. This approach allows for the direct integration of pluripotent stem cells into the 3D construct bypassing early neural differentiation steps (embryoid bodies and neural rosettes). The streamlined process provides a system that can be manipulated to support a variety of experimental applications. The similar growth and gene expression responses indicate the feasibility of generating patient-specific brain tissue models. We are in the progress of developing 3D neural tissue models of Alzheimer's and Parkinson's disease to identify disease mechanisms and for investigating drugs targeting neurodegenerative diseases.

Disclosures: W.L. Cantley: None. **C. Du:** None. **S. Lomoio:** None. **T. DePalma:** None. **E. Peirent:** None. **D. Kleinknecht:** None. **M. Hunter:** None. **T.J.F. Nieland:** None. **M. Schomer:** None. **G. Tesco:** None. **D.L. Kaplan:** None.

Nanosymposium

185. Neural Stem Cells: Reprogramming, Regeneration, and Transplantation

Location: SDCC 2

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 185.05

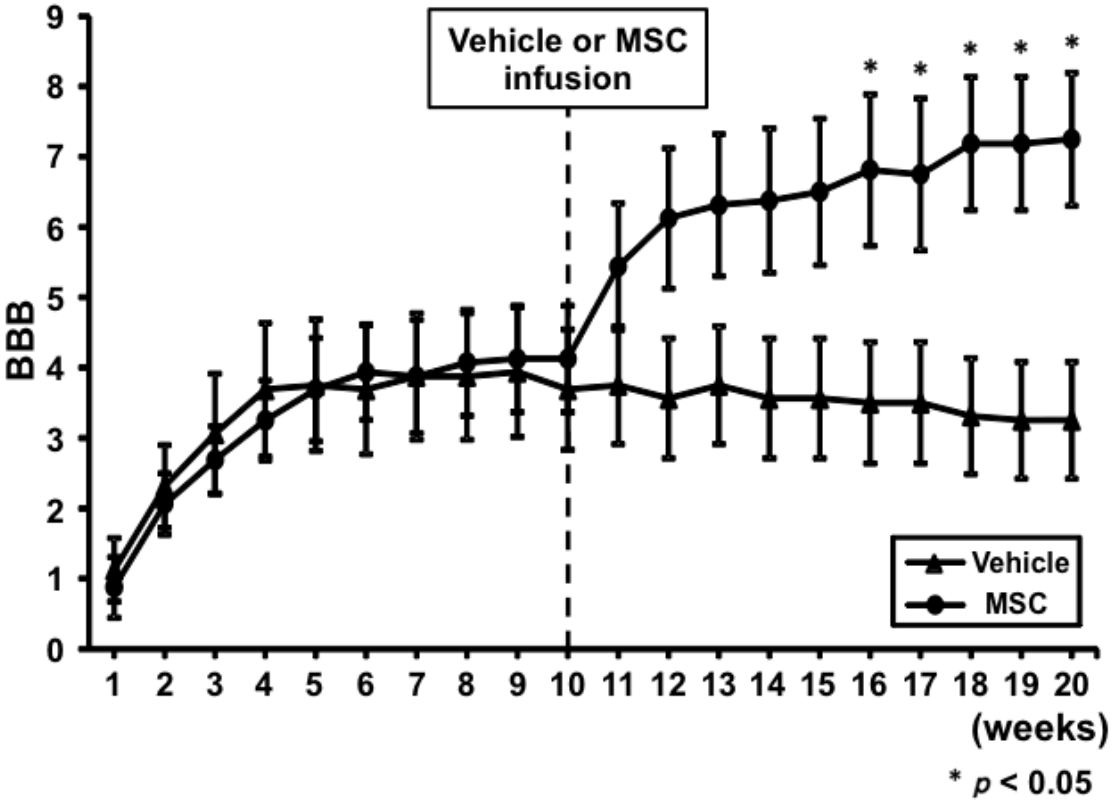
Topic: A.04. Transplantation and Regeneration

Support: JSPS KAKENHI
the AMED Translational Research Network Program
the BLRD and RR&D Services of Department of Veterans Affairs
the NMSS
the CT Stem Cell Research Program

Title: Intravenous infusion of mesenchymal stem cells promotes functional recovery in a model of chronic spinal cord injury

Authors: *T. MORITA[1], M. SASAKI[2], Y. K. SASAKI[2], M. NAKAZAKI[2], H. NAGAHAMA[2], S. OKA[2], J. D. KOCSIS[3], O. HONMOU[2], T. YAMASHITA[1]
[1]Orthopedic surgery, [2]Neural Regenerative Med., Sapporo Med. Univ. Sch. of Med., Sapporo-City, Japan; [3]Neurol., Yale Univ. Sch. of Med., New Haven, CT

Abstract: Intravenous infusion of mesenchymal stem cells (MSCs) derived from bone marrow improves behavioral function in rat models of spinal cord injury (SCI). However, most studies have focused on the acute or subacute phase of SCI. The purpose of this study was to investigate whether intravenously deliveredMSCs improve functional and structural outcome after contusive chronic SCI.Rats receiveda severe contusion at the T9 level spinal cordand received at random intravenous infusion of MSCs (1.0×10^6) or vehicle (DMEM) 10 weeks after the induction of SCI. Open field locomotor function was assessed using the Basso,Beattie, and Bresnahan (BBB) locomotor rating scale weekly until 20 weeks post-SCI (Figure). Motor recovery was greater in the MSC-treated group with rapid improvement beginning in earlier post-infusion times than in the vehicle-treated group. GFP^+MSCs were found in the injured spinal cord parenchyma the day after GFP-MSC infusion, and the percentage of intravenously infused cells accumulating in the injured spinal cord was at least 5.5%.Blood spinal cord barrier (BSCB) integrity was assessed by the intravenous infusion of Evans Blue (EvB) with spectrophotometric quantitation of its leakage into the parenchyma. In the vehicle-infused group, intense EvB staining was distributed within the spinal cord lesion. On the other hand, BSCB leakage was significantly reduced in the MSC-treated rats. Immunohistochemical staining for RECA-1 and PDGFR-bshowed increased microvasculature/repair-neovascularization in MSC-treated rats. There was extensive remyelination around the lesion center and increased sprouting of the corticospinal tract and serotonergic fibers after MSC infusion. These results indicate that the systemic infusion of MSCs results in functional improvement that is associated with structural changes in the chronically injured spinal cord including stabilization of the BSCB, axonal sprouting/regeneration and remyelination.



Disclosures: T. Morita: None. **M. Sasaki:** None. **Y.K. Sasaki:** None. **M. Nakazaki:** None. **H. Nagahama:** None. **S. Oka:** None. **J.D. Kocsis:** None. **O. Honmou:** None. **T. Yamashita:** None.

Nanosymposium

185. Neural Stem Cells: Reprogramming, Regeneration, and Transplantation

Location: SDCC 2

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 185.06

Topic: C.10. Brain Injury and Trauma

Support: PSI Foundation
U of T Open Fellowship

Title: Investigating the mechanism of regulation of select tight junctions implicated in neurovascular dysfunction by human umbilical cord perivascular cells after modelled traumatic brain injury

Authors: *T. BARRETTO[1,2], E. PARK[2], E. LIU[2], D. GALLAGHER[4], A. J. BAKER[5,3]
[1]Inst. of Med. Sci., Univ. of Toronto, Toronto, ON, Canada; [3]Critical Care, [2]St. Michael's Hosp., Toronto, ON, Canada; [4]Create Fertility Ctr., Toronto, ON, Canada; [5]St. Michael's Hosp., Univ. of Toronto, Inst. of Med. Scienc, Toronto, ON, Canada

Abstract: Traumatic Brain Injury (TBI) is the leading cause of morbidity and life-years lost in North America thus advancement of clinical therapeutics is an urgent issue. Primary injury occurs when the brain is impacted with sufficient force to cause trauma. A secondary injury phase continues for weeks to months after the initial insult and is composed of cellular and molecular mechanisms that contribute to blood brain barrier breakdown, axonal breakdown and glutamate toxicity among other events. This secondary injury disrupts tight junction (TJs) complexes such as occludin and the intercellular adaptor, ZO1 leading to a compromised blood brain barrier (BBB) and axonal integrity. Human umbilical cord derived perivascular cells (HUCPVCs) are known to express mesenchymal, neurotrophic and vascular factors. The pleiotropic activity of these factors may potentially protect the neurovascular unit and rescue white matter damage after TBI.
Rats were subjected to a fluid percussion injury (FPI) and systemically infused with 1.5 x 10^6 cells at 1.5h post-injury and sacrificed at acute time points for analysis. **Vascular leakage** was assessed using an Evan's blue assay and expressed in μg of dye per gram of tissue. At 24h and 48h vascular leakage was 6.4 μg and 15.5 μg vs. 1.7 μg in sham rats. HUCPVC treated rats had 5.5 μg and 3.3 μg at 24 and 48 hours, respectively. **Vascular density** assessed by RECA-1 immunohistochemistry (IHC) at 24h and 48h showed that vascular density was reduced by 40% in injured animals relative to sham and cell-treated animals. IHC for **neurofilament integrity** as assessed with NF200 revealed aggregate formation in axons and reduced axonal length in cortical sections of FPI animals relative to sham and cell-treated animals. Cortical tissue at the injury site was extracted at 24h and 48h for Western blot analysis to examine the expression of TJ complexes and neurofilament breakdown. At 24h and 48h, NF200 expression was increased by 200% and 140% respectively in injured animals relative to sham animals. HUCPVC administration reduced NF200 expression to sham levels by 48h. Evaluation of the **Occludin-ZO1 complex** formation by immunoprecipitation and western blot analysis indicated a 100% increase in complex formation at 24h in FPI animals. Modeled TBI demonstrated increased vascular leakage and axonal irregularities. The infusion of HUCPVCs following injury was associated with reduced vascular leakage suggesting a potential therapeutic strategy to address vascular disruption after TBI. In addition to the therapeutic potential of these cells, they can be used as a tool to understand some of the complex secondary mechanisms that contribute to breakdown of the BBB

Disclosures: T. Barretto: None. **E. Park:** None. **E. Liu:** None. **D. Gallagher:** A. Employment/Salary (full or part-time):; Create Fertility Centre. **A.J. Baker:** None.

Nanosymposium

185. Neural Stem Cells: Reprogramming, Regeneration, and Transplantation

Location: SDCC 2

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 185.07

Topic: A.03. Stem Cells and Reprogramming

Support: DFG, German Research Foundation
Berlin Institute for Medical Systems Biology (BIMSB)

Title: iPSC-derived neuronal/astrocyte composite cultures identify functional and bioenergetic defects in Leigh syndrome patients carrying SURF1 mutations

Authors: *G. INAK[1], R. JUETTNER[1], A. ZINK[2], P. LISOWSKI[3], B. MLODY[1], M. GOTTHARDT[1], R. KUEHN[1], E. E. WANKER[1], M. SCHUELKE[2], A. PRIGIONE[1]
[1]Max Delbrueck Ctr. for Mol. Med., Berlin, Germany; [2]Charité Universitaetsmedizin, Berlin, Germany; [3]Berlin Inst. for Med. Systems Biol. (BIMSB), Berlin, Germany

Abstract: Leigh syndrome (LS) is a rare untreatable neurological disorder. Pathognomonic features include basal ganglia defects and lactate acidosis. LS becomes apparent in infants following a metabolic stress, leading to death in two-three years. LS is caused by mutations of nuclear DNA (nDNA) or mitochondrial DNA (mtDNA) in more than 75 genes of the respiratory chain. LS research presently lacks good model systems for mechanistic studies, which hampers the discovery of therapies. This is particularly the case for the nuclear gene *SURF1*, a hotspot for LS mutations whose impairment is not pathogenic in mouse models. Here, we generated induced pluripotent stem cells (iPSCs) carrying *SURF1* mutations and obtained human composite cultures composed of electrophysiologically active dopaminergic neurons and functional astrocytes. Composite culture derived from LS patients carrying *SURF1* mutations show defects in mitochondrial movement, bioenergetics, and mitochondrial membrane polarization and impaired neuronal firing over time. We obtained CRISPR/Cas9-based genome corrected iPSCs to confirm the normalization of these phenotypes. This approach allows us to determine which dysfunctions are specifically due to the *SURF1* mutation. Finally, high-content analysis (HCA) of mitochondrial neuronal health can be used to screen the insults and stresses that can show toxicity specifically in patient neural cultures. This HCA approach may be used in the future to identify stresses that are responsible for the decompensation and “crises” observed in the patients. The platform may unveil agents capable of preserving the neural homeostasis in LS by protecting against its susceptibility to insults. This may enable the development of novel treatment strategies against a debilitating and so far untreatable condition.

Disclosures: G. Inak: None. **R. Juettner:** None. **A. Zink:** None. **P. Lisowski:** None. **B. Mlody:** None. **M. Gotthardt:** None. **R. Kuehn:** None. **E.E. Wanker:** None. **M. Schuelke:** None. **A. Prigione:** None.

Nanosymposium

185. Neural Stem Cells: Reprogramming, Regeneration, and Transplantation

Location: SDCC 2

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 185.08

Topic: A.03. Stem Cells and Reprogramming

Support: 3iRegeneration TEKES

Title: Caudalised brain organoids for modelling human brain development

Authors: *S. M. MOLCHANOVA[1], M. CHEREPKOVA[1], S. ABDURAKHMANOVA[2], T. P. TAIRA[3], T. OTONKOSKI[1], M. M. BESPALOV[1]
[1]Fac. of Medicine, Res. Programs Unit, Mol. Neurol., [2]Fac. of Medicine, Inst. of Biomedicine, [3]Vet. Biosci., Univ. of Helsinki, Helsinki, Finland

Abstract: Defects in the development of synaptic connectivity and neuronal networks very likely underlie pathological changes, seen in neurodevelopmental disorders, such as autism spectrum disorder and schizophrenia. Although we now understand a lot about synaptic development of the rodent's brain, the transfer of this knowledge to the human neurons has been for so far very challenging. Here, we describe the *in vitro* model of developing human neuronal network.
We generate human neuroectodermal stem cells (hNESC) from pluripotent stem cells (PSC) that can be expanded for at least 50 passages, likely possess a caudal identity (HoxC4-expressing), and can differentiate into neurons, astrocytes and oligodendrocyte precursors. In suspension, NESC form brain organoids, containing self-organized structures resembling developing brain ventricles. Brain organoids can grow in a rotating culture for 3 months and survive for up to 5-6 months. By the age of 4 months, most of the neurons show repetitive action potential firing and spontaneous synaptic excitatory and inhibitory currents. The first synaptic currents start to appear at the age of two months, and develop gradually after that - as a result, nearly 70 % of the neurons are synaptically connected in 4-month-old organoids. Synaptic development is accompanied by the cell growth and extension of the dendritic tree, seen as a change in membrane resistance, cell capacitance and dendritic length, estimated from biocytin staining. The synaptic development is correlated with the change in the electric behaviour of the neurons. Cells in 2-month-old organoids either are not able to maintain the stable membrane potential, or display the voltage transients, seen as a shift of the membrane potential in a square-like shape. When organoids mature, voltage transients disappear and are substituted by the spontaneous action potential firing, occurring either irregularly or in bursts. This is accompanied by the decrease in occurrence of spontaneous calcium waves, recorded using calcium-sensitive fluorophores.
The sequential developmental evens, shown in brain organoids *in vitro*, resemble the process of

activity-driven synaptic maturation, described for neonatal rodent brain. Our data prove that developing neurons with human genetic background, cultured in organoid-like shape, may be used as *in vitro* model for studying the human synaptic development in healthy and pathological conditions.

Disclosures: S.M. Molchanova: None. **M. Cherepkova:** None. **S. Abdurakhmanova:** None. **T.P. Taira:** None. **T. Otonkoski:** None. **M.M. Bespalov:** None.

Nanosymposium

186. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC 30B

Time: Sunday, November 4, 2018, 1:00 PM - 3:45 PM

Presentation Number: 186.01

Topic: C.01. Brain Wellness and Aging

Support: National Natural Science Foundation of China, 31471149 and 81527901

Title: A genome-wide RNAi screen identifies conserved epigenetic modulators that prevent healthy aging

Authors: *J. YUAN[1], S.-Y. CHANG[1], S.-G. YIN[2], X. CHENG[2], X.-J. LIU[1], Z.-Y. LIU[1], X.-L. KANG[1], J.-A. YIN[1], Q. JIANG[1], P. HAO[2], L. JIANG[2], S.-Q. CAI[1]
[1]Inst. of Neuroscience, CAS, Shanghai City, China; [2]Inst. Pasteur of Shanghai,Chinese Acad. of Sci., shanghai, China

Abstract: It has been assumed for a long time that lifespan and healthspan strongly correlate, but the two can be clearly dissociated. Although life expectancy increases globally, increasing longevity is scarcely accompanied by an extended healthspan. Thus how to achieve healthy aging emerges as one of the most challenging heath issues. Here we report that two conserved epigenetic modulators prevent healthy aging via repressing mitochondrial functions.
By genome-wide RNAi screening of candidate genes regulating the age-related serotonin and dopamine loss, which are known to cause behavioral deterioration in *C. elegans*, we identified a neuronal epigenetic reader BAZ-2 and a neuronal histone 3 lysine 9 methyltransferase SET-6 as modulators of aging. By occupying at the promoter regions, these epigenetic modulators repressed the expression of nuclear genes encoding mitochondrial proteins and hence reduced mitochondrial functions, a mechanism conserved in mouse cultured neurons and human cells; deletion of these epigenetic modulators prevented age-related deterioration in the worm's food-induced behavior, food intake, and male virility by improving mitochondrial functions. Furthermore, the expression levels of their human homologues increased in normal aging human brains and positively correlated with Alzheimer's disease progression.
Thus, our genome-wide RNAi screen in *C. elegans* reveals conserved mechanisms underlying biological regulation of healthy aging, providing a new insight for achieving healthy aging.

Disclosures: J. Yuan: None. **S. Chang:** None. **S. Yin:** None. **X. Cheng:** None. **X. Liu:** None. **Z. Liu:** None. **X. Kang:** None. **J. Yin:** None. **Q. Jiang:** None. **P. Hao:** None. **L. Jiang:** None. **S. Cai:** None.

Nanosymposium

186. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC 30B

Time: Sunday, November 4, 2018, 1:00 PM - 3:45 PM

Presentation Number: 186.02

Topic: C.01. Brain Wellness and Aging

Support: DFG FOR926 CP1
DFG FOR926 SP2
DFG SFB645
DFG BI-1227/5

Title: A chronic low dose of delta-9-tetrahydrocannabinol restores cognitive function in old mice by histone acetylation

Authors: *A. BILKEI-GORZO[1], O. ALBAYRAM[1], A. DRAFFEHN[2], K. MICHEL[1], A. PIYANOVA[1], H. OPPENHEIMER[3], M. DVIR-GINZBERG[3], I. RACZ[1], T. ULAS[2], S. IMBEAULT[1], I. BAB[3], J. SCHULTZE[2], A. ZIMMER[1]
[1]Inst. of Mol. Psychiatry, Univ. of Bonn, Bonn, Germany; [2]Genomics and Immunoregulation, LIMES Inst., Bonn, Germany; [3]Inst. of Dent. Sci., Hebrew Univ., Jerusalem, Israel

Abstract: Brain aging is accompanied by a number of cellular and molecular changes that may ultimately lead to cognitive deficits. One of these changes is a decline in the activity of the endocannabinoid system characterised by diminished 2-arachidonoylglycerol levels and reduced coupling between cannabinoid CB1 receptors and Gi-protein. Reduced CB1 receptor signalling in $CB1^{-/-}$ or GABA/$CB1^{-/-}$ mice leads to accelerated brain ageing, therefore we asked whether activation of CB1 receptors could alleviate symptoms of brain ageing. We showed that the normal age-related decline of cognitive functions can be counteracted with a chronic low dose of Δ9-tetrahydrocannabinol (THC). Thus, both mature (12-month-old) and old (18-month-old) mice receiving THC showed similar learning and memory performance in the Morris water-maze, novel object location recognition and social recognition tests as vehicle-treated young (2-month-old) animals. The same treatment in young animals did not influence or even worsened their learning ability. The restoration of the memory performance in mature animals was accompanied by an enhanced expression of synaptic marker proteins and an increased spine density in the hippocampus. Most strikingly, THC treatment facilitated a rebalanced hippocampal gene transcription in old mice so that their expression profiles closely resembled that of young THC-free animals, while the expression pattern of THC-treated young mice was similar as in vehicle-treated mature animals. This indicates that the enhanced CB1 tone achieved through low-dose

THC treatment may have normalized the weak cannabinoid signalling signature in mature animals and thus reverted some of the age-related changes in gene expression, whereby several genes with antiaging effects were upregulated while genes contributing to aging were downregulated. Together with changes in gene expression pattern, THC-treatment enhanced acetylation and decreased trimethylation of histone 3 and 4 in the hippocampus of mature animals. Changes in the epigenetic landscape are critical for the long lasting beneficial effect of THC on old animals, because pharmacological inhibition of histone acetylation completely blocked all anti-aging effects of THC. Thus, chronic low dose THC-treatment has a long lasting anti-aging effect and restoration of CB1 signalling in old individuals could be an effective strategy to treat or prevent age-related cognitive impairments.

Disclosures: A. Bilkei-Gorzo: None. **O. Albayram:** None. **A. Draffehn:** None. **K. Michel:** None. **A. Piyanova:** None. **H. Oppenheimer:** None. **M. Dvir-Ginzberg:** None. **I. Racz:** None. **T. Ulas:** None. **S. Imbeault:** None. **I. Bab:** None. **J. Schultze:** None. **A. Zimmer:** None.

Nanosymposium

186. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC 30B

Time: Sunday, November 4, 2018, 1:00 PM - 3:45 PM

Presentation Number: 186.03

Topic: C.01. Brain Wellness and Aging

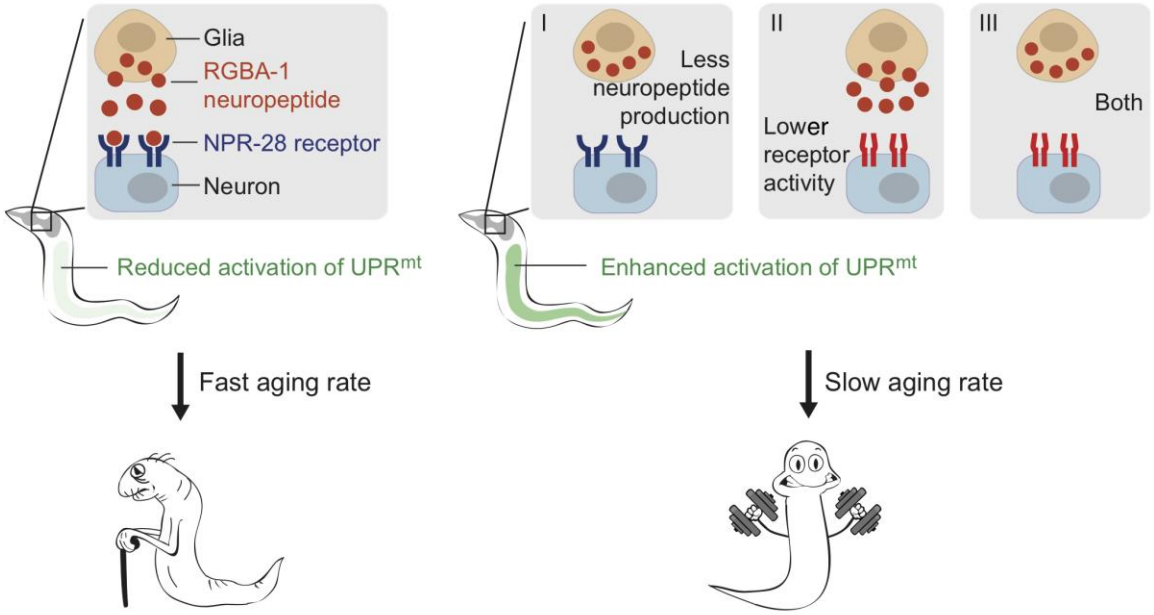
Support: National Natural Science Foundation of China 31471149 and 81527901

Title: Natural variation in glia-neuron signaling modulates aging rate

Authors: *G. GAO[1], J.-A. YIN[1], X.-J. LIU[1], Z.-Q. HAO[2], K. LI[1], X.-L. KANG[1], H. LI[3], Y.-H. SHAN[4], W.-L. HU[4], H.-P. LI[2], S.-Q. CAI[1]
[1]Inst. of Neurosci., Shanghai City, China; [2]CAS-MPG Partner Inst. for Computat. Biol., Shanghai, China; [3]Inst. of Biochem. and Cell Biol., Shanghai, China; [4]Inst. of Plant Physiol. and Ecology, Shanghai, China

Abstract: Aging is the major risk factor for neurodegenerative disorders, cancer, and diabetes. As the aging population is growing rapidly around the world, how to age with well-preserved functions emerges as one of the most important health issues. The rate of behavioral and cognitive decline is remarkably different among aging individuals. By dissecting the genetic basis of this variability, we discover the first genetic pathway underlying natural variation in aging rate in *Caenorhabditis elegans*. We find that natural isolates of *C. elegans* show diverse lifespan and varied rates of decline in many behaviors including male virility, feeding, and locomotion. DNA polymorphisms in a novel neuropeptide-coding gene, named *rgba-1*, and its receptor gene *npr-28* modulate the rate of decline in worm mating behavior. Glia-derived RGBA-1 neuropeptides activate NPR-28 signaling, which acts in serotonergic and dopaminergic

neurons to accelerate aging. Down-regulation of this signaling largely prevents age-related decline in male virility and feeding. Furthermore, this signaling involves protein deacetylase SIR-2.1-dependent activation of mitochondrial unfolded protein response (UPR^{mt}), a pathway that modulates aging. Population genetic analysis shows that genomic regions surrounding *rgba-1* and *npr-28* may have been subjected to selective sweep (with Tajima's *D* values of − 2.31 and − 1.47, respectively). Thus, natural variation in neuropeptide-mediated glia-neuron signaling modulates the rate of aging. Besides, our further studies on long-lived wild strains with vigorous behaviors identify other candidate genes that modulate the rate of behavioral aging and longevity. Our work thus paves a new avenue to study age-related behavioral decline and opens a door for comprehensive understanding the biological regulation of healthy aging.
The sample sizes in our study were determined from related previous analyses in the literature. All behavioral experiments were repeated on at least three days. The experimenters were blind to the genotype or treatment.



Disclosures: G. Gao: None. **J. Yin:** None. **X. Liu:** None. **Z. Hao:** None. **K. Li:** None. **X. Kang:** None. **H. Li:** None. **Y. Shan:** None. **W. Hu:** None. **H. Li:** None. **S. Cai:** None.

Nanosymposium

186. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC 30B

Time: Sunday, November 4, 2018, 1:00 PM - 3:45 PM

Presentation Number: 186.04

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant NS080913

Title: Origins of age-related neurogenesis decline

Authors: *A. IBRAYEVA[1], E. PU[1], M. BAY[1], D. JÖRG[2], D. BERG[3], H. SONG[3], B. SIMONS[2], M. BONAGUIDI[1]
[1]Dept. of Stem Cell Biol. and Regenerative Med., Broad CIRM Ctr. At USC, Los Angeles, CA; [2]Cavendish Lab., Cambridge Univ., London, United Kingdom; [3]Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Neural stem cells (NSC) must balance the production of newborn cells with their own maintenance to continually modify circuits throughout life. However, time significantly diminishes neurogenesis in the adult rodent hippocampus. The cellular and molecular mechanisms driving stem cells out of balance remain largely unknown. We developed *in vivo* single cell linage tracing, computational modeling approaches, single cell RNA-sequencing and systems level data science to comprehensively investigate neural stem cell adaptation and restoration during aging. We identify NSC loss, slowing kinetics and cell fate choice switches as reasons why neurogenesis declines during aging. Strikingly, we elucidate that these changes occur early in adulthood, between 3 and 6 months of age in mouse. We also identify mechanisms mediating slowing NSC expansion and define the molecular signatures of NSC deep quiescence. Our study elucidates cellular and molecular origins of neurogenesis decline and may serve as a new mammalian stem cell model to study early-onset cellular aging.

Disclosures: A. Ibrayeva: None. **E. Pu:** None. **M. Bay:** None. **D. Jörg:** None. **D. Berg:** None. **H. Song:** None. **B. Simons:** None. **M. Bonaguidi:** None.

Nanosymposium

186. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC 30B

Time: Sunday, November 4, 2018, 1:00 PM - 3:45 PM

Presentation Number: 186.05

Topic: C.01. Brain Wellness and Aging

Support: NIH R01 NS094171
NIH R00 NS076646
NIH R01 DC014423
NIH R01 GM054657
NIH T32 GM007240
ANR-16-CE15-0001-01
ANR-11-LABX-0054

Title: An epidermal antimicrobial peptide and its neuronal receptor regulate dendrite degeneration in aging and infection

Authors: *L. E[1], T. ZHOU[2], S. KOH[3], M. CHUANG[5], R. SHARMA[4], N. PUJOL[6], A. D. CHISHOLM[7], C. EROGLU[8], H. MATSUNAMI[2], D. YAN[2]
[1]Mol. Genet. and Microbiology, Duke Univ., Durham, NC; [2]Duke Univ., DURHAM, NC; [3]Cell Biol., [4]Duke Univ., Durham, NC; [5]UCSD, La Jolla, CA; [6]4Centre d'Immunologie de Marseille-Luminy, Marseille, France; [7]Univ. of California San Diego, La Jolla, CA; [8]Cell Biol Dept, Duke Univ, DUMC, Durham, NC

Abstract: Infections have been identified as possible risk factors for aging-related neurodegenerative diseases, but it remains unclear whether infection-related immune molecules have a causative role in neurodegeneration during aging. Here, we reveal an unexpected role of an epidermally-expressed antimicrobial peptide, NLP-29 (neuropeptide-like protein 29), in triggering aging-associated dendrite degeneration in *C. elegans*. The age-dependent increase of *nlp-29* expression is regulated by the epidermal *tir-1*/SARM - *pmk-1*/p38 MAPK innate immunity pathway. We further identify that an orphan G protein-coupled receptor NPR-12 (neuropeptide receptor 12) acts in neurons as a receptor for NLP-29, and also demonstrate that autophagic machinery is involved cell-autonomously downstream of NPR-12, to transduce degeneration signals. Moreover, we show that fungal infections cause dendrite degeneration using a similar mechanism as in aging, through NLP-29, NPR-12 and autophagy. Finally, we present evidence to show that NLP-29/antimicrobial peptide can cause the degeneration of NPR-12-expressing rat cortical neurons in the same manner as in *C. elegans* neurons, in support of an evolutionarily conserved mechanism linking infection, aging and neurodegeneration. Our findings reveal an important causative role of antimicrobial peptides, their neuronal receptors and the autophagy pathway in aging- and infection-associated dendrite degeneration.

Disclosures: L. E: None. **T. Zhou:** None. **S. Koh:** None. **M. Chuang:** None. **R. Sharma:** None. **N. Pujol:** None. **A.D. Chisholm:** None. **C. Eroglu:** None. **H. Matsunami:** None. **D. Yan:** None.

Nanosymposium

186. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC 30B

Time: Sunday, November 4, 2018, 1:00 PM - 3:45 PM

Presentation Number: 186.06

Topic: C.01. Brain Wellness and Aging

Support: NIH

Title: Endophilin A1- mediated synaptic failure links to mitochondrial stress in Alzheimer's disease

Authors: *Q. YU, F. DU, S. YAN
Higuchi Biosci. Center, Sch. of Pharmacy, Uni, Lawrence, KS

Abstract: Synaptic dysfunction and mitochondrial dysfunction are early pathological features of Alzheimer's disease (AD)-affected brains. However, the underlying mechanisms and strategies to rescue synaptic and mitochondrial injury remain largely unknown. Endophilin A1 is a brain-specific protein enriched in synaptic terminals. It has been reported to play a critical role in endocytosis, a critical process for neurotransmitters clearance from synaptic cleft and dendritic spine morphogenesis and stability. We have previously demonstrated that endophilin A1 protein level was significantly increased in AD-affected human brains and Aβ-producing AD mouse model, suggesting that Endophilin A1 may potentially be an important intracellular player in the synaptic alterations relevant to the pathogenesis of AD. However, to date, the direct effect of Endophilin A1 on Aβ-induced synaptic impairment *in vivo* AD mice has not yet been explored. Here, we establish the *in vivo* consequences of upregulation of Endophilin A1 expression in Aβ-rich environments, leading to alterations in synaptic transmission and vesicle release as shown by a decline in long-term potentiation (LTP) and blocking synaptic vesicle release and learning and memory impairment in AD mice. Notably, increasing endophilin A1 augments cerebral Aβ accumulation and interferes with APP processing by activation of gamma-secretase. Furthermore, increased expression of endophilin A1 impaired mitochondrial respiratory function and produced reactive oxygen species (ROS) together with activation of p38 MAP kinase. Our results indicate that Endophilin A1-mediated signal transduction *via* mitochondrial ROS/p38 MAP kinase contributes to Aβ-induced mitochondrial dysfunction, synaptic injury, and cognitive decline. Blockade of endophilin A1-mediated signaling protects against Aβ-induced synaptic damage. Thus, these studies significantly enhance our understanding of the AD pathogenesis for exploring the effective therapeutic strategy for AD via endophilin A1-involved synaptic dysfunction.

Disclosures: Q. Yu: None. **F. Du:** None. **S. Yan:** None.

Nanosymposium

186. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC 30B

Time: Sunday, November 4, 2018, 1:00 PM - 3:45 PM

Presentation Number: 186.07

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant

Title: PINK1-mediated mitochondrial quality control contributes to amyloid pathology in Alzheimer's disease

Authors: *F. DU, Q. YU, S. YAN
Higuchi Biosci. Center, Sch. of Pharmacy, Uni, Lawrence, KS

Abstract: Mitochondrial defect is an early pathological feature of the Alzheimer's disease (AD). Aberrant mitochondrial dynamics, perturbed bioenergetics function, especially mitochondrial dysfunction, and excessive reactive oxygen species (ROS) are observed in AD brains. Evidence has shown that Amyloid-β (Aβ) peptide has the deleterious effects on mitochondrial function. The defective mitochondria are progressively accumulated in axons and synapses over the lifetime of AD-affected neurons. PTEN-induced putative kinase 1 (PINK1) is critical to the maintenance of mitochondrial integrity and function by promoting the removal of damaged mitochondria *via* mitophagy-a selective form of autophagy whereby defective mitochondria are specifically engulfed by autophagosomes and targeted for degradation in the lysosomes. In the present study, we demonstrate for the first time that PINK1 is associated with AD pathology. Restoring neuronal PINK1 function strikingly reduces Aβ levels, amyloid-associated pathology, oxidative stress, as well as mitochondrial and synaptic dysfunction. In contrast, PINK1-deficient mAPP mice augmented cerebral Aβ accumulation, mitochondrial abnormalities, impairments in learning and memory, as well as synaptic plasticity at earlier age in comparison with mAPP mice. Notably, gene therapy-mediated PINK1 overexpression promotes the clearance of damaged mitochondria by augmenting autophagy signaling *via* activation of autophagy receptors (OPTN and NDP52), thereby alleviating Aβ-induced loss of synapses and cognitive decline in AD mice. Loss of PINK1 activity or blockade of PINK1-mediated signaling fails to reverse Aβ-induced detrimental effects. Our present study offers new insights into PINK1-dependent amyloid pathology through autophagy signaling and mitochondrial quality, contributing to the synaptic and cognitive dysfunction in the pathogenesis of AD. Thus, activation of PINK1 may represent a new therapeutic avenue for halting AD progression at the early stage through mitochondrial quality control combined with eliminating amyloid pathology.

Disclosures: F. Du: None. **Q. Yu:** None. **S. Yan:** None.

Nanosymposium

186. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC 30B

Time: Sunday, November 4, 2018, 1:00 PM - 3:45 PM

Presentation Number: 186.08

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant NS062184
NIH Grant MH096093

Title: An MRI study of the effect of mutant amyloid precursor protein (APP) decoupled from effect of plaque on axonal transport in the live mouse brain

Authors: *C. MEDINA[1], F. CHAVES[2], R. E. JACOBS[3], E. L. BEARER[4]
[1]Pathology, Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM; [2]Univ. of New Mexico,

Albuquerque, NM; [3]Zilkha Neurogenetic Inst., USC Keck Sch. of Med., Los Angeles, CA; [4]Dept. of Pathology, UNM Sch. of Med., Albuquerque, NM

Abstract: The amyloid precursor protein (APP), the precursor to Aβ plaques,, mediates cargo-motor attachments for axonal transport. In APP KO mice transport is decreased. In old transgenic mice expressing mutated human (APP^{SwInd}) linked to Familial Alzheimer's Disease, with both over-expression of mutated protein and plaques, axonal transport is altered, as detected by time-lapse manganese-enhanced magnetic resonance imaging (MEMRI) in living mouse brains. We seek to answer whether expression of mutated APP effects transport dynamics independent of plaque, and do plaques alone contribute to transport defects? To explore this, we used the Tet-Off system to decouple expression of APP^{SwInd} from presence of plaques, and then studied transport using our MEMRI technique in three experimental groups of 6 month-old transgenic mice equal numbers of both genders, in which APP^{SwIn} was manipulated by doxycycline: Group A (+ plaques, + APP^{SwInd}) (n=12); Group B (+ plaques, no APP^{SwInd}) (n=12), and group C (no plaques, + APP^{SwInd}) (n=12). MEMRI allows us to observe axonal transport in live animals with T_1-weighted MRI. Time-lapse MR images were captured before and a successive time points after stereotactic injection of Mn^{2+} (3-5nL) into CA3 of the hippocampus. Images of multiple individuals were aligned and processed with our automated computational pipeline, and statistical parametric mapping (SPM) performed. After imaging, brains were harvested for biochemistry or histopathology. Paired T-tests within-group between time points support the impression that APP^{SwInd} expression alone may affect transport destinations and rates of accumulation. Histology and biochemistry showed that Groups A and B but not C displayed plaques, and APP^{SwInd} was expressed 3.2-fold over normal at sacrifice in Groups A and C but not B, with Aβ detected only in Groups A and B. Cholinergic neurons that project to hippocampus from the medial septal nucleus were decreased in Group C ($p=0.0006$ by ANOVA, n=15). Isolated hippocampal vesicles contained Mn^{2+}, as well as Trk (NGF receptor), Rab 5 and 7 (associated with transport vesicles), suggesting a distinct vesicle population is affected by these APP mutations. These surprising results implicate APP^{SwInd} in transport defects, separable from the effect of plaque.

Disclosures: C. Medina: None. **F. Chaves:** None. **R.E. Jacobs:** None. **E.L. Bearer:** None.

Nanosymposium

186. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC 30B

Time: Sunday, November 4, 2018, 1:00 PM - 3:45 PM

Presentation Number: 186.09

Topic: C.01. Brain Wellness and Aging

Support: JPCOFUND/0004/2015 - NAB3
IF/00998/2012/CP0182/CT0004

EC TrafficInAD-334366

Title: Cellular aging potentiates synapse loss due to neuronal beta-amyloid production by increasing APP endocytosis

Authors: *C. G. ALMEIDA, T. BURRINHA
NOVA Med. Sch. - UNL, CEDOC - Chronic Dis. Res. Ctr. NMS-UNL, Lisbon, Portugal

Abstract: Aging is the main risk factor for the most common neurodegenerative disorder, Alzheimer's disease (AD). The neurodegenerative process in AD is initially characterized by synaptic loss accompanied by β-Amyloid (Aβ) accumulation. Aβ can accumulate in the "normal" aging brain. Defective clearance of Aβ has been postulated as responsible for Aβ accumulation in the late-onset AD, however, whether the production of Aβ is also potentiated with aging is not well established. We set out to investigate if and how cellular aging-drives alterations of intracellular trafficking that potentiate Aβ production and thus cause synaptic decline. To study neuronal aging, we used primary mouse cortical neurons aged in culture. We confirmed that cortical neurons (E16) undergo a stereotyped process of differentiation, maturation and aging in 28 days *in vitro* (DIV). At 28 DIV, neurons accumulate lipofuscin, the hallmark of aging, mainly in lysosomes of the cell body. We found that aged neurites evidence a dramatic rise in endogenous intracellular Aβ production. Since Aβ is produced upon endocytosis and consequent proteolysis of the amyloid precursor protein (APP) by its secretases, we measured APP endocytosis by pulse-chase experiments using immunofluorescence quantitative analysis and biochemical analysis in aged neurons compared to mature neurons (21 DIV). Unexpectedly, we found an enhancement of APP endocytosis and processing in aged neurons without alterations on total APP levels. We found early endosomes up-regulated. We confirmed that this up-regulation of APP processing and endocytosis in aged mouse brain. Importantly, in aged neurons, there is a decrease in the number of synapses with prominent loss of spines. We thus asked if this synaptic decline could be reversed by inhibition of Aβ production. We found that both γ- and β-secretase inhibition can partially rescue aging-synaptic decline. Overall our data indicate that an increase in APP endocytosis contributes to augment Aβ production with aging which impacts synaptic function, even in normal aged neurons.

Disclosures: C.G. Almeida: None. **T. Burrinha:** None.

Nanosymposium

186. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC 30B

Time: Sunday, November 4, 2018, 1:00 PM - 3:45 PM

Presentation Number: 186.10

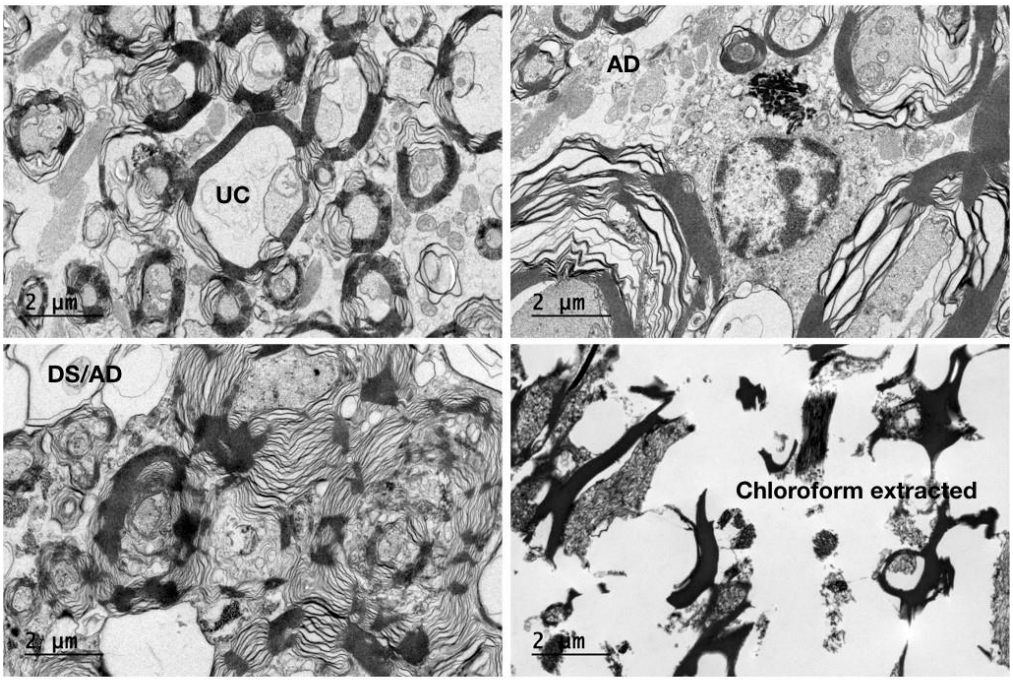
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: HD R01HD067731

Title: Myelin redundancy: A brain biomarker for "aging" versus Alzheimer's disease in Down syndrome

Authors: *A. N. VAN HOEK, L. DAI[1], J. R. KORENBERG[2]
[1]Pediatrics, Univ. of Utah, Salt Lake City, UT; [2]Pediatrics, Univ. of Utah, Salt Lake Cty, UT

Abstract: A major challenge for accelerating therapeutics of Alzheimer's Disease (AD) and "normal" Aging is the identification of dynamic neuronal and glial biomarkers that distinguish them, supporting Down syndrome (DS) as the ideal model. The pathology of aging involves degenerative neuronal and myelin features and genetic causes like AD, that also characterize 100% with DS by age 35 as harbingers of dementia affecting ~70%. However, DS-AD dementia merges with signs of accelerated aging seen in DS with three copies of the HS Chr 21 gene APP encoding the amyloid plaque protein, but without biomarkers for the age-related waning of capacities not related to AD. We examined the architecture of myelin in 22 cervical spinal cord samples obtained from the NIH NeuroBioBank (NBB) and our NIH DS study, with diagnoses of DS (41-76y), AD (54-60y) or normal control (50-74y) by genetic (confocal microscopy) and morphological (transmission electron microscopy) analyses of 11 single donor glutaraldehyde (GA) and formalin (F) fixed tissues. The results thus far indicate that DS myelin (n=6, F and GA fixed tissues) exhibited striking age-related redundancy and exaggerated ballooning (Figure bottom-left). In contrast, myelin in AD (n=4; 54, 60y) was ballooned but non-redundant, revealing compacted myelin sheaths (top-right). Myelin of aged controls (52-58y) was less ballooned and more compact (top-left). Chloroform extraction eliminated ballooned myelin laminae resulting in large empty regions in DS retaining compacted myelin (bottom-right). These results indicate that aged and less so young DS but not AD is associated with redundant myelin sheaths that are readily extracted in contrast to normal myelin. This biomarker of normal aging in DS may suggest a linear decrease in conduction velocity and consequent cognitive loss in DS. Although its severity may result from aberrant repair by the Chr 21 encoded gene OLIG2, the redundancy biomarker may reflect physiologic and modifiable in vivo dysfunction that constitutes a therapeutic target for non-AD aging, whether or not related to Alzheimer's neuropathology.



Disclosures: L. Dai: None. **J.R. Korenberg:** None.

Nanosymposium

186. Brain Wellness and Aging: Molecular Mechanisms

Location: SDCC 30B

Time: Sunday, November 4, 2018, 1:00 PM - 3:45 PM

Presentation Number: 186.11

Topic: C.01. Brain Wellness and Aging

Support: EFOP-3.6.3-VEKOP-16-2017-00002

Title: Effetct of healthy aging on blood-brain barrier morphology and function. Does it have any impact on the memory and the protein expression? A comparative study in aged and young rats

Authors: *F. ERDO[1], K. TÓTH[2], Á. BAJZA[3], B. PÉTERFIA[3], E. TÓTH[2], A. CSORBA[4], L. BORS[3], D. MÁTHÉ[5], G. PERLAKI[6], G. ORSI[6], J. MOLNÁR[7], I. WILHELM[8], I. GYERTYAN[9]
[1]Fac. of Information Technol. and Bionics, Pázmány Péter Catholic Univ., Budapest, Hungary; [2]MTA TTK Inst. of Cognitive Neurosci. and Psychology, Budapest, Hungary; [3]Fac. of Information Technol. and Bionics, Pázmány Péter Catholic Univ., Budapest, Hungary; [4]Univ. of Szeged, Fac. of Pharmacy, Deparment of Pharmacognosy, Szeged, Hungary; [5]Semmelweis University, Fac. of Medicine, Dept. of Biophysics and Radiation Biol., Budapest, Hungary;

[6]MTA-PTE Clin. Neurosci. MR Res. Group, Pécs, Pécs, Hungary; [7]Solvo Biotech., Szeged, Hungary; [8]MTA-SZBK Szeged, Szeged, Hungary; [9]Semmelweis University, Dept. of Pharmacol., Budapest, Hungary

Abstract: Objective Severeal articles are published about increased permeability and altered morphology of the blood-brain barrier (BBB) with advanced age. Our study aimed to compare the structure of brain microvessels and function of P-glycoprotein (P-gp) at the BBB and its behavioral consequences in young and aged Wistar rats.
Methods Male Wistar rats 2-3 months (young) and 14-16 months (middle aged) were studied. Dual and triple-probe microdialysis techniques were used to compare BBB permeability for quinidine (QND) in young and aged rats in presence and absence of a specific P-gp inhibitor (PSC-833). Concentrations of QND were analyzed by LCMS-MS. Comparative MR imaging of the brains was performed to study anatomical changes, and also single photon emission computed tomography (SPECT) imaging was applied for comparison P-gp functionality. For ultrastructural analysis, electronmicroscopy was performed. The efflux transporter expression at the BBB was studied at RNA and protein levels. For behavioral analysis Morris-Water maze, New Object Recognition and Pot Jumping tests were used.
Results The control level of QND in absence of PSC-833 was higher in aged than in young rats. In presence of PSC-833, the brain levels increased less in aged than in young animals suggesting lower expression level or impaired functionality of P-gp in old subjects. In MR imaging the extension of cerebral ventricles increased significantly and there were also characteristic ultrastructural changes at the BBB with aging by electronmicroscopy. The P-gp expression seems to be decreased both at protein and at RNA levels in aged rats. However, there was no significant cognitive impairement observed with healthy aging in the behavioral tests.
Conclusions Our results indicate many differences between young adult and aged rats in the structure and function of the BBB. These findings suggest a lower expression and/or reduced P-gp function with aging but, on the other hand, there was no memory and learning deficit observed in the applied behavioral assays in aged subjects. In summary, it can be concluded that healthy aging is a risk factor for increased permeability of BBB, which results in a higher CNS exposure to dangerous xenobiotics and bacterial components in old subjects.

Disclosures: F. Erdo: None. **K. Tóth:** None. **Á. Bajza:** None. **B. Péterfia:** None. **E. Tóth:** None. **A. Csorba:** None. **L. Bors:** None. **D. Máthé:** None. **G. Perlaki:** None. **G. Orsi:** None. **J. Molnár:** None. **I. Wilhelm:** None. **I. Gyertyan:** None.

Nanosymposium

187. Alzheimer's Disease: Synapses, Mechanisms, and Models

Location: SDCC 33

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 187.01

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

Support: NIA Grant P01-AG016765
NIH Grant P51-OD011107

Title: Developing a monkey model of Alzheimer's disease focused on women's health

Authors: *D. BECKMAN[1], K. DONIS-COX[1], S. OTT[1], W. G. JANSSEN[2], M. G. BAXTER[2], J. H. MORRISON[1]
[1]California Natl. Primate Res. Ctr., UC Davis, Davis, CA; [2]Dept. of Neurosci. and Friedman Brain Inst., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Soluble oligomers of the Aβ peptide (AβOs) are toxins that target and disrupt synapses, and generation of AβOs has been recently recognized as a likely initiating event in Alzheimer's disease (AD). There is a translational gap in AD studies, with promising drugs developed based on work in rodent models demonstrating minimal translation in AD patients in clinical trials. Additionally, although women have a two-fold greater lifetime risk of developing AD compared to men, females have not been a focus of preclinical studies. Thus, we sought to develop a model of AβO toxicity in female rhesus monkeys, to take advantage of the highly developed cortical structures in this species, as well as the similarities in the endocrine system between rhesus monkeys and humans. Repeated intracerebroventricular injections of AβOs were performed in 4 adult female rhesus monkeys. Controls consist of 2 animals injected with scrambled Aβ peptide and 3 non-injected animals (age range: 11-19 years old). High-resolution confocal microscopy and morphometric analysis of alexa filled neurons were used to evaluate synaptic, neuronal, and glial markers in the dorsolateral prefrontal cortex (dlPFC) and hippocampus after Aβ injections. Cerebrospinal fluid (CSF) and brain tissue were also collected and analyzed for biomarkers of AD pathology, including: phosphorylated Tau protein (pTau), total Tau, $A\beta_{1\text{-}42}$, $A\beta_{1\text{-}40}$ and TNF-α levels. AβO injection into the lateral ventricle of the brain induces loss of thin spines in targeted dlPFC neurons, an area highly vulnerable in aging and AD. Further, AβOs associate with the synaptic marker PSD95, inducing loss of more than 60% of local excitatory synapses. AβOs induced a robust neuroinflammatory response in the hippocampus, with numerous activated ameboid microglia and TNF-α release. Finally, AβOs increased CSF levels of $A\beta_{1\text{-}42}$, pTau Ser396 and pTau Ser199, but not $A\beta_{1\text{-}40}$ or total Tau. No similar changes were observed in the scrambled Aβ injected animals nor the non-injected controls. These initial findings from detailed quantitative analysis of effects of AβO administration on synapses in a female nonhuman primate model, are a very promising step toward understanding the mechanism of early AD pathogenesis in the primate brain, and may help develop an effective disease-modifying therapy of high relevance to women's health.

Disclosures: D. Beckman: None. **K. Donis-Cox:** None. **S. Ott:** None. **W.G. Janssen:** None. **M.G. Baxter:** None. **J.H. Morrison:** None.

Nanosymposium

187. Alzheimer's Disease: Synapses, Mechanisms, and Models

Location: SDCC 33

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 187.02

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

Support: FAPERJ
CAPES
CNPq
ISN

Title: Targeting translation impairment to restore cognitive deficits in Alzheimer's disease models

Authors: *M. M. OLIVEIRA[1], M. V. LOURENCO[1], F. LONGO[2], N. KASICA[3], W. YANG[4], T. MA[5], F. G. DE FELICE[6], E. KLANN[7], S. T. FERREIRA[1]
[1]Inst. of Med. Biochem. Leopoldo de Meis, Federal Univ. of Rio De Janeiro, Rio de Janeiro, Brazil; [2]Ctr. for Neural Sci., New York Univ., New York, NY; [3]Wake Forest Baptist Hlth., Winston-Salem, NC; [4]Wake Forest Baptist Med. Ctr., Winston Salem, NC; [5]Intrnl. Medicine-Geriatrics, Wake Forest Sch. of Med., Winston Salem, NC; [6]Fed Univ. Rio De Janeiro, Rio de Janeiro, Brazil; [7]Ctr. for Neural Sci., New York Univ. Ctr. for Neural Sci., New York, NY

Abstract: Alzheimer's disease (AD) is the major form of dementia, with no efficient treatment approved. It becomes essential, thus, to elucidate the precise mechanisms affected in these patients, offering new targets. The amyloid cascade hypothesis dictates that synapse loss is a consequence of synaptotoxic effects triggered by amyloid beta oligomers (AbOs), the major neurotoxins involved in AD. Although complex, the effects triggered by AbOs inflict damage in pathways that are central to neural activity and synapse consolidation. Protein synthesis downregulation appears as a central candidate to AbO-induced synaptic impairment, due to its central role on synaptic consolidation. We and other groups have shown that the eukaryotic initiation factor 2 alpha (eIF2a), a central regulator of protein synthesis, presents elevated activity in AD brains and AD models. eIF2a promotes the uncoupling of the ternary complex, the machinery responsible for the majority of cellular translation. Modulating this pathway, thus, emerges as an attractive therapeutic approach. ISRIB is a small synthetic molecule that boosts eIF2B activity, enhancing the translational process dependent of the ternary complex. Recent evidences indicate that ISRIB counteracts protein synthesis impairment induced by the activation of the endoplasmic reticulum stress pathways, a mechanism that is directly regulated by eIF2alpha activity. We sought to investigate whether ISRIB could counteract the cognitive impairment induced by AbOs. For this, we used a well-established model in our lab to study AbOs toxicity in vivo, consisting of a single injection of an AbOs suspension

intracerebroventricularly (i.c.v.). Mice injected with AbOs present memory loss in different memory tasks even 10 days post-injection. Our results indicate that ISRIB prevents AbO-induced cognitive impairment in the Novel Object Recognition (NOR) task and in the Contextual Fear Conditioning (CFC) task, indicating that boosting the translation could counteract neurotoxic effects induced by AbOs. The hippocampus of mice injected with both AbOs and ISRIB presented lower levels of ATF4, when compared to the hippocampus of AbOs-injected mice. We therefore sought to investigate whether ISRIB could prevent AbO-induced protein synthesis impairment. We found that ISRIB rescued proteostasis in both cultured neurons and hippocampal slices. Finally, chronic injection of ISRIB in 10 to 13-month old APP/PS1 had neuroprotective effects in different memory paradigms. Our data indicate that ISRIB could have a neuroprotective effect over AbOs activity, unraveling an alternative mechanism that could be exploited as a therapeutic target.

Disclosures: M.M. Oliveira: None. **M.V. Lourenco:** None. **F. Longo:** None. **N. Kasica:** None. **W. Yang:** None. **T. Ma:** None. **F.G. De Felice:** None. **E. Klann:** None. **S.T. Ferreira:** None.

Nanosymposium

187. Alzheimer's Disease: Synapses, Mechanisms, and Models

Location: SDCC 33

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 187.03

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

Support: NIH grant R01 NS086890
NIH grant DP1 DA041722
NIH grant RF1 AG057409
NIH grant R01 AG056259
NIH grant P30 NS076411

Title: S-Nitrosylation of Uch-L1 contributes to synaptic damage in models of Alzheimer’s disease

Authors: *T. NAKAMURA[1], C. OH[1], L. LIAO[1], A. J. ROBERTS[2], J. R. YATES, III[1], S. A. LIPTON[1,2,3]
[1]Mol. Med., [2]Neurosci., The Scripps Res. Inst., LA Jolla, CA; [3]Dept. of Neurosciences, Univ. of California, San Diego, Sch. of Med., LA Jolla, CA

Abstract: Emerging evidence suggests that dysfunction in the ubiquitin-proteasome system (UPS) plays an important role in the pathogenesis of age-related neurodegenerative diseases, including Alzheimer’s disease (AD). For instance, the ubiquitin C-terminal hydrolase Uch-L1 is typically downregulated in AD brains. Restoration of Uch-L1 activity in an animal model of AD

improves UPS activity, and alleviates synaptic injury and memory loss (Gong *et al. Cell*, 2006). However, the underlying mechanism of Uch-L1 dysfunction in AD, particularly in sporadic cases, remains unknown. In a variety of neurodegenerative disorders, reactive nitrogen species (RNS) produce nitrosative stress and contribute to neuronal damage. In AD, oligomerized amyloid-β (Aβ) peptide can trigger the generation of excessive RNS, resulting in aberrant protein S-nitrosylation, representing a covalent reaction of NO-related species with a critical cysteine thiol group, to modulate protein function (Nakamura *et al. Neuron*, 2013). Here, we show that human postmortem AD brains and AD transgenic mouse models manifest S-nitrosylated Uch-L1 protein (SNO-Uch-L1). In cell-based and transgenic mouse models of AD, we found that Aβ oligomers trigger SNO-Uch-L1 formation, thus inhibiting Uch-L1 deubiquitination activity. Importantly, expression of non-nitrosylatable Uch-L1 protects dendritic spines from Aβ oligomer-induced damage, consistent with the notion that S-nitrosylation of Uch-L1 contributes to Aβ-related synaptic injury. Thus, these findings link UPS dysfunction and aberrant redox signaling to Aβ-induced synaptic damage in AD. Additionally, our studies suggest that S-nitrosylation and thus inhibition of Uch-L1 activity may represent a potential new target for AD therapy and possibly other diseases associated with nitrosative stress.

Disclosures: T. Nakamura: None. **C. Oh:** None. **L. Liao:** None. **A.J. Roberts:** None. **J.R. Yates:** None. **S.A. Lipton:** None.

Nanosymposium

187. Alzheimer's Disease: Synapses, Mechanisms, and Models

Location: SDCC 33

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 187.04

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

Support: BWF PDEF 1017399
AARFD-16-442630

Title: cindr, the *Drosophila* homolog of CD2AP, plays a conserved role in synapse function and protein turnover

Authors: *S. A. OJELADE, T. V. LEE, N. GIAGTZOGLOU, J. SHULMAN
Neurol., Baylor Col. of Med., Houston, TX

Abstract: Discoveries through human genome-wide association studies have implicated numerous loci that associate with an increased risk for Alzheimer’s disease (AD), but their roles in AD pathogenesis remain obscure. We previously found that *cindr*, a conserved, *Drosophila* homolog of the AD susceptibility locus, *CD2AP*, modulates Tau-mediated neurodegeneration. CD2AP is an actin-binding, adaptor protein required for mammalian kidney function, but its role in the nervous system and in AD remains unresolved. Therefore, we generated a *cindr* null

mutant in *Drosophila* and characterized its requirements for neuronal function and maintenance. Cindr is expressed robustly in the *Drosophila* nervous system and is enriched at presynaptic boutons, where it associates/interacts with other presynaptic proteins such as Synapsin and Synaptotagmin. In flies lacking *cindr*, the adult brain develops normally, and there is no overt evidence for age-dependent neurodegeneration. Instead, *cindr* mutants show impaired synaptic maturation, and neurotransmission due to reduced basal, presynaptic calcium levels. Moreover, *cindr* interacts both physically and genetically with *Leonardo* (*leo*), the ortholog of 14-3-3 Zeta, and they function in concert to affect protein turnover via regulation of the Ubiquitin-Proteasome System (UPS). Studies of *CD2AP* null mice validate and support a conserved function in synaptic proteostasis, as loss of CD2AP similarly impacts proteasome activity, and affects the degradation of proteins including Synapsin, Synaptophysin and PMCA. In an analysis of 838 postmortem human brains, we further show that CD2AP protein levels are anti-correlated with synaptic proteins, including Synapsin, and this relationship is altered in AD. Using a cross-species experimental paradigm, we discovered a conserved role of *cindr/CD2AP* in synapse structure and function, and suggest a potential interaction with Tau-induced proteinopathy and resulting synaptotoxicity in AD.

Disclosures: S.A. Ojelade: None. **T.V. Lee:** None. **N. Giagtzoglou:** None. **J. Shulman:** None.

Nanosymposium

187. Alzheimer's Disease: Synapses, Mechanisms, and Models

Location: SDCC 33

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 187.05

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

Support: CNPq
FAPERJ
HFSP
ISN
Alzheimer Society Canada
INNT/Brazil
CIHR

Title: Exercise-linked FNDC5/irisin corrects synapse and memory defects in mouse models of Alzheimer's disease

Authors: *M. V. LOURENCO[1], O. ARANCIO[2], S. T. FERREIRA[3], F. G. DE FELICE[4]
[1]Fed Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [2]Dept of Pathol, Columbia Univ., New York, NY; [3]Fed. Univ. Rio de Janeiro, Rio de Janeiro, Brazil; [4]Fed Univ. Rio de Janeiro, Rio de Janeiro, Brazil

Abstract: Defective brain hormonal signaling has been associated with neurodegenerative diseases, particularly Alzheimer's disease (AD), a disorder characterized by synapse and memory failure. Irisin is an exercise-induced myokine released upon cleavage of membrane-bound precursor protein FNDC5, recently reported to be expressed in the hippocampus, a key memory center in the brain. We show that irisin levels are reduced in AD hippocampi and cerebrospinal fluid, and in experimental models of AD. Knockdown of brain FNDC5/irisin impaired long-term potentiation and novel object recognition memory in mice. Conversely, boosting brain levels of FNDC5/irisin rescued synaptic plasticity and memory in AD mouse models. Peripheral overexpression of FNDC5/irisin rescued memory impairment, whereas blockade of either peripheral or brain irisin attenuated the neuroprotective actions of physical exercise on synaptic plasticity and memory in AD mice. By showing that FNDC5/irisin is an important mediator of the beneficial effects of exercise in the diseased brain, our findings place FNDC5/irisin as a novel agent capable of opposing synapse failure and memory impairment in AD.

Disclosures: M.V. Lourenco: None. **O. Arancio:** None. **S.T. Ferreira:** None. **F.G. De Felice:** None.

Nanosymposium

187. Alzheimer's Disease: Synapses, Mechanisms, and Models

Location: SDCC 33

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 187.06

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

Support: UK Dementia Research Institute
European Research Council Consolidator Award ALZSYN
Alzheimer's Research UK
Alzheimer's Society
Medical Research Scotland

Title: Reducing tau in synapses is associated with amelioration of behavioural deficits ina novel model of Alzheimer's disease

Authors: *T. L. SPIRES[1], E. K. PICKETT[1], J. TULLOCH[1], A. G. HERRMANN[1], O. NETSYK[1], P. JAIN[1], S. DUNNETT[1], S. S. SEDEH[1], M. FJELDSTAD[1], W. CALKIN[1], L. MURISON[1], R. J. JACKSON[1], J. MCQUEEN[1], R. PITSTICK[2], C.-A. MCKENZIE[1], E. ALLISON[1], G. CARLSON[2], C. SMITH[1], I. OREN[1], O. M. HARDT[3], C. M. HENSTRIDGE[1]
[1]The Univ. of Edinburgh, Edinburgh, United Kingdom; [2]McLaughlin Res. Inst., Great Falls, MT; [3]McGill, Montreal, QC, Canada

Abstract: Alzheimer's disease (AD) is pathologically defined by the deposition of amyloid beta in plaques and tau in neurofibrillary tangles in the brain. Strong evidence supports the notion that amyloid beta is the trigger that initiates disease while tau is the bullet that causes neurodegeneration; however understanding the cascade leading from amyloid beta to tau remains one of the frustratingly large knowledge gaps in the field. One potential site of this cascade is within synapses. Synapse loss is the strongest pathological correlate of cognitive decline in AD, and previous work implicates both amyloid beta and tau in synapse degeneration. Here we tested the hypothesis that amyloid beta and tau interact to cause synaptic dysfunction and behavioural impairments in a novel model of AD. We observe that removing endogenous mouse tau protects plaque-bearing APP/PS1 mice from synaptic plasticity and behavioural deficits without preventing plaque-associated synapse loss. Mice expressing both APP/PS1 and human tau transgenes develop an age-related hyperactivity phenotype, which completely recovers when tau levels are lowered by transgene suppression. This functional recovery was accompanied by a reduction in the proportions of pre and postsynaptic terminals containing tau. In human AD brain samples, we also observed tau in pre and postsynaptic terminals, supporting a potential role for tau in synaptic dysfunction. These data indicate that the amyloid cascade may occur at least in part in synapses where tau promotes amyloid beta mediated synapse dysfunction, suggesting lowering tau at synapses as a potential therapeutic approach in AD.

Disclosures: T.L. Spires: None. **E.K. Pickett:** None. **J. Tulloch:** None. **A.G. Herrmann:** None. **O. Netsyk:** None. **P. Jain:** None. **S. Dunnett:** None. **S.S. Sedeh:** None. **M. Fjeldstad:** None. **W. Calkin:** None. **L. Murison:** None. **R.J. Jackson:** None. **J. McQueen:** None. **R. Pitstick:** None. **C. McKenzie:** None. **E. Allison:** None. **G. Carlson:** None. **C. Smith:** None. **I. Oren:** None. **O.M. Hardt:** None. **C.M. Henstridge:** None.

Nanosymposium

187. Alzheimer's Disease: Synapses, Mechanisms, and Models

Location: SDCC 33

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 187.07

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

Support: EMBO Long-Term Fellowship (ALTF 590-2016)
Massachusetts Alzheimer Disease Research Center (P50AG005134)
JPB foundation
ERC (project RATLAND)

Title: Tau silences neuronal circuits and blocks the effects of amyloid- β *in vivo*

Authors: *M. A. BUSCHE[1], S. WEGMANN[1], S. DUJARDIN[1], J. SCHIANTARELLI[1], T. KAMATH[1], I. NELKEN[2], B. T. HYMAN[1]

[1]Neurol., Massachusetts Gen. Hosp., Charlestown, MA; [2]Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Alzheimer´s disease is characterized by widespread amyloid-β (Aβ) plaques and tau neurofibrillary tangles (NFTs) in the brain. The relationship of these two pathological lesions to one another is a central mystery of Alzheimer biology. Here we employed in vivo two-photon calcium-imaging of large populations of layer 2/3 cortical neurons in a novel mouse model expressing both human Aβ and tau. Our recordings reveal a strong tau-dependent suppression of activity and silencing of a vast number of neurons (63.01 ± 2.3 %), which dominates over Aβ-dependent neuronal hyperactivity. We show that NFTs are neither sufficient nor required for the silencing, which instead is dependent on soluble tau. We demonstrate that by repressing tau gene expression the silencing phenotype can be rapidly rescued in tau mice (fractions of silent neurons before treatment: 50.84 ± 3.49 %, after treatment: 25.92 ± 2.57 %). Surprisingly, however, the same treatment was much less effective in the presence of Aβ (fractions of silent neurons before treatment: 64.25 ± 4.21 %, after treatment: 61.87 ± 2.28 %). Together, our new data demonstrate that soluble tau not only impairs neuronal circuits, but also blocks the effects of Aβ, which may help explain the failure of the numerous clinical trials directed at reducing Aβ in the brains of Alzheimer patients to reverse cognitive deficits, as abnormal tau remains even after clearance of Aβ.

Disclosures: M.A. Busche: None. **S. Wegmann:** None. **S. Dujardin:** None. **J. Schiantarelli:** None. **T. Kamath:** None. **I. Nelken:** None. **B.T. Hyman:** None.

Nanosymposium

187. Alzheimer's Disease: Synapses, Mechanisms, and Models

Location: SDCC 33

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 187.08

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

Support: NS37853 (C.I.)
AG051179 (M.I.)

Title: Aβ1-42 causes intracellular calcium dysregulation and arcuate npy neuron dysfunction through Cav1.3-like calcium currents

Authors: *G. WANG[1], M. ISHII[2], A. HILLER[3], C. IADECOLA[3]
[1]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY; [2]Feil Family Brain and Mind Res. Inst., [3]Weill Cornell Med., New York, NY

Abstract: Alzheimer’s disease (AD) is associated with early hypothalamic dysfunction leading to weight loss and metabolic dysregulation (*Cell Metab.* 2015, 22, 761). Dyshomeostasis of

intracellular calcium $[Ca^{2+}]_i$ is a major mechanism by which Aβ alters neuronal function (*Cell* 2012, 148: 1204). Voltage-gated L-type Ca^{2+} channels (LTCC) are key modulators of $[Ca^{2+}]_i$, spontaneous firings (SF) and reactive oxygen species (ROS) in neurons. We previously found that $[Ca^{2+}]_i$ increased and a low voltage-threshold-activated (LTA) L-type Ca^{2+} current present in hypothalamic arcuate (ARC) neuropeptide Y (NPY) neurons from mice overexpressing mutated amyloid precursor protein (tg2576) (*SfN* 2017). Here we tested whether LTA LTCC-dependent mechanisms are involved in the $[Ca^{2+}]_i$ dyshomeostasis and dysfunction induced by APP overexpression or $A\beta_{1\text{-}42}$ in NPY neurons. Using whole-cell current-clamp on ARC NPY neurons, we found increased SF in tg2576 slices and $A\beta_{1\text{-}42}$ (100 nM)-treated WT slices, an effect inhibited by the L-type Ca^{2+} channel blocker nimodipine (NMD) (Hz, tg2576 4.01±0.57; NMD 1.94±0.66; $P<0.05$, N=10. WT 2.48±0.53; $A\beta_{1\text{-}42}$ 3.9±0.61; NMD 1.9±0.46; $P<0.05$, N=5-8), but not by N-type or P/Q-type Ca^{2+} channel blockers ($P>0.05$, N=4). We then compared $[Ca^{2+}]_i$ in ARC and cortical (COR) NPY neurons from WT and tg2576 mice using Fura-2. Baseline $[Ca^{2+}]_i$ was higher in ARC and COR NPY neurons from tg2576 than those from WT mice, which was reduced by NMD (340/380nm, ARC NPY: WT 0.17±0.02; tg2576 0.47±0.05; NMD 0.29±0.04. COR NPY: WT 0.33±0.12; tg2576 0.82±0.07; NMD 0.62±0.04. $P<0.05$; N=5-33). Next, whole-cell voltage-clamp in WT ARC NPY neurons found that the peak currents (PC) of LTCC I/V curves were shifted to lower threshold potentials after application of $A\beta_{1\text{-}42}$ compared to vehicle (-20 vs 0mV; $P<0.05$, n=6). Similarly, application of $A\beta_{1\text{-}42}$ to ARC NPY neurons from dihydropyridine insensitive ($DHP^{-/-}$) $Ca_V1.2$ mice shifted the PC of LTCC I/V curves to -20mV, which was reversed by NMD (pA at -20mV; veh -460±56.1A; $A\beta_{1\text{-}42}$ -1189±92.2; NMD -686.5 ±148.6; $P<0.05$, N=5). Finally, using the mitochondrial ROS dye MitoSox red, we found that $A\beta_{1\text{-}42}$ increased mitochondrial ROS in ARC but not in COR NPY neurons of $DHP^{-/-}$ $Ca_V1.2$ mice, an effect inhibited by NMD (2μM) (ARC NPY: $A\beta_{1\text{-}42}$ by 37.1±9.7%; NMD by 14.5±7.5%; $P<0.05$, N=10-20). Since $DHP^{-/-}$ $Ca_V1.2$ mice have functional $Ca_V1.2$ but are insensitive to NMD, it is likely that APP overexpression or $A\beta_{1\text{-}42}$ in ARC NPY neurons disrupts $[Ca^{2+}]_i$ via $Ca_V1.3$ L-type Ca^{2+} influx, leading to high SF and mitochondrial ROS formation. The data raise the possibility that $Ca_V1.3$ in ARC NPY neurons mediate the Ca^{2+} dysregulation underlying hypothalamic dysfunction in AD.

Disclosures: G. Wang: None. **M. Ishii:** None. **A. Hiller:** None. **C. Iadecola:** None.

Nanosymposium

187. Alzheimer's Disease: Synapses, Mechanisms, and Models

Location: SDCC 33

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 187.09

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

Support: NIH Grant AG017926
NIH Grant AG08200-27

NIH Grant AG5138

Title: A peptide derived from the PS1/γ-secretase-mediated cleavage of ephrinB2 rescues the angiogenic function of brain endothelial cells expressing PS1 FAD mutants

Authors: *A. GEORGAKOPOULOS[1], Y. YOON[2], N. WARREN, 10128[1], G. VOLOUDAKIS[1], N. K. ROBAKIS[3]
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Psychiatry and Neurosci., Icahn Sch. of Med., New York, NY; [3]Dept Psychiat & Neurosci., Mount Sinai Hlth. Syst., New York, NY

Abstract: Vascular dysfunction has been linked to the onset of Alzheimer's Disease (AD). AD brains exhibit impaired brain vasculature pathology and there is a strong association between cognitive decline and cerebrovascular abnormalities. Interestingly the changes in the microvasculature precede cognitive decline and neurodegeneration. One of the mechanisms that may lead to this pathology is endothelial dysfunction and decreased angiogenesis which affect the integrity of vascular architecture and plasticity, ultimately impairing neuronal health and function.
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 (ECs) of blood vessels stimulates angiogenesis and the cytoplasmic domain of ephrinB2 is necessary for this function.
We found that Presenilin1 (PS1), which plays a central role in familial AD (FAD), regulates the EphB4-Fc-induced processing of ephrinB2 in primary ECs in a γ-secretase-dependent manner producing cytosolic peptide ephrinB2/CTF2 (efnB2/CTF2). We also found that EphB4-Fc-induced sprouting, tube formation and VE-cadherin angiogenic complexes depend on PS1/γ-secretase (Warren et al., 2018) and that ECs from PS1 FAD brains have decreased angiogenic functions as they fail to increase sprouting, tube formation and angiogenic complexes in response to angiogenic factor EphB4-Fc.
We had previously shown that overexpression of efnB2/CTF2 peptide significantly increases EC sprouting, tube formation and VE-cadherin angiogenic complexes *in vitro* (Warren et al, 2018). Here we show that overexpression of efnB2/CTF2 significantly increases sprouting of PS1 FAD mutant ECs *in vitro*. To improve the angiogenic function of this peptide we prepared a small peptide based on the sequence of efnB2/CTF2, which contains its C-terminal sequence necessary for angiogenic function (Warren et al., 2018). This peptide is more stable compared to efnB2/CTF2 and is able to penetrate the cells as it contains a TAT sequence at its N-terminus. WT or PS1 FAD brain ECs treated with this peptide have significantly increased sprouting *in vitro* compared to cells treated with control peptide. The above show that the angiogenic function of PS1 FAD mutant brains ECs is rescued by this small peptide providing a candidate agent for treatment of impaired vascular functions observed in AD brains.

Disclosures: A. Georgakopoulos: None. **Y. Yoon:** None. **N. Warren:** None. **G. Voloudakis:** None. **N.K. Robakis:** None.

Nanosymposium

187. Alzheimer's Disease: Synapses, Mechanisms, and Models

Location: SDCC 33

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 187.10

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

Support: NIH Grant R01AG053588)
NIH Grant R00AG037716
Alzheimer's Association NIRG-12-242803
Alzheimer's Association AARG-16-442863)

Title: The regulatory role of GHSR in Alzheimer's disease related hippocampal synaptic dysfunction

Authors: *J. TIAN[1], L. GUO[1], S. SUI[1], C. DRISKILL[1], A. PHENSY[1,2], J. ZIGMAN[2], R. H. SWERDLOW[3], S. KROENER[4], H. DU[1]
[1]The Univ. of Texas At Dallas, Richardson, TX; [2]UT-southwestern, Dallas, TX; [3]Dept Neurol, Univ. Kansas Sch. Med., Kansas City, KS; [4]Sch. of Behavioral and Brain Sci., Univ. of Texas at Dallas Sch. of Behavioral and Brain Sci., Richardson, TX

Abstract: Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by progressive cognitive impairments mainly affecting the aging population. Selective hippocampal deficits, including synaptic failure, are a defining pathology of Alzheimer's disease (AD). However, the molecular mechanisms that lead to hippocampal synaptic injury remain a long-standing scientific question. Recent studies have highlighted the role of growth hormone secretagogue receptor1a (GHSR1a or ghrelin receptor) in regulating hippocampal synaptic function. But whether GHSR1a deregulation contributes to hippocampal pathology in AD has never been comprehensively studied. Here, we found abnormally increased GHSR1a expression in the hippocampi from postmortem AD brains as well as AD animal models (5xFAD mice). Furthermore, we demonstrate a physical interaction between amyloid beta (Aβ) and GHSR1a, which suppresses GHSR's function that leads to hippocampal synaptic stress and impaired cognitive function. Genetic deletion of GHSR (GHSR Null mice) replicates the hippocampal synaptic injury and cognitive deficits seen in the age- and gender- matched 5xFAD mice, further suggesting a functional loss of GHSR1a in hippocampal pathology in AD. The deleterious effect of Aβ-mediated GHSR1a deregulation on hippocampal synaptic function is likely to be a result of defective GHSR1a downstream signaling and its failure to control dopamine receptor D1 (DRD1). The simplest interpretation of our results is that abnormal GHSR1a regulation is a primary pathology accompanying AD and plays a critical role in mediating hippocampal lesions via its interplay with Aβ. Therefore, GHSR1a may be a potential therapeutic target for the correction of hippocampal synaptic failure and cognitive deficits in AD.

Disclosures: J. Tian: None. **L. Guo:** None. **S. Sui:** None. **C. Driskill:** None. **A. Phensy:** None. **J. Zigman:** None. **R.H. Swerdlow:** None. **S. Kroener:** None. **H. Du:** None.

Nanosymposium

187. Alzheimer's Disease: Synapses, Mechanisms, and Models

Location: SDCC 33

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 187.11

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

Support: NIH R01 AG053588

Title: Cyclophilin d- oscp interaction mediates mitochondrial f1fo atp synthase dysfunction in Alzheimer's disease

Authors: *E. GAUBA, L. GUO, H. DU
Dept. of Mol. & Cell Biol., Univ. of Texas At Dallas, Richardson, TX

Abstract: Synaptic mitochondrial dysfunction in Alzheimer’s Disease (AD) is strongly associated with F1FO ATP synthase deregulation, which results in inefficient OXPHOS and collapsed mitochondrial membrane potential, as well as excess mitochondrial Permeability Transition pore (mPTP) formation. Our studies have determined the physical interaction between a F1FO ATP synthase key subunit called Oligomycin Sensitivity Conferring Protein (OSCP) and Amyloid β (Aβ), as well as the interaction between Aβ and the key mPTP regulator Cyclophilin D (CypD) in AD brains. Given the known interplay of OSCP with CypD, it has raised an intriguing question that whether Aβ is a factor promoting the formation of OSCP/CypD complex in AD-related pathological settings, thus inducing excess mPTP formation and aggravating synaptic mitochondrial dysfunction in AD. For the present study, CypD deficient mice were crossed with 5xFAD mice (an AD mouse model with human APP/Aβ overexpression). The mice at different ages were used to isolate synaptic mitochondria brain to perform mitochondrial studies and making brain cryosections for immunostaining and interaction studies. We found that the interaction between OSCP/CypD elevates in Aβ-rich conditions in the AD mouse brains along with reduced synaptic mitochondrial function and F1FO ATP synthase dysfunction. Moreover, the OSCP/Aβ interaction decreases with CypD depletion in a dose dependent manner in AD-related conditions. Our further biochemical studies showed that Aβ enhances OSCP/CypD binding affinity/ Lastly, the dose-dependent CypD depletion restored the decreased OSCP levels in the AD mice brain together with attenuated mitochondrial OXPHOS function, restored ATP levels, and mitigated mitochondrial calcium handling capacity as well as alleviated F1FO ATP synthase enzymatic activity in AD mouse brains. Similarly, depleting the CypD/OSCP interaction also relieved memory loss in AD mice brain. In conclusion, these results convey a triad of the proteins interactions and depicts that Aβ promotes CypD/OSCP interaction, which is potentially a critical cause of mitochondrial dysfunction in AD brain.

Disclosures: E. Gauba: None. **L. Guo:** None. **H. Du:** None.

Nanosymposium

187. Alzheimer's Disease: Synapses, Mechanisms, and Models

Location: SDCC 33

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 187.12

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

Support: JPB Foundation

Title: Innate immune system modulates gamma-secretase with aging and in Alzheimer's disease

Authors: *J.-Y. HUR[1], G. R. FROST[1], X. WU[1], S. PAN[1], C. CRUMP[1], J. WANG[2], J. TCW[2], A. MCKENZIE[3], Y. SAGI[4], K. R. SADLEIR[5], R. RISSMAN[6], R. VASSAR[5], B. ZHANG[3], D. S. JOHNSON[7], E. MASLIAH[6], P. GREENGARD[4], A. GOATE[2], Y. LI[1]
[1]Chem. Biol., Mem. Sloan Kettering Cancer Ctr., New York, NY; [2]Neurosci., [3]Genet. and Genomic Sci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]Mol. and Cell. Neurosci., Rockefeller Univ., New York, NY; [5]Sch. of Med., Northwestern Univ., Chicago, IL; [6]Neurosciences, Univ. of California San Diego, La Jolla, CA; [7]Pfizer, Cambridge, MA

Abstract: Alzheimer’s disease (AD) is caused by synaptic and neuronal loss in the brain that eventually results in cognitive decline. Late onset AD (LOAD) generally has a late onset (> 65 years of age) and is responsible for over 95% of AD cases. Aging is the highest risk factor for LOAD, but the underlying mechanism causing LOAD is poorly understood. One of the characteristic hallmarks of AD is senile plaques containing the amyloid β-peptide (Aβ). Aβ is produced from the amyloid precursor protein by sequential proteolytic cleavages by β-secretase and γ-secretase. γ-Secretase is an aspartyl protease complex, containing presenilin (PS), nicastrin, Aph-1, and Pen-2. Regulation of γ-secretase involves both obligatory subunits and modulatory proteins. The role of these essential components has been well studied, however, little is known about the presence and function of γ-secretase modulatory proteins (GSMPs). Here, we used γ-secretase modulators (GSMs) to identify GSMPs. We identified a GSMP that is an innate immune response protein and is induced by multiple proinflammatory cytokines. GSMP directly binds γ-secretase. Down-regulation of GSMP in cells reduces γ-secretase activity for Aβ production. Expression of this GSMP is increased with aging and in AD mouse models. Furthermore, this GSMP protein is upregulated in a subset of LOAD patients that exhibit higher γ-secretase activity for Aβ production. These findings reveal an unprecedented mechanism in which γ-secretase is modulated by GSMP under neuroinflammatory conditions and contributes to the pathogenesis of a subpopulation of LOAD patients.

Disclosures: J. Hur: None. **G.R. Frost:** None. **X. Wu:** None. **S. Pan:** None. **C. Crump:** None. **J. Wang:** None. **J. Tcw:** None. **A. McKenzie:** None. **Y. Sagi:** None. **K.R. Sadleir:**

None. **R. Rissman:** None. **R. Vassar:** None. **B. Zhang:** None. **D.S. Johnson:** None. **E. Masliah:** None. **P. Greengard:** None. **A. Goate:** None. **Y. Li:** None.

Nanosymposium

188. Alzheimer's Disease and Other Dementias: Tau and TDP-43 Proteinopathies

Location: SDCC 5

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 188.01

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

Support: NINDS NS085770
NIA AG013854

Title: Distribution of tdp-43 pathology in hippocampal synaptic relays suggests trans-synaptic propagation in primary progressive aphasia

Authors: *D. T. OHM, P. JAMSHIDI, G. KIM, K. BOLBOLAN, S. WEINTRAUB, E. H. BIGIO, M. M. MESULAM, C. GEULA
Northwestern Univ., Chicago, IL

Abstract: Aggregation and propagation of misfolded proteins in the form of abnormal inclusions is a common feature of neurodegenerative diseases. A hallmark of frontotemporal lobar degeneration (FTLD) is the abnormal aggregation of inclusions containing hyperphosphorylated tau or the 43-kDa transactive response element DNA-binding protein (TDP-43) (FTLD-TDP). While pathologic spread has been suggested to act through axonal pathways and prion-like mechanisms, existing evidence from the human brain is limited to qualitative and semi-quantitative observations at the gross anatomical level. Using unbiased stereology, this study aimed to quantitatively investigate potential trans-synaptic propagation of abnormal TDP-43 precipitates in the well-established neural circuitry of the hippocampus, which encompasses a highly ordered chain of intrinsic single synaptic connections that link cytoarchitectonically distinct zones. Whole-hemisphere sections from brains of five participants with clinical diagnoses of primary progressive aphasia (PPA)—a neurodegenerative disorder in which language is the most salient deficit— were examined. All brain specimens had post-mortem diagnoses of FTLD-TDP. We have shown that mature TDP-43 inclusions in these brains display a clinically concordant distribution that favors the language-dominant hemisphere. Bilateral whole-hemisphere brain sections were immunohistochemically stained using an antibody to phosphorylated TDP-43 (pS409/410-2). Four PPA participants were right-handed and had asymmetric left hemisphere atrophy, and one was left-handed with asymmetric right hemisphere atrophy. TDP-43-positive mature (darkly stained, fibrillar) and pre-inclusions (diffuse nuclear and/or cytoplasmic staining, potential precursors to mature inclusions) were quantified in the granule cell layer of the dentate gyrus (DG) and the pyramidal cell layers of CA3, CA2, and CA1. The highest density of mature TDP-43 inclusions were found in the granule neurons of

DG, followed by significantly fewer inclusions in the pyramidal neurons of CA3 (one synaptic relay away), and still fewer inclusions in CA1 and CA2 ($p<0.05$) pyramidal neurons (two synapses away). TDP-43 pre-inclusions, however, showed highest densities in either DG or CA3, followed by lower densities in CA1 and CA2. Our quantitative results suggest trans-synaptic propagation of intracellular TDP-43 inclusions. Moreover, the relationship between patterns of pre- and mature inclusions corroborates the concept that pre-inclusions are present prior to the formation of mature TDP inclusions and develop through progressive stages into dark mature aggregates.

Disclosures: D.T. Ohm: None. **P. Jamshidi:** None. **G. Kim:** None. **K. Bolbolan:** None. **S. Weintraub:** None. **E.H. Bigio:** None. **M.M. Mesulam:** None. **C. Geula:** None.

Nanosymposium

188. Alzheimer's Disease and Other Dementias: Tau and TDP-43 Proteinopathies

Location: SDCC 5

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 188.02

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

Title: Discovery and development of diagnostics and therapeutics for TDP-43 proteinopathies

Authors: T. AFROZ[1], T. SEREDENINA[1], V. DARMENCY[1], C. BOUDOU[1], J. KOCHER[1], M. CHAUHAN[1], A. MARCHAND[1], H. KROTH[1], O. ADOLFSSON[1], A. PUROHIT[2], D. PATERSON[2], L. MARTARELLO[2], M. NEUMANN[3], J. STOEHR[1], A. PFEIFER[1], *A. MUHS[1]
[1]AC Immune SA, Lausanne, Switzerland; [2]Biogen, Inc., Cambridge, MA; [3]Dept. of Neuropathology, Univ. of Tübingen, Tübingen, Germany

Abstract: TDP-43 is a multifunctional and essential RNA-binding protein, whose abnormal cytoplasmic aggregation characterizes the affected neurons in majority of patients with amyotrophic lateral sclerosis (ALS) and in about 45% of patients with frontotemporal dementia (FTD). Moreover, TDP-43 copathology is found in sub-populations of Alzheimer’s disease (AD), Huntingtons’ disease (HD), Lewy body diseases, and Pick’s disease, among others. Neurodegenerative diseases linked to deposition of TDP-43 are therefore classified as TDP-43 proteinopathies. Even though the loss of normal nuclear localization and cytoplasmic TDP-43 aggregation correlates with neurodegeneration, the exact mechanisms of neurotoxicity remain elusive. Nonetheless, recent research suggests that similar to other protein aggregation diseases, TDP-43 proteinopathies follow the prion paradigm through templated conversion and spread of pathologic conformers across the central nervous system. Antibody-mediated clearance of pathological TDP-43 aggregates therefore represents an attractive strategy for therapeutic intervention. However, the lack of tools for accurate diagnosis and monitoring of disease progression have impeded the research and development of therapeutics for TDP-43 proteinopathies. We have generated a set of antibodies targeting different regions of TDP-43 that

specifically recognize pathological TDP-43 inclusions in post-mortem brain tissue from ALS and FTD patients. These antibodies display high affinity and selectivity for misfolded TDP-43 *in vitro* and are currently being evaluated for their therapeutic potential. To complement the therapeutic approach, we are generating small molecules suitable for further development as positron emission tomography (PET) ligands. We have identified a set of small molecules that specifically bind to pathological TDP-43 in post-mortem brain tissue and display suitable CNS PET properties. Additional compounds are currently being synthesized and evaluated with the goal to develop PET ligands with high affinity for TDP-43 while being selective over amyloid-beta and tau aggregates.

Disclosures: **T. Afroz:** A. Employment/Salary (full or part-time):; AC Immune SA. **T. Seredenina:** A. Employment/Salary (full or part-time):; AC Immune SA. **V. Darmency:** A. Employment/Salary (full or part-time):; AC Immune SA. **C. Boudou:** A. Employment/Salary (full or part-time):; AC Immune SA. **J. Kocher:** A. Employment/Salary (full or part-time):; AC Immune SA. **M. Chauhan:** A. Employment/Salary (full or part-time):; AC Immune SA. **A. Marchand:** A. Employment/Salary (full or part-time):; AC Immune SA. **H. Kroth:** A. Employment/Salary (full or part-time):; AC Immune SA. **O. Adolfsson:** A. Employment/Salary (full or part-time):; AC Immune SA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AC Immune SA. **A. Purohit:** A. Employment/Salary (full or part-time):; Biogen, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen, Inc. **D. Paterson:** A. Employment/Salary (full or part-time):; Biogen, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen, Inc. **L. Martarello:** A. Employment/Salary (full or part-time):; Biogen, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen, Inc. **M. Neumann:** F. Consulting Fees (e.g., advisory boards); AC Immune SA. **J. Stoehr:** A. Employment/Salary (full or part-time):; AC Immune SA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AC Immune SA. **A. Pfeifer:** A. Employment/Salary (full or part-time):; AC Immune SA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AC Immune SA. **A. Muhs:** A. Employment/Salary (full or part-time):; AC Immune SA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AC Immune SA.

Nanosymposium

188. Alzheimer's Disease and Other Dementias: Tau and TDP-43 Proteinopathies

Location: SDCC 5

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 188.03

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

Support: National Institute on Aging of the National Institutes of Health under Award Number R01AG054449
Florida Department of Health, Ed and Ethel Moore Alzheimer's Disease Research Program (8AZ06)
KU Leuven Postdoctoral Mandate Funding (PDM/17/185)

Title: Clinicopathological correlations of mixed pathology in Alzheimer's disease

Authors: *J. M. SCHAEVERBEKE[1,2], F. S. H. AL-SHAIKH[2], N. O. AZU[2], K. J. VINSON[2], A. M. LIESINGER[2], N. ERTEKIN-TANER[3], O. A. ROSS[2], R. DUARA[5], N. R. GRAFF-RADFORD[4], D. W. DICKSON[2], M. E. MURRAY[2]
[1]KU Leuven, Leuven, Belgium; [2]Neurosci., [3]Neuroscience, Neurol., [4]Neurol., Mayo Clin., Jacksonville, FL; [5]Mount Sinai Med. Ctr., Miami Beach, FL

Abstract: Alzheimer's disease (AD) is neuropathologically characterized by neurofibrillary tangles (NFT) and amyloid-β plaques. However, mixed pathologies often co-occur in older AD patients. These include Lewy body disease (LBD), hippocampal sclerosis (HpScl) (of a TDP-43 etiology), and vascular disease. For clinical trial design, it is of crucial importance to assess whether these "mixed AD" cases differ in their clinicopathologic characteristics. The FLorida Autopsied Multi-Ethnic (FLAME) cohort was queried for AD cases, and sub-classified based upon mixed LBD and HpScl pathologies. The cases were limited to a Braak NFT stage>IV and those lacking known mutations. The final cohort (n=1491) consisted of 6 groups as shown in Table 1: pure AD [lacking Lewy body or HpScl pathology], AD-amygdala predominant Lewy bodies (AD-ALB), AD-LBD, AD-HpScl, AD-ALB-HpScl, and AD-LBD-HpScl. Standard neuropathologic procedures were performed. Clinical progression was assessed using age onset of cognitive symptoms, disease duration, and by examining the mini-mental state examination score (MMSE) proximal to death. Age onset ($p=0.002$) and age at death ($p<0.001$) differed across AD groups, with AD-HpScl having the oldest age. Disease duration also differed with AD-ALB found to have the longest disease duration ($p<0.001$). Neither education ($p=0.978$) nor final MMSE score differed ($p=0.512$). Vascular disease was most commonly observed in AD-HpScl and AD-ALB-HpScl, but not in AD-LBD-HpScl ($p=0.003$). Interestingly, higher TDP-43, but lower NFT Braak stage, was observed in AD-LBD as compared to AD-ALB. The frequency of *APOE*-ε4 carriers was highest in AD cases with multiple proteinopathies (AD-LBD-HpScl and AD-ALB-HpScl) ($p=0.002$), although these cohorts were the smallest in size. Mixed AD cases significantly differ with regard to clinicopathologic characteristics. Co-existing HpScl is typically observed in older patients, while the longest disease duration is seen in AD-ALB. Our findings could implicate a larger clinical window for treatment in these groups. In particular the high co-morbidity of vascular disease provides an opportunity for prophylactic treatment.

Clinicopathologic characteristics

Characteristics	AD	AD-ALB	AD-LBD	AD-HpScl	AD-ALB-HpScl	AD-LBD-HpScl	*P*-value

Number (% total of n=1491)	819 (55%)	218 (15%)	332 (22%)	77 (5%)	13 (1%)	32 (2%)	---
Age at death, yr.	81 (75, 86)	81 (75,86)	80 (74,86)	88 (83,91)	86 (81,89)	82 (80,89)	<0.001
Females (% total of AD type)	455 (56%)	116 (53%)	158 (48%)	49 (64%)	7 (54%)	17 (53%)	0.100
Education, yr.	14 (12,16)	14 (12,16)	14 (12,16)	13 (12,16)	14 (12,16)	12 (12,16)	0.978
Clinical findings							
Age of onset, yr.	72 (65,78)	70 (62,76)	72 (66,78)	75 (70,80)	74 (66,78)	71 (67,76)	0.002
Disease duration, yr.	9 (6,11)	10 (7,13)	9 (6,11)	8 (6,10)	9 (6,12)	9 (6,12)	<0.001
MMSE Final score	13 (6,20)	11 (6,15)	12 (5,18	16 (11,19)	8 (6,9)	10 (6,15)	0.512
Postmortem findings							
Vascular disease	234/815 (29%)	54/217 (25%)	71/331 (21%)	32/77 (42%)	6/13 (46%)	7/32 (22%)	0.003
TDP-43	194/559 (35%)	74/191 (39%)	123/280 (44%)	77 (100%)	13 (100%)	31 (100%)	<0.001
NFT Braak stage	VI (V,VI)	VI (V,VI)	V (V,VI)	VI (V,VI)	VI (V,VI)	VI (V,VI)	<0.001
Thal amyloid phase	5 (5,5)	5 (5,5)	5 (5,5)	5 (5,5)	5 (5,5)	5 (5,5)	5 (5,5)
APOE e4+	335/572 (58%)	124/187 (66%)	190/281 (68%)	40/61 (66%)	12/12 (100%)	24/30 (80%)	0.002
MAPT (H1H1)	248/422 (59%)	78/134 (58%)	145/243 (60%)	30/44 (68%)	2/6 (33%)	17/27 (63%)	0.639

Disclosures: J.M. Schaeverbeke: None. **F.S.H. Al-Shaikh:** None. **N.O. Azu:** None. **K.J. Vinson:** None. **A.M. Liesinger:** None. **N. Ertekin-Taner:** None. **O.A. Ross:** None. **R. Duara:** None. **N.R. Graff-Radford:** None. **D.W. Dickson:** None. **M.E. Murray:** None.

Nanosymposium

188. Alzheimer's Disease and Other Dementias: Tau and TDP-43 Proteinopathies

Location: SDCC 5

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 188.04

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

Support: NIH F32 AG053036
NIH P01 AG017586

Title: Detection of Alzheimer's disease (AD) specific tau pathology in co-morbid frontotemporal lobar degeneration-tau (FTLD-tau) with a conformation-selective anti-tau monoclonal antibody

Authors: *G. S. GIBBONS, S.-J. KIM, J. L. ROBINSON, L. CHANGOLKAR, D. J. IRWIN, V. M. LEE, J. Q. TROJANOWSKI
Ctr. for Neurodegenerative Dis. Res., Univ. of Pennsylvania, Philadelphia, PA

Abstract: A major challenge of neuropathological phenotyping frontotemporal lobar degeneration-tau (FTLD-tau) is assessing the extent of co-occurring Alzheimer's disease (AD) tau pathology since current diagnostic antibodies detect hyperphosphorylated tau present in both FLTD-tau and AD. Therefore, we utilize GT-38, an AD tau selective monoclonal antibody that does not detect FTLD-tau pathology, to systematically evaluate and Braak stage AD neurofibrillary tangle (NFT) tau co-pathology in a large series of 158 cases of FTLD-tau. We selected consecutive cases of progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Pick's disease (PiD) to evaluate AD NFT tau pathology with GT-38 immunohistochemical staining of the hippocampus, entorhinal cortex, pons, locus coeruleus, and visual cortex according to National Institute on Aging-Alzheimer's Association (NIA-AA) neuropathological criteria. Overall, 63% of FTLD-tau cases had some degree of co-occurring AD NFT tau pathology (i.e. Braak $\geq$ B1) with 70/158=B1, 26/158=B2, 3/158=B3. We tested whether AD co-pathology is more frequent within a specific FTLD-tau subtype and found increased frequency with PSP (χ^2 (6, n =158) = 15.19; p = 0.019). Patients were grouped with no/negligible AD NFT tau (Braak B0/B1) or medium/high level AD NFT tau (Braak B2/3) to assess whether higher Braak stages associated with advanced age. B2/3 stage patients were older than patients with B0/1 AD tau co-pathology (mean difference 7.511 ± 1.833 years; $p < 0.01$ by two-tailed t-test). Next, we will investigate the hypothesis that co-occurring AD tau pathology correlates with clinical symptoms including episodic memory deficits by analysis of clinical neuropsychiatric examination records. This study will provide insight into the clinical significance of co-occurring AD with FTLD-tau and demonstrates that the AD tau selective antibody GT-38 provides a unique tool for neuropathological staging of AD tau pathology.

Disclosures: G.S. Gibbons: None. **S. Kim:** None. **J.L. Robinson:** None. **L. Changolkar:** None. **D.J. Irwin:** None. **V.M. Lee:** None. **J.Q. Trojanowski:** None.

Nanosymposium

188. Alzheimer's Disease and Other Dementias: Tau and TDP-43 Proteinopathies

Location: SDCC 5

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 188.05

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

Support: Methodist Hospital Foundation

Title: Network tau spreading in human neurodegeneration

Authors: *J. C. MASDEU[1], B. PASCUAL[1], Q. FUNK[1], E. ROCKERS[1], P. ZANOTTI-FREGONARA[1], M. YU[1], N. PAL[1], C. KARMONIK[1], B. SPANN[1], G. ROMAN[1], P. SCHULZ[2]
[1]Neurol., Houston Methodist Res. Inst., Houston, TX; [2]Neurol., McGovern Med. Sch. of UT Hlth., Houston, TX

Abstract: Objective and Rationale: Trans-neuronal misfolded tau propagation, in a prion fashion, has been shown in tissue culture and experimental animals, but not *in vivo* in humans. We tried to determine whether tau deposition in non-fluent primary progressive aphasia (nfPPA) follows a network pattern. **Methods:** Eight nfPPA patients, all PET amyloid-negative, and eight healthy controls had ^{18}F-AV-1451 tau PET. The SUV ratio over the cerebellar gray matter was calculated for t = 80-100 min. The two groups were compared using SPM. MRI tractography was performed in the nfPPA group. Additionally, in a different group of 35 healthy subjects with similar age as the nfPPA patients, we determined normal network functional connectivity with BOLD MRI using the voxel most often activated in syntactic tasks as seed. **Results:** nfPPA patients had impaired language production and increased ^{18}F-AV-1451 uptake in two major clusters ($p < 0.05$ FWE corrected): the larger in Broca's area (inferior premotor frontal cortex) and the smaller in the syntactic comprehension area of the left temporal lobe, which was also the area most heavily connected to Broca's area in the MRI connectivity analysis in healthy subjects. Furthermore, MR tractography revealed abnormal thinning, most pronounced anteriorly, of the left arcuate fasciculus, connecting the frontal and temporal nodes of the language network. **Conclusions:** Increased ^{18}F-AV-14510 signal in nfPPA most likely reflects binding to abnormal tau. Binding was greatest in Broca's area, where degeneration begins in nfPPA, and, to a lesser extent, in the posterior node of the syntactic network. The arcuate fasciculus was thinned in the left hemisphere suggesting that it is the pathway traveled by misfolded proteins associated with neuronal and axonal degeneration. Our findings provide *in vivo* evidence that, in neurodegenerative dementia, misfolded tau propagates in a prion-like manner.

Disclosures: J.C. Masdeu: 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, Biogen, Avanir, Novartis, Abbvie, Jannssen. F. Consulting Fees (e.g., advisory boards); General Electric Healthcare. **B. Pascual:** None. **Q. Funk:** None. **E. Rockers:** None. **P. Zanotti-Fregonara:** None. **M. Yu:** None. **N. Pal:** None. **C. Karmonik:** None. **B. Spann:** None. **G. Roman:** None. **P. Schulz:** None.

Nanosymposium

188. Alzheimer's Disease and Other Dementias: Tau and TDP-43 Proteinopathies

Location: SDCC 5

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 188.06

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

Support: ALS ASSOCIATION STARTER GRANT

Title: Reduced C9ORF72 function exacerbates gain-of-toxicity from ALS/FTD-causing repeat expansion in C9ORF72

Authors: *Q. ZHU[1], J. JIANG[1], T. GENDRON[2], M. MCALONIS-DOWNES[1], P. KING[1], Y. ZHANG[2], M. MALDONADO[1], A. E. TAYLOR[3], S. GARCIA[4], M. J. RODRIGUEZ[4], B. MYERS[1], S. G. DASTIDAR[5], J. KIM[4], C. HEYSER[4], A. R. L. SPADA[5], L. PETRUCELLI[2], S. D. CRUZ[1], J. RAVITS[3], C. LAGIER-TOURENNE[6], D. W. CLEVELAND[1]
[1]Ludwig Inst., Univ. of California San Diego, LA Jolla, CA; [2]Neurosci., Mayo Clin., Jacksonville, FL; [3]UCSD, San Diego, CA; [4]Neurosciences, Univ. of California at San Diego, La Jolla, CA; [5]Duke Univ., Durham, NC; [6]Massachusetts Gen. Hosp., Cambridge, MA

Abstract: Hexanucleotide GGGGCC expansions in C9ORF72 are the most frequent genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). While repeat expansion has been established to produce one or more toxic products, in affected individuals the repeat expansion also reduces mRNAs encoding C9ORF72, a predicted guanine exchange factor. Using mice that express a human C9ORF72 gene with 450 repeats but which does not encode the C9ORF72 protein, we determine that disruption of one or both endogenous C9ORF72 alleles enhances cognitive deficits, hippocampal neuron loss, and glial activation. Reduction in C9ORF72 is also found to suppress repeat-mediated elevation in autophagy, accompanied by accelerated accumulation of dipeptide-repeat proteins produced by AUG-independent translation of repeat-containing RNAs. More strikingly, disruption of one or both endogenous C9ORF72 alleles provokes or accelerates premature death of animals overexpressing 66 GGGGCC repeats by means of somatic brain transgenesis mediated by adeno-associated virus respectively. These efforts provide direct support for disease mechanism in ALS/FTD from reduced C9ORF72 function synergizing with repeat-dependent gain-of-toxicity.

Disclosures: Q. Zhu: None. **J. Jiang:** None. **T. Gendron:** None. **M. McAlonis-Downes:** None. **P. King:** None. **Y. Zhang:** None. **M. Maldonado:** None. **A.E. Taylor:** None. **S. Garcia:** None. **M.J. Rodriguez:** None. **B. Myers:** None. **S.G. Dastidar:** None. **J. Kim:** None. **C. Heyser:** None. **A.R.L. Spada:** None. **L. Petrucelli:** None. **S.D. Cruz:** None. **J. Ravits:** None. **C. Lagier-Tourenne:** None. **D.W. Cleveland:** None.

Nanosymposium

188. Alzheimer's Disease and Other Dementias: Tau and TDP-43 Proteinopathies

Location: SDCC 5

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 188.07

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

Support: NIH: R21AG042066

Title: TDP-43 protein variants as biomarkers in frontotemporal dementia

Authors: *L. VENKATARAMAN[1], G. KHAN[2], B. T. HARRIS[2], M. R. SIERKS[1]
[1]Arizona State Univ., Tempe, AZ; [2]Neurol., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Frontotemporal dementia (FTD) is the second leading cause of early onset dementia following Alzheimer’s disease. It involves atrophy of the frontal & temporal regions of the brain affecting language, memory, & behavior. TDP-43 pathology is found in most FTD & ALS cases. It plays a role in transcription, translation & serves as a shuttle between the nucleus & cytoplasm. Prior to its aggregation, TDP-43 exists as polyubiquitinated, hyperphosphorylated C-terminal fragments that correlate well with FTD disease progression. Reagents that can selectively recognize specific TDP variants associated with onset & progression of FTD can be effective diagnostic & therapeutic tools. A combination of phage display library & AFM based panning was used to select biomarker candidates that selectively bound to TDP variants present in FTD individuals but not healthy controls. The scFvs were screened against TDP-43 immunoprecipitated from pooled FTD (n=3), ALS (n=2) & healthy, cognitively normal control brain tissue homogenates (n=2). Eight scFvs that had significantly higher binding to pooled FTD over healthy controls were selected for further characterization to be tested with individual FTD brain tissue homogenate. The scFv candidates were able to select individual FTD brain tissue homogenates (n=7) over healthy controls (n=5) in sandwich ELISA. To test the utility of these scFvs as potential blood based biomarkers for neurodegenerative diseases, we tested the anti-TDP scFvs with FTD-TDP (n=12), FTD-Tau (n=12) & healthy control sera (n=8). The scFvs readily selected the FTD sera samples over the controls indicating that these TDP variants are present in blood & may also serve as therapeutic targets.

Disclosures: L. Venkataraman: None. **G. Khan:** None. **B.T. Harris:** None. **M.R. Sierks:** None.

Nanosymposium

188. Alzheimer's Disease and Other Dementias: Tau and TDP-43 Proteinopathies

Location: SDCC 5

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 188.08

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

Support: The study is partly supported by the HKU Seed Funding for Basic Science Research (201311159171)

Title: Impact of silica nanoparticles-induced neurodegeneration and cognitive impairment, an example on the effect of environmental pollutant

Authors: *R. C. CHANG[1,2], R. YOU[1], Y. LIU[1,3], C. HUANG[1,3], H. W. LI[4], Y. S. HO[5]
[1]Lab. of Neurodegenerative Diseases, LKS Fac. of Medicine, Univ. of Hong Kong, Hong Kong, China; [2]State Key Lab. of Brain and Cognitive Sciences, The Univ. of Hong Kong, Hong Kong, China; [3]Dept. of Anaesthesiology, LKS Fac. of Medicine, The Univ. of Hong Kong, Hong Kong, China; [4]Dept. of Chemistry, Hong Kong Baptist Univ., Hong Kong, China; [5]Sch. of Nursing, The Hong Kong Polytechnic Univ., Hong Kong, China

Abstract: Silica nanoparticles(SiO_2-NPs) are one of the most broadly exploited nanomaterials and have been utilized in a variety of industries. They are also the most common component in a number of airborne pollutants, including mineral dust and particulate matter (PM),found in ambient air as well as circulated air in households and workplaces. Air pollution has been considered to be a risk factor for inducing Alzheimer's disease (AD). After inhalation, SiO_2-NPs penetrate the epithelium of the respiratory tract and are then translocated to the brain via either the circulatory system or the olfactory nerve. However, the role of SiO_2-NPs in neurodegeneration is largely unknown. Here, we evaluated the effects of SiO_2-NPs-exposure on behavior, neuropathology, and synapse in young adult mice and primary cortical neuron cultures. Male C57BL/6N mice (3 months old) were exposed to either vehicle (sterile PBS) or fluorescein isothiocyanate-tagged SiO_2-NPs (NP) using intranasal instillation. Behavioral tests were performed after 1 and 2 months of exposure. We observed decreased social activity at both time points as well as anxiety and cognitive impairment after 2 months in the NP-exposed mice. NP deposition was primarily detected in the medial prefrontal cortex and the hippocampus. Neurodegeneration-like pathological changes, including reduced Nissl bodies, increased tau phosphorylation, and neuroinflammation, were also present in the brains of NP-exposed mice. Furthermore, we observed NP-induced impairment in exocytosis along with decreased synapsin I and increased synaptophysin expression in the synaptosome fractions isolated from the frontal cortex as well as primary neuronal cultures. Extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) were also activated in the frontal cortex of NP-exposed mice. Moreover, inhibition of ERK activation prevented NP-mediated changes in exocytosis in

cultured neurons, highlighting a key role in the changes induced by NP exposure. In conclusion, intranasal instillation of SiO_2-NPs results in mood dysfunction and cognitive impairment in young adult mice and causes neurodegeneration-like pathology and synaptic changes via ERK activation. The results may explain why air pollution can be a risk factor for developing AD.

Disclosures: R.C. Chang: None. **R. You:** None. **Y. Liu:** None. **C. Huang:** None. **H.W. Li:** None. **Y.S. Ho:** None.

Nanosymposium

188. Alzheimer's Disease and Other Dementias: Tau and TDP-43 Proteinopathies

Location: SDCC 5

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 188.09

Topic: C.03. Parkinson’s Disease

Support: NIH Grant NS079858 to Z. Mao
NIH Grant AG023695 to Z. Mao
NIH Grant NS095269 to Z. Mao
Michael J. Fox Foundation to Z. Mao
NIH Grant AG058866 to W. LI
NNSF of China No. 31371400 to Q. Yang
NNSF of China No. 31671060 to Q. Yang

Title: Chaperone-mediated autophagy is activated by ER stress via p38 for dopaminergic neuron survival

Authors: *W. LI[1], J. ZHU[1,3], J. DOU[2], H. SHE[1], K. TAO[1,4], H. XU[1], Q. YANG[1,4], Z. MAO[1]
[1]Dept. of Pharmacol., [2]Dept. of Radiation Oncology, Emory Univ. Sch. of Med., Atlanta, GA; [3]New York Univ. at Buffalo, Buffalo, NY; [4]The Fourth Military Med. Univ., Xi'an, China

Abstract: The interplay between endoplasmic reticulum (ER) and lysosomes is essential for coordinating a network of key cellular processes in response to stress. How signals are transduced from ER to lysosomes remains elusive. Here we demonstrate that in dopaminergic neuron-like SN4741 cells, ER stress activates chaperone-mediated autophagy (CMA). ER stressors lead to a PERK-dependent activation and recruitment of MKK4 to lysosomes, activating a lysosomal pool of p38 MAPK. Lysosomal p38 MAPK directly phosphorylates the CMA receptor LAMP2A at T211 and T213, which induces its change to an active conformation and membrane accumulation and causes CMA activation. Loss of the ER-CMA coupling sensitizes cells to ER stress-induced death. Neurotoxins associated with Parkinson's disease fully engages ER-p38 MAPK-CMA pathway in the mouse brain and uncoupling it results in a greater loss of SNc dopaminergic neurons. Thus, CMA triggered by ER stress protects dopaminergic neurons from stress *in vitro* and *in vivo*.

Disclosures: W. Li: None. **J. Zhu:** None. **J. Dou:** None. **H. She:** None. **K. Tao:** None. **H. Xu:** None. **Q. Yang:** None. **Z. Mao:** None.

Nanosymposium

189. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC 25

Time: Sunday, November 4, 2018, 1:00 PM - 2:30 PM

Presentation Number: 189.01

Topic: C.03. Parkinson’s Disease

Support: CIHR Doctoral Award
MJFF

Title: The role of Parkinson's disease-linked lrrk2 protein at cortico- and thalamo-striatal synapses

Authors: *N. KUHLMANN[1], L. CAO[2], M. J. FARRER[2], A. J. MILNERWOOD[3]
[1]Neurosci., [2]Med. Genet., Univ. of British Columbia, Vancouver, BC, Canada; [3]McGill Univ., Montreal Neurolog. Inst., Montreal, QC, Canada

Abstract: The striatum is the gateway to the basal ganglia: GABAergic spiny projection neurons (SPNs) receive converging glutamatergic inputs from the cortex and the thalamus, as well as dopaminergic modulation from the substantia nigra, and form the sole output pathways. Altered striatal circuitry and plasticity is implicated in numerous psychiatric and neurodegenerative disorders, including Parkinson's disease (PD). While mutations in the PD-linked LRRK2 gene perturb several cellular functions, the effects on striatal plasticity are unknown. We previously reported that the LRRK2-G2019S mutation increases glutamatergic transmission in cultured cortical neurons and striatal slices from young G2019S knock-in (GKI) male mice, suggesting a role in early pathophysiology. However, glutamatergic inputs from the cortex and thalamus differ considerably in their striatal synaptic targets, NMDA/AMPA ratios, plasticity and vulnerability in PD, with a substantial loss of thalamic inputs in PD patients and animal models. Thus, we sought to examine whether the LRRK2-G2019S mutation has pathway-specific effects, using selective optogenetic activation of cortical or thalamic inputs while recording from SPNs in striatal slices from 2-month-old male GKI and wild-type (WT) littermates. We report that both pathways show greater initial glutamatergic release followed by rapid depletion, as evidenced by a decrease in light-evoked paired-pulse ratios and stability of responses over time. We further examined whether there were any input-specific differences in mGluR-dependent LTD, and whether these effects could be rescued by acute inhibition of LRRK2 kinase activity. This work extends the LRRK2 literature by demonstrating early pathophysiological changes in both cortical and thalamic evoked glutamatergic release, and examines the potential for therapeutic intervention by modulating LRRK2 kinase activity.

Disclosures: L. Cao: None. **M.J. Farrer:** None. **A.J. Milnerwood:** None.

Nanosymposium

189. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC 25

Time: Sunday, November 4, 2018, 1:00 PM - 2:30 PM

Presentation Number: 189.02

Topic: C.03. Parkinson's Disease

Support: Parkinson Society of Canada
CIHR
CERC

Title: Effects of LRRK2 kinase inhibition on cellular phenotypes in a VPS35 p.D620N knock-in mouse model of Parkinson's disease

Authors: *C. KADGIEN[1], M. FARRER[2], A. J. MILNERWOOD[3]
[2]Ctr. for Applied Neurogenetics, [1]Univ. of British Columbia, Vancouver, BC, Canada; [3]McGill Univ., Montreal Neurolog. Inst., Montreal, QC, Canada

Abstract: The pathogenic D620N (DN) mutation in vacuolar protein sorting 35 (VPS35) is linked to late-onset, autosomal-dominant Parkinson's disease (PD). VPS35 is a core component of the retromer complex, a Rab effector involved in endosomal recycling and intracellular trafficking of multiple neurotransmitter receptors including GluA1-containing AMPARs. Here we explore retromer localization, binding of known interactors & novel cargoes, AMPAR trafficking, and early synaptic dysfunction in a novel D620N knock-in mouse model of PD. We have uncovered reduced WASH-complex binding to VPS35, accumulation of dendritic VPS35 clusters, and altered glutamatergic transmission in brains and cultured cortical neurons from knock-in animals. Mutations in another protein, LRRK2, are also linked to late-onset autosomal dominant Parkinson's disease and result in similar patterns of aberrant synaptic transmission in knock-in mouse models. LRRK2 co-immunoprecipitates with VPS35 and has been linked to glutamate and dopamine release and post-synaptic endosomal recycling of neurotransmitter receptors. Recent publications have identified Rab GTPases as substrates of the LRRK2 kinase domain. Here we use LRRK2 kinase inhibition to explore VPS35 and LRRK2 interactions that regulate synapse function in VPS35 knock-in and wild-type mice. Many genes linked to PD appear to be involved in synaptic transmission; thus, understanding the role of VPS35, LRRK2, and their functional interactions are important for uncovering how disruptions of neurotransmission lead to neurodegeneration in PD.

Disclosures: C. Kadgien: None. **M. Farrer:** None. **A.J. Milnerwood:** None.

Nanosymposium

189. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC 25

Time: Sunday, November 4, 2018, 1:00 PM - 2:30 PM

Presentation Number: 189.03

Topic: C.03. Parkinson’s Disease

Support: CIHR
Parkinson Canada
FRSQ

Title: Rab GTPases and the presynapse in Parkinson's disease

Authors: *A. KAMESH[1], A. J. MILNERWOOD[2]
[1]Montreal Neurolog. Inst., McGill Univ., Montreal, QC, Canada; [2]McGill Univ., Montreal Neurolog. Inst., Montreal, QC, Canada

Abstract: Vacuolar protein sorting 35 (VPS35) is one of three components of the retromer tricomplex that functions to regulate endosomal recycling. The D620N mutation in VPS35 causes autosomal dominant Parkinson’s disease (PD). Cardinal symptom development in patients with VPS35 D620N mutation are indistinguishable from idiopathic PD, therefore studying this mutation may provide invaluable insight into the etiology of PD. Cultured cortical neurons from VPS35 D620N knock-in mice (VKIs) have altered glutamate transmission, and dopamine release is augmented in the dorsolateral striatum of brain slices from VKI mice; however, it is unknown whether these synaptic alterations are mechanistically related, or not. Rab GTPases are involved in presynaptic vesicle cycling between endosome compartments and plasma membrane. We hypothesize that VPS35 D620N mutations in mice alter presynaptic Rab GTPase function similarly in cortical and nigrostriatal synapses, leading to changes in glutamate vesicle release in the cortex and dopamine vesicle release in the striatum. We conducted biochemical analysis of the levels and phosphorylation state of specific Rabs involved in vesicular trafficking (Rab 5, 7, 11, and 27), and immunofluorescence staining of VPS35, glutamate, and dopamine transporters (vGLUT1 and VMAT2, respectively). In addition to nigrostriatal dopamine release, corticostriatal and thalamostriatal glutamatergic inputs were assayed by optogenetic stimulation and recording of EPSCs in striatal projection neurons. Further identifying the mechanism by which VPS35 D620N mutations alter glutamate and dopamine transmission may uncover common therapeutic targets in VPS35 and idiopathic PD.

Disclosures: A.J. Milnerwood: None.

Nanosymposium

189. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC 25

Time: Sunday, November 4, 2018, 1:00 PM - 2:30 PM

Presentation Number: 189.04

Topic: C.03. Parkinson’s Disease

Support: Parkinson's Canada
FRQS

Title: Alterations in spindle coordination in the LRRK2-G2019S mouse model of Parkinson's disease

Authors: *Y. ZHANG[1], A. J. DUSZKIEWICZ[2], A. PEYRACHE[3], A. J. MILNERWOOD[4]
[1]Neurol. & Neurosurg., [2]Montreal Neurolog. Inst. and Hosp., [3]Montreal Neurolog. Inst., McGill Univ., Montreal, QC, Canada; [4]McGill Univ., Montreal Neurolog. Inst., Montreal, QC, Canada

Abstract: Parkinson’s disease (PD) is a progressive, multi-system disorder whose onset begins many years prior to clinical diagnosis (based on motor dysfunction), and manifests as a range of neurological and neuropsychiatric symptoms. Mutations in the LRRK2 gene are the most common cause of late onset PD, with mutation in the G2019S kinase domain conferring most risk. Many patients have reported experiencing major sleep disturbances early on in life; dopamine regulates sleep-wake cycles, and recent evidence suggests that dopamine function and transport are induced early on in PD. Young LRRK2-G2019S knock-in (LRRK2-KI) mice exhibit elevated dopamine/glutamate release and some phenotypes similar to dopamine-transporter (DAT)-depleted mice. DAT-depleted mice have disturbed sleep-wake cycles and altered sleep architecture. We examined these phenotypes in LRRK2-KI mice in the context of motor function and physiological alterations during sleep-wake cycles. Since sleep spindles are transmitted from the thalamus to the cortex via glutamatergic connections and synchronized via cortico-cortical excitation, we suspected that cortical and thalamic glutamatergic regulation of spindle entrainment would be altered in the LRRK2-KI model. LRRK2-KI mice were bilaterally implanted with electrode arrays in frontal/parietal cortices to reveal coordination of sleep spindles across the cortex. We also tested LRRK2 kinase inhibition for physiological and behavioral rescue, in hopes of further validating LRRK2 as a target for PD neuroprotection. Results in LRRK2-KI mice will be compared with VPS35-KI PD mutants.

Disclosures: Y. Zhang: None. **A.J. Duszkiewicz:** None. **A. Peyrache:** None. **A.J. Milnerwood:** None.

Nanosymposium

189. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC 25

Time: Sunday, November 4, 2018, 1:00 PM - 2:30 PM

Presentation Number: 189.05

Topic: C.03. Parkinson's Disease

Support: Healthy Brains for Healthy Lives (BV)
Fonds de Recherche Sante Quebec (BV, AJM)
Canadian Institutes for Health Research (SEM, MJF)
Parkinson Canada (CAK, AJM)
Canada Excellence Research Chairs (MJF)
Michael J Fox Foundation (AJM)
Ellen Foundation (AJM)

Title: Influence of genetic background on induced synucleinopathy in neuronal models of Parkinson's disease

Authors: *B. VIEIRA[1], S. E. MACISAAC[2], C. A. KADGIEN[2], M. J. FARRER[2], A. J. MILNERWOOD[1]
[1]Neurol. & Neurosurg., Montreal Neurolog. Inst., Montreal, QC, Canada; [2]Neurosci., Ctr. for Applied Neurogenetics, Vancouver, BC, Canada

Abstract: Parkinson's disease (PD) is pathologically defined by aggregates composed of the protein alpha-synuclein (α-syn) known as Lewy Bodies (LBs) and Lewy Neurites (LNs). Interestingly, α-syn is normally enriched in presynaptic terminals but, for reasons unknown, misfolds into abnormal toxic conforms (oligomers, or fibrils) in PD. Transformation of α-syn is believed to impair multiple cellular processes (axonal transport, endo/lysosomal sorting, ubiquitin-proteasome and mitochondria) that may ultimately lead to cell death. Although treatments are effective for some motor symptoms, none prevent or slow the progression of the disease.
Mutations in α-syn, LRRK2 and VPS35 cause autosomal dominant late-onset parkinsonism that is similar to idiopathic PD. Importantly, these proteins are all involved in regulating endosome/lysosome protein sorting in neurons.
We investigated toxic α-syn treatment, inoculated as pre-formed fibrils (PFFs), and its effects upon neuronal survival, neuritic architecture, aberrant α-syn phosphorylation and aggregation. In cultures from WT, LRRK2 knock-out (LKO) and LRRK2 G2019S knock-in (GKI), cortical neurons are differentially sensitive to PFF-induced damage. Learning from mouse data, we have extended the assay into human neuron scenarios.
Indeed, LKO neurons are protected, whereas GKIs are more vulnerable to PFF-induced toxicity. In addition, levels of the lysosome protein LAMP1 are increased upon PFF treatment and

LAMP1 is basally elevated in resistant LKO neurons. Conversely, vulnerable GKI neurons exhibit base elevations in the autophagy marker p62, suggesting autophagic impairment, which might contribute to increased vulnerability. Thus, the endo-lysosomal pathways may be manipulated to increase resistance to α-syn pathology, and potentially provide neuroprotective targets for PD.

Disclosures: B. Vieira: None. **S.E. Macisaac:** None. **C.A. Kadgien:** None. **M.J. Farrer:** None. **A.J. Milnerwood:** None.

Nanosymposium

189. Parkinson's Disease: LRRK2 Mechanisms, Targets, and Pathways

Location: SDCC 25

Time: Sunday, November 4, 2018, 1:00 PM - 2:30 PM

Presentation Number: 189.06

Topic: C.03. Parkinson’s Disease

Support: Parkinson Center of Oregon Pilot Grant
NIH Grant 1R35GM124780

Title: Genetic modifiers of lrrk2 g2019s parkinson's disease-related phenotypes in *Drosophila*

Authors: *I. MARTIN[1], S. LAVOY[1], V. CHITTOOR[1], C. CHOW[2]
[1]Oregon Hlth. and Sci. Univ., Portland, OR; [2]Univ. of Utah, Salt Lake City, UT

Abstract: Disease phenotypes can be variable among carriers of a pathogenic mutation. Background genetic variation is a strong driver of disease variability, in addition to differences in age and environmental exposure. To investigate the genotype-phenotype relationship that determines the expressivity of a pathogenic mutation, numerous genetic backgrounds must be studied. This can be efficiently achieved using model organism collections such as the *Drosophila* Genetic Reference Panel (DGRP). We use the DGRP to determine the impact of genetic background on the locomotor phenotype of a LRRK2 G2019S *Drosophila melanogaster* model of Parkinson’s disease. We uncovered variability in the LRRK2 G2019S locomotor phenotype in different DGRP backgrounds and identified candidate genetic modifiers via a genome-wide association study. Genes involved in the outgrowth and regulation of neuronal projections are enriched in these candidate modifiers. RNAi functional testing of candidates nominated by GWAS reveals several targets that modify both age-related dopamine neuron loss and associated locomotor dysfunction in the *Drosophila* LRRK2 G2019S model. These results demonstrate how natural genetic variation can be used as a powerful tool to identify genes that modify disease-related phenotypes.

Disclosures: I. Martin: None. **S. Lavoy:** None. **V. Chittoor:** None. **C. Chow:** None.

Nanosymposium

190. Stroke Recovery: Non-Pharmacological Approaches and Novel Diagnostics

Location: SDCC 32

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 190.01

Topic: C.09.Stroke

Support: NIH grant AG045656
ALZHEIMER ASSO ZEN-15-321972

Title: Brain repair via *in situ* astrocyte-to-neuron conversion

Authors: *G. CHEN[1], Z. GUO[1], L. ZHANG[1], Y. CHEN[1], J. YIN[1], Z. WU[1], Y. WANG[1], L. GE[2]
[1]Biol., Penn State Univ., University Park, PA; [2]Chinese Acad. of Sciences, Inst. of Zoology, Kunming, China

Abstract: Glial scar is widely associated with brain and spinal cord injury, stroke, glioma, and neurodegenerative disorders such as Alzheimer's disease. Reactive glia initially exert neuroprotective role but later form glial scar to inhibit neuroregeneration. **Currently, there is no effective way to reverse glial scar back to neural tissue**. We have recently developed an innovative *in vivo* cell conversion technology to directly convert reactive glial cells into functional neurons inside the mouse brain (**Guo et al., Cell Stem Cell, 2014, selected as BEST of 2014 article**). This is achieved through *in vivo* expression of a single neural transcription factor NeuroD1 in the reactive astrocytes in injured mouse brain or Alzheimer's disease mouse model. **Our *in vivo* cell conversion technology makes use of internal glial cells to regenerate new neurons with 90% conversion efficiency, making it possible for the first time in history to reverse glial scar back to neural tissue**. Such internal cell conversion method will avoid cell transplantation and immune rejection. **More importantly, our recent study in a stroke model demonstrated that in vivo neuroregeneration efficiency can be as high as 100 times of the internal regeneration capability in the cerebral cortex after injury, an unprecedented efficiency in regenerative medicine**. We have further discovered a cocktail of small molecules that can directly convert cultured human astrocytes into functional neurons (**Zhang et al., Cell Stem Cell, 2015**), paving the way for a potential drug therapy for human brain repair. We have also successfully converted reactive glial cells into neurons using NeuroD1 in non-human primate brains, making an important step toward future clinical trials.
This project was supported by grants from NIH, Alzheimer's Association, and Charles H. Skip Smith Endowment Fund. G.C. is Verne M. Willaman Chair in Life Sciences at Penn State University.

Disclosures: G. Chen: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); I am a co-founder

of NeuExcell Therapeutics Inc.. **Z. Guo:** None. **L. Zhang:** None. **Y. Chen:** None. **J. Yin:** None. **Z. Wu:** None. **Y. Wang:** None. **L. Ge:** None.

Nanosymposium

190. Stroke Recovery: Non-Pharmacological Approaches and Novel Diagnostics

Location: SDCC 32

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 190.02

Topic: C.09.Stroke

Support: NIH Grant R01-AG033570
NIH Grant RC1-AG036208-01
UIC Grant CCTS-0512-06
AHA Grant 15PRE25080088
NIH Grant T32-HL007692-25
NIH Grant P01-AI089556

Title: Treatment with activated mesenchymal stem cells increases long-term functional recovery following ischemic stroke via reduction of microglia activation and induction of oligodendrogenesis

Authors: *M. K. TOBIN[1], K. LOPEZ[1], M. R. PERGANDE[2], A. M. BARTHOLOMEW[3], S. M. COLOGNA[2], O. LAZAROV[1]
[1]Anat. and Cell Biol., [2]Chem., [3]Surgery, Bioengineering, Univ. of Illinois at Chicago, Chicago, IL

Abstract: Stroke is the most common cause of adult disability worldwide with few treatment options and normal brain repair mechanisms fail to promote recovery. The mechanisms behind this failure are largely unknown but loss of trophic support as well as contribution of inflammation have been posited as important mediators of the failure of endogenous repair mechanisms. To address this lack of understanding we utilized both *in vitro* studies as well as a rat model of ischemic stroke. Further, because mesenchymal stem cells (MSCs) secrete various neurotrophic factors and are known to dampen immune responses we examined their efficacy for treating stroke. Activation with interferon-γ has been shown to enhance the paracrine effects of MSCs so our studies utilized both naïve MSCs (nMSC) as well as interferon-γ-activated MSCs (aMSCγ). Rats administered MSCs have a more rapid and sustained improvement compared to vehicle treated animals with improvements in both sensory and motor deficits with significantly reduced infarct volumes. Furthermore, 1 week after stroke both nMSC and aMSCγ significantly reduce microglia activation which is sustained 3 weeks after stroke suggesting that functional recovery results from attenuation of post-stroke inflammation. Interestingly, primary microglia treated with MSC conditioned media exhibit a reduction in expression of the proinflammatory cytokines IL-6 and TNF-α up to 48 hours in culture with increases of the pro-regenerative IL-10

and IL-4 up to 7 days in culture suggesting that MSCs convert microglia from a proinflammatory phenotype to an anti-inflammatory phenotype. In contrast to previous literature, we see reductions in proliferation in the SVZ in vehicle treated animals with no changes in new neurons or oligodendrocytes after stroke. With MSC treatment, however, there is rescue of total cell proliferation in the SVZ as well as an increase in oligodendrocyte progenitor cells 24 hours after stroke suggesting that MSC treatment induces oligodendrocyte differentiation. This is substantiated by *in vitro* studies demonstrating that neural stem cells grown in conditioned media from nMSC, and to a larger extent aMSCγ, differentiate into oligodendrocytes. Moreover, 1 week after stroke, aMSCγ treated animals have increased myelin levels in the ipsilateral hemisphere compared to vehicle and nMSC treated animals suggesting that not only do aMSCγ induce oligodendrocyte differentiation but these cells become myelinating oligodendrocytes. Taken together, these results suggest that aMSCγ improve functional recovery following ischemic stroke by decreasing post-stroke inflammation and promoting myelin-producing oligodendrocytes.

Disclosures: M.K. Tobin: None. **K. Lopez:** None. **M.R. Pergande:** None. **A.M. Bartholomew:** None. **S.M. Cologna:** None. **O. Lazarov:** None.

Nanosymposium

190. Stroke Recovery: Non-Pharmacological Approaches and Novel Diagnostics

Location: SDCC 32

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 190.03

Topic: C.09.Stroke

Support: Leducq Foundation

Title: Activity dependent optimization of vascular function after stroke

Authors: *M. BALBI, D. XIAO, L.-P. BERNIER, M. VANNI, J. BOYD, J. LEDUE, B. MACVICAR, T. H. MURPHY
Psychiatry, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Stroke represents a leading cause of death and disability worldwide. Optogenetic stimulation used to enhance stroke recovery has shown potential benefits when applied weeks after injury. However, benefits of acute brain stimulation have not been reported. Changes in gamma oscillations (20-50 Hz) have been observed in several neurological disorders but the relationship between gamma oscillations and cellular pathologies is unclear. We investigated the effect of the gamma-wave modulation in the acute phase - within 1 hr - after stroke. We combined multimodal approaches employing optogenetics in conjunction with laser speckle imaging, two photon microscopy, electrophysiology and behavioral tasks. Transgenic VGAT-ChR2 mice were implanted with a transcranial chronic window and subjected to photothrombotic

stroke while awake in the target area of somatomotor cortex. Optogenetic stimulation at 40 Hz ipsilateral to the stroke side resulted in a significantly higher increase in blood flow over the course of the first week following stroke (Stroke n= 8 vs Stroke + stimulation n= 10: p= 0.0148). Stroke area and stroke volume were significantly reduced in mice that received the stimulation (Area: Stroke n= 8 vs Stroke + stimulation n= 10, p= 0.0010; Volume: Stroke n= 8 vs Stroke + stimulation n= 10, p= 0.0249). Assessment of motor function showed a significant improvement over time in mice that received stimulation (NDS: Stroke n= 8 vs Stroke + stimulation n= 10, p< 0.0001. Tapered beam test: Stroke n= 9 vs Stroke + stimulation n= 10, Group x time effect: p <0.0001). Microglia activation was assessed to investigate whether the stimulation at this specific frequency would induce local activation of these cells. Electrophysiological recordings *in vivo* showed an increase in synchronization in the areas associated to the stimulated one. Two photon microscopy was used to characterize the effects of stimulation on interneurons and excitatory cells. In this study, we describe the beneficial effects of acute, 40 Hz brain stimulation at gamma range: reduced lesion volume and improved motor function after stroke.

Disclosures: M. Balbi: None. **D. Xiao:** None. **L. Bernier:** None. **M. Vanni:** None. **J. Boyd:** None. **J. LeDue:** None. **B. MacVicar:** None. **T.H. Murphy:** None.

Nanosymposium

190. Stroke Recovery: Non-Pharmacological Approaches and Novel Diagnostics

Location: SDCC 32

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 190.04

Topic: C.09.Stroke

Support: NIH NINDS R35 NS097265

Title: Food for thoughts: Imaging the dietary effects on brain ischemic stroke

Authors: *I. SHAKED, R. LIU, C. MATEO, B. FRIEDMAN, D. KLEINFELD
Univ. of California At San Diego, LA Jolla, CA

Abstract: Among diseases characterized by cerebrovascular inflammation, ischemic stroke presents a major threat to human health, killing about 200 thousand people annually in the United States alone. **However, mechanistic evidence of the instantaneous inflammatory response to cerebrovascular injury, which initiates infarcts, is missing.**
Ischemic stroke follows the formation of blood clots inside brain blood vessels. Paradoxically, these clots may be stabilized by proximate feedback, such as hyper-immune cell activation. As a means to understand these processes and modify them, it is crucial to be able to monitor clot formation in real time. Toward this essential goal, I have applied my background in neuro-immunology (*Shaked et al. 2009 Immunity; Wang & Shaked 2013 Immunity*; *Shaked et al. 2015 Nat Immunol*) to my current investigation of the initiation of vascular stroke at the level of a

single vessel, an area of research pioneered in the Kleinfeld laboratory. My background has allowed me to bring a new focus to the laboratory and address the role of platelet-neutrophil interactions. These are a potential initiating step in cerebrovascular clot formation. Herein, I'll present state-of-the-art in vivo imaging of cerebral blood flow in individual cerebral vessels in mice, concurrent with the delivery of amplified ultra-short laser pulses target microscopic lesions to the wall of a targeted microvessel (*Nishimura et al. 2006 Nat Meth*). I further show the effect of hyperlipidemia and hyperglycemia on the immediate and early inflammatory response to vascular injury and cerebral blood flow. Our data demonstrate that delivery of minimal laser pulses (which corresponds to a fluence of $F_T \sim$1-5J/cm^2), which hardly have effect under normal conditions, are sufficient under metabolic burden (hyperlipidemia and hyperglycemia) to induces significant blood clots, containing activated platelets and neutrophils. These data are a step contributing to our understanding of the linkage between metabolic and inflammatory burden in the context of brain blood supply.

Disclosures: I. Shaked: None. **R. Liu:** None. **C. Mateo:** None. **B. Friedman:** None. **D. Kleinfeld:** None.

Nanosymposium

190. Stroke Recovery: Non-Pharmacological Approaches and Novel Diagnostics

Location: SDCC 32

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 190.05

Topic: C.09.Stroke

Support: Croatian Science Foundation under the project IP-06-2016-1892
European Regional Development Fund, Operational Programme Competitiveness and Cohesion, grant agreement No. KK.01.1.1.01.0007, CoRE - Neuro

Title: *In vivo* bioluminescence imaging shows an increase of Gap43 and Casp3 activity in Tlr2-deficient mouse brain after ischemic lesion

Authors: *S. GAJOVIC[1], D. GORUP[1], S. SKOKIC[1], J. KRIZ[2]
[1]Univ. of Zagreb Sch. of Med., Zagreb, Croatia; [2]Laval Univ., Quebec, QC, Canada

Abstract: Tlr2-deficient mice have reduced neuroinflammation after brain ischemic lesion. Following necrosis after ischemia, TLR2 (Toll-like receptor 2) proteins recognize DAMPs (damage associated molecular patterns) and activate innate immune response in the brain. The aim of this study was to evaluate the consequences of Tlr2-deficiency accompanied by reduced inflammation on brain repair after ischemic lesion. To monitor time evolution of brain response after ischemic lesion, in vivo imaging was used. The lesion size was assessed by MRI (magnetic resonance imaging), and the molecular events by BLI (bioluminescence imaging). For BLI, Gap43-luc/GFP transgenic mice was used to get advantage of two different imaging modalities.

Using free luciferin as a substrate, the insight in Gap43 activity (corresponding to the axonal outgrowth and repair) was obtained. In another approach, the caged luciferin, DEVD-luciferin (VivoGlo, Promega), was cleaved through enzymatic activity of caspase and released in free form to react with luciferase. This enabled to image Casp3/7 activity being a marker for neural stress and apoptosis after ischemic lesion. Tlr2 loss-of-function male mice were compared to their wild type controls. Ischemic lesion was induced by tMCAO (transient medial cerebral artery occlusion) for 60 min, and brain imaging and analysis were performed in four time points until 28 days after ischemia. MRI was performed by 7T Bruker BioSpec 70/20 USR, and BLI by Perkin Elmer IVIS Spectrum. The functional test of animal behavior and protein analysis by Western blot of brain samples complemented imaging data. The multimodal imaging allowed to correlate the photon flux recorded by BLI to the lesion size obtained by MRI. This enabled normalizing the bioluminescence signal among different animals, which resulted in statistically significant differences between tested (Tlr2-deficient) and control group. In Tlr2-deficient mice Gap43 bioluminescence was higher until 28 days after ischemia, and Casp3/7 activity increased 14 days onward as compared to the wild type animals. Synaptic markers DLG4 and synaptophysin were higher in Tlr2-deficient mice. In conclusion, multimodal in vivo imaging showed enhanced elements of repair in Tlr2-deficient mice.

Disclosures: S. Gajovic: None. **D. Gorup:** None. **S. Skokic:** None. **J. Kriz:** None.

Nanosymposium

190. Stroke Recovery: Non-Pharmacological Approaches and Novel Diagnostics

Location: SDCC 32

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 190.06

Topic: C.09.Stroke

Support: CIHR I-26004

Title: Reduced expression of conserved dopamine neurotrophic factor in the platelets of stroke patients

Authors: *R. K. MISHRA[1], H. JOSHI[2], S. GABRIELE[2], A. SIDDIQI[2], M. RATHBONE[2], W. OCZKOWSKI[2], B. CONNOLLY[2], D. BARANOWSKI[2], J. GABRIELE[2]
[1]Psych & Behav Sci., McMaster Univ. Hsc-4N 78, Hamilton, ON, Canada; [2]McMaster Univ., Hamilton, ON, Canada

Abstract: Stroke, a leading cause of adult disability, recovery, and rehabilitation, is still not well understood at the molecular level. Recently, there has been an increasing effort to understand the biochemical and molecular mechanisms of recovery and neuronal plasticity. Neurotrophic factors (NTFs) are an important group of secreted proteins regulating the development, maintenance, function, and plasticity of neuronal populations. NTFs have been receiving more

attention as potential therapeutics with regards to assisting in recovery in various models of stroke. Cerebral dopamine neurotrophic factor (CDNF) is a vertebrate specific paralogue derived from the same ancestral gene of human MANF, but is thought to have a different function. The role of CDNF in neuro-inflammation has been investigated with respect to Parkinson's Disease, bipolar disorder, and other psychiatric disorders. Recently, there is emerging research linking CDNF expression to therapeutic recovery in stroke. Expression of CDNF has been detected throughout the human brain. Additionally, CDNF expression is also detected in non-neuronal tissues such as the heart, liver, lungs, skeletal muscles, spleen, testis, and thymus. The objective of this study was to investigate CDNF mRNA expression in peripheral blood of patients with stroke. Recent studies have demonstrated that alterations of gene expression in peripheral blood are characteristic of a wide range of diseases including neuronal injuries and cancer. Two cohorts (n=54 controls, n=23 stroke; n=94 controls, n=44 stroke) of stroke patients along with control subjects were recruited. Peripheral blood was collected and RNA from platelets was extracted. CDNF gene expression in platelets was quantified by real time qPCR. In both cohorts of patients, CDNF expression was significantly ($p < 0.01$) reduced (first cohort 70% reduction, second cohort 46% reduction) in platelets of stroke patients compared to those of control subjects. There were no age related changes in CDNF expression. Since most of the stroke subjects were on medication, it is difficult to conclude whether the reduction in CDNF expression was due to stroke or therapeutics. In conclusion, these studies demonstrate the translation of neurological event into a peripheral circulatory change and further studies could be directed towards the interplay of CNS, hematopoietic derivatives and utilizing CDNF as a therapeutic tool. This work was supported by CIHR, Canada

Disclosures: R.K. Mishra: None. **H. Joshi:** None. **S. Gabriele:** None. **A. Siddiqi:** None. **M. Rathbone:** None. **W. Oczkowski:** None. **B. Connolly:** None. **D. Baranowski:** None. **J. Gabriele:** None.

Nanosymposium

190. Stroke Recovery: Non-Pharmacological Approaches and Novel Diagnostics

Location: SDCC 32

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 190.07

Topic: C.09.Stroke

Support: NIH Grant R21NS099869

Title: Nanoelectroporated cells for brain injury therapy

Authors: *N. HIGUITA-CASTRO[1], J. MOORE[2], M. BALCH[1], H. N. HARRIS[1], W. LAURENCE[1], R. STEWARD[1], A. SUNYECZ[1], C. K. SEN[1], S. KHANNA[1], C. L. RINK[1], D. GALLEGO-PEREZ[1,2]
[1]Dept. of Surgery, [2]Dept. of Biomed. Engin., The Ohio State Univ., Columbus, OH

Abstract: Angiogenic cell therapies promote nerve repair and neurological recovery by providing growth factors and scaffolding to support nerve growth. Current approaches rely on the use of progenitor stem-like cells, which pose significant risks due to uncontrolled differentiation, tumorigenesis, genetic abnormalities, etc. Although induced-endothelial cells (iECs) derived through direct cell reprogramming could present a safer alternative, currently there is no example of directly reprogrammed iECs for brain injury therapies. Moreover, reprogramming methodologies rely heavily on viral vectors, which pose additional safety concerns. We developed a novel non-viral approach to generate iECs through nanochannel-mediated direct cell reprogramming. Here we are reporting for the first time on the use of iECs for the implementation of angiogenic cell therapies for the injured brain. Skin fibroblasts were reprogrammed into iECs using a novel transcription factor cocktail of Etv2, Foxc2, and Fli1 (EFF). These iECs were subsequently injected intracranially to increase brain perfusion and functional recovery in mice with ischemic stroke. Once brain injury was confirmed, the mice were intracranially injected with EFF-iECs or control fibroblasts (CT). MRI, open field test, laser speckle imaging (LSI) and immunohistochemistry (IHC) were used to evaluate the response of the injured brain to iEC-based therapy. No negative changes in mice well-being were observed as a result of intracranial cell delivery. MRI analysis shows that injured brains treated with EFF-iECs exhibit an 80% recovery from injury. Brains treated with CT show less than 40% recovery. Similarly, open field tests indicate that mice treated with EFF-iECs show about a 70% improvement in locomotion vs. <40% for CT. LSI revealed a significant increase in brain perfusion in response to EFF-iEC therapy compared to CT. IHC also revealed increased tissue vascularization based on stromal overexpression of endothelial markers such as Pecam-1 and vWF. Our results established the ability of iECs derived from mouse fibroblasts to increase brain tissue perfusion *in vivo* both in healthy and injured brains. We report that EFF-iECs have the ability to induce a remarkable increase in blood flow in injured brains, thus suggesting that iECs can modulate the formation of blood-conducting vasculature in the injured brain *in vivo*. Our results show the feasibility of using iEC-based cell therapies to aid tissue repair and functional recovery after brain injury.

Disclosures: N. Higuita-Castro: None. **J. Moore:** None. **M. Balch:** None. **H.N. Harris:** None. **W. Laurence:** None. **R. Steward:** None. **A. Sunyecz:** None. **C.K. Sen:** None. **S. Khanna:** None. **C.L. Rink:** None. **D. Gallego-Perez:** None.

Nanosymposium

190. Stroke Recovery: Non-Pharmacological Approaches and Novel Diagnostics

Location: SDCC 32

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 190.08

Topic: C.09.Stroke

Support: NIH NRSA F31NS105486

Title: Corticospinal tract morphometry at the cervical spinal cord in chronic hemiparetic stroke

Authors: *H. KARBASFOROUSHAN[1], J. COHEN-ADAD[3], J. P. DEWALD[2]
[1]Neurosci., [2]Physical Therapy and Human Movement Sci., Northwestern Univ., Chicago, IL; [3]MGH - Harvard Med. Sch., Charlestown, MA

Abstract: Previous neuroimaging studies of individuals with chronic stroke have frequently tested the morphological changes (e.g. white matter integrity/ volume) of corticospinal tract in the brain. However, white matter changes of corticospinal tract in spinal cord in these individuals has never been tested. Considering that lateral corticospinal tract passes through a very distinct region (posterior and lateral portion) of the spinal cord, it allows us to test the white matter integrity of damaged corticospinal tract post hemiparetic stroke. The goal of this study therefore is to use high resolution anatomical MRI and DTI of cervical spinal cord and novel analyses approaches to test the morphological changes of lateral corticospinal tract post stroke. 20 individuals with chronic (>1yr) hemiparetic subcortical stroke and 20 age-matched controls were recruited to participate in this study. The MRI scans were collected on a 3T Siemens Trio magnetic resonance scanner at the Northwestern University Center for Translational Imaging. High resolution T2-weighted anatomical and diffusion weighed images were obtained over C1-C5. T2 weighted images were acquired with 0.8 x 0.8 x 0.8 isotropic resolution. DTI used spin echo single-shot echo planner imaging with b=1000 in 30 directions, 4 averages, four images with b=0 and resolution of 0.8 x 0.8 x 5 mm. Images were inspected and excluded from analysis if image quality was poor. Quantitative analysis of white matter integrity was done using Spinal Cord Toolbox (SCT) V.3.1.0, including spinal cord segmentation, registration to the probabilistic SCT template and extraction of metrics (fractional anisotropy) with partial volume correction. Voxel wise analysis over all spinal cord FA maps was continued in SPM12 in Matlab 2018b. Using voxel-wise corrected p value < 0.001 and p cluster-level corrected < 0.05, the white matter regions with decrease white matter integrity were identified. The stroke patients compared to healthy controls showed significant decrease in white matter integrity of lateral corticospinal tract of paretic side. ROIs analysis of lateral corticospinal tract also illustrated significant decrease in paretic side of individuals with stroke compared to age-match controls.

Disclosures: H. Karbasforoushan: None. **J. Cohen-Adad:** None. **J.P. Dewald:** None.

Nanosymposium

190. Stroke Recovery: Non-Pharmacological Approaches and Novel Diagnostics

Location: SDCC 32

Time: Sunday, November 4, 2018, 1:00 PM - 3:15 PM

Presentation Number: 190.09

Topic: C.09.Stroke

Support: NIH NICHD Grant K01HD079584
NIH NICHD Grant K12HD055931

Title: Influence of descending cortical projections on spinal reflex excitability in post-stroke individuals

Authors: *A. J. LOPEZ[1], J. XU[2], S. P. EICHOLTZ[2], M. R. BORICH[2], T. M. KESAR[2]
[1]Atlanta, GA; [2]Rehabil. Med., Emory Univ., Atlanta, GA

Abstract: Combining peripheral electrical stimulation with transcranial magnetic stimulation (TMS) at specific inter-stimulus intervals can index descending corticofugal influences on spinal reflex excitability. Subthreshold TMS pulses sent before or after peripheral nerve stimulation modulates the Hoffmann's reflex (H-reflex). Short-latency facilitation (SLF) of the H-reflex occurs when a TMS pulse is sent 1-5 ms *after* peripheral nerve stimulation, and long-latency facilitation (LLF) occurs when a TMS pulse is delivered *before* peripheral nerve stimulation. Post-stroke individuals have abnormally elevated spinal reflex excitability. However, the influence of descending corticofugal projections on spinal alpha motoneurons for post-stroke individuals remains unknown. The purpose of this study was to evaluate the influence of these projections on spinal reflex excitability in post-stroke individuals using TMS-conditioned H-reflex responses. Ten neurologically-unimpaired, adult participants (8 females, 2 males; 24 ± 3 years-old) and eight post-stroke participants (6 females, 2 males; 60 ± 4 years-old) completed a single experimental session. The unconditioned (UC) H-reflex was obtained by delivering peripheral nerve stimulation to the posterior tibial nerve at an intensity that elicited an H-reflex amplitude at 20% Mmax in the soleus muscle. Subsequently, SLF and LLF (conditioned H-reflexes) were collected in an analogous manner. For SLF, TMS was delivered over the soleus motor cortex hotspot 1.5 ms following peripheral nerve stimulation. For LLF, TMS was delivered 10 ms before peripheral stimulation. Subthreshold TMS (85% of resting motor threshold) was delivered for both SLF and LLF conditions. For post-stroke individuals, compared to UC H-reflex amplitude, conditioned H-reflex amplitude was significantly greater for LLF ($p < .005$), but not significantly greater for SLF ($p > .22$). Also, LLF was significantly greater than SLF ($p < .01$). Stroke survivors showed a significant reduction in SLF compared to able-bodied ($p < .03$). These results provide the first characterization of SLF and LLF in individuals post-stroke. Reduced excitability of direct descending corticofugal projections in individuals post-stroke may be related to reduced descending inhibition of spinal segmental reflexes, resulting in heightened spinal reflex excitability. Our future work will aim to determine how the excitability of descending cortical projections onto spinal motor neurons is modulated by rehabilitation interventions.

Disclosures: A.J. Lopez: None. **J. Xu:** None. **S.P. Eicholtz:** None. **M.R. Borich:** None. **T.M. Kesar:** None.

Nanosymposium

191. Auditory Processing: Adaptation, Learning, and Memory

Location: SDCC 24

Time: Sunday, November 4, 2018, 1:00 PM - 2:30 PM

Presentation Number: 191.01

Topic: D.06. Auditory & Vestibular Systems

Support: ERC grant to IN (project RATLAND)

Title: Adaptation to simple sounds in the auditory field of insular cortex in anesthetized rats

Authors: *M. M. JANKOWSKI[1,2], A. POLTEROVICH[1,2], A. KAZAKOV[1,2], A. YARON[1,2], I. NELKEN[1,2]
[1]Edmond and Lily Safra Ctr. for Brain Sci., [2]The Dept. of Neuroscience, The Silberman Inst. of Life Sci., The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: The insular cortex is multi-modal cortical structure of mammalian brain composed of functionally distinct subregions characterized by different patterns of connectivity with other brain areas. Rat Insular cortex possess an auditory responsive field which is anatomically separated from other auditory cortical fields. While simple sound response properties of neurons in the insular auditory field have been described, we are not aware of any study of higher-order processing in this area. Stimulus specific adaptation (SSA) is the specific decrease in the response to a frequent ('standard') stimulus, which does not generalize, or generalizes only partially, to another, rare stimulus ('deviant'). Here we studied SSA in the insular auditory field. We used two approaches for recording neuronal activity in the insular cortex of halothane anesthetized rats. First, we characterized the location of insular auditory field in Sabra-R rats using widely spaced arrays of 9 single tungsten electrodes inserted vertically to various layers of the insular cortex and the claustrum, delineating the antero-posterior and medio-lateral coordinates of the field. Subsequently, we performed series of recordings using high-density silicone probes (neuropixels) to delineate dorso-ventral coordinates of the field and its microstructure. Both approaches revealed presence of the auditory responsive neurons in the insular cortex. Histological verification revealed that auditory responsive neurons were most frequently detected in the granular insular cortex between +0.24 mm to -1.08 mm posterior to bregma. Insular cortex neurons showed pronounced adaptation to repeated simple sounds and weak/moderate SSA. Consistent with the strong adaptation, these neurons failed the accepted test for deviance detection, showing responses to deviants that were substantially smaller than the responses to the same tones within sequences that contained multiple frequencies. Under anesthesia, the neuronal responses in the rat insular auditory field are therefore less capable of signaling deviance than neurons in primary auditory cortex.

Disclosures: M.M. Jankowski: None. **A. Polterovich:** None. **A. Kazakov:** None. **A. Yaron:** None. **I. Nelken:** None.

Nanosymposium

191. Auditory Processing: Adaptation, Learning, and Memory

Location: SDCC 24

Time: Sunday, November 4, 2018, 1:00 PM - 2:30 PM

Presentation Number: 191.02

Topic: D.06. Auditory & Vestibular Systems

Support: BRiC INAIL 2016-DiMEILA17
ONR Global N62909-15-1-2002
D1 Funds Università Cattolica

Title: Cochlear deafferentation induced by noise exposure in rodent models causes structural and functional changes in the auditory cortex

Authors: M. V. PODDA[1], F. PACIELLO[2], S. COCCO[1], R. ROLESI[2], D. TROIANI[1], A. R. FETONI[2,3], G. PALUDETTI[2], *C. GRASSI[1]
[1]Inst. of Human Physiology, Univ. Cattolica, Roma, Italy; [2]Dept. of Head and Neck Surgery, IRCCS Fondazione Policlinico Universitario A. Gemelli, Univ. Cattolica del Sacro Cuore, Rome, Italy; [3]Inst. of Cell Biol. and Neurobio., CNR, Rome, Italy

Abstract: Exposure to oto-neurotoxic exogenous factors (e.g., noise exposure, ototoxic drugs) can induce auditory-related functional impairments in humans and animals. Specifically, exposure to intense noise can induce progressive hearing deficit, increase of the threshold of hearing sensitivity, damage to cochlear structures and deficit in the time coding of auditory signals in the auditory system (*Fetoni et al., 2015*). Despite the well-established evidence documenting peripheral damages and hearing loss following noise exposure (NIHL), there is a substantial lack of knowledge on possible alterations in central structures. The present study addresses the effects of noise exposure on cochlear functions and on cortical plasticity in rodents (rats and mice). Animals were exposed to noise (100 dB, 60 min/day for 10 days) and sacrificed 30 days after the onset of noise session. At peripheral level, we evaluated auditory function by Auditory Brainstem Response (ABR) recordings and the extent of cochlear damage with rhodamine-phalloidin staining. Golgi-Cox staining was used to evaluate neuronal morphological changes in the auditory cortices, by comparing spine density and dendritic branching of layer 2/3 and 5-6 pyramidal neurons in noise-exposed and normal-hearing animals. Electrophysiological recordings were also performed in auditory cortex brain slices to evaluate basal synaptic transmission at layer 2/3 horizontal connections. Our results demonstrate that noise exposure induces a significant threshold elevation (about 40-45 dB) in the middle-high frequency region. Morphological data show a marked outer hair cell (OHC) loss, more pronounced in the region of the cochlear middle turn (about 30% of OHC loss). Moreover, the acoustic trauma decreases spine density in layer 2/3 of auditory cortex pyramidal neurons, both in apical (spine loss of about 30%) and basal (about 40%) dendrites. Basal synaptic transmission at layer 2/3 horizontal

connections was significantly reduced in noise-exposed animals compared to normal-hearing animals as revealed by analysis of input-output curves (p=0.01). Our results indicate that exposure to noise induces cochlear damage leading to hearing loss and that peripheral damage up-spreads to central structures, causing functional and structural changes. These central alterations might be related to auditory disorders such as tinnitus or to cognitive dysfunctions often associated with hearing impairments.

Disclosures: M.V. Podda: None. **F. Paciello:** None. **S. Cocco:** None. **R. Rolesi:** None. **D. Troiani:** None. **A.R. Fetoni:** None. **G. Paludetti:** None. **C. Grassi:** None.

Nanosymposium

191. Auditory Processing: Adaptation, Learning, and Memory

Location: SDCC 24

Time: Sunday, November 4, 2018, 1:00 PM - 2:30 PM

Presentation Number: 191.03

Topic: D.06. Auditory & Vestibular Systems

Support: NIH/NIGMS SC1 GM122645

Title: Layer 5 parvalbumin-expressing neurons: A distinct functional group of GABAergic neurons with nhibitory interhemispheric projections

Authors: *A. J. APICELLA[1], P. FEYEN[2]
[1]Biol. Department, Neurosci. Inst., Northwestern Univ., San Antonio, TX; [2]Biology, Neurosci. Inst., UTSA, San Antonio, TX

Abstract: Parvalbumin-expressing neurons (CC-Parv) connect the two hemispheres of multiple cortical areas, project through the corpus callosum, and are a functional part of the cortical circuit. Around 40% of all parvalbumin-expressing neurons ranging from layers 2/3 to layer 6 connect contralateral auditory, visual and motor cortices . Here we investigate in detail a subclass of these neurons with soma localization restricted to layer 5. Specifically, we assess whether layer 5 CC-Parv neurons possess anatomical and molecular mechanisms which regulate intrinsic excitability and modulate the gating of interhemispheric inhibition. In order to investigate these cellular characteristics, we use viral tracing to determine the anatomical and electrophysiological properties of layer 5 CC-Parv and parvalbumin-expressing (Parv) neurons of the mouse auditory cortex (AC). We show that layer 5 CC-Parv neurons have larger dendritic fields characterized by longer dendrites that branched farther from the soma, relative to layer 5 Parv neurons dendritic fields which are categorized by shorter dendrites that branch in closer proximity to the soma. The layer 5 CC-Parv neurons also show distinct firing characteristics, namely, lower firing rates, delayed action potential (AP) responses to threshold currents, and lower instantaneous frequencies compared to the layer 5 Parv neurons. Kv1.1 containing K^+ channels are the main source of the AP repolarization of the layer 5 CC-Parv and have a major role in determining both

the spike delayed response, firing rate and instantaneous frequency of these neurons. With respect to processing of auditory frequency information, our morphological data invites us to speculate that layer 5 CC-Parv-neurons may be broadly tuned due to a larger dendritic field, while layer 5 Parv neurons may be highly tuned due to a smaller dendritic field.

Disclosures: P. Feyen: None.

Nanosymposium

191. Auditory Processing: Adaptation, Learning, and Memory

Location: SDCC 24

Time: Sunday, November 4, 2018, 1:00 PM - 2:30 PM

Presentation Number: 191.04

Topic: D.06. Auditory & Vestibular Systems

Support: NIH/NICHD (DP1-HD091947)
NIH/NIBIB (P41-EB018783)
NIH/NICHD (R25-HD088157)
NIH/NIMH (P50-MH109429)
US Army Research Office (W911NF-14-1-0440)
Fondazione Neurone

Title: Distinct neural selectivities for music, speech, and song in human auditory cortex

Authors: S. V. NORMAN-HAIGNERE[1,2,3], J. J. FEATHER[3], *P. BRUNNER[4,5], A. RITACCIO[4,5], J. H. MCDERMOTT[3,6], G. SCHALK[4,5,7], N. G. KANWISHER[3]
[1]HHMI Postdoctoral Fellow of the Life Sci. Res. Fndn., Chevy Chase, MD; [2]Dept. d'Études Cognitives, École Normale Supérieure, PSL Res. University, CNRS, Paris, France; [3]Dept. of Brain and Cog Sci., MIT, Cambridge, MA; [4]Nat. Ctr. for Adapt. Neurotechnologies, Wadsworth Ctr, NYSDOH, Albany, NY; [5]Dept. of Neurol., Albany Med. Col., Albany, NY; [6]Program in Speech and Hearing Biosci. and Technol., Harvard Univ., Cambridge, MA; [7]Dept. of Biomed. Sci., State Univ. of New York, Albany, NY

Abstract: Music is ubiquitous across human cultures. How is it represented in the brain? fMRI studies have reported that cortical responses to music overlap with responses to speech and language, suggesting that music co-opts mechanisms adapted for other functions. However, we have previously found that when fMRI voxel responses are modeled as the weighted sum of responses from multiple neural populations, distinct selectivities for music and speech emerge. This finding suggests that the apparent overlap reported in prior studies is due to the coarse nature of fMRI, which blurs responses from nearby neural populations. To test this hypothesis, we measured cortical responses to a diverse set of natural sounds with human electrocorticography (ECoG), which has high spatial and temporal resolution, and which can sample from relatively large regions of the cortex. We observed clear selectivity for speech in

some electrodes, and for music in others, validating our prior fMRI findings. Unexpectedly, we also observed electrodes that responded primarily to music with vocals (i.e. singing), and whose response could not be explained as purely a sum of music and speech selectivity. All category-selective responses developed quickly (within 200 to 500 ms of stimulus onset), and could not be explained by standard acoustic features. Music and song-selective responses were most prominent in anterior regions of the superior temporal gyrus (although a more posterior music-selective response was also observed), while speech selectivity was most prominent in the middle STG. These findings reveal that music and speech have distinct representations in the brain, but also that music itself is processed via multiple neural populations, one specific to the analysis of singing.

Disclosures: S.V. Norman-Haignere: None. **J.J. Feather:** None. **P. Brunner:** None. **A. Ritaccio:** None. **J.H. McDermott:** None. **G. Schalk:** None. **N.G. Kanwisher:** None.

Nanosymposium

191. Auditory Processing: Adaptation, Learning, and Memory

Location: SDCC 24

Time: Sunday, November 4, 2018, 1:00 PM - 2:30 PM

Presentation Number: 191.05

Topic: D.06. Auditory & Vestibular Systems

Support: Leon Levy Neuroscience Fellowship

Title: Neural correlates of delayed auditory feedback during speech production investigated by electrocorticography

Authors: *M. OZKER, M. MCALISTER, L. FANDA, J. SHUM, P. DUGAN, D. FRIEDMAN, W. DOYLE, O. DEVINSKY, A. FLINKER
Dept. of Neurol., NYU Sch. of Med., New York City, NY

Abstract: Accurate and fluent production of speech critically depends on hearing one's self. The auditory system continuously monitors self-generated vocal sounds to detect vocalization errors, which allows for the online adjustment of motor actions to achieve intended vocalization. When auditory feedback is disrupted, vocalization is altered to compensate for the disruption (e.g. speaking loudly when listening to music over headphones). To study auditory feedback control during speech production, we used a delayed auditory feedback (DAF) paradigm, which strongly disrupts speech fluency by causing stutter-like speech, characterized by syllable repetitions, prolonged words and longer pauses. While delaying speech in real time is a common therapeutic approach in stutterers, where it interestingly improves speech fluency, the underlying neural mechanism remains understudied and poorly understood. Here, we employed rare neurosurgical electrocorticography (ECoG) recordings directly from cortex. Subjects were visually presented with 3-syllable words and 8-word sentences in separate sessions. As they read aloud the

presented stimuli, their voice was recorded by a microphone and played back to them with 0, 50, 100 or 200 millisecond delays through earphones. Behaviorally, articulation duration increased significantly with increasing amount of delays for both word reading (For 0, 50, 100 and 200 ms delay: 0.72, 0.75, 0.78, 0.81; $F = 38.4$, $p = 10^{-9}$) and sentence reading (2.77, 3, 3.49, 3.82; $F = 111$, $p = 10^{-16}$). Neural responses in the high-gamma broadband frequencies (70-150 Hz) were used as the primary measure of neural activity. Auditory electrodes over the superior temporal gyrus showed increased neural responses as delays increased both for word reading ($F = 98$, $p = 10^{-16}$) and for sentence reading ($F = 123$, $p = 10^{-16}$). Motor electrodes showed increased neural responses for increasing delays only for sentence reading ($F = 37$, $p = 10^{-9}$) but not for word reading ($F = 3.6$, $p = 0.06$). This represents one of the first reports of delayed auditory feedback in human electrophysiology. The data suggests that while auditory cortex encodes mismatches between intended and produced speech, motor cortex is preferentially engaged only when articulation demand increases during production of longer, more complex speech segments.

Disclosures: M. Ozker: None. **M. McAlister:** None. **L. Fanda:** None. **J. Shum:** None. **P. Dugan:** None. **D. Friedman:** None. **W. Doyle:** None. **O. Devinsky:** None. **A. Flinker:** None.

Nanosymposium

191. Auditory Processing: Adaptation, Learning, and Memory

Location: SDCC 24

Time: Sunday, November 4, 2018, 1:00 PM - 2:30 PM

Presentation Number: 191.06

Topic: D.06. Auditory & Vestibular Systems

Support: NSF DGE-1137475

Title: Statistical learning of infant distress sounds during maternal experience

Authors: *J. SCHIAVO[1], R. C. FROEMKE[2,3]
[1]New York Univ. Med. Ctr., New York, NY; [2]Otolaryngology, NYU Med., New York, NY; [3]Skirball Inst., New York, NY

Abstract: Statistical learning is a process in which animals can become sensitive to regularities in sensory input and distributions of core stimulus features (Thiessen 2016). Sensitivity to stimulus-relevant variability enables generalization across sounds, such as vocalizations, that may vary in lower level features. While some neural correlates of generalization have been identified, links between cortical plasticity and statistical learning to enable generalization across stimulus-relevant features is poorly understood.
Here, we take advantage of maternal pup retrieval behavior in mice, in which mothers retrieve nest-isolated pups based on ultrasonic vocalizations (USVs) (Ehret 2005). While pup USVs follow a general structure (Liu et al. 2003), calls are variable across lower level features, such as temporal modulation. Mother mice must be sensitive to distributional statistics of these calls to

generalize over a range of vocalizations. Importantly, pup-naïve virgins do not behaviorally respond to USVs, but begin retrieving after experience with pups (Marlin et al. 2015). This behavior therefore serves as an ideal model to assess plasticity mechanisms underlying the sensitization of the virgin auditory cortex to USV statistics as these calls gain behavioral relevance during initial maternal experience.
Using *in vivo* two-photon imaging, we found that USV-responsive excitatory neurons in retrieving virgins (N=9), but not non-retrieving virgins (N=11), respond invariantly to USVs morphed in the temporal domain. Interestingly, inhibitory neurons are widely tuned in both retrieving (N=3) and naïve females (N=5), resulting in an excitatory-inhibitory tuning mismatch in naïve auditory cortex. When we tracked the excitatory and inhibitory populations across co-housing with pups, we find that excitatory neurons begin to respond invariantly to morphs 24 hours prior to the onset of pup retrieval, and the excitatory and inhibitory populations come to match 24 hours post-retrieval onset. Finally, we can alter cortical responses to temporally-morphed calls by altering exemplar statistics during initial pup experience (N=3). Our results show a form of cortical plasticity underlying statistical learning for maternal behavior.

Disclosures: J. Schiavo: None. **R.C. Froemke:** None.

Nanosymposium

192. Sleep: Hot Topics

Location: SDCC 7

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 192.01

Topic: F.08. Biological Rhythms and Sleep

Support: Israel Science Foundation (690/15)

Title: Sleep upregulates chromosome dynamics and enables activity-dependent nuclear maintenance

Authors: *L. APPELBAUM[1], D. ZADA[1], I. BRONSHTEIN-BERGER[2], T. LERER-GOLDSHTEIN[1], Y. GARINI[2]
[1]The Fac. of Life Sci. and The Multidisciplinary Brain Res. Ctr., [2]Dept. of Physics and the Inst. for Nanotechnology, Bar Ilan Univ., Ramat Gan, Israel

Abstract: Sleep is essential to all animals with a nervous system. Nevertheless, the core cellular function of sleep is unknown, and there is no conserved molecular marker to define sleep across phylogeny. We used fluorescent telomere and centromere markers to visualize 3D changes in chromosome dynamics in single cells of live zebrafish. Time-lapse imaging revealed that sleep increases chromosome dynamics by two-fold in individual neurons but not in non-excitable cell types. Genetic suppression and pharmacological induction of sleep reduces and increases chromosome dynamics, respectively. Simultaneous imaging of spontaneous neuronal activity

and chromosome dynamics, as well as optogenetic stimulation, showed that neuronal activity reduces chromosome dynamics. Moreover, by synchronized enhancement of chromosome dynamics, sleep enables the consolidated repair of DNA double-strand breaks (DSBs) in specific neuronal networks. These results establish chromosome dynamics as a marker to define single sleeping cells, and propose that the restorative function of sleep is activity-dependent nuclear maintenance.

Disclosures: L. Appelbaum: None. **D. Zada:** None. **I. Bronshtein-Berger:** None. **T. Lerer-Goldshtein:** None. **Y. Garini:** None.

Nanosymposium

192. Sleep: Hot Topics

Location: SDCC 7

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 192.02

Topic: F.08. Biological Rhythms and Sleep

Support: NS070911
NS094390
NS095824
NS082010

Title: Serotonergic regulation of sleep in zebrafish larvae

Authors: *G. OIKONOMOU, M. ALTERMATT, J. CHO, V. GRADINARU, D. PROBER
Caltech, Pasadena, CA

Abstract: The role of serotonin (5-HT) in sleep has been the subject of a long debate. Classical studies in the 1960s showed that either inhibition of tryptophan hydroxylase (TPH), the rate-limiting enzyme in 5-HT biosynthesis, or ablation of the raphe, the main source of serotonergic innervation for the brain, result in insomnia. Thus, 5-HT was initially thought to have a sleep-promoting role. However, later studies showed that raphe activity and 5-HT release are increased during wakefulness and reduced during sleep, giving rise to the current view of a wake-promoting role for the serotonergic system, which does not account for the earlier observations. We revisited this question in zebrafish, a diurnal vertebrate which has emerged as a promising model for the study of sleep. Here we provide diverse evidence in support of a sleep-promoting role for the serotonergic system in zebrafish larvae. We show that 5-HT receptor agonists promote sleep, while pharmacological inhibition of TPH inhibits sleep. Furthermore, *tph2* mutant larvae which lack 5-HT in the raphe are more active, sleep less, and show increased maximal arousal and reduced sleep depth. Chemogenetic ablation of the raphe phenocopies the activity and sleep phenotypes of *tph2* mutants, while optogenetic activation of the raphe reduces activity and increases sleep. These results suggest a sleep-promoting role for the serotonergic system in a

simple diurnal vertebrate system, setting the stage for a better understanding of how 5-HT regulates the sleep/wake cycle.

Disclosures: G. Oikonomou: None. **M. Altermatt:** None. **J. Cho:** None. **V. Gradinaru:** None. **D. Prober:** None.

Nanosymposium

192. Sleep: Hot Topics

Location: SDCC 7

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 192.03

Topic: F.08. Biological Rhythms and Sleep

Support: VA Merit Award BX00155605
VA Merit Award BX003520

Title: Chemo-genetic activation of corticotropin releasing factor neurons in the hypothalamic paraventricular nucleus acutely disrupts sleep in mice

Authors: *S. KUMAR[1,2,3], K.-C. HSIEH[1,2,4], D. MCGINTY[1,5], R. SZYMUSIAK[1,4,6]
[1]Veteran Affairs Med. Ctr., Los Angeles, CA; [2]Websciences Intl., Los Angeles, CA; [3]Dept. of Pharmaceut. and Biomed. Sci., California Hlth. Sci. Univ., Clovis, CA; [4]Dept. of Med., [5]Depatment of Psychology, [6]Dept. of Neurobio., UCLA, Los Angeles, CA

Abstract: Introduction: Activation of corticotropin releasing factor (CRF) neurons in the paraventricular nucleus of the hypothalamus (PVN) orchestrates endocrine and behavioral responses to acute stress, including sleep disruption. We hypothesized that selective activation of CRF neurons in the PVN acutely disturbs sleep. We examined the effects of chemo-genetic activation of CRF neurons in the PVN on spontaneous sleep-wake and EEG measures in mice. **Methods:** 7 male CRF-ires-Cre mice received bilateral injections of pAAV-hSyn-DIO-hM3D(Gq)-mCherry excitatory DREADD targeting the PVN. Mice were also implanted with EEG/EMG electrodes. Mice were maintained 12/12 hr light dark cycle. Three weeks after AAV injections intraperitoneal injections of vehicle or CNO (1 mg/kg), were administered at zeitgeiber time (ZT) 0 in a repeated measure experiments. EEG and EMG were recorded undisturbed for eight hrs post-injection. EEG slow-wave activity (SWA) in NREM sleep (% change from baseline values) and sleep wake measures were quantified during 8 hour post-injection. **Results:** During first 4-hr post-injection, percent time awake increased following 1 mg CNO compared to vehicle (72.6±6.8%/39.8±3.4%, p=0.001) whereas NREM time (26.5±6.6%/54.9±2.6%, p=0.002) and REM time (0.7±0.4%/5.3±0.9%, p=0.001) decreased. In following 4-hr period, wake time (33.0±3.9%/26.3±2.9%, p=0.194), NREM time (60.1±3.4%/65.5±2.6%, p=0.236) and REM time (6.9±0.6%/8.2±0.5%, p=0.115) did not differ between and CNO and vehicle conditions. EEG slow-wave activity (SWA) in NREM sleep in

first 4-hrs post-injection did not differ between experimental conditions (102.72±0.07% versus 106.81±0.03%, p=0.598) but was elevated over baseline levels in CNO-treated mice during the second 4-hrs (120.32±0.07%/94.20±0.02%, p=0.004). Wake bout duration was increased in both first and second 4 hrs following CNO injection whereas NREM bout increased only during the second 4-hr period. There were no between treatment differences in REM bout duration. **Conclusion:** Acute activation of CRF neurons in the hypothalamic PVN acutely suppresses sleep, followed by a homeostatic response to sleep loss.

Disclosures: S. Kumar: None. **K. Hsieh:** None. **D. McGinty:** None. **R. Szymusiak:** None.

Nanosymposium

192. Sleep: Hot Topics

Location: SDCC 7

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 192.04

Topic: H.01. Animal Cognition and Behavior

Support: R01AG054551
Fidelity Biosciences

Title: Cholinergic modulation of hippocampal activity across the sleep-wake cycle

Authors: *S. N. GOMPERTS, H. ZHOU, K. NEVILLE, N. KAUSAR, N. GOLDSTEIN, S. KABU, R. YE, S. NGUYEN, N. GELWAN
Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Calcium is a critical second messenger in neurons that contributes to learning and memory. To determine how the coordination of action potentials of neuronal ensembles with the hippocampal local field potential (LFP) is reflected in dynamic calcium activity, we recorded hippocampal calcium activity with endoscopic imaging of the genetically encoded fluorophore GCaMP6 along with concomitant LFP across the sleep-wake cycle of freely behaving mice. Dynamic calcium activity was markedly more robust in exploratory behavior and REM sleep than in quiet wakefulness and slow wave sleep, behavioral states that differ with respect to theta and septal cholinergic activity. Chemogenetic activation of septal cholinergic neurons expressing the excitatory hM3Dq DREADD increased calcium activity and reduced sharp wave ripples (SWRs). Furthermore, muscarinic acetylcholine receptor (mAChR) inhibition reduced calcium activity while increasing SWRs. These results demonstrate that hippocampal dynamic calcium activity depends on behavioral and theta state as well as endogenous mAChR activation.

Disclosures: S.N. Gomperts: None. **H. Zhou:** None. **K. Neville:** None. **N. Kausar:** None. **N. Goldstein:** None. **S. Kabu:** None. **R. Ye:** None. **S. Nguyen:** None. **N. Gelwan:** None.

Nanosymposium

192. Sleep: Hot Topics

Location: SDCC 7

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 192.05

Topic: F.08. Biological Rhythms and Sleep

Support: NSF/STTR grant #622766, to Mobile Sleep Technologies
NIH grant #1R43AG056250-01 to Mobile Sleep Technologies

Title: Auditory stimulation during sleep transiently increases delta power and all-night proportion of NREM stage 3 sleep while preserving total sleep time and continuity

Authors: *M. M. SCHADE[1], D. M. ROBERTS[3], D. GARTENBERG[3], G. M. MATHEW[2], O. M. BUXTON[2,4]
[1]Biobehavioral Hlth., Pennsylvania State Univ., Harrisburg, PA; [2]Biobehavioral Hlth., Pennsylvania State Univ., University Park, PA; [3]Mobile Sleep Technologies, Washington, DC; [4]Harvard Univ., Cambridge, MA

Abstract: Background: Phase-locked auditory stimulation during NREM sleep increases power spectral density (PSD) in the delta frequency range of the EEG ("deep sleep enhancement"). We manually administered sounds during both N2 and N3 sleep, not phase-locked to delta waves, to evaluate an "Enhance" and "Disrupt" condition night relative to a night without acoustic stimuli ("Sham"). We hypothesized that an Enhance condition with sound stimuli would induce more %N3 sleep compared to Sham; and that a Disrupt condition would reduce %N3 compared to Sham, and induce more neurocortical arousals.
Methods/Analyses: Participants (8 healthy adults 36-49, 5 female) slept 4 consecutive nights in an inpatient lab with polysomnography. Nights 1 & 3 (Habituation, Sham) were nonintervention nights; nights 2 & 4 were Enhance or Disrupt conditions (random order). Enhance sounds (pink noise pulses presented at an interval of .8 Hz) were played during N2 and N3. Disrupt sounds (environmental sounds known to cause arousals) were played during N2, N3, and REM. In order to further characterize the specificity of acoustic stimuli, the disrupt sounds varied in inter-burst interval, sound type, frequency, and pressure level. PSD in the delta band (.5-4Hz) of the EEG was extracted for each night and evaluated during N2, N3, and across all sleep stages. Delta band PSD and sleep outcomes were compared across Sham, Disrupt, and Enhance using mixed linear modeling for repeated measures and included the interaction between condition and order of Enhance/Disrupt.
Results: Sounds were played for 24.8% of TST on Disrupt and 25.2% of TST on Enhance (n.s.). Total Sleep Time did not differ among conditions. When Enhance stimuli were presented during N2 or N3, Delta PSD was transiently increased. There was a significant interaction between condition and the order of Disrupt or Enhance ($p<.01$) on %N3 sleep, where the %N3 sleep was

increased in Enhance vs. Sham (M=3.1%, ±4.3%) when Enhance was presented before Disrupt ($p<.05$). Sleep continuity did not differ between Enhance and Sham (n.s.). In contrast, sleep continuity was worse on Disrupt vs. Sham ($p<.0001$; M=5.6/hr, ±3.3/hr).
Conclusions: Despite playing sound for a similar proportion of TST as Disrupt, sleep continuity did not suffer on the Enhance night. We were able to preserve TST and increase %N3 by playing pink noise sounds during N2 & N3, which has not yet been reported in conjunction with delta-band PSD increases. We attribute the significant order interaction with condition to a rebound effect on the Sham nights that followed Disrupt, rendering Sham similar to "enhanced" sleep.

Disclosures: M.M. Schade: 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.; Mobile Sleep Technologies (through the Pennsylvania State University). **D.M. Roberts:** A. Employment/Salary (full or part-time):; Mobile Sleep Technologies. **D. Gartenberg:** A. Employment/Salary (full or part-time):; Mobile Sleep Technologies. **G.M. Mathew:** 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.; Mobile Sleep Technologies (through the Pennsylvania State University). **O.M. Buxton:** 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.; Mobile Sleep Technologies (through the Pennsylvania State University).

Nanosymposium

192. Sleep: Hot Topics

Location: SDCC 7

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 192.06

Topic: F.08. Biological Rhythms and Sleep

Title: Sleep stage classification using deep learning on electrocardiography (ECG) data only

Authors: *A. M. JONES[1], B. R. SHETH[2]
[1]Neurosci. Grad. Program, USC, Los Angeles, CA; [2]Dept Elec, Comp Eng, Univ. of Houston, Houston, TX

Abstract: While it is widely acknowledged that sleep is of, for, and by the brain, there is mounting evidence that sleep is also of, for, and by the body. The autonomic nervous system, which controls the body viscera, also participates in, and is a window into, sleep. Measurement of heart rate variability is a proxy for the state of the autonomic system, which is known to be affected by the state of arousal, i.e. sleep or wake (W). With this understanding, our objective is an automated method of accurately determining sleep stages using only ECG, and its successful

achievement is a cheaper, more practical, and easier-to-administer alternative to polysomnography. Sleep is, *ipso facto*, a non-stationary process, with long-term cyclic patterns, short-term continuity of sleep stages, and between-stage transitions of differing frequency. Popular machine learning algorithms assume time independence; consequently, sleep staging with these methods is barely above chance levels. Instead, we built a deep learning, time-dependent, recurrent neural network. Deep networks are effective at feature extraction, and bidirectional layers allow the model to simultaneously use past and future information while sleep staging a 30s epoch—as human scorers do. The model used the target epoch to be classified along with 3-9 epochs before and after as input, which was processed by several convolution layers to extract 32 features for each epoch. These features were the input to two bidirectional GRU layers, the output of which was the sleep stage. The epochs trained and tested on were randomly selected, spaced as far apart as possible, and class-balanced. Using the raw ECG as input, our model classified 5 stages (S1/S2/S3/REM/W) on unseen subjects at an accuracy 3X chance level (62%, for the class-balanced data), with a Cohen's $\kappa = 0.53$—better than a recently published method (Fonseca et al., PhysiolMeas., 2015) with $\kappa = 0.49$ for 4 classes (S1+S2/S3/REM/W), and $\kappa = 0.56$ for 3 classes (S1+S2+S3/REM/W). However, the accuracy must be higher to be useful to the community of clinicians. To that end, we are currently: 1) including time-frequency transforms of the raw ECG signal as part of the input; 2) expanding the hyperparameter search of possible network architectures; 3) improving the model design to use the entire night of sleep for every subject (which will lead to class imbalances); 4) using ensembles of models, with the assumption that each "expert" model will be better at classifying one specific stage; 5) further exploring if different models from a common ensemble would work better on different subgroups of subjects; and 6) attempting a multiple-pass process to bootstrap and refine stage predictions.

Disclosures: A.M. Jones: None. **B.R. Sheth:** None.

Nanosymposium

192. Sleep: Hot Topics

Location: SDCC 7

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 192.07

Topic: F.08. Biological Rhythms and Sleep

Support: NIH R01EY019466
NSF BCS 1539717
Center for Vision Research, Brown University
FY17 OVPR Seed Grant, Brown University

Title: REM sleep has two distinct roles in learning: Stabilization of pre-sleep learning and promotion of new post-sleep learning

Authors: *M. TAMAKI, A. BERARD, T. WATANABE, Y. SASAKI
Cognitive, Linguistic & Psychological Sci., Brown Univ., Providence, RI

Abstract: The role of REM sleep in learning has remained controversial. REM sleep has been suggested to be involved in stabilization of learning or unlearning. Using the texture discrimination task (TDT; Karni & Sagi, 1991), a standard visual perceptual learning (VPL) task, the present study examined whether REM sleep plays multifaceted roles in learning. It is known that performance improvement of TDT is retinotopic, and that 2 trainings on TDT with orthogonal background line orientations lead to both retrograde and anterograde interferences, if there is no time interval between the blocks (Yostumoto et al., 2009). First, we tested whether REM sleep stabilizes VPL trained before sleep (pre-sleep VPL). The 2-block TDT training with orthogonal background orientations were separated by a 2-hr sleep interval. The 2nd TDT training was assumed to retrogradely interfere with pre-sleep VPL, unless pre-sleep VPL was stabilized during sleep. The results showed that pre-sleep VPL was stabilized when REM sleep was present during sleep. Theta activity during REM sleep was enhanced retinotopically in correlation with stabilization of pre-sleep VPL. These show REM sleep eliminates retrograde interference via theta activity. Second, we tested whether REM sleep eliminates anterograde interference from pre-sleep VPL to VPL trained after sleep (post-sleep VPL), thereby promotes post-sleep VPL. Two TDT trainings were separated by a 2-hr sleep interval. Post-sleep VPL occurred only when REM sleep was observed. The amount of post-sleep VPL was significantly correlated with the REM-sleep duration. Third, we tested whether REM sleep was involved in pre-sleep interference caused by 2 TDT trainings with no interval, which resulted in no learning. The amount of interference was correlated with REM-sleep duration, indicating longer REM sleep followed greater pre-sleep interference. However, when these trainings were conducted with the same background orientation, which led to learning, the performance of TDT was enhanced after sleep in correlation with theta activity that increased retinotopically during REM sleep, but not with the duration of REM sleep. Together, our results show that theta activity during REM sleep and the duration of REM sleep are involved in different aspects of facilitation of VPL. Theta activity during REM sleep is involved in stabilization of pre-sleep VPL. In contrast, the duration of REM sleep plays a role in elimination of interferences caused by VPL training. This process may clear up irrelevant synapses and make more spaces, resulting in promoting new post-sleep learning. These suggest REM sleep protects and promotes learning trained before and after sleep.

Disclosures: M. Tamaki: None. **A. Berard:** None. **T. Watanabe:** None. **Y. Sasaki:** None.

Nanosymposium

192. Sleep: Hot Topics

Location: SDCC 7

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 192.08

Topic: F.08. Biological Rhythms and Sleep

Support: NIH K99-MH111748
Harvard Society of Fellows
NIH S10-OD010759
NIH P41-EB015896

Title: Focal thalamic activity at the moment of awakening identified through simultaneous EEG and fast fMRI

Authors: *L. D. LEWIS[1], G. BONMASSAR[1], K. GUPTA[2], K. SETSOMPOP[1], R. STICKGOLD[3], B. R. ROSEN[1], J. R. POLIMENI[1]
[1]MGH/Harvard Med. Sch., Boston, MA; [2]Wellesley Col., Wellesley, MA; [3]Ctr. For Sleep and Cognition, Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: The process of awakening from sleep can be abrupt, with major changes in behavior and neural activity occurring within hundreds of milliseconds. Such shifts in arousal and alertness are signaled by striking alterations in cortical electrophysiological dynamics that can be detected in the scalp EEG. The neural circuit mechanisms that regulate arousal transitions are not well understood, but animal studies have suggested an important role for the thalamus, and have identified individual thalamic nuclei that can regulate arousal in local regions of cortex. We aimed to use whole-brain imaging in humans to identify the activity patterns within individual thalamic nuclei that are associated with changes in cortical arousal state, focusing on the moment of awakening from sleep. We performed simultaneous EEG and fast (TR=247 ms) fMRI at ultra-high field (7 Tesla) to measure signals within individual nuclei of the thalamus and analyze their relationship to cortical electrophysiology. We studied subjects as they fell asleep in the scanner, using a button-pressing task to index behavioural state, and tracked electrophysiological arousal through spontaneous alpha rhythms. We anatomically identified the mediodorsal thalamus, pulvinar, and lateral geniculate nucleus (LGN), and extracted their mean fMRI signal timecourses relative to sleep onset and spontaneous awakening. We identified a pattern of thalamic activation that occurred selectively at the moment of awakening, preceding the change in cortical EEG state by hundreds of milliseconds. Analyzing fMRI timecourses within each individual anatomically segmented nucleus suggested that these patterns were local to specific higher-order thalamic nuclei, including the mediodorsal nucleus, whereas the LGN did not exhibit analogous patterns during awakening. These results identify a focal set of thalamic nuclei engaged selectively at transitions between arousal states, suggesting possible mechanisms for regulating cortical electrophysiological state. In addition, they demonstrate that fast fMRI at ultra-high field can identify rapid activity dynamics in small, deep brain nuclei that signal upcoming changes in cortical electrophysiology and behavior, with potential broader applications for studying the neural circuits regulating diverse arousal, cognitive, and attentional states.

Disclosures: L.D. Lewis: None. **G. Bonmassar:** None. **K. Gupta:** None. **K. Setsompop:** None. **R. Stickgold:** None. **B.R. Rosen:** None. **J.R. Polimeni:** None.

Nanosymposium

192. Sleep: Hot Topics

Location: SDCC 7

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 192.09

Topic: F.08. Biological Rhythms and Sleep

Support: NIH IRP Y1AA3009

Title: Increases in brain activation within an autonomic network following one night of total sleep deprivation

Authors: *E. SHOKRI-KOJORI[1], S. B. DEMIRAL[2], D. TOMASI[3], C. E. WIERS[4], A. ZEHRA[5], C. FREEMAN[6], V. RAMIREZ[1], T. SRIVASTAVA[4], G.-J. WANG[3], N. D. VOLKOW[7]
[1]Natl. Inst. on Alcohol Abuse and Alcoholism, [2]NIDCD, [3]NIH, Bethesda, MD; [5]Lab. of Neuroimaging, [4]Natl. Inst. On Alcohol Abuse and Alcoholism, Bethesda, MD; [6]Natl. Inst. of Alcohol Abuse and Alcoholism, Bethesda, MD; [7]NIH/NIDA, Bethesda, MD

Abstract: While good sleep is essential for our physical and mental health, sleep deprivation (SD) is known to result in complex changes to autonomic (ANS) and central (CNS) nervous systems. However, it is largely unknown how SD affects the interaction between ANS and CNS. Recently, we have documented an autonomic brain network that included a range of posterior sensory cortices and the dorsal attention stream. This network exhibited significant interactions with vascular sympathetic tone as indexed by low frequency (LF, < 0.1 Hz) fluctuations in the pulse signal. Considering the evidence that SD increases sympathetic vascular modulation, we hypothesized that SD alters brain activity within this network and its association with autonomic signaling. In a group of 20 healthy individuals (10 females, 22-72 years old), we measured brain resting state activity with fMRI (10 min) and concurrently recorded the pulse signal, once after rested wakefulness (RW) and once after one night of total SD. In addition, participants performed a visual attention task (VAT, $n = 16$) and reported their mood ($n = 18$) following RW and SD conditions. SD relative to RW, elevated LF fluctuations in the pulse signal and significantly increased fractional amplitude of LF fluctuations (fALFF) in areas with marked overlap with the autonomic network ($p_{FWE} < 0.05$). Participants performed worse on the VAT and had worse mood following SD ($p < 0.05$). Increases in fALFF following SD positively correlated with changes in performance in VAT ($p = 0.03$) suggesting that these changes in brain activity may reflect a compensatory phenomenon. The autonomic network also showed significant SD-related increases in synchrony with pulse amplitude in LF ($p = 0.015$), an effect that was most pronounced within the cuneus (a core region of the autonomic network) ($p_{FWE} < 0.05$). Our results support that enhanced sympathetic modulation of vasculature in SD may also impact brain resting activity in a manner that would be essential for maintaining attention. While

SD has been associated with poorer attentional processing, our data highlight that enhanced interactions between ANS and CNS may hint at compensatory mechanisms which mitigate the symptoms of SD. Thus, future work could involve studying ANS-CNS interactions in attention disorders.

Disclosures: E. Shokri-Kojori: None. **S.B. Demiral:** None. **D. Tomasi:** None. **C.E. Wiers:** None. **A. Zehra:** None. **C. Freeman:** None. **V. Ramirez:** None. **T. Srivastava:** None. **G. Wang:** None. **N.D. Volkow:** None.

Nanosymposium

192. Sleep: Hot Topics

Location: SDCC 7

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 192.10

Topic: F.08. Biological Rhythms and Sleep

Support: Military Operational Medicine Research Program

Title: Dissecting the impact of a brain insult on human sleep homeostatic and circadian processes *in vivo* and *ex vivo*

Authors: M. ST. PIERRE[1], C. PATTINSON[2], A. GRILLAKIS[1], J. MANTUA[1], A. MCKEON[1], V. CAPALDI[1], *C. L. GRAY[3], J. GILL[2], A. M. YARNELL[4], A. BRAGER[1]
[1]Behavioral Biol., Walter Reed Army Inst. of Res., Silver Spring, MD; [2]Natl. Inst. of Nursing Res., Bethesda, MD; [3]Morehouse Sch. of Medicine/ MRC F-F14, Atlanta, GA; [4]Leadership and Behavioral Sci., United States Military Acad., West Point, NY

Abstract: Despite evidence of the recuperative value of sleep, the mechanisms of brain insult on increased physiological sleepiness remain unclear. Here, we examined if brain insult alters the daily rhythm of physiological sleepiness and/or the homeostatic response to sleep loss. We measured the ability to maintain wakefulness - a measure of physiological sleepiness - across forced wakefulness (FW) in (asymptomatic) individuals (~ 25 y.o.) with prior concussion (3-12 months ago; mTBI; n=6) and age-matched controls (CON; n=6). At-home actigraphic sleep at baseline was ~ 8 h. After an in-lab baseline night, the participants underwent 40 h of FW followed by an 8 h sleep opportunity (recovery). Overnight polysomnography (PSG) at baseline revealed significant differences for total sleep time decrease for mTBI vs. CON; p=0.005), percent wake (increase for mTBI vs. CON; p=0.008), deep NREM sleep (decrease for mTBI vs. CON; p=0.028), and latency into REM sleep (decrease for mTBI vs. CON; p=0.047). Despite PSG differences at baseline, rates of accumulated physiological sleepiness across FW were similar between mTBI vs. CON (p=0.161). Rates of dissipated physiological sleepiness across the recovery period were also similar for mTBI vs. CON (p=0.101). During recovery, PSG total sleep time (decrease; p=0.007) and wake (increase; p=0.013) remained significantly different

between mTBI vs. CON. These data are preliminary evidence that the homeostatic component of sleep may be only marginally impacted by brain insult. Differences in wake and REM output in participants with concussion suggest evidence of circadian disruption. To examine this, we are extracting, sequencing, and analyzing (bioinformatics) clock-controlled micro-RNA inputs and outputs derived from saliva. To conclude, these data present a first-ever look at the impact of concussion on circadian processes and reject a long-standing assumption that all dynamics of the sleep homeostatic system are residually impacted by brain insult.

Disclosures: M. St. Pierre: None. **C. Pattinson:** None. **A. Grillakis:** None. **J. Mantua:** None. **A. McKeon:** None. **V. Capaldi:** None. **C.L. Gray:** None. **J. Gill:** None. **A.M. Yarnell:** None. **A. Brager:** None.

Nanosymposium

192. Sleep: Hot Topics

Location: SDCC 7

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 192.11

Topic: F.08. Biological Rhythms and Sleep

Title: Under slept and Overanxious: The neural correlates of sleep-loss induced anxiety in the human brain

Authors: *E. B. SIMON[1], M. P. WALKER[2]
[1]Berkeley, CA; [2]Univ. of California, Berkeley, CA

Abstract: Introduction: Sleep loss causally triggers anxiety. Disturbed sleep, including Non-REM slow-wave activity (SWA), is comorbid with all anxiety disorders, while sleep deprivation increases anxiety in healthy individuals. However, the underlying brain mechanisms of this effect remain unknown. Anxiety disorders are associated with hyperactivation in the extended limbic network, yet hypoactivation in medial prefrontal cortex (mPFC). Here, we test the hypothesis that: sleep-loss induced anxiety is triggered by amplified activity within the limbic network due to impaired top-down regulation by mPFC, while Non-REM SWA palliative restores this network and thus reduces anxiety.
Methods: 18 healthy adults (20.2±1.5 years old, 9F) entered a repeated-measure, crossover study involving two experimental sessions after: (1) a normal night of polysomnography-recorded sleep, and (2) 24-hours of sleep-deprivation. In each session, participants viewed emotionally evocative videos during a functional MRI scan as an assay of affective brain reactivity. Anxiety was measured using the State-Trait Anxiety Inventory following each session.
Results: Sleep-deprivation triggered a 30% increase in anxiety ($p < 0.01$). Fitting the neural profile observed in anxiety disorders, sleep-deprivation resulted in amplified reactivity within the amygdala and dorsal anterior cingulate, yet marked hypoactivity in mPFC ($p<0.001$). Most critical, the degree of mPFC disengagement predicted 1) the magnitude of sleep deprivation-

induced anxiety across individuals ($p<0.05$), and 2) the loss of top-down mPFC-amygdala connectivity following sleep-loss ($p<0.05$). Finally, and focusing on the sleep rested night, greater amounts of Non-REM SWA predicted the palliative overnight reduction in anxiety ($p<0.05$), further associated with greater re-engagement of mPFC activity the next day. Conclusions: These data establish a neuropathological model explaining the anxiogenic impact of sleep loss: impaired mPFC activity resulting in a loss of top-down regulation of limbic brain reactivity. Conversely, Non-REM SWA services an overnight anxiolytic benefit upon these affective brain systems. More generally, our findings emphasize sleep as a novel therapeutic target for the amelioration of anxiety in non-clinical and clinical populations.

Disclosures: E.B. Simon: None. **M.P. Walker:** None.

Nanosymposium

192. Sleep: Hot Topics

Location: SDCC 7

Time: Sunday, November 4, 2018, 1:00 PM - 4:00 PM

Presentation Number: 192.12

Topic: F.08. Biological Rhythms and Sleep

Title: Sleep-more in Seattle: Later high school start times are associated with better student sleep and academic performance

Authors: *G. DUNSTER[1], L. DE LA IGLESIA[1], C. NAVE[1], J. FLEISCHER[2], S. PANDA[2], H. O. DE LA IGLESIA[1]
[1]Univ. of Washington, Seattle, WA; [2]Salk Inst., La Jolla, CA

Abstract: Teenagers typically have later chronotypes; yet, the vast majority of high schools in the United States start before 8:30 am leading to a teenage sleep epidemic. This has resulted in recommendations from groups like the American Association of Pediatrics calling for delays in school start times (SST) to combat this health crisis. However, whether delaying school start times as a single measure results in better student sleep has not been demonstrated with rigorous quantitative methods. In the Fall of 2016, Seattle Public School District in the state of Washington voted to delay their secondary SST from 7:50 to 8:45. To assess the effects of this delay, we monitored sleep-wake cycles in students using automatic wristwatch data loggers in two local high schools for two months during the Spring quarters before and after the delay. After the delayed SST, students woke up significantly later in the morning but did not go to sleep significantly later at night, resulting in a net significant increase in their daily sleep duration. In addition, mean waveforms of activity show a significant difference between years in the timing of activity. Importantly, although exposure to morning daylight was delayed in association with later SST exposure to evening light was not. Additionally, student grades improved and their daytime sleepiness decreased. Finally, students from our more ethnically diverse, low-income study site had significantly fewer absences and tardies during their first period of school after

they delayed SST. This is the first study to show the benefits of later SST in teenagers using automatic sleep recording in a naturally occurring experimental setting. Our results indicate that later SST are not only associated with healthier sleep habits but also with better academic performance and school attendance.

Disclosures: G. Dunster: None. **L. de la Iglesia:** None. **C. Nave:** None. **J. Fleischer:** None. **S. Panda:** None. **H.O. de la Iglesia:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.01

Topic: H.02. Human Cognition and Behavior

Support: Flanders Research Foundation FWO 1509318N (RB)
Biotechnology and Biological Sciences Research Council BB/H008217/1 (LKT)
ERC Advanced Investigator Grant no 669820 (LKT)

Title: Perceptual and conceptual processing across the adult lifespan

Authors: *R. BRUFFAERTS[1], L. K. TYLER[2], B. RANDALL[2], K. A. TSVETANOV[3], C. CAN[2], A. CLARKE[2]
[1]Neurosciences, KULeuven, Leuven, Belgium; [2]Univ. of Cambridge, Cambridge, United Kingdom; [3]Dept. of Psychology, Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Neural responses to visual objects are increasingly delayed[1] and reduced across the human lifespan. However, it is unclear if these age-related changes impact the cognitive processing of objects. Previously, we demonstrated that neural activity can be modelled with a visuoperceptual model in an early time window (50-150 ms) and a semantic model in a later time window (150-400 ms) in young adults[2] showing the time-course of visual and semantic processing. Here, using MEG, we tested how representations of visuoperceptual and semantic information change with age, and asked if age-related changes relate to performance and cognition.
Eighty-five subjects (24-87 years, 44 male) of the Cam-CAN cohort[3] performed a visual object naming task during MEG recording. Accuracy was high (90.9%, SD 5.3%), but decreased with age (r: -0.476, $P < 0.001$), while fluid intelligence (Cattell Culture Fair) declined with age (r: -0.712, $P < 0.001$), and crystallized intelligence did not change with age.
MEG time courses for each subject were fitted to a visuoperceptual (HMax) and a semantic model (feature norms) using multiple linear regression[2]. Model fits were averaged within an early and later time window to quantify visual and semantic components respectively. Both components decreased across the lifespan (visual $r = -0.279$ $P = 0.010$; semantic $r = -0.238$, $P =$

0.028): less visuosemantic information was contained in the neural signal of mature controls. The peak time of the visual component was delayed across the lifespan ($r = 0.237$, $P = 0.028$), but was not correlated with its magnitude ($r = 0.082$, $P = 0.443$): neural slowing does not influence how visuosemantic information is represented.
The visual component moderated the effect of age on fluid intelligence ($R^2 = 0.573$, $F(80, 4) = 26.9$, $P < 0.001$, interaction: $\beta = 4.24$, $P = 0.021$) suggesting that in mature controls, a greater visual component was associated with higher fluid intelligence. The visual component moderated the relationship between the semantic component and naming accuracy ($R^2 = 0.207$, $F(80, 4) = 5.23$, $P < 0.001$, int. $\beta = 0.007$, $P = 0.048$) indicating subjects with a higher visual and a higher semantic component showed higher accuracy. This pattern was observed in younger subjects, and mature subjects with high accuracy.
We show that less visuosemantic information is contained in the neural signal of mature controls, but could not be explained by neural slowing. Better performance and cognition was linked to a higher amount of visual information in the neural signal, supporting the brain maintenance hypothesis: successful ageing is underpinned by retaining youth-like neural function[4].
[1]Price, 2017 [2]Clarke, 2015 [3]Shafto, 2014 [4]Nyberg, 2012

Disclosures: R. Bruffaerts: None. **L.K. Tyler:** None. **B. Randall:** None. **K.A. Tsvetanov:** None. **C. Can:** None. **A. Clarke:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.02

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant AG019731

Title: Age-related changes in memory representational networks

Authors: *Z. A. MONGE[1], M. RITCHEY[2], R. E. CABEZA[1]
[1]Ctr. for Cognitive Neurosci., Duke Univ., Durham, NC; [2]Boston Col., Chestnut Hill, MA

Abstract: Preliminary evidence indicates that increased age is associated with changes in memory representational quality (MRQ). However, it is unclear if there are also age-related changes in how information is *shared* between brain regions (i.e., informational connectivity). Here, we investigated age-related changes in memory representational networks. During fMRI scanning, 20 younger adults (YAs) and 16 older adults (OAs) studied negative, positive, and neutral pictures. Later, outside of the scanner, participants completed a memory recognition task, in which they were presented previously presented pictures and novel lures. Participants indicated whether the item was old or new. To construct the representational networks, first,

within each ROI (AAL atlas; 90 ROIs), we constructed *representational timeseries*. For each ROI and for each event we used a support vector machine that was trained to discriminate the three emotional stimuli categories (i.e., negative, positive, neutral) for every single event except for one event being tested (multi-voxel pattern analysis with a leave-one-out cross-validation procedure). For the event being tested, we outputted the classifier-determined probability that the event belonged to the classified emotional category (i.e., how confident the classifier was in its decision). The representational timeseries from each ROI were correlated with each other to construct, for each participant, a *representational network*, which were then analyzed within a graph theoretical framework. A modularity analysis (on the study averaged representational network) revealed that there were three groups of brain regions (i.e., modules) that shared more information with each other relative to other regions - posterior occipitotemporal cortex, anterior temporal/ventral prefrontal cortex (PFC), and frontoparietal modules. Irrespective of memory, we found that within the OAs (compared to YAs) the strength of connections from the posterior occipitotemporal cortex ($p<.001$) and frontoparietal ($p<.0001$) modules was attenuated but preserved within the anterior temporal/ventral PFC module ($p=.99$). Furthermore, we found when comparing memory hits to misses, that memory-related between-anterior temporal/ventral PFC module connection reconfiguration was greater within the YAs than OAs ($p<.05$). In sum, it appears that there are age-related changes in how brain regions share information with each other, and in service of memory, that OAs do not as flexibly reconfigure information sharing from anterior temporal/ventral PFC regions. Perhaps this finding reflects OAs greater reliance on semantic knowledge in service of memory.

Disclosures: Z.A. Monge: None. **M. Ritchey:** None. **R.E. Cabeza:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.03

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant AG05806
Wharton Pension Research Council / Boettner Institute / TIAA-CREF

Title: Neural and behavioral correlates of episodic memory are associated with temporal discounting in older adults

Authors: *K. M. LEMPERT[1], D. A. WOLK[2], J. W. KABLE[1]
[1]Dept. of Psychology, [2]Hosp. of the Univ. of Pennsylvania, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Older adults face many tradeoffs between smaller rewards available immediately and larger delayed rewards. When making such intertemporal choices, people generally prefer rewards sooner rather than later, a tendency called temporal discounting. The effects of age on temporal discounting have been inconsistent across studies, perhaps due to substantial variability in the extent of cognitive decline with age. Furthermore, if variability in cognitive decline among older adults underlies variability in temporal discounting, a secondary question is the *specific* cognitive process that declines in older adults, leading to steeper discounting. One neural system that deteriorates with aging, and has been shown to promote patient choice, is the episodic memory system. We examined the association between episodic memory ability and temporal discounting in older adults. In addition, we investigated whether temporal discounting was associated with a neural measure of cognitive decline, white matter hyperintensity (WMH) volume. These white matter lesions (detectable as areas of hyperintense signal in brain white matter on FLAIR MRI) are ubiquitous in older adults regardless of cognitive status, are thought to relate to small vessel ischemic disease, and can predict global cognitive impairment, including impairment in episodic memory retrieval. 100 older adults (ages 58-93; mean age = 72.01; N = 76 cognitively normal; N = 24 with mild cognitive impairment, MCI) completed a neuropsychological testing battery, as well as an intertemporal choice task and a risky decision making task. A composite episodic memory retrieval score significantly predicted discount rate, even when controlling for age, gender, race, and years of education ($\beta = -0.48$; $p = 0.005$). Specifically, individuals with better episodic memory tended to discount delayed rewards less. Moreover, overall WMH burden (available for N = 71; N = 15 MCI) was positively associated with temporal discounting, even when controlling for intracranial volume, age, gender, and education ($\beta = 0.55$; $p = 0.009$). Highlighting the specificity of these findings, there was no relationship between episodic memory and risk aversion ($r = 0.03$; $p = 0.76$), or between WMH burden and risk aversion ($\beta = 0.01$; $p = 0.925$). There was also no significant relationship between executive function and temporal discounting ($r = -0.03$; $p = 0.76$). While this study was cross-sectional, it suggests that temporal discounting may increase as episodic memory declines with aging.

Disclosures: K.M. Lempert: None. **D.A. Wolk:** None. **J.W. Kable:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.04

Topic: H.02. Human Cognition and Behavior

Support: University of Iowa Social Sciences Grant
Dana Foundation

Title: Age differences in the neural correlates of loss aversion

Authors: *K. HALFMANN[1], W. HEDGCOCK[2], N. L. DENBURG[3]
[1]Psychology, Univ. of Wisconsin - Platteville, Platteville, WI; [2]Marketing, Univ. of Minnesota, Minneapolis, MN; [3]Neurol., Univ. of Iowa, Iowa City, IA

Abstract: Most decisions offer a potential loss or gain. Humans tend to avoid risks with potential losses - a bias called loss aversion (Kahneman and Tversky, 1979). Age relates to changes in loss aversion, but the direction of results are mixed (e.g., Johnson, Gachter, and Hermann, 2006; Strough et al., 2008). Similarly, older adults tend to emphasize positive relative to negative information in decision processing, which may reduce loss aversion and increase risk taking (Pachur, Mata, and Hertwig, 2017). We asked whether there were age-related differences in the neural substrates of loss aversion. Indeed, processing decisions engages a value system (i.e., prefrontal, parietal, and striatal regions), and recent research suggests that older adults who make more suboptimal decisions show more temporal variability in the ventral striatum (Samanez-Larkin et al., 2010). Thus, we predicted that there would be age-related differences in the value system during a mixed gain/loss task. Forty-nine individuals participated in this research: 33 healthy older adults (*Mdn*=77 years; 48.5% female) and 16 younger adults (*Mdn*=22 years; 50% female). Participants chose between a sure $0 or a 50/50 chance to gain or lose a monetary reward while undergoing functional magnetic resonance imaging (fMRI). Participants were asked to indicate whether they would take ("accept") this gamble or reject the gamble (take $0) on each trial, where 1=*Strongly Accept*, 2=*Weakly Accept*, 3=*Weakly Reject*, 4=*Strongly Reject*. We did not observe behavioral differences in loss aversion by age. However, older adults showed reduced blood oxygen level dependent signal (BOLD) signal relative to younger adults in the medial prefrontal cortex and dorsal striatum (i.e., caudate). These brain areas served as regions of interest (ROIs) in our following analyses. We defined striatal ROIs based on individual participant anatomy, because the striatum lies adjacent to the ventricles and aging is associated with ventricular expansion. Older adults showed greater temporal variance in the BOLD signal in the left and right dorsal striatum and (to a lesser extent) the medial prefrontal cortex relative to younger adults. Taken together, our results suggest that aging relates to less activation and more variable activation in the value system during a mixed gain/loss task. Although we did not observe a behavioral difference between younger and older adults in loss aversion, choice behavior does not fully show age effects on decision processing (Lighthall, Huettel, and Cabeza, 2014). These results have implications for how older adults process financial decisions.

Disclosures: K. Halfmann: None. **W. Hedgcock:** None. **N.L. Denburg:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.05

Topic: H.02. Human Cognition and Behavior

Support: NIA R00-AG042596
NIA R01-AG044838
NIA T32-AG000029

Title: Time preferences and neural representation of subjective value across adulthood

Authors: *K. L. SEAMAN[1], C. PUTTINGER[2], R. MATA[2], D. H. ZALD[3], G. R. SAMANEZ-LARKIN[1]
[1]Ctr. for Cognitive Neurosci., Duke Univ., Durham, NC; [2]Dept. of Psychology, Univ. of Basel, Basel, Switzerland; [3]Dept Psychol, Vanderbilt Univ., Nashville, TN

Abstract: Many everyday decisions involve a tradeoff between the immediate satisfaction of obtaining a reward and the long-term well-being that can be obtained by waiting. The decision to accept a smaller, sooner reward instead of waiting for a larger, later reward is known as temporal discounting. A number of behavioral studies have examined temporal discounting across the adult life span, with mixed results. While several studies have reported a decrease in temporal discounting with age (e.g. Eppinger et al., 2012), many studies have also reported no age effects on discounting behavior (e.g. Rieger & Mata, 2013) or a increase in discounting with age (e.g. Read & Read, 2004). In addition to this inconclusive behavior, there is little empirical evidence directly linking psychological and neural systems with adult age differences in subjective value representation in the brain. Thus, in Study 1 we examined neural subjective value representations when monetary rewards are integrated with time delays across adulthood. 75 healthy participants between the ages of 22 and 83 completed an incentive-compatible task, participants made choices between either (1) a smaller magnitude reward with a shorter time delay and (2) a larger magnitude reward with a longer time delay while undergoing fMRI. Subjective values were computed using individual discount rates estimated using a hyperbolic discount function. We found that subjective value correlated with activity in the medial prefrontal cortex, but no consistent evidence for age differences in either preferences or the neural representations of subjective value across adulthood. We evaluated the reliability of this effect with a pre-registered systematic literature review and meta-analysis of existing studies examining temporal discounting in different age groups (e.g. younger adults vs. older adults) or in adult age-heterogeneous samples (Study 2). We predicted a nonsignificant or small negative effect of age on discount rates. Our initial search identified 2688 independent studies and after screening, we found 32 studies met our inclusion criteria. Within these studies, we found heterogeneity in terms

of experimental design (e.g. extreme-group vs. continuous age), methodology (e.g. delay discounting vs. intertemporal choice), and quantification of discounting behavior (e.g. proportion of immediate choices vs. parameters from a computational model). This heterogeneity in experimental design is likely the reason for the inconsistency in the literature. Overall, the studies together suggest that both decision preferences and the neural systems supporting this decision behavior remain stable across adulthood.

Disclosures: K.L. Seaman: None. **C. Puttinger:** None. **R. Mata:** None. **D.H. Zald:** None. **G.R. Samanez-Larkin:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.06

Topic: H.02. Human Cognition and Behavior

Support: German Research Foundation (DFG) (SFB 940/2 B7)
German Ministry of Education and Research (BMBF EMOTISK 16SV7243)

Title: Effects of human aging on model-based control during learning and decision-making

Authors: *B. EPPINGER[1,2], M. WALTER[3], S.-C. LI[2]
[1]Concordia Univ., Montreal, QC, Canada; [2]Lifespan Developmental Neuroscience, Fac. of Psychology, TU Dresden, Dresden, Germany; [3]Univ. of St. Gallen, St. Gallen, Switzerland

Abstract: In this talk I will present findings from three experiments on the effects of human aging on the interplay of goal-directed (model-based) and habitual (model-free) learning and decision mechanisms. Across all three experiments we used variants of a sequential decision-making task developed by Daw and colleagues (2011). In the first experiment, we examined how the distinctiveness of learnt reward associations affects model-based decision making. We show that older adults engage less in model-based control than younger adults. However, age differences in model-based decision making are insensitive to the distinctiveness of learnt reward associations (Eppinger et al., 2013). In the second experiment we varied the transition structure of the task to see how changes in model-based representations are reflected in event-related potential (ERP) components in younger adults. Results of this study show that the P300 ERP component is sensitive to the distinctiveness of the transition structure and reflects an integration of model-based and model-free information during decision-making (Eppinger et al., 2017). In the third experiment we applied the same experimental manipulation as in Experiment 2 in an age-comparative design. In younger adults we replicate the results from the second experiment. In older adults we show increased model-based behavior in the condition with more predictable state transitions. Taken together, findings from this series of three experiments show that age

differences in model-based control are, in part, due to age-related deficits in the representation of the transition structure of the task environment. This may reflect a more general underlying problem of older adults in the representation of cognitive state spaces.

Disclosures: B. Eppinger: None. **M. Walter:** None. **S. Li:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.07

Topic: H.02. Human Cognition and Behavior

Support: National Science Foundation (SES-1450624) to DSO and NCE
Elder Justice Foundation to RNS

Title: Uncovering age-related vulnerabilities in trust-related decision making: A brain-behavior analysis

Authors: *N. C. EBNER[1], D. S. OLIVEIRA[1], G. R. TURNER[2], R. N. SPRENG[3]
[1]Univ. of Florida, Gainesville, FL; [2]Psychology, York Univ., North York, ON, Canada; [3]Montreal Neurolog. Inst., McGill Univ., Montreal, QC, Canada

Abstract: Fraud costs older adults billions of dollars annually. Financial abuse constitutes one of the most common forms of elder mistreatment, with devastating consequences for health and independent living. A rapidly aging population, combined with age-related changes in decision making, render fraud targeting older adults a growing public-health concern. Technological advances are opening novel avenues for fraud. Older adults increasingly navigate the Internet to manage assets online and are at increased risk of becoming victims of cyber social-engineering attacks, such as spear-phishing emails, which lure users into visiting web pages that procure personal information or into clicking on malicious downloads. We adopted a multi-contextual, ecologically valid approach to uncover age-related vulnerabilities on the level of brain and behavior in trust-related decision making. Study 1 recorded the browsing activity of 100 young (M = 22 yrs, SD = 4.1, 56% female) and 58 older (M = 72 yrs, SD = 6.8, 43% female) adults over 21 days. Throughout the study, participants, unbeknownst to them, received simulated spear-phishing emails. A large number of users (43%) were susceptible to the spear-phishing attacks, with older women constituting the most vulnerable group (B = 0.98, z = 2.02, p = 0.04). There was a discrepancy, particularly among older users (B = -0.78, z = -2.11, p = 0.04), between self-reported susceptibility awareness and behavior. Examining specific risk profiles, higher susceptibility to online fraud was associated with lower memory (B = -1.38, CI = [-36.4, -0.5], odds ratio = 0.25, p = 0.01) and lower positive affect (B = -2.34, CI = [-76.0, -0.7], p = 0.02, odds ratio = 0.10) among users aged 75−89. In a complementary study, we contrasted brain

structure and function in 13 older adults who were victims of fraud (M = 70 yrs, SD = 4.6, 54% female) with 13 older adults who had avoided an attempted fraud (M = 69 yrs, SD = 4.6, 54% female). The exploited group showed cortical thinning in anterior insula and posterior superior temporal cortices and reduced functional connectivity within default and salience networks, while between-network connectivity was increased. Thus, alterations in brain regions implicated in trust-related decision making may signal heightened fraud risk in older adults. Our data advance understanding of brain and behavioral processes underlying age-related vulnerabilities to fraud online and in-person. Determination of cognitive, socio-affective, and neurobiological risk profiles is crucial to develop prevention tools against victimizations in aging, which can have dramatic consequences for individual and societal health and well-being.

Disclosures: N.C. Ebner: None. **D.S. Oliveira:** None. **G.R. Turner:** None. **R.N. Spreng:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.08

Topic: H.02. Human Cognition and Behavior

Title: Dissociation in neural components of memory-dependent value judgments is maintained in healthy aging

Authors: *N. R. LIGHTHALL[1], L. B. CONNER[1], N. C. EBNER[2]
[1]Univ. of Central Florida, Orlando, FL; [2]Univ. of Florida, Gainesville, FL

Abstract: Across the lifespan, past experiences shape our judgments about the value of current choice options. Relatively little research has examined how processes like episodic encoding and retrieval demand affect the neural mechanisms of value judgments, thus it is presently unclear if and how such memory components interact with value-related processing. In addition, normal aging is associated with declines in both episodic encoding and retrieval, suggesting that the involvement of these memory processes may enhance age differences in value-based neural processing. The present fMRI study compared brain activation underlying memory-dependent value judgments in younger versus older adults, and determined how such activation was modulated by encoding and retrieval. Stimuli included product images with consumer review excerpts from an online shopping website. In initial encoding blocks, participants provided valence ratings for a series of consumer reviews. Each product was presented either with one consumer review (low retrieval demand) or two different reviews on non-consecutive trials (high retrieval demand). In subsequent value judgment blocks, participants estimated the average consumer rating for each product presented at encoding. To assess episodic encoding, the final task block included a memory test for product attributes (neutral details) mentioned in the

original consumer reviews, intermixed with foil attributes. Parametric analysis of value processing showed that older compared to younger adults exhibited less robust brain activity in sensory regions when making judgments from memory. Within and across age groups, retrieval demand was associated with activation of fronto-parietal regions that were notably distinct from regions associated with value judgments. Performance on the product attribute memory task was associated with increased activity in the dorsolateral prefrontal cortex during the judgment phase; however, participants' value-related activation was not modulated by their level of attribute-memory. Taken together, these results indicate that episodic encoding and retrieval demand can affect brain regions recruited during memory-dependent value judgments, but the network of regions associated with value judgments themselves function relatively independent of memory components. In addition, although the neural correlates of value processing are affected by age, dissociations in memory-related components of value judgments appear to be maintained in healthy aging.

Disclosures: N.R. Lighthall: None. **L.B. Conner:** None. **N.C. Ebner:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.09

Topic: H.02. Human Cognition and Behavior

Support: NIH-NINDS-NS-054775

Title: Changes in economic rationality and brain morphometry in human aging

Authors: *H.-K. CHUNG[1], A. TYMULA[2], I. LEUNG[3], M. VALENZUELA[3], P. W. GLIMCHER[4]
[1]Psychology, New York Univ., New York, NY; [2]Sch. of Econ., [3]Brain & Mind Ctr. and Sydney Med. Sch., Univ. of Sydney, Sydney, Australia; [4]Ctr. Neural Sci., New York Univ. Ctr. for Neural Sci., New York, NY

Abstract: There is growing interest in studying the neural mechanisms underlying decision-making across the lifespan. We previously (Tymula, et al., 2013) identified several age-related changes of risk attitudes and choice consistency: Highly functional elders are not only more likely to make fundamental choice errors but also more risk-averse. Neuroanatomical evidence shows that the decrease of grey matter (GM) volume in right posterior parietal cortex (rPPC) better predicts risk preference than age per se (Grubb et al., 2016). Here, in study one we extended this work by searching for a neuroanatomic locus correlating with economic rationality in healthy aging brain. In study two, we recruited an "on-the-path-to-dementia" sample and measured their cognitive abilities including rationality in choice. Economists have established

normative theories with a clear statement of the axioms that any rational person should obey to maximize subjective value (utility). One of the fundamental axioms of rational choice is the General Axiom of Revealed Preference (GARP) that defines the necessary and sufficient conditions for being a utility maximizer. We adopted the experimental paradigm designed by Harbaugh and colleagues (2001) to quantify the level of economic rationality in humans as defined by GARP violations. In the first study, we recruited highly functional elders 65+ years and used whole-brain voxel-based morphometry (VBM) to search for correlations between grey mater density and economic rationality. The results show that a reduction in ventrolateral prefrontal gray matter volumes best accounts for age-related declines in rationality. Interestingly, analyzing a large-scale database of previous functional magnetic resonance imaging (fMRI) studies in Neurosynth, we found that this brain area shows strong co-activation patterns with nearly all of the value-associated regions including posterior parietal cortex, ventromedial prefrontal cortex, dorsal lateral prefrontal cortex, striatum, and others - despite the fact that it has received very little attention in fMRI studies. In the second study, we recruited adults who are still healthy but have been identified to be on a path to dementia. Our preliminary data confirms our hypothesis: This population shows more serious impairment of economic rationality. They violated GARP more often and made more severe GARP violations than high functional elders in the study one. Taken together, these findings highlight the importance of furthering and harnessing our understanding of the brain function and behavior in aging to better develop intervention for long term health.

Disclosures: H. Chung: None. **A. Tymula:** None. **I. Leung:** None. **M. Valenzuela:** None. **P.W. Glimcher:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.10

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R21AG058206
NIH Grant R24AG0F4355
NIH Grant F31DA042574
NIH Grant T32AG000030
NIH Grant T32NS073547

Title: Neural mechanisms of motivational integration and cognitive control: Implications for healthy aging

Authors: *D. YEE[1], T. S. BRAVER[2]
[1]Washington Univ. In St. Louis, Saint Louis, MO; [2]Psychological and Brain Sci., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Motivational incentives play an influential role in decision-making and cognitive control. However, few studies have examined how different incentive categories are integrated in terms of their motivational influence. Recent evidence has suggested key interactions of motivational integration and cognitive control in terms of behavior, but its underlying neural mechanisms are unknown. We conducted an fMRI study to examine whether the combined diverse incentives (money, liquids) are in represented as a neural common currency in value-sensitive brain regions, and whether/how this putative motivational signal modulates cognitive control regions in prefrontal cortex. To test our hypothesis, we developed an innovative task paradigm that quantifies dissociable and integrative effects of liquid valence (appetitive, neutral, aversive) and monetary rewards (e.g., low, medium, high) on cognitive control. In the study, participants (N=51, 25 fem, 18-38 years) performed a cued task-switching paradigm to earn varying monetary reward amount (e.g., low, medium, high) across trials. Critically, post-trial performance feedback - in the form of oral liquid delivery - signaled successful task performance (accurate and fast responses) and attainment of monetary reward. Thus, the symbolic meaning of the liquid was held constant, and the liquid valence was blocked. A general linear model was performed to extract a time course of beta coefficients for the nine motivation experimental conditions (3 levels of money, 3 liquids). Preliminary results revealed distinct temporal profiles of BOLD activation for monetary rewards and liquid incentives in the striatum, anterior cingulate, and frontoparietal network, with highest monetary rewards eliciting earlier BOLD activation compared to medium and lower monetary reward trials. Dorsal striatum activation was associated with liquid salience (intensity), whereas left medial frontal gyrus activation was association with liquid valence. These results provide evidence of putative dissociable neural mechanisms for motivational incentive integration in a cognitive control context in healthy young adults. Critically, these mechanisms are directly relevant for understanding the motivational and cognitive changes in aging, as older adults are well known to paradoxically demonstrate decline in cognitive function but enhancement of motivational processing. Current directions include using multivariate approaches to elucidate motivation-control interactions in PFC, and collecting fMRI data from older adults to understand how neural mechanisms underlying they key interaction is altered throughout the lifespan.

Disclosures: D. Yee: None. **T.S. Braver:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.11

Topic: H.02. Human Cognition and Behavior

Support: HDSA Human Biology Project

Title: Reward-dependent cognition in pre-symptomatic and symptomatic Huntington's disease

Authors: *M. SHARP[1], P. WASSERMAN[2], K. MARDER[2], D. SHOHAMY[3]
[1]Neurol., McGill Univ., Montreal, QC, Canada; [2]Columbia Univ. Med. Ctr., New York, NY; [3]Columbia Univ., New York, NY

Abstract: Striatal neurons are impacted earliest in the course of Huntington's disease and striatal atrophy is a sensitive marker of disease progression. It is also known that patients with Huntington's disease, even in the earliest stages of the disease, have subtle cognitive impairments, but the specific cognitive mechanisms underlying these symptoms and their relation to striatal function remain poorly understood. Remarkably, despite the extensive literature demonstrating the crucial role of the striatum in signalling reward, there has been very little focus on studying reward-related cognitive processes in patients with Huntington's disease. Here we aimed to fill this gap by measuring reward learning and reward-guided memory in pre-symptomatic Huntington's patients (n=36), symptomatic patients (n=34) and healthy controls (n=18). We adapted a probabilistic reinforcement learning task in which participants gradually learned to associate stimuli with reinforcing outcomes. On each trial, at the time of feedback, participants were also shown a trial-unique image that, by its category assignment, indicated whether they were correct or incorrect on that trial. This allowed us to measure the influence of reward on two processes: reinforcement learning and reward-modulated episodic memory.
As predicted, results show that learning and memory were worse in the symptomatic Huntington's patients. Importantly, the same measures were also impaired in pre-symptomatic patients, demonstrating sensitivity of these tasks to early stages of the disease. We additionally found a relationship between task performance and estimated disease burden, which is calculated using the mutation length (number of CAG trinucleotide repeats) and age, among pre-symptomatic and symptomatic patients. Specifically, increased disease burden was strongly associated with worse reinforcement learning and, paradoxically, weakly associated with greater selectivity of memory for rewarded images. The degree to which learning and memory are impaired was also associated with measures of executive function. These results suggest that specific striatal-dependent cognitive mechanisms are impaired in patients with Huntington's disease and that measures of reward-guided cognition could be used as a marker of disease, even in the earliest and pre-symptomatic stages.

Disclosures: M. Sharp: None. **P. Wasserman:** None. **K. Marder:** None. **D. Shohamy:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.12

Topic: H.02. Human Cognition and Behavior

Support: VR521-2013-2589
Humboldt Research Award
af Jochnick Foundation

Title: Does frontostriatal white matter integrity mediate the dopaminergic influence on value learning in old age?

Authors: *L. DE BOER[1], B. GARZON[1], J. AXELSSON[2], K. RIKLUND[2], L. NYBERG[2], L. BÄCKMAN[1], M. GUITART-MASIP[1]
[1]Aging Res. Center, Karolinska Institutet, Solna, Sweden; [2]Umea Univ., Umea, Sweden

Abstract: The ability to learn about probabilistic rewards and to make optimal decisions is impaired in normal aging. Previous research has shown reduced processing of reward information in striatum and prefrontal cortex (PFC) in older persons. We have recently shown that the strength of the BOLD signal reflecting expected value at the time of choice in ventromedial prefrontal cortex (vmPFC) mediates age effects in choice performance on a two-armed bandit task. This signal is modulated by dopamine (DA) D1 receptor availability in nucleus accumbens (NAcc; doi: 10.7554/eLife.26424). These results suggest that value representations in vmPFC emerge through an iterative gating process within corticostriatal loops centered in NAcc that is modulated by DA. Here we extend these findings by investigating whether integrity of the white matter tract connecting vmPFC and NAcc is linked to the effects of D1 receptor availability on the strength of the expected-value signal in vmPFC. We will analyze diffusion tensor images acquired on the same 30 young and 30 older adults that participated in the previously reported experiment that involved performance on a two-armed bandit task along with fMRI and PET DA D1 data collected with [11C]SCH23390. Tractography analysis will identify the white matter pathway connecting NAcc to the voxels in vmPFC, representing expected value in individual subjects. We will relate measures of integrity of these paths to performance on the two-armed bandit task, the strength of the expected value signal in vmPFC and D1 receptor availability in NAcc. Previous work has shown that reduced integrity of the white matter pathway between vmPFC and NAcc is related to reduced probabilistic reward learning performance in older individuals. We therefore expect that the integrity of the white matter pathway connecting NAcc and vmPFC will predict performance in the two-armed bandit as well as the strength of the expected value signal in vmPFC. We also expect that the integrity of the white matter pathway connecting NAcc and vmPFC is associated with the effects of D1

receptor availability in NAcc on the strength of the expected value signal in vmPFC. These results will elucidate one mechanism by which DA decline contributes to impaired cognitive abilities in normal aging.

Disclosures: L. De Boer: None. **B. Garzon:** None. **J. Axelsson:** None. **K. Riklund:** None. **L. Nyberg:** None. **L. Bäckman:** None. **M. Guitart-Masip:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.13

Topic: H.02. Human Cognition and Behavior

Support: VA VA 5I01CX000501
NIH ADNI U01 AG024904
DOD W81XWH-12-2-0012

Title: Cognitive aging and the anterior cingulate cortex: Glucose metabolism, amyloid, and APOE genotype

Authors: *J. V. PARDO[1], S. M. NYABWARI[2], J. T. LEE[3]
[1]Psychiatry, Univ. of Minnesota Dept. of Psychiatry, Minneapolis, MN; [2]Neurosci., Univ. of Minnesota, Minneapolis, MN; [3]Cognitive Neuroimaging Unit, Minneapolis VAHCS, Minneapolis, MN

Abstract: Identifying and understanding the role of biomarkers for cognitive decline during aging is important. We showed previously the anterior cingulate cortex (ACC) and adjacent medial prefrontal cortex (mPFC) are key to aging-related metabolic dysfunction correlating with age-associated cognitive decline (Pardo et al., 2007). Here, we examine using the ADNI dataset the hypothesis that ACC metabolism functions as a mediator in the age and executive function relationship driven by amyloid deposition; i.e., the decline in ACC metabolism with age during otherwise healthy aging is an important explanatory factor in the observed age and cognition relationship, perhaps related to neural dysfunction induced by fibrillar amyloid. FDG and amyloid PET scans from ADNI were normalized to Talairach space via the Neurostat program (S. Minoshima, U. Washington). We performed an ACC/mPFC region-of-interest analysis for each scan. We obtained data from 231 cognitively normal participants (age 59-93 years, mean 74, SD 6). Participants' ages and animal fluency scores, which served as a measure of executive performance, were also obtained from ADNI and were matched to their respective ACC amyloid and FDG uptake means. In agreement with our previous study, significant correlations arose between age and metabolism [$r = -0.44$, $p = 2(10)^{-12}$]; metabolism and fluency [$r = -0.23$, $p = 4(10)^{-4}$]; and age and fluency [$r = -0.26$, $p = 2(10)^{-4}$]. These findings motivated a mediation

model in which ACC metabolism functions as a mediator in the relationship between age and fluency score. The Sobel test for mediation showed significance in the indirect effect of ACC metabolism on the age and fluency relationship at the .05 significance level, suggesting ACC metabolism functions as a mediator in the age and fluency relationship. The direct effect or the effect of age on fluency when controlling for ACC metabolism was not zero. As such ACC metabolism was a partial mediator between age and fluency, not a complete mediator. No significant correlation between age and amyloid ($r = 0.12$, $p = .06$) or amyloid and fluency ($r = 0.09$, $p = .17$) surfaced. Surprisingly, resting metabolism was positively correlated with amyloid in the healthy elders ($r = 0.15$, $p = .02$). Since APOE4 is associated with ACC amyloid deposition (Pardo & Lee, 2018), the results suggest ACC metabolism is in part a mediator of the relationship between age and cognition, while fibrillary amyloid deposition dependent on genotype is not directly responsible for these relationships. These findings motivate the creation and use of novel interventions targeting the ACC to prevent or treat the decline in cognitive function associated with normal aging.

Disclosures: J.V. Pardo: None. **S.M. Nyabwari:** None. **J.T. Lee:** None.

Nanosymposium

193. Human Cognition and Behavior: Decision Making and Cognitive Aging

Location: SDCC 23

Time: Sunday, November 4, 2018, 1:00 PM - 4:30 PM

Presentation Number: 193.14

Topic: H.02. Human Cognition and Behavior

Support: Heart and Stroke Foundation
Canadian Institutes of Health Research Project Grant
The Imagination Institute

Title: Creative thinking is associated with dissociable patterns of intrinsic functional connectivity in older and younger adults

Authors: *A. ADNAN[1], R. BEATY[3], J. LAM[2], N. SPRENG[4], G. R. TURNER[2]
[1]Psychology, York Univ., Toronto, ON, Canada; [2]Psychology, York Univ., North York, ON, Canada; [3]Harvard Univ., Boston, MA; [4]Montreal Neurolog. Inst. and Hosp., Montreal, QC, Canada

Abstract: The default-executive coupling hypothesis of aging posits that increased functional coupling between the default network (DN) and executive control regions occurs in response to increased cognitive control demands in older adulthood (Turner and Spreng, 2015). Preliminary work from our lab (Adnan et al., in prep) has shown that there is greater default-executive coupling in older adults, compared to young adults, during a divergent thinking (DT) task. However, whether this task-based pattern of functional coupling is reflected in intrinsic

connectivity patterns and predictive of creative ability, in older adults is unknown. This study sought to investigate patterns of intrinsic connectivity that are predictive of DT in young and older adults. **Methods:** 22 young and older adults completed a battery of DT tasks outside the scanner and a multi-echo resting state scan. Functional connectivity analyses were implemented using the CONN toolbox. Default and executive control regions (including the salience and fronto parietal networks; SN; FPN) were defined using an apriori functional parcellation scheme (Gordon et al., 2014). DT was specified as a regressor of interest at the first level and simple main effects of creativity were examined in young and older adults independently and using a direct contrast. **Results:** Consistent with previous work, young adults showed greater intrinsic connectivity both within DN and SN and also between DN-SN and DN-FPN, that was positively related to DT. In older adults, intrinsic connectivity within the DN and between DN-SN positively covaried with DT. A direct contrast between groups showed that young adults had a wider range of both within (SN-SN, DN-DN and FPN-FPN) and between network (FPN-SN, SN-DN and FPN-DN) intrinsic connectivity that was predictive of DT. In contrast, only within DN connectivity and between DN-SN connectivity was associated with DT in older adults. **Summary:** Our results provide early evidence for age differences in intrinsic connectivity profiles that predict creative thought. Consistent with previous work, young adults showed a similar pattern of default-executive coupling characterized by a significantly higher number of connections within networks and between networks. In contrast, creative thought in older adults was associated with a smaller range of both within and between network coupling, primarily implicating default and salience nodes of the executive control network. Creativity in later life is associated with a more circumscribed pattern of intrinsic function connectivity, implicating associative processes mediated by the default network and frontally-mediated control processes.

Disclosures: A. Adnan: None. **R. Beaty:** None. **J. Lam:** None. **N. Spreng:** None. **G.R. Turner:** None.

Nanosymposium

194. Biomarker and Drug Discovery: Drug Delivery and Assay Development

Location: SDCC 4

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 194.01

Topic: I.05. Biomarker and Drug Discovery

Title: Imaging neurogenic inflammation in the skin: A translational measure of TRPA1 activation

Authors: *V. JOSEPH[1], X. YANG[2], S. GAO[2], W. THEESE[2], J. LIN[2], R. WEIMER[1], R. BAUER[2]
[1]Biomed. Imaging, [2]Genentech, Inc., South San Francisco, CA

Abstract: Transient receptor potential ankyrin 1 (TRPA1) is a polymodal sensor for irritants expressed on nociceptive neurons, sensory neurons in the lung, skin, and GI, and non-neuronal cells in the lung and epithelium. Activation of TRPA1 can induce nociceptive pain, itch, cough, and inflammation. Several groups have developed small molecule inhibitors (SMIs) targeting TRPA1 for the potential treatment of pain, itch, and respiratory diseases. However, direct sampling of the target tissue to assess the pharmacodynamics of these molecules is not feasible in the clinic. Here we describe the development of a translational, functional assay of TRPA1 activity in the skin that can be used as a pharmacodynamic biomarker in human clinical trials. Laser speckle contrast imaging (LSCI) is a non-invasive imaging technique that combines high spatial and temporal resolution to study blood flow. TRPA1 activation in the skin by application of TRPA1-specific agonist allyl-isothiocyanate (AITC) induces neurogenic inflammation resulting in an increase in dermal blood flow that can be measured with LSCI. We hypothesized that TRPA1 SMI activity could be assessed by its ability to inhibit this blood flow response. We tested this hypothesis in two rodent models. Topical application of 5% AITC to the rat ear significantly induced dermal blood flow and this was blocked by genetic deletion of TRPA1 in knockout animals (n=6). Oral dosing of a TRPA1 SMI dose-dependently attenuated dermal blood flow in response to both 5% AITC on rat ear (n=6) and 25% AITC on guinea pig ear (n=5).

We optimized this assay for human use by conducting a feasibility and test-retest clinical imaging study. The forearms of 22 subjects were imaged during a single session. AITC (5%, 10%, 15%, 20%) and vehicle were applied on the forearm, and subjects reported their pain and itch on a scale of 0-10. Tolerable pain and/or itch and an increase in dermal blood flow were induced at every concentration tested, with 10% and 15% being the most robust with the fewest adverse events. To test reproducibility of this assay, 22 subjects were imaged twice, under identical conditions, 2 weeks apart. Both arms were imaged at each session and each arm received identical applications of 10% and 15% AITC. Dermal blood flow response to 10% and 15% AITC were highly reproducible within-subject across sessions (ICC= 0.74-0.87) enabling the potential of detecting a drug effect with as few as 3-5 subjects.

LSCI provides an *in vivo* measure of TRPA1-dependent activity and can demonstrate proof of activity of TRPA1 inhibitors. Our assay requires few subjects, is easily implemented, and could therefore be a useful pharmacodynamic readout in clinical trials.

Disclosures: X. Yang: A. Employment/Salary (full or part-time):; Genentech, Inc. **S. Gao:** A. Employment/Salary (full or part-time):; Genentech, Inc. **W. Theese:** A. Employment/Salary (full or part-time):; Genentech, Inc. **J. Lin:** A. Employment/Salary (full or part-time):; Genentech, Inc. **R. Weimer:** A. Employment/Salary (full or part-time):; Genentech, Inc. **R. Bauer:** A. Employment/Salary (full or part-time):; Genentech, Inc..

Nanosymposium

194. Biomarker and Drug Discovery: Drug Delivery and Assay Development

Location: SDCC 4

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 194.02

Topic: I.05. Biomarker and Drug Discovery

Support: Neuroscience program
College of Medicine
Department of chemistry and biochemistry
Field Neurosciences Institute
John G. Kulhavi Professorship in Neuroscience at CMU

Title: G1 and G4 PAMAM dendrimers delivery to the brain after systemic and intracranial injections in C57BL/6J mice

Authors: *B. SRINAGESHWAR[1,5,6], S. T. PERUZZARO[2,5], M. M.-M. ANDREWS[2,5], A. WEDSTER[2,5], A. DILS[5,6], J. STURGIS[5,6], P. OTERO[2,5], S. CLIMIE[2,5], K. JOHNSON[3], A. HIETPAS[3], J. KIPPE[2,5], B. CLARK[3], A. N. STEWART[2,5], O. V. LOSSIA[2,5,6], D. STORY[2,5,4], A. AL-GHARAIBEH[2,5], A. ANTCLIFF[2,5,6], N. MUNRO[2,5], R. CULVER[2,5], D. SWANSON[3], G. L. DUNBAR[2,5,4,7], A. SHARMA[3], J. ROSSIGNOL[2,5,6]
[1]Neurosci., Central Michigan Univ., Chennai, India; [2]Neurosci., [3]Chem. and Biochem., [4]Dept. of Psychology, Central Michigan Univ., Mount Pleasant, MI; [5]Field Neurosciences Inst. Lab. for Restorative Neurol., Mount Pleasant, MI; [6]Col. of Med., Mount Pleasant, MI; [7]Field Neurosciences Inst., Saginaw, MI

Abstract: Dendrimers are 3-dimensional nanoparticles that are branched having various applications in the field of biomedicine. Previous evidences show that the G4 dendrimers having 100% amine surface (G4-NH2) are highly toxic to cells in vitro and in vivo due to their amine groups that are highly positive charged. Therefore, to reduce the toxicity, we have modified the 100% amine surface of the dendrimers to have more neutral functional groups in such a way that the dendrimers have only 10% of the surface covered with NH2 and 90% of the surface covered with hydroxyl groups (-OH; known as G4-90/10). Our in vitro data shows that these modified dendrimers are taken up the cells (neurons and different types of stem cells) in vitro and neurons and glial cells in vivo. The toxicity assay shows that these modified dendrimers are less toxic compared to the 100% amine surface dendrimers. Following injection of these modified dendrimers into C57BL/6J mice via carotid artery (single dose) and tail-vein (multiple dose) showed that these dendrimers reach the brain by crossing the blood-brain barrier (BBB) and localize into the neuron and glial cells. Analysis of the presence of dendrimers in peripheral organs following carotid injections showed that these dendrimers are not present in the lungs, liver, spleen and kidneys proving that most of the dendrimers following carotid injections

reached the brain. However, as expected some dendrimers reached the peripheral organs following multiple tail-vein injections. Localizing into the kidneys showed that these dendrimers get eliminated out of the biological system thereby do not cause any side effects as seen in other type of nanoparticles that gets retained in the biological system. Moreover, prolonged presence of dendrimers (G1-90/10 and G4-90/10) upto 3 weeks following unilateral intracranial injections into the striatum showed that these dendrimers have the tendency to migrate in the brain via corpus callosum at different rates depending on their size. Our research findings showed that the (1) dendrimers are uptaken by the neuronal culture in vitro; (2) dendrimers alone can cross the BBB when injected via carotid artery and tail-vein, and are uptaken by neurons and glial cells in vivo; and (3) the G1 and G4 dendrimers migrate in the brain following unilateral injections into the striatum upto 3 weeks and there is a difference in migration between the G1 and the G4 dendrimers owing to their size difference. The future aspect involves delivering cargo such as drugs/biomolecules to the brain using dendrimers in vivo.

Disclosures: B. Srinageshwar: None. **S.T. Peruzzaro:** None. **M.M. Andrews:** None. **A. Wedster:** None. **A. Dils:** None. **J. Sturgis:** None. **P. Otero:** None. **S. Climie:** None. **K. Johnson:** None. **A. Hietpas:** None. **J. Kippe:** None. **B. Clark:** None. **A.N. Stewart:** None. **O.V. Lossia:** None. **D. Story:** None. **A. Al-Gharaibeh:** None. **A. Antcliff:** None. **N. Munro:** None. **R. Culver:** None. **D. Swanson:** None. **G.L. Dunbar:** None. **A. Sharma:** None. **J. Rossignol:** None.

Nanosymposium

194. Biomarker and Drug Discovery: Drug Delivery and Assay Development

Location: SDCC 4

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 194.03

Topic: I.05. Biomarker and Drug Discovery

Support: Chinese FRFCU 2016QN81017
Chinese NSF 61673346
Chinese NSF 81600982
Chinese NSF 81527901

Title: Dynamic observation of focused ultrasound induced blood-brain barrier opening in cat brain via contrast-enhanced 7T MRI

Authors: *X. YU[1,2], X. FENG[1], T. HE[1], C.-H. TSAI[4], W.-Y. CHAI[5,4], K. WANG[1,3], H.-L. LIU[1,4], H.-Y. LAI[1,2]
[1]Interdisciplinary Inst. of Neurosci. and Technology, QAAS, Zhejiang Univ., Zhejiang, China; [2]Dept. of Neurobiology, Sch. of Med., [3]Col. of Biomed. Engin. and Instrument Sci., Zhejiang Univ., Hangzhou, China; [4]Dept. of Electrical Engin., Chang Gung Univ., Taoyuan, Taiwan; [5]Dept. of Diagnos. Radiology and Intervention, Chang Gung Mem. Hosp., Taoyuan, Taiwan

Abstract: Focused ultrasound (FUS), together with microbubbles (MBs) injected into blood vessels, can induce reversible disruption of tight junctions between endothelial cells and increase the permeability of cerebral capillaries, thus open the blood-brain barrier (BBB) locally, temporarily and non-invasively. Before MB-mediated FUS can be translated to clinical use in drug delivery for central nervous system diseases, its safe and effective range for BBB opening need to be systematically confirmed across different animal species which have different skull thicknesses. Our research aims at evaluating its dynamics in middle-size animal, cats, under a series of FUS exposure levels via contrast-enhanced T1-weighted images (T1-WIs) of 7T MRI and Evans Blue (EB) brain staining.

Before FUS exposure in each cat, it was administered with MBs intravenously (i.v., 1.5μL/ kg) and EB dye (1 ml/kg). Cats were exposed to 0.6, 0.8 and 1.0 mechanical index (MI) FUS for 30s and 60s, respectively. Whole brain T1-WIs (TR=2300 ms, TE=18 ms, BW=100 Hz, Voxel size: $0.5\times0.5\times1.0$ mm^3) were recorded by 7T research system (Siemens, Erlangen, Germany) before FUS, and 0.5-h, 3.5-h, 6.5-h and 1-day post-FUS. The MRI contrast-agents, Gd-DTPA (0.3 mmol/kg), were i.v. injected at each timepoint to evaluate the BBB permeability. To localize the spatial distribution of BBB opening, animals were deeply anesthetized and sacrificed to get EB-stained brains. The signal intensity (SI) changes of T1-WIs in the region of FUS exposure were depicted along the timeline.

Image analysis showed that 0.6-MI FUS for 60s was not able to induce BBB opening in cat brain; BBB opening induced by 0.8-MI FUS (30s) recovered after 6.5 h; effects of 0.8 MI (60s) and 1.0 MI (30s) still existed after 6.5h, but vanished 1 day after FUS. Result of EB staining was consistent with image analysis.

Moreover, when the exposure time was constant, higher MI led to stronger and longer BBB opening effect. Additionally, when a FUS exposure was applied 120s after MB injection rather than immediately after injection, even if its exposure time doubled, the induced permeability was lower at early stage, implying that the interval between MB injection and FUS exposure might also be one of the influencing factors for BBB disruption.

Our study suggests that MB-mediated FUS, together with 7T MRI, might potentially be applied to the nonhuman primates and further clinical situations.

Disclosures: X. Yu: None. **X. Feng:** None. **T. He:** None. **C. Tsai:** None. **W. Chai:** None. **K. Wang:** None. **H. Liu:** None. **H. Lai:** None.

Nanosymposium

194. Biomarker and Drug Discovery: Drug Delivery and Assay Development

Location: SDCC 4

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 194.04

Topic: I.05. Biomarker and Drug Discovery

Support: NIH grant R01NS092838

NIH grant R21NS09004

Title: Physiology and clinical potential of the cerebrospinal/perivascular therapy delivery route

Authors: *M. PAPISOV[1], V. BELOV[2], P. GIFFENIG[1], J. APPLETON[1], B. DURCANOVA[1], C. GILLOOLY[1], J. PASS[1]
[2]Radiology, [1]Massachusetts Gen. Hosp., Boston, MA

Abstract: The goal of our studies was to investigate the mechanisms and overall kinetics of the in vivo transport of solutes administered to the cerebrospinal fluid (CSF) CSF to the perivascular spaces and further along the perivascular spaces into the CNS parenchyma. Organ-level solute transport was studied in real time by quantitative PET. Experimental macromolecules were labeled with ^{124}I or ^{89}Zr and administered intrathecally (IT) at various locations to rats and monkeys. Dynamic imaging data and static images were acquired using Siemens MicroPET Focus 220 imager coupled with Neurologica CereTom CT imager. At the microscopic level, the studies were carried out by fluorescence photoimaging after intrathecal administration of fluorophore-labeled macromolecules binding various cell surface components. The initial solute distribution in the CSF (and, therefore, the exposure of perivascular entrances leading to various subcompartments of CNS) were found to depend on the injection site and volume. The site/volume effect can be utilized to deliver a therapeutic from a distal lumbar administration site predominantly to the cerebro-cervical CSF (up to >90% of the injected dose) or to a segment of the spinal cord from approximately T1 to the administration site. Targeting of only the cervical or cerebral region is physiologically unachievable. Solute transport in the CSF was found to be non-direcational and driven by pulsatile flows remixing the CSF along the entire compatment (rapidly in the cerebro-cervical region, slowly in the spine). No detectable influence of directional flux was detected anywhere in the CSF. Solute clearance from the CSF to the blood was found to be macromolecule size dependent. The lymphatic drainage existing in rodents (ca. 3% of the total drainage in rats) was not found in primates (<0.3%). IT administered solutes were found to rapidly enter the internal (intrafissural, intrasulcal) tight spaces and from there to distribute further through multiple perivascular channels abundant in all CNS compartments through their entire depth. The intrafussiral/sulcal and perivascular transport dynamics are consistent with active pulsation-driven processes (Taylor dispersion) and not with directional bulk flows. Thus, the mechanistic landscape of the cerebrospinal solute transport significantly differs from the paradigm suggesting that CSF and interstitial bulk flows prevail outside and inside the CNS, respectively. Our data explain the known but insufficiently understood effects of IT administered drugs. The observed transport timeframes suggest strong potential for developing highly effective CNS targeted IT therapies in the near future.

Disclosures: M. Papisov: None. **V. Belov:** None. **P. Giffenig:** None. **J. Appleton:** None. **B. Durcanova:** None. **C. Gillooly:** None. **J. Pass:** None.

Nanosymposium

194. Biomarker and Drug Discovery: Drug Delivery and Assay Development

Location: SDCC 4

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 194.05

Topic: I.05. Biomarker and Drug Discovery

Title: Nanoparticle delivery of CRISPR into the brain rescues a mouse model of fragile X syndrome from exaggerated repetitive behaviors

Authors: *H. LEE[1], N. MURTHY[2], B. LEE[1], S. PANDA[1], R. GONZALES[1], K. LEE[3]
[1]Cell. and Integrative Physiol., The Univ. of Texas Hlth. Sci. Ctr. at S, San Antonio, TX; [2]Univ. of California, Berkeley, Berkeley, CA; [3]GenEdit, Berkeley, CA

Abstract: Technologies that can edit genes in the brains of adult animals safely may revolutionize the treatment of neurological diseases and the understanding of brain function. Here, we demonstrate that intracranial injection of clustered regularly interspaced short palindromic repeats (CRISPR)-Gold, a non-viral delivery vehicle for the CRISPR associated protein 9 (Cas9) ribonucleoprotein (RNP), can edit genes in the brains of adult mice in multiple mouse models. CRISPR-Gold can deliver both Cas9 and Cpf1 RNPs, and can edit all of the major cell types in the brain, including neurons, astrocytes and microglia, with undetectable levels of toxicity at the doses used. We also show that CRISPR-Gold designed to target the metabotropic glutamate receptor 5 (mGluR5) gene can efficiently reduce local mGluR5 levels in the striatum after an intracranial injection and can rescue mice from the exaggerated repetitive behaviors caused by fragile X syndrome, a common single-gene form of autism spectrum disorders. CRISPR-Gold may significantly accelerate the development of brain-targeted therapeutics and enable the rapid development of focal brain-knockout animal models. **Rigorous study design and reporting:** To provide maximal quality, reproducibility, and transparency in our data, we have designed our experiments to be randomized where possible and have adequate controls, and we will report all data. **Biological justification of using males for behavioral studies in WT and *Fmr1* KO mice:** The *FMR1* gene is present in the X chromosome and we can only produce male littermates of WT and *Fmr1* KO mice. Therefore, we justify that we will need to use only male WT and *Fmr1* KO for all the behavior tests in our proposed study. All experiments in this proposal except behavior tests have been designed to incorporate sex as a biological variable; thus, equal numbers of male and female mice will be utilized.

Disclosures: H. Lee: None. **N. Murthy:** None. **B. Lee:** None. **S. Panda:** None. **R. Gonzales:** None. **K. Lee:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GenEdit.

Nanosymposium

194. Biomarker and Drug Discovery: Drug Delivery and Assay Development

Location: SDCC 4

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 194.06

Topic: I.05. Biomarker and Drug Discovery

Title: A nanostructured carbon nanotube array for *in vitro* neural diseases study through a size-based extracellular vesicle capture

Authors: *Y.-T. YEH[1], Y. ZHOU[2], Y. MAO[1], M. TERRONES[1]
[1]The Pennsylvania State Univ., University Park, PA; [2]Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: Extracellular Vesicles (EV) contains information that represents status of the host cells at the moment of their excretions. Preliminary study shows that EV is an important biomarker for different neural diseases and cancer metastasis. To have a better understanding of EVs, the first key step is to isolate EVs from the extracellular matrix. However, since a population of EVs is heterogeneous mixture, this challenges existing technologies to obtain an effective isolation. Currently, Currently, based on their biogenesis and sizes, EVs are divided into three groups, including exosomes (30-100 nm in diameter), microvesicles (100- 1000 nm in diameter), and apoptotic bodies (800 – 5000 nm in diameter). In this report, we developed a handheld platform that captures and separates a mixture of EVs according to their sizes. After capture, this platform is compatible with downstream analysis, such as cell culture and genomic sequencing. In briefly, we synthesized a nanostructured array made of aligned carbon nanotubes (CNTs). This porous array has a gradient of inter-tubular distance ranging from 20-800 nm, which covers the sizes for both exosomes and microvesicles. We applied this technology to study communications of neuroglia from a mouse model. We built a CNT array with 100 and 500 nm inter-tubular distance to capture and separate EVs that are excreted from primary cell culture of the glia cells. Our results showed that both exosomes and microvesicles are successfully isolated and separated by CNT arrays with different inter-tubular distance. Furthermore, we integrated this platform and established an *in vitro* model to study neurotransmission. After EVs isolation, this biocompatible CNT arrays serves as a primary culture substrate that allows us to study and monitor how EVs are uptaken by other neuron cells as recipients. Our preliminary results show feasibilities of study transmissions of EVs between neuroglia to neurons, by using SH-SY5Y cells as a model of a recipient. At the moment, we are applying this technology to answer the following questions: 1) What contents (e.g. genome and protein expression) of an EV population are excreted from different types of neurons, 2) whether the EV profiles are altered when an external stimulus (e.g. heat, electrical pulse, and viral infection) is applied, and 3) If so, what is the difference. We believe this technology is an effective approach to analyze EVs.

Disclosures: Y. Yeh: None. **Y. Zhou:** None. **Y. Mao:** None. **M. Terrones:** None.

Nanosymposium

194. Biomarker and Drug Discovery: Drug Delivery and Assay Development

Location: SDCC 4

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 194.07

Topic: I.05. Biomarker and Drug Discovery

Support: NIH Grant R00 NS070821
NIH Grant R01 MH109544
Icahn School of Medicine Capital Campaign
Translational and Molecular Imaging Institute
City College of New York, Grove School of Engineering

Title: Automated hippocampal subfield segmentation using 7T MRI in patients with epilepsy

Authors: *J. ALPER[1,4], R. E. FELDMAN[5], A. PAI[5], J. W. RUTLAND[5], K.-H. HUANG[5], L. XIE[8], L. FLEYSHER[6], A. L. RUS[6], L. V. MARCUSE[9], M. C. FIELDS[9], H.-M. LIN[7], B. N. DELMAN[5], P. R. HOF[2], P. BALCHANDANI[3]
[1]Translational and Mol. Imaging Inst., [2]Neurosci., [3]Radiology, Icahn Sch. of Med. At Mount Sinai, New York, NY; [4]Biomed. Engin., City Col. of New York, New York, NY; [5]Radiology, [7]Population Hlth. Sci. and Policy Dept., [6]Icahn Sch. of Med. at Mount Sinai, New York, NY; [8]Biomed. Engin., Univ. of Pennsylvania, Philadelphia, PA; [9]Neurol., Mount Sinai Hosp., New York, NY

Abstract: Epilepsy is a widely prevalent, disabling neurological condition, characterized by recurrent seizures. In 20-30% of focal epilepsy patients, the source of epilepsy is not clearly identifiable on clinical MRI scans, making treatment decisions difficult. Identification of hippocampal subfields associated with epilepsy [1] may elucidate underlying mechanisms of seizure genesis and aid treatment planning. Higher resolution and contrast afforded by ultrahigh-field MRI units, such as 7 Tesla (7T), allow for more precise measurements of subfields than clinical strength scanners. We evaluated asymmetry differences in subfield volumes between epilepsy patients and healthy controls using Automatic Segmentation of Hippocampus Subfields (ASHS) software [2].
Thirty epilepsy patients (ages 19-56) and thirty gender and age matched (+/-3 years) controls (ages 20-55) underwent MRI scanning at 7T (Magnetom, Siemens). Imaging protocol included MP2RAGE (TR=6000 ms, TI1=1050 ms, TI2=3000 ms, TE=5.06 ms, voxel=0.8x0.8x0.8 mm^3) and T_2TSE (TR=9000 ms, TE=69 ms, voxel=0.45x0.45x2 mm^3) acquired at a coronal oblique orientation. Using ASHS, differences in subfield volume asymmetries were evaluated between patients and controls. Subfield volumes include: CA1, CA2, CA3, DG, and subiculum on each side. Asymmetry for each subfield volume was compared between patients and controls, by

calculating an asymmetry index. Subanalysis on a subset of sixteen patients with lateralized, mesial-temporal lobe epilepsy (MTE) against side-matched controls was performed by calculating an asymmetry index specialized to the side with seizure onset. We regressed for age and gender and used a signed rank statistical test on the data.
Epilepsy patients exhibited greater right-left volume asymmetry in CA1 ($p=0.0428$) and DG ($p=0.0074$) compared with controls. Subanalysis on the MTE patients revealed reduced CA2 asymmetry ($p=0.0017$) in patients compared to controls. Results of the right-left asymmetry analysis are concordant with the literature on hippocampal subfield changes associated with epilepsy, and may reflect atrophy and modified signaling in pyramidal cells [3]. Results of the MTE subanalysis may suggest a natural asymmetry which occurs in healthies as well. Future work includes accounting for total intracranial volume, increasing sample size, and comparing to Freesurfer 6.0 automated segmentation. Identifying subfield biomarkers to better characterize hippocampal involvement in epilepsy can result in better treatment planning and monitoring in epilepsy.
1. Kim et al. Epilepsy research, 2015.
2. Yushkevich et al. Hum Brain Mapp, 2015.
3. Wittner et al. Brain, 2009.

Disclosures: J. Alper: None. **R.E. Feldman:** None. **A. Pai:** None. **J.W. Rutland:** None. **K. Huang:** None. **L. Xie:** None. **L. Fleysher:** None. **A.L. Rus:** None. **L.V. Marcuse:** None. **M.C. Fields:** None. **H. Lin:** None. **B.N. Delman:** None. **P.R. Hof:** None. **P. Balchandani:** None.

Nanosymposium

194. Biomarker and Drug Discovery: Drug Delivery and Assay Development

Location: SDCC 4

Time: Sunday, November 4, 2018, 1:00 PM - 3:00 PM

Presentation Number: 194.08

Topic: I.05. Biomarker and Drug Discovery

Title: Analysis of cerebrospinal fluid by data-independent acquisition mass spectrometry reveals biomarkers specific for Parkinson's disease

Authors: *M. ROTUNNO[1], M. LANE[1], P. WOLF[1], W. ZHANG[1], P. OLIVA[1], C. SCHERZER[2], R. ALCALAY[3], K. ZHANG[1], L. SHIHABUDDIN[1], P. SARDI[1]
[1]Sanofi, Inc., Framingham, MA; [2]Brigham and Women's Hospital, Harvard Med., Boston, MA; [3]Dept. of Neurology, Columbia Univ., New York, NY

Abstract: Parkinson’s disease (PD) is the second most common neurodegenerative disorder. Treatments are available to address PD motor symptoms, but not disease progression or cognitive decline. Demonstrating disease modification in clinical trials is still a substantial challenge because of the high disease heterogeneity and variability in progression as well as subjectivity in clinical scoring. To develop novel therapeutics for PD, there is an urgent need to

identify biomarkers for patient stratification in clinical trials. In this study, we used cutting edge data-independent acquisition (DIA) mass spectrometry to identify PD-specific biomarkers in patient cerebrospinal fluid (CSF). To identify novel biomarkers with minimal false discovery, two independent cohorts were analyzed by DIA mass spectrometry. An initial discovery cohort of 53 PD and 72 control (CTRL) patient samples was analyzed, identifying 53 proteins with significant changes (nominal p-value ≤ 0.05) in PD relative to CTRL out of the 342 detectable proteins. A second cohort of 28 PD and 43 CTRL samples were analyzed as above and identified 41 proteins with significant changes in PD. Thirteen proteins showed significant changes in both cohorts, some of which are previously reported to be altered in PD (*i.e.*, EPHA4 and SERPINC1). Three members of a specific protein family, which are cleaved into bioactive peptides, were amongst these 13 proteins . Further, peptide-level quantification of the detectable members of this protein family (7 total) revealed that specific regions of all 7 proteins are decreased in Parkinson's disease samples. Together, these data may implicate altered processing, localization, and/or function of this entire protein family for the first time in PD.

Disclosures: **M. Rotunno:** A. Employment/Salary (full or part-time):; Sanofi, Inc. **M. Lane:** A. Employment/Salary (full or part-time):; Sanofi, inc. **P. Wolf:** A. Employment/Salary (full or part-time):; Sanofi, inc. **W. Zhang:** A. Employment/Salary (full or part-time):; Sanofi, inc. **P. Oliva:** A. Employment/Salary (full or part-time):; Sanofi, inc.. **C. Scherzer:** None. **R. Alcalay:** None. **K. Zhang:** A. Employment/Salary (full or part-time):; Sanofi, inc. **L. Shihabuddin:** A. Employment/Salary (full or part-time):; Sanofi, inc. **P. Sardi:** A. Employment/Salary (full or part-time):; Sanofi, inc..

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.01

Topic: A.07. Developmental Disorders

Support: NIH grant HD055741
NIH grant MH101653

Title: Longitudinal diffusion tensor imaging study of infants at low and high risk for autism

Authors: *J. J. WOLFF[1], M. R. SWANSON[2], Y. PERALTA[1], M. STYNER[2], K. BOTTERON[3], S. R. DAGER[4], J. T. ELISON[1], A. M. ESTES[4], H. C. HAZLETT[2], R. T. SCHULTZ[5], J. PIVEN[2]
[1]Univ. of Minnesota Twin Cities, Minneapolis, MN; [2]Univ. of North Carolina, Chapel Hill, NC; [3]Washington Univ. in St. Louis, St. Louis, MO; [4]Univ. of Washington, Seattle, WA; [5]Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: Background: We have previously identified differences in white matter fiber tract development between high familial risk infants who did and did not meet diagnostic criteria for ASD (Wolff et al. 2012), a finding independently reported by other research groups (e.g. Solso et al. 2016). To build upon this existing body of work, we conducted a new study to: 1) examine the trajectories for white matter pathways between high-risk infants with ASD (HR-ASD) and low-risk controls(LR), and 2) examine white matter development in relation to autism symptom severity. **Methods:** Our study included prospective, longitudinal DTI data collected at ages 6, 12, and 24 months for 54 high-risk siblings diagnosed with ASD at age 2 years and 114 low-risk control infants. DTI data were collected on identical 3T scanners during natural sleep. White matter regions of interest were deterministically segmented yielding 7 bilateral projection and association pathways, 3 divisions of the corpus callosum, and 2 cerebellar tracts. Symptom severity scores calculated based on ADOS assessment at age 2 years. Trajectories between outcome groups were examined using linear mixed effects models, and relations of DT-MRI to behavior were examined using ordinal regression. **Results:** There were significant main effects for the anterior internal capsule, genu and body of the corpus callosum, corticospinal tracts, and superior cerebellar peduncles (all $p < .015$). For growth trajectories (group X age), HR-ASD differed from LR controls on all pathways showing a main effect with the addition of the pontine crossing tract (all $p < .04$). Growth trajectories for HR-ASD relative to LR controls were uniformly characterized higher FA at age 6 months followed by slower growth thereafter. FA development from 6 to 24 months (rate of change) was significantly associated with symptom severity in 4 pathways: the genu ($\chi2 = 9.3$, $p = 0.002$, OR = 4.6) and body of the corpus callosum ($\chi2 = 6.2$, $p = 0.013$, OR = 4.5); left ALIC ($\chi2 = 4.8$, $p = 0.029$, OR = 3.4); and PCT ($\chi2 = 4.4$, $p = 0.037$, OR = 2.0). These relationships were characterized by faster growth rate associated with more severe ASD. **Conclusions:** Early development of white matter includes both exuberant growth (myelination, arborization) and regressive events (axon elimination). The present results support that these developmental processes may be altered in infants who develop ASD. This work also provides evidence that a faster rate of change in structural connectivity is associated with more severe impairment by toddlerhood, a result consistent with reports identifying that "faster" or "more" is not necessarily better early in the development of ASD.

Disclosures: J.J. Wolff: None. **M.R. Swanson:** None. **Y. Peralta:** None. **M. Styner:** None. **K. Botteron:** None. **S.R. Dager:** None. **J.T. Elison:** None. **A.M. Estes:** None. **H.C. Hazlett:** None. **R.T. Schultz:** None. **J. Piven:** None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.02

Topic: A.07. Developmental Disorders

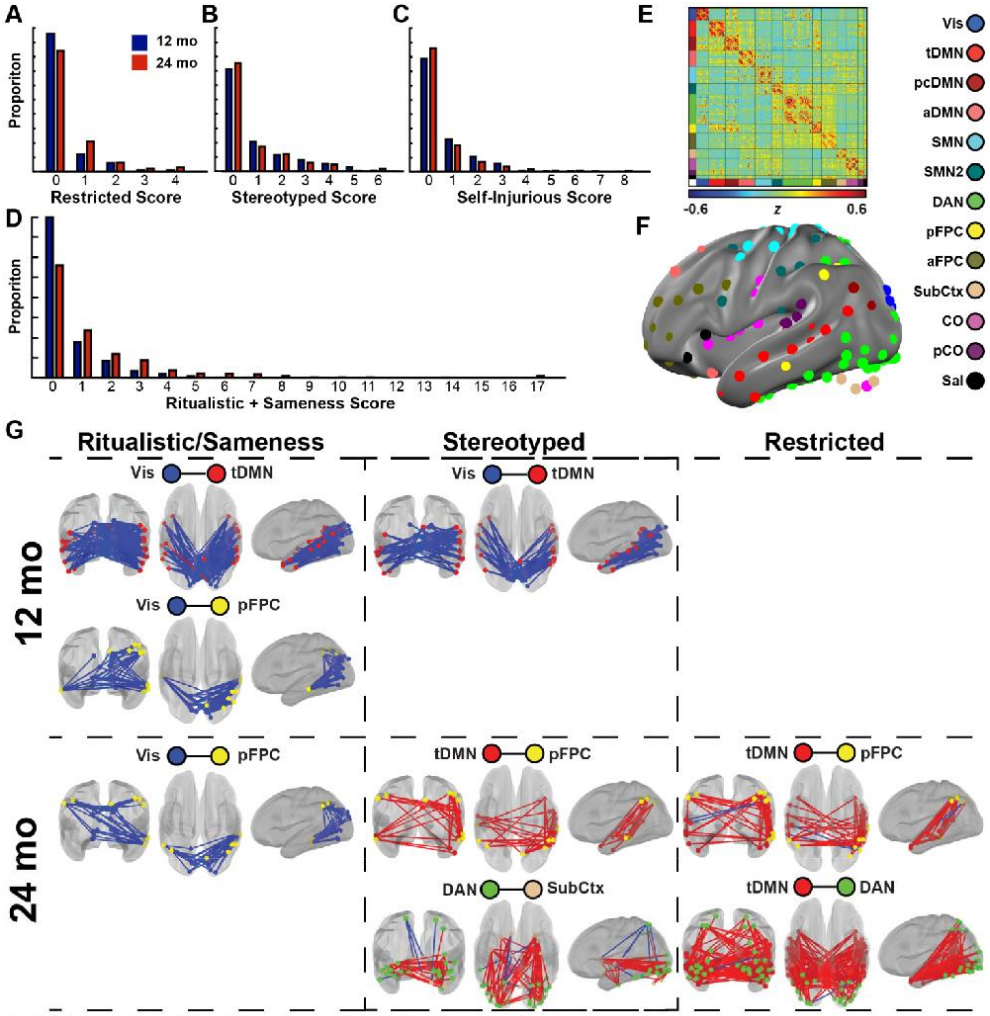
Support: NIH Grant R01HD055741
NIH Grant HD079124
NIH Grant R01MH093510
NIH Grant K01MH103594
NIH Grant K01MH101653
NIH Grant P30NS098577
NIH Grant HD087011

Title: Restricted and repetitive behavior and brain functional connectivity in infants at risk for developing autism spectrum disorder

Authors: *A. T. EGGEBRECHT[1], C. J. MCKINNON[3], A. TODOROV[2], J. J. WOLFF[4], J. T. ELISON[4], C. M. ADAMS[2], A. Z. SNYDER[5], A. M. ESTES[8], L. ZWAIGENBAUM[9], K. N. BOTTERON[2], R. C. MCKINSTRY[2], N. MARRUS[2], A. C. EVANS[10], H. C. HAZLETT[11], S. R. DAGER[8], S. J. PATERSON[12], J. PANDEY[13], R. T. SCHULTZ[13], M. A. STYNER[11], G. GERIG[14], B. L. SCHLAGGAR[15], S. E. PETERSEN[6], J. PIVEN[11], J. R. PRUETT, JR[7], .. FOR THE IBIS NETWORK[11]
[1]Mallinckrodt Inst. of Radiology, Washington Univ. Sch. of Med., St Louis, MO; [2]Washington Univ. Sch. of Med., St. Louis, MO; [3]Univ. of Chicago, Chicago, IL; [4]Univ. of Minnesota, Minneapolis, MN; [5]Radiol Dept, [6]Div. Neurol, Dept Neurol, [7]Dept Psych-Child, Washington Univ. Sch. Med., Saint Louis, MO; [8]Univ. of Washington, Seattle, WA; [9]Univ. of Alberta, Edmonton, AB, Canada; [10]Montreal Neurolog. Inst., Quebec, QC, Canada; [11]Univ. of North Carolina at Chapel Hill, Carborro, NC; [12]Temple Univ., Philadelphia, PA; [13]Children's Hosp. of Philadelphia, Philadelphia, PA; [14]New York Univ., New York, NY; [15]Dept Neurol, Div. Child Neurol, Washington Univ, Sch. Med., Saint Louis, MO

Abstract: Restricted and repetitive behaviors (RRBs), detectable by 12 months (mo) in many infants later diagnosed with autism spectrum disorder (ASD), may represent some of the earliest behavioral markers of one of the diagnostic features of ASD. Brain functional connectivity (fc) underlying the emergence of these key behaviors has yet to be elucidated. Behavioral and resting-state fc magnetic resonance imaging data were collected from 167 children at high and low familial risk for ASD, at 12 and 24 m (n=38 at both time points). Fifteen infants met criteria for ASD at 24 months. We divided RRBs into four subcategories (restricted, stereotyped, ritualistic/sameness, and self-injurious behavior) and used a data-driven approach (fcMRI enrichment; Eggebrecht et al., 2017) to identify functional brain networks associated with the development of each RRB subcategory.Our primary findings (summarized in the Figure) reveal that neural correlates of RRB subcategories are distinct between 12 and 24 mo, with the single exception of decreasing fc between visual and control networks associated with greater severity of ritualistic/sameness behavior at both 12 and 24 mo. Greater severity of two RRB subcategories, ritualistic/sameness and stereotyped behavior, was associated with decreasing fc between visual and default mode networks at 12 mo. At 24 mo, both stereotyped and restricted behavior were associated with increasing fc between default mode and control networks. Additionally, at 24 mo, stereotyped behavior was also associated with increasing fc between the dorsal attention and subcortical networks, while restricted behavior was also associated with

increasing fc between default mode and dorsal attention networks. No significant functional network level brain-behavior relationships were observed for self-injurious behavior. These observations mark the earliest known description of functional brain systems underlying RRBs, reinforce the construct validity of RRB subcategories in infants, and implicate specific neural substrates for future interventions targeting RRBs.



Restricted and repetitive behaviors and functional connectivity in infants
The number of items endorsed for each RBS-R factor at both 12 months old (mo; blue) and 24 mo (red): **A** the restricted behavior factor includes four items pertaining to limited range of focus, interest, or activity (e.g., preoccupation with part of object); **B** the stereotyped behavior factor includes six items relating to repeated, purposeless movements (e.g., arm flapping); **C** the self-injurious factor includes eight items relating to repeated actions that can cause injury to the body (e.g., hair pulling); **D** the ritualistic/sameness factor includes seventeen items relating to performing activities of daily living in a similar manner or resistance to change (e.g., arranging/ordering). **E** An Infomap-sorted mean fcMRI matrix derived from the correlation structure between 230 functionally-defined regions of interest (ROIs). **F** Left lateral view of the ROIs on the brain surface, colored according to network assignment. **G** Patterns of RRB-fc relationships across age and behavior displayed in functional network pairs significantly associated with a given behavior based on data-driven enrichment analyses. Red lines denote severity of behavior is associated with increasing functional connectivity between ROIs. Blue lines denote severity of behavior is associated with decreasing functional connectivity between ROIs.

Disclosures: A.T. Eggebrecht: None. **C.J. McKinnon:** None. **A. Todorov:** None. **J.J. Wolff:** None. **J.T. Elison:** None. **C.M. Adams:** None. **A.Z. Snyder:** None. **A.M. Estes:** None. **L. Zwaigenbaum:** None. **K.N. Botteron:** None. **R.C. McKinstry:** Other; receives acting, modeling, and speaking fees from Siemens Healthcare. **N. Marrus:** None. **A.C. Evans:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent

holder, excluding diversified mutual funds); founder and a member of the Board of Directors of Biospective Inc. **H.C. Hazlett:** None. **S.R. Dager:** None. **S.J. Paterson:** None. **J. Pandey:** None. **R.T. Schultz:** None. **M.A. Styner:** None. **G. Gerig:** None. **B.L. Schlaggar:** None. **S.E. Petersen:** None. **J. Piven:** None. **J.R. Pruett:** None. **.. for the IBIS Network:** None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.03

Topic: A.07. Developmental Disorders

Support: NICHD 2P50HD055784-08

Title: Atypical circuit level brain activity in infants at high risk for autism spectrum disorder

Authors: *A. DICKINSON[1], A. T. MARIN[2], A. SCHEFFLER[1], D. SENTURK[1], S. S. JESTE[3]
[2]Semel Inst. for Neurosci. and Human Behavior, [1]UCLA, Los Angeles, CA; [3]68-237A, UCLA Semel Inst. of Biobehavioral Sci., Los Angeles, CA

Abstract: Heterogeneous genetic and environmental etiologies of autism spectrum disorder (ASD) converge upon circuit level brain disruption well before behavioral symptoms emerge (Geschwind, 2009). The dynamics of neural oscillations in the alpha range (6-12 Hz) are sensitive to circuit level development and can therefore be used to detect atypical change. Alpha oscillations can be measured using electroencephalography (EEG) and quantified through robust measures including peak alpha frequency and alpha phase coherence (Dickinson *et al.,* 2017). Here we prospectively study EEG from infants who are at high risk for ASD (15-20%) due to an older sibling with ASD (Charman *et al.*, 2017), in order to: 1) characterize trajectories of brain development in infants at high risk for ASD, and 2) determine if early EEG measures predict later cognitive function and social communication skills. Method: Spontaneous EEG data were collected during the first year of life (3, 6, 9 & 12 month) from high and low risk infants as part of an ongoing UCLA Autism Center of Excellence project (NICHD 2P50HD055784-08). Here we focus on 3 month data. Infants were grouped into 'High risk' (ADOS-t CSS ≥ 4, N=9) and 'typically developing' (CSS<4, N=51) groups based on the presence of social communication impairments and restricted and repetitive behaviors at 18 months. Future 36 month ADOS assessments will confirm diagnoses. The Mullen scales of early learning were used to assess overall development at 18 months. Alpha phase coherence was used to establish connectivity between every possible electrode pair, and a robust curve fitting procedure was used to quantify peak alpha frequency. Results: 1) FDR-corrected analyses reveal that frontal left hemisphere alpha phase coherence is increased at 3 months in the group of infants who demonstrate ASD behaviors at 18 months (ASD: M=0.37; typical: M=0.28; P<.0002). 2) Across all participants, occipital peak alpha frequency at 3 months was inversely correlated with non-verbal

development at 18 months (R=-.56, P=.02). Conclusions: The present data suggest that the dynamics of circuit level activity are altered as early as 3 months of age in participants who later show increased ASD behaviors. The early hyperconnectivity demonstrated here is consistent with structural findings of increased white matter during infancy in ASD (Wolff et al., 2012). We will discuss the potential utility of electrophysiological markers of circuit development to 1) identify children who show ASD-related neurodevelopmental disruptions during the first year of life, 2) support individualized prognoses, and 3) inform neurobiological targets of early intervention.

Disclosures: A. Dickinson: None. **A.T. Marin:** None. **A. Scheffler:** None. **D. Senturk:** None. **S.S. Jeste:** None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.04

Topic: A.07. Developmental Disorders

Support: R01-DC010290

Title: An EEG biomarker quantifying sensitive period onset in Autism Spectrum Disorder

Authors: *L. J. GABARD-DURNAM[1], H. TAGER-FLUSBERG[2], C. A. NELSON[3]
[1]Boston Childrens' Hosp., Boston, MA; [2]Boston Univ., Boston, MA; [3]Richard David Scott Chair in Pediatric Developmental Med. Res., Harvard Med. Sch., Boston, MA

Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder which some think may result from dysregulated sensitive periods in development. Neural measures of sensitive periods in animal models have shown that the timing of sensitive periods is regulated by maturing inhibition, which shifts the balance of spontaneous neural activity and experience-induced neural activity (the S/E ratio). Specifically, the S/E ratio decreases during sensitive period onset relative to pre-sensitive period levels. The present study translated the S/E ratio measure of sensitive period onset into human ASD neurodevelopment with longitudinal high-density electroencephalography (EEG) from 3 to 12 months of age. Specifically, this study tested how the language phoneme sensitive period manifests in ASD neurodevelopment, as language deficits are frequent ASD symptoms. We hypothesized that reduced neural inhibition in ASD may delay the developmental timing when inhibition is robust enough to reduce the S/E ratio (i.e. delayed sensitive period opening). Data were contributed by 79 typically developing infants (TD), 67 high-risk infants without ASD at 3 years (HR-), and 24 high-risk infants with ASD diagnoses at 3 years of age (HR+). Spontaneous EEG power was collected with a silent baseline EEG recording, while experience-induced EEG power was generated by a phoneme oddball

paradigm. All EEG data were processed through HAPPE software, optimized for developmental EEG data, and the S/E power ratio was calculated over auditory cortex. The S/E ratio in TD infants decreased between 3 and 6 months of age, consistent with the native phoneme sensitive period onset behaviorally ($p < 0.05$, $n = 79$). However, the S/E ratio in HR+ infants remained elevated at 6 months of age, and was significantly higher than both HR- and TD infants ($p = 0.015$, $n = 170$), consistent with a delayed phoneme sensitive period. Post-hoc analyses showed the elevated 6-month S/E ratio in the HR+ infants was due to elevated spontaneous EEG power, consistent with the model of hyper-excitability in early ASD neurodevelopment. The S/E ratio was significantly negatively associated with later expressive language at 18 months ($p < 0.05$, $n = 170$). These findings suggest early auditory sensitive periods may be delayed in ASD with ramifications for later language development. Moreover, the S/E ratio may serve as a translational sensitive period biomarker that can link ASD animal model insights to human brain development.

Disclosures: L.J. Gabard-Durnam: None. **H. Tager-Flusberg:** None. **C.A. Nelson:** None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.05

Topic: A.07. Developmental Disorders

Support: NIH Grant F01-DC010290
NIH Grant R21 DC 08637
NIH Grant 1T32MH112510
Autism Speaks 1323
American Brain Foundation
Autism Science Foundation
Nancy Lurie Marks Family Foundation

Title: EEG markers of language development in infants and toddlers at risk for autism spectrum disorder

Authors: *C. L. WILKINSON[1], L. J. GABARD-DURNAM[1], A. R. LEVIN[2], K. KAPUR[2], H. TAGER-FLUSBERG[3], C. NELSON[1]
[1]Developmental Med., [2]Neurol., Boston Children's Hosp., Boston, MA; [3]Psychological and Brain Sci., Boston Univ., Boston, MA

Abstract: Language development in children with autism spectrum disorder (ASD) varies greatly. While many children first present with delayed language skills, roughly one quarter go on to have age-appropriate language skills by school age, and an estimated 30% will be minimal

verbal. One of the best predictors of later achievement in children with autism is language acquisition. Despite this, we still know little about the neurobiological correlates of language development in infants and toddlers at high risk for autism. Here we present the results from baseline EEG data longitudinally collected from infants, as part of the Infant Sibling Project, aimed at comparing infants with familial risk of developing ASD (HR) with low risk controls (LR). Each infant was seen at multiple intervals between 3 and 36 months, for EEG collection, developmental evaluation, using the Mullen Scales of Early Learning (MSEL), and eventual ASD evaluation at 18, 24, or 36 months. Data analyzed for this analysis was collected from 112 infants (54LR, 58HR). Ordinary least squares modeling of longitudinal baseline power from 3 to 24 months over several frequency bands was used to determine each infant's estimated 6-month intercept and estimated slope. Multivariate linear regression was then used to characterize the relationship between EEG measures and the MSEL verbal quotient at 24 months, either with or without risk group included in the model. Models included parental education and sex as covariates. Including risk group status improved model fit (Adjusted $R^2 = 0.168$ (without risk); 0.263 (with risk)), and MSEL predicted scores using this model significantly correlated with actual scores ($r = 0.71$, 95% CI: 0.60-0.80). Two-way interactions between risk and EEG measures were assessed to further characterize differences in EEG-language associations between LR and HR infants. Significant interaction effects were observed for 6-month intercepts of low frequency bands, delta ($p<0.05$) and theta ($p=0.007$), as well as estimated slopes of high-alpha ($p<0.05$) and beta ($p=0.002$). These data support a growing body of research showing early brain differences between LR and HR infants regardless of ASD diagnosis. It also emphasizes the need to characterize EEG biomarkers of language development in ASD within a high-risk population. Future work will further characterize these differences between risk groups, and determine the effect of ASD as a possible mediator of EEG predictors of language within the high-risk group.

Disclosures: C.L. Wilkinson: None. **L.J. Gabard-Durnam:** None. **A.R. Levin:** None. **K. Kapur:** None. **H. Tager-Flusberg:** None. **C. Nelson:** None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.06

Topic: A.07. Developmental Disorders

Support: NIH RO1 MH107802

Title: Atypical visual network connectivity in toddlers with autism spectrum disorders

Authors: *B. CHEN[1], A. C. LINKE[2], C. H. FONG[3], L. OLSON[4], S. REYNOLDS[1], M. KINNEAR[1], R.-A. MUELLER[1], I. FISHMAN[1]

[2]Psychology, [1]San Diego State Univ., San Diego, CA; [3]Psychology, SDSU, San Diego, CA; [4]Joint Doctoral Program in Clin. Psychology, SDSU / UC San Diego, San Diego, CA

Abstract: Introduction

Behavioral signs of autism spectrum disorders (ASDs) appear in the first years of life; however, little is known about neural networks and brain connectivity in ASDs during this critical developmental period. Previous studies have identified early anatomical abnormalities in toddlers with ASDs including increased cortical surface and brain volume, as well as extra-axial cerebrospinal fluid (Shen & Piven, 2017). Less is known about functional network organization early in life in ASDs. Using resting state fMRI (rs-fMRI), we examined functional connectivity patterns in toddlers with and without ASDs.

Methods

T1-weighted anatomical MRI and rs-fMRI data were acquired from 10 toddlers with ASDs (7 males; 26±4 months) and 15 typically developing (TD) toddlers (11 males; 22±5 months) during natural sleep. Group Independent Component Analysis (ICA) was applied to rs-fMRI data to generate 20 spatial components. Of those, 10 independent components (ICs) were identified as non-artifact resting-state functional connectivity networks (RFNs), similar to adult RFNs reported by Smith et al (2009). Mean time series were extracted from thresholded RFN masks and entered into a 10x10 pairwise correlation matrix, for each participant. Group differences in RFN connectivity were examined with two-sample t-tests applied to the correlation matrices. The Mullen Scale of Early Learning was administered to assess visual reception, motor, and language development.

Results

Group comparisons revealed significantly weaker connectivity between medial and lateral visual RFNs in toddlers with ASDs compared to TD peers ($p=0.03$, FDR corrected). Connectivity between the medial and lateral visual RFNs was negatively correlated with age in both ASD ($r=-0.76$) and TD ($r=-0.52$) toddlers. Moreover, it was negatively correlated with Mullen Visual Receptive scores in ASD ($r=-0.34$) but not in TD toddlers ($r=-0.14$).

Conclusions

Findings suggest increasing segregation between specialized visual networks in TD toddlers with age. This process may occur earlier in toddlers with ASD, potentially in line with some evidence on atypically increased reliance on visual functioning in older children with ASD. This is further supported by the finding of better visuo-spatial abilities in toddlers with advanced segregation (reduced BOLD synchronization) between the visual networks.

References

Shen, M. D., & Piven, J. (2017). Brain and behavior development in autism from birth through infancy. *Dialogues in clinical neuroscience*, *19*(4), 325.

Smith, S. M., et al. (2009). Correspondence of the brain's functional architecture during activation and rest. *PNAS*, *106*(31), 13040-13045.

Disclosures: B. Chen: None. **A.C. Linke:** None. **C.H. Fong:** None. **L. Olson:** None. **S. Reynolds:** None. **M. Kinnear:** None. **R. Mueller:** None. **I. Fishman:** None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.07

Topic: A.07. Developmental Disorders

Title: Modeling brain overgrowth in psychiatric disorders using human pluripotent stem cells

Authors: *S. CHETTY
Stanford, CA

Abstract: A number of psychiatric disorders, such as autism and schizophrenia, are associated with severe mental impairments and disturbances, social and behavioral deficits, and poor cognitive abilities. Severe cases of these disorders are frequently associated with alterations in brain growth and size. Changes in brain structure and size precede the onset of clinical symptoms, suggesting that understanding the mechanisms regulating brain growth could provide a window of opportunity for early intervention.
Directed differentiation of human pluripotent stem cells (hPSCs) is a promising approach for disease modeling. Here, we generate hiPSCs from patients with psychiatric disorders associated with brain overgrowth or undergrowth. We differentiate patient-specific hiPSC lines into various neuronal and glial lineages and investigate the molecular and cellular mechanisms contributing to changes in brain size. In particular, we identify cell types in the brain that are especially prone to alterations in cell proliferation, survival, and telomere shortening. Our results show an important role for the neuroimmune system in regulating these cellular changes. Based on these mechanistic insights, we identify novel therapeutic targets for regulating brain size in psychiatric disorders.

Disclosures: S. Chetty: None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.08

Topic: A.07. Developmental Disorders

Support: NSF GRFP 1321850
NIH K MH097972

NIH R01 MH101173
NIMH R21 MH096582
NINDS, 2P50NS22343
NIH R21 MH102578

Title: Atypical links between resting state EEG and fMRI measures in autism spectrum disorders

Authors: *L. E. MASH[1,2], B. KEEHN[3], Y. GAO[1,2], J. TOWNSEND[4], T. T. LIU[5], R.-A. MUELLER[1]
[1]Psychology, San Diego State Univ., San Diego, CA; [2]SDSU/UC San Diego Joint Doctoral Program in Clin. Psychology, San Diego, CA; [3]Speech, Language, and Hearing Sci., Purdue Univ., West Lafayette, IN; [4]Neurosciences, [5]Radiology, UCSD, La Jolla, CA

Abstract: Functional connectivity (FC) has been found to be broadly atypical in autism spectrum disorders (ASDs). However, studies of resting state FC in this population have been almost exclusively unimodal (using a single imaging technique only). EEG and fMRI yield fundamentally different measures of network connectivity, precluding straightforward comparisons between modalities. Because these methods have complementary advantages in temporal and spatial resolution, multimodal integration is critical for improved understanding of underlying brain activity. In simultaneous EEG/fMRI studies of typically developing (TD) adults, EEG alpha power has been consistently found to relate positively to thalamic and negatively to cortical blood oxygen level-dependent (BOLD) activity (Goldman et al., 2002). Thalamocortical BOLD activity may also become increasingly desynchronized with reduced alpha power (Allen et al., 2017). Both reduced EEG alpha power (Wang et al., 2013) and atypical thalamocortical BOLD coupling (Nair et al., 2015; Woodward et al., 2017) have been reported in ASDs. The current study tested group differences in EEG alpha power, thalamic BOLD activity, and the relationship between these measures in a cohort of individuals with ASDs and TD peers.
17 high-functioning adolescents (ages 12-17) with ASDs and 17 TD individuals matched for age and scanner motion underwent eyes-open, resting state EEG recordings and fMRI scans, in two separate sessions. EEG alpha power was calculated from six occipital electrodes. Amplitude of the low frequency function (ALFF), a measure of BOLD amplitude, was calculated for the thalamus. As in previous studies, we found that both absolute (p = .006) and relative (p = .02) alpha power were reduced in ASD compared to TD participants. No significant group differences were found in thalamic ALFF. In the TD group, a positive association between alpha power and thalamic ALFF was found (r = .51, p = .037), mirroring findings from the simultaneous EEG/fMRI literature. However, no significant association was found in the ASD group (r = -.14, p = .59). Group differences in slopes were significant (β = -3.03, p = .02). These results did not significantly change after covarying for nonverbal IQ, sex, and handedness. Our findings replicate previous reports of reduced EEG alpha power in ASDs. Furthermore, the expected relationship between EEG alpha power and thalamic ALFF was present only in the TD adolescents, whereas absence of this link in the ASD group may suggest a potentially atypical relationship between vigilance and thalamic activity in ASDs.

Disclosures: L.E. Mash: None. **B. Keehn:** None. **Y. Gao:** None. **J. Townsend:** None. **T.T. Liu:** None. **R. Mueller:** None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.09

Topic: A.07. Developmental Disorders

Support: European Commission
Wellcome Trust
YAMAHA Sports Challenge Fellowship
CREST of JST
ERATO of JST

Title: Neural retainability in autism

Authors: *T. WATANABE[1,2], G. E. REES[3,4], N. MASUDA[5]
[1]RIKEN Ctr. for Brain Sci., Saitama, Japan; [2]UCL Inst. of Cogntive Neurosci., London, United Kingdom; [3]UCL Inst. of Cognitive Neurosci., London, United Kingdom; [4]UCL Wellcom Ctr. for Human Neuroimaging, London, United Kingdom; [5]Dept. of Engin. Mathematics, Univ. of Bristol, Bristol, United Kingdom

Abstract: The timescale of intrinsic neural activity is considered to represent how long the brain region retains information. Higher-order brain regions show highly retainable and auto-correlated intrinsic neural signals, which may allow integration of neural information across long time periods. Here, based on theoretical implications that autistic behaviours should be underpinned by atypical information processing, we examined neural retainability in autism by measuring the magnitude of the autocorrelation of resting-state functional MRI signals publicly shared in ABIDE. We first found that high-functioning adults with autism spectrum disorder (ASD) had significantly smaller neural retainability in bilateral primary sensory and visual cortices, whereas their right caudate showed larger retainability compared to a sex-/IQ-/age-matched control group. We then identified significant associations between this atypically reduced neural retainability in the sensory/visual areas and the overall severity of ASD and between the atypically enhanced retainability in the right caudate and severity of cognitive inflexibility of this condition. These cross-sectional observations were confirmed in an independent longitudinal dataset recorded from an adolescent population. Finally, we found that such atypical neural retainability could be supported by atypical local grey matter volumes in autism. These findings suggest that individuals with ASD have atypical neural dynamics in sensory-related focal brain areas, which could be a basis of their more complex cognitive symptoms.

Disclosures: T. Watanabe: None. **G.E. Rees:** None. **N. Masuda:** None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.10

Topic: A.07. Developmental Disorders

Support: NIH Grant R01-MH081023
NIH Grant K01-MH09797

Title: Anatomical correlates of language connectivity-based subgrouping in autism spectrum disorder

Authors: *Y. GAO[1], J. S. KOHLI[1], C. H. FONG[2], A. C. LINKE[2], I. FISHMAN[2], R. A. CARPER[2], R.-A. MUELLER[2]
[1]Clin. Psychology, San Diego State University/ UC San Diego, San Diego, CA; [2]Psychology, San Diego State Univ., San Diego, CA

Abstract: Introduction: Autism Spectrum Disorders (ASDs) are heterogeneous developmental disorders associated with both atypical functional connectivity (FC) and anatomy. Language impairments are pervasive, but their neural underpinnings remain elusive, partly due to the heterogeneity across the ASDs population. Recent research supports the study of more homogeneous subsets of ASDs. The present study explored anatomical differences between subgroups of children with ASDs identified by distinct patterns of intrinsic FC within the language network.
Methods: FC analyses were conducted with 6-minute eyes-open resting state fMRI scans from 51 ASD and 50 typically developing (TD) youths, ages 8-17 years. Groups were matched on age, PIQ, head motion, gender, and handedness (all *p*s>.69). ASD subgroups were obtained using Gaussian finite mixture modeling of the FC between 14 language network regions (from meta-analysis by Rodd et al., 2015). After quality assurance, T1-weighted anatomical scans were analyzed by subgroup. Local Gyrification Index (lGI), the ratio of cortical surface area buried within sulcal folds to the outer brain surface area, was calculated using FreeSurfer v.5.3.0. LGI was analyzed using a general linear model including age as a covariate. Results were corrected for multiple comparisons using Monte Carlo null-z simulations (cluster forming threshold $p<.01$).
Results: Based on the lowest Bayesian Information Criterion, a 2-group solution best fit the ASD language network FC patterns. ASD Group 1 showed significantly greater intrinsic FC than TD group for 15 connections between language regions ($qs_{FDR}<.05$). Between the two ASD subgroups, Group 1 showed greater intrinsic FC for 37 connectivity pairs ($qs_{FDR}<.05$). The same group also displayed higher Verbal IQ and lower symptom severity (Autism Diagnostic

Observational Schedule- Total Score, Autism Diagnostic Interview- Social subscale score; *p*s<.05). ASD Group 1 showed predominantly greater lGI with clusters of medium to large effect sizes located bilaterally in inferior temporal regions and in the right inferior parietal lobule, whereas a cluster of increased lGI was observed in the left middle frontal gyrus in ASD Group 2. Conclusion: Different subgroups within an ASDs cohort showed strikingly distinct patterns of atypical FC of the language network. Less robust differences in cortical morphology (gyrification) were also found for these subgroups. Findings support the need to identify subgroups within larger ASD cohorts that may reflect divergent neurodevelopmental and behavioral trajectories.

Disclosures: Y. Gao: None. **J.S. Kohli:** None. **C.H. Fong:** None. **A.C. Linke:** None. **I. Fishman:** None. **R.A. Carper:** None. **R. Mueller:** None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.11

Topic: A.07. Developmental Disorders

Title: Functional connectivities are more informative than anatomical variables in diagnostic classification of autism

Authors: *A. JAHEDI[1], A. EILL[2], Y. GAO[4], J. S. KOHLI[3], C. H. FONG[3], R. A. CARPER[3], B. BAILEY[1], R.-A. MUELLER[3]
[1]Dept. of Mathematics and Statistics, [2]Biomed. Informatics, [3]Psychology, San Diego State Univ., San Diego, CA; [4]Clin. Psychology, San Diego State University/ UC San Diego, San Diego, CA

Abstract: Background: Previous studies have used different neuroimaging modalities for diagnostic classification of autism spectrum disorders (ASD) through machine learning. The question whether various modalities may be differentially informative has not been tested. In this study, conditional random forest (CRF) was applied to anatomical MRI (aMRI), diffusion tensor imaging (DTI), and functional connectivity MRI (fcMRI) to address this question.
Methods: The dataset included 47 typically developing (TD) and 46 ASD participants, matched on age, motion, and non-verbal IQ. FcMRI data consisted of a matrix of 220x220 functionally defined regions of interest (ROIs), yielding 24090 variables. The aMRI data had 397 variables (including cortical volume, thickness, surface area, mean curvature, and local gyrification index), and the DTI data consisted of 192 variables derived from John Hopkins University white matter tract labels (Mori et al., 2015). Analysis 1 combined the top 100 variables based on mean decrease in accuracy (MDA) from each modality in CRF. Analysis 2 combined the top 19 variables from each modality (based on performance separated by modality). Analysis 3 used larger ROIs for fcMRI (101x 101 matrix = 5050 variables) to reduce bias favoring the large

numbers of fcMRI variables. Analysis 4 used 100 randomly chosen variables per modality. Negative MDA and sets of variables with out-of-bag error rate > 0.4 were discarded. This process was run through 1 million iterations.
Results: In analysis 1, the top 100 variables from each modality reached 88% accuracy. 93% of the top 100 belonged to the fcMRI modality. An accuracy of 93% was achieved for analysis 2, with top MDAs for all 19 fcMRI variables. Analysis 3, using the top 100 variables from each modality, reached an accuracy of 83% and 87% of the top 300 were fcMRI variables. The combined accuracy for the top 19 variables from each modality (which were ran separately) was 80%, and once again, fcMRI variables showed highest MDA. In analysis 4, average MDA for fcMRI variables was significantly higher than for other modalities (p<2.2e-16).
Conclusion: Findings from multiple analyses consistently suggest that resting state fcMRI variables may be more informative for prediction of diagnostic status (ASD vs. TD) than variables from aMRI and DTI. However, differences in original numbers of variables and granularity (e.g., size of ROIs) between modalities complicate direct and unbiased comparison.

Disclosures: A. Jahedi: None. **A. Eill:** None. **Y. Gao:** None. **J.S. Kohli:** None. **C.H. Fong:** None. **R.A. Carper:** None. **B. Bailey:** None. **R. Mueller:** None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.12

Topic: A.07. Developmental Disorders

Support: NIH R01-MH081023
NIH K01-MH097972

Title: Gender-related differences in intrinsic functional connectivity in children and adolescents with autism spectrum disorders

Authors: *L. OLSON[1], A. C. LINKE[2], L. E. MASH[2], M. REITER[1], R.-A. MUELLER[3], I. FISHMAN[3]
[1]Joint Doctoral Program in Clin. Psychology, SDSU / UC San Diego, San Diego, CA; [2]Psychology, [3]San Diego State Univ., San Diego, CA

Abstract: Autism Spectrum Disorders (ASDs) are much more prevalent in boys than girls (~4:1 ratio). Most imaging studies in ASDs therefore include few girls. Although a growing body of research is beginning to highlight possible gender differences in ASD clinical presentation, less is known about female variants at the neural level. We investigated gender-related differences in intrinsic functional connectivity (iFC) within and between functional networks in children and adolescents with and without ASDs.

Resting-state functional MRI data for 141 children and adolescents (ages 7-18 years) were selected from the Autism Brain Imaging Database Exchange (ABIDE I and II; n = 111; DiMartino et al., 2014 & 2017) and an in-house sample (n = 31). Within each diagnostic group, boys and girls were matched on age, handedness, cognitive functioning, head motion, and study site (ASD n = 70—35 females, TD n = 72—36 females). ASD boys and girls were also matched on symptom severity. Group independent component analysis and dual-regression were used to generate resting-state functional networks (RFNs) for each subject. RFNs were categorized into three domains: sensorimotor, default mode, and higher-order. iFC was estimated by generating RFN-RFN correlation matrices. Between-subjects t-tests were used to test for gender and diagnosis effects on iFC, controlling for site and motion.
In the TD group, girls showed significantly higher connectivity within the default mode network (DMN) than boys, $t_{(70)} = -2.87$, $p = 0.005$, after controlling for study site and motion. There were no gender effects in within- or between-network connectivity for any domain in the ASD group. Girls with ASDs, however, showed significantly higher variability (standard deviation) in their within-DMN connectivity compared to ASD boys, $t_{(10)} = -5.3704$, $p = 0.001$, whereas no gender effects were observed in iFC variability in the TD group.
We observed a pattern of increased within-DMN connectivity in TD girls compared to TD boys that was absent when comparing girls and boys with ASDs. This suggests that gender-related differences in network differentiation may have an atypical expression in ASDs. Additionally, the finding of increased interindividual variability among girls with ASDs may fully explain this null funding in the ASD group. It suggests the existence of multiple highly distinct female variants of ASDs, which will need to be considered in studies with greater inclusion of female participants.

Disclosures: L. Olson: None. **A.C. Linke:** None. **L.E. Mash:** None. **M. Reiter:** None. **R. Mueller:** None. **I. Fishman:** None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.13

Topic: A.07. Developmental Disorders

Support: Autism Speaks 10085

Title: Response to own name in noise differs in autistic adolescents with severe language impairments

Authors: *S. SCHWARTZ[1], L. WANG[2], B. SHINN-CUNNINGHAM[2], H. TAGER-FLUSBERG[3]

[1]Grad. Program for Neurosci., [2]Biomed. Engin., [3]Psychological and Brain Sci., Boston Univ., Boston, MA

Abstract: Your name is one of the most common things you hear, beginning at birth. It becomes a highly salient stimulus, eliciting an orienting response that leads you to turn quickly towards its source upon hearing it. Children and adults show a positive event-related potential response (ERP) to their own name, but not other peoples' names, over parietal-occipital channels around 300 milliseconds post-stimulus (a P3), in attentive and inattentive states, and even in sleep and comatose states. However, recent evidence suggests that adults with autism (ASD) have a smaller P3 to their own name when compared to typically developing (TD) adults (Nijhof et al., 2018). These findings align with research showing that failure to orient to one's own name is an early sign of the disorder. Prior work has also found a relationship between the ability to segregate streams and extract salient speech from noise and integrity of language in ASD (Boatman et al., 2001; Russo et al., 2009; Wang et al., 2016). Our work expanded on prior findings by investigating ERPs to names in both quiet and multispeaker noise contexts, in TD listeners and ASD listeners with a range of language abilities. Subjects ages 13-23 heard 486 audio-recordings of their own and two unfamiliar names in a passive ERP paradigm while they watched a silent movie. Additionally, we quantified expressive and receptive language in ASD subjects with parent report measures, including the Vineland Adaptive Behavior Scales and an in-house validated list of words used and understood (Plesa Skwerer et al., 2016). In quiet, TD subjects showed a P3 to their own name relative to other names during the first 30 presentations of each name ($p=0.05$), replicating prior studies that only presented this many trials. However, ERP topography changed as TD listeners were exposed to more repetitions of each name. From an analysis all usable trials, TD subjects showed a habituated frontal ERP to their own name at around 250 ms relative to other names ($p<0.05$) but no clear P3. When names were presented in noise, response to own name was significantly larger than to other names, lasting from 300-700 ms, along parietal-occipital channels (a prolonged P3) ($p<0.05$). In contrast, subjects with ASD showed no difference in response to their own and other names in either quiet or noise. Within ASD, receptive and expressive language positively correlated with P3 response to own name, but not other names, when embedded in noise ($p<0.05$). Future work should continue to explore how ASD individuals with co-existing language impairments process sound and if their ability to extract salient speech from noisy environments has any influence on their ability to process language.

Disclosures: S. Schwartz: None. **L. Wang:** None. **B. Shinn-Cunningham:** None. **H. Tager-Flusberg:** None.

Nanosymposium

266. Autism: Structural and Functional Correlates in Children

Location: SDCC 32

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 266.14

Topic: A.07. Developmental Disorders

Support: NIH Grant R01-MH081023
NIH Grant K01-MH097972
NIH Grant R01-MH103494

Title: The cingulum and cingulate U-fibers in children and adolescents with autism spectrum disorders

Authors: *J. HAU[1,2], S. ALJAWAD[2], N. BAGGETT[2], R. CARPER[2], I. FISHMAN[2], R.-A. MÜLLER[2]
[1]Brain Develop. Imaging Lab., San Diego, CA; [2]San Diego State Univ., San Diego, CA

Abstract: Background
Postmortem studies show an abnormal increase of axons in superficial white matter and decrease in deep white matter underlying cingulate cortex in autism spectrum disorders (ASD). The cingulum is the major deep fiber tract subserving the cingulate cortex and limbic areas. It is involved in social cognition, emotion processing and motor control, and has been implicated in ASD. While the main bundle portion, the *cingulum proper* (cg) has been widely studied, the extensive system of superficial U-fiber tracts (cgU) that connect the cingulate gyrus with adjacent gyri has received little attention. We aimed to replicate findings of altered microstructure in cg, investigate possible altered micro and macro-structure in cgU, and examine relationships between cg and cgU and behavior in children and adolescents with ASD.
Methods
61 ASD and 54 typically developing (TD) participants (7-18 years) were selected from 179 after quality control and matching for age, non-verbal IQ and head motion. GE 3T scanner acquired (diffusion: b=1000s/mm^2, 61 directions, 1.9 x 1.9 x 2mm^3, field map, reverse PE b0s in ~½ of ASD and TD for improved field map correction; T1: FSPGR, 1mm^3). Eddy current distortions and head motion were corrected. Probabilistic tractography was performed in native space with 5000 seeds per voxel from cingulate cortex (cg) and each of rostral anterior, caudal anterior, posterior and isthmus cingulate cortex (cgU), excluding gray matter outside ipsilateral cingulate, parahippocampal and entorhinal gyri (cg) and adjacent cingulate cortex (cgU). Tract measures (FA, MD, RD and volume) were analyzed (group, age, group x age, dropout, pipeline) using linear regression (cg) and repeated measures ANCOVA across hemispheres (cgU). Partial correlations (age, dropout, pipeline) with behavioral measures (ADOS-2, ADI-R scores) were run on measures of each tract.
Results
RD was increased in left cg in ASD (p=.023). Hemisphere x group x age was significant for posterior cgU volume (p=.011). *Post-hoc*: Posterior cgU volume decreased with age in TD and ASD on left and decreased with age in ASD (p=.013, r=-.323) but not TD (n.s., r=.001) on right. Bilateral caudal anterior cgU MD was positively correlated with symptom severity. Right rostral and caudal anterior and left posterior cgU volume were negatively associated with repetitive behaviors. Left posterior cgU volume was positively, FA negatively, associated with social deficits.
Conclusion

Findings implicate both the cingulate's primary (cg) and short association (cgU) tracts in ASD, and suggest that localized segments of cgU contribute differentially to repetitive and social behaviors in ASD.

Disclosures: J. Hau: None. **S. Aljawad:** None. **N. Baggett:** None. **R. Carper:** None. **I. Fishman:** None. **R. Müller:** None.

Nanosymposium

267. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: SDCC 24

Time: Monday, November 5, 2018, 8:00 AM - 11:00 AM

Presentation Number: 267.01

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

Support: NEI EY006311
NIA AG18031
NIA AG038834
Research to Prevent Blindness (RPB)
Louisiana Biotechnology Research Network (LBRN)

Title: Progressive envelopment of sporadic Alzheimer's disease (AD) neuronal nuclei by microbiome-derived lipopolysaccharide (LPS); selective inhibition of neurofilament light chain (NF-L) gene expression

Authors: *W. J. LUKIW[1], L. CONG[2], Y. ZHAO[3], V. JABER[4]
[1]Neurosci. Ctr., Louisiana State Univ. Neurosci. Ctr. of Excellence, New Orleans, LA; [2]Dept. of Neurology, Shengjing Hospital, China Med. Univ., Shenyang, Liaoning Province,, China; [3]LSUHSC-NO Neurosci., New Orleans, LA; [4]LSU Neurosci. Ctr., New Orleans, LA

Abstract: The remarkable co-localization of highly pro-inflammatory lipopolysaccharide (LPS) with sporadic Alzheimer's disease (AD)-affected neuronal nuclei suggests that there may be some novel pathogenic contribution of this heat stable neurotoxin to neuronal activity and neuron-specific gene expression, such as decreased transcriptional output. In this report we show for the first time: **(i)** the progressive association and envelopment of sporadic AD neuronal nuclei with LPS; and **(ii)** a selective repression in the output of neuron-specific neurofilament light (NF-L) chain messenger RNA (mRNA), perhaps as a consequence of this association. Interestingly, down-regulation of NF-L mRNA and NF-L expression is a characteristic attribute of AD neocortex and hippocampus, and accompanies neuronal atrophy, synaptic deficits and an associated loss of neuronal architecture. To study this phenomenon further, human neuronal-glial (HNG) cells in primary cultures were incubated with LPS, and microRNA and DNA arrays, LED-Northern and Western blots were used to analyze transcription patterns for the 3 member neuron-specific intermediate filament-gene family NF-H, NF-M and NF-L. As in sporadic AD

limbic-regions, down-regulated transcription products for the NF-L intermediate filament protein were particularly significant. These results support our novel hypothesis **(i)** that internally-sourced, microbiome-derived neurotoxins contribute to a progressive disruption in the read-out of the brain's neuron-specific genetic-information; **(ii)** that the presence of LPS-enveloped neuronal nuclei is associated with a down-regulation in NF-L expression, a key neuron-specific cytoskeletal component; and **(iii)** this may have a bearing on progressive neuronal atrophy, loss of synaptic-contact and disruption of neuronal architecture, all of which are characteristic pathological features of sporadic-AD brain. This is the first report that demonstrates a neuron-specific effect of a human GI-tract microbiome-derived neurotoxin on decreased NF-L mRNA abundance and decreased NF-L expression in AD brain.Supported through an unrestricted grant to the LSU Eye Center from Research to Prevent Blindness (RPB); the Louisiana Biotechnology Research Network (LBRN) and NIH grants NEI EY006311, NIA AG18031 and NIA AG038834 (WJL).

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

Nanosymposium

267. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: SDCC 24

Time: Monday, November 5, 2018, 8:00 AM - 11:00 AM

Presentation Number: 267.02

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

Support: NIH/NIA Grant AG034113
NIH/NIA Grant AG057496
Cure Alzheimer's Fund
Hobby Foundation
American Cancer Society IRG 81-001-26

Title: Meningeal lymphatic vessels play a key role in age-dependent cognitive decline and in Alzheimer's disease pathology

Authors: *S. DA MESQUITA[1], A. LOUVEAU[1], A. VACCARI[2], I. SMIRNOV[1], R. CORNELISON[3], K. M. KINGSMORE[3], C. CONTARINO[5], D. RAPER[1], K. E. VIAR[1], R. D. POWELL[1], W. BAKER[1], N. DABHI[1], J. M. MUNSON[6], M. LOPES[4], C. C. OVERALL[1], S. T. ACTON[2], J. KIPNIS[1]
[1]Dept. of Neurosci., [2]Dept. of Electrical & Computer Engin. and Dept. of Biomed. Engin., [3]Dept. of Biomed. Engin., [4]Dept. of Pathology, Univ. of Virginia, Charlottesville, VA; [5]Dept. of Mathematics, Univ. of Trento, Povo, Italy; [6]Dept. of Biomed. Engin. & Mechanics, Virginia Tech, Col. of Engin., Blacksburg, VA

Abstract: The brain parenchyma is devoid of lymphatic vasculature. In the parenchyma, exchange mechanisms at the blood-brain and blood-cerebrospinal fluid (CSF) barriers and the dispersion of interstitial fluid along perivascular spaces (glymphatic route) into the CSF, are the main routes of excretion of brain metabolic byproducts and waste, such as amyloid beta. The (re)discovery of lymphatic vessels in the meninges, with an access to the subarachnoid space, led us to re-evaluate the fluid dynamics and macromolecule drainage within/from the central nervous system (CNS). Herein, we show that impaired drainage of CSF, induced by interference with meningeal lymphatic structure and function, impacts on mechanisms of macromolecule influx through the glymphatic perivascular route and of macromolecule efflux from the brain parenchyma. Prolonged meningeal lymphatic dysfunction in young-adult mice ultimately results in learning and memory deficits. On the other hand, boosting meningeal lymphatic function in old mice leads to improved paravascular brain perfusion by CSF and better performance in cognitive tasks. Ablation of meningeal lymphatics in transgenic mouse models of Alzheimer's disease (AD) led to worsened amyloid pathology not only in the brain parenchyma but also in the dura, both pathological features that closely resemble what is observed in the CNS of AD patients. Altogether, these findings show that meningeal lymphatic vessels play a central role in brain homeostasis in young and aged mice, as well as in AD pathophysiology.

Disclosures: S. Da Mesquita: None. **A. Louveau:** None. **A. Vaccari:** None. **I. Smirnov:** None. **R. Cornelison:** None. **K.M. Kingsmore:** None. **C. Contarino:** None. **D. Raper:** None. **K.E. Viar:** None. **R.D. Powell:** None. **W. Baker:** None. **N. Dabhi:** None. **J.M. Munson:** None. **M. Lopes:** None. **C.C. Overall:** None. **S.T. Acton:** None. **J. Kipnis:** None.

Nanosymposium

267. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: SDCC 24

Time: Monday, November 5, 2018, 8:00 AM - 11:00 AM

Presentation Number: 267.03

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

Support: CIHR MOP-142487

Title: Upregulation of MIF in Alzheimer’s disease

Authors: *W. SONG[1], S. ZHANG[1], J. ZHAO[2], Y. ZHANG[2], Y. ZHANG[1], F. CAI[1], L. WANG[2]
[1]The Univ. of British Columbia, Vancouver, BC, Canada; [2]Guangdong Gen. Hosp., Guangzhou, China

Abstract: Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine. Chronic inflammation induced by amyloid β proteins (Aβ) is one prominent neuropathological feature in Alzheimer’s disease (AD) brain. In the present study, we reported that MIF expression was upregulated in the brain of AD patients and AD model mice. Elevated MIF concentration

was detected in the cerebrospinal fluid of AD patients but not the patients suffering from mild cognitive impairment and vascular dementia. Reduced MIF expression impaired learning and memory in the AD model mice. MIF expression largely associates with Aβ deposits and microglia. Binding assay revealed a direct association between MIF and Aβ oligomers. Neurons instead of glial cells were responsible for secretion of MIF upon stimulation by Aβ oligomers. In addition, overexpression of MIF significantly protected neuronal cells from Aβ-induced cytotoxicity. Our study suggests that neuronal secretion of MIF may serve as a defense mechanism to compensate for declined cognitive function in AD, and increased MIF level could be a potential AD biomarker.

Disclosures: W. Song: None. **S. Zhang:** None. **J. Zhao:** None. **Y. Zhang:** None. **Y. Zhang:** None. **F. Cai:** None. **L. Wang:** None.

Nanosymposium

267. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: SDCC 24

Time: Monday, November 5, 2018, 8:00 AM - 11:00 AM

Presentation Number: 267.04

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

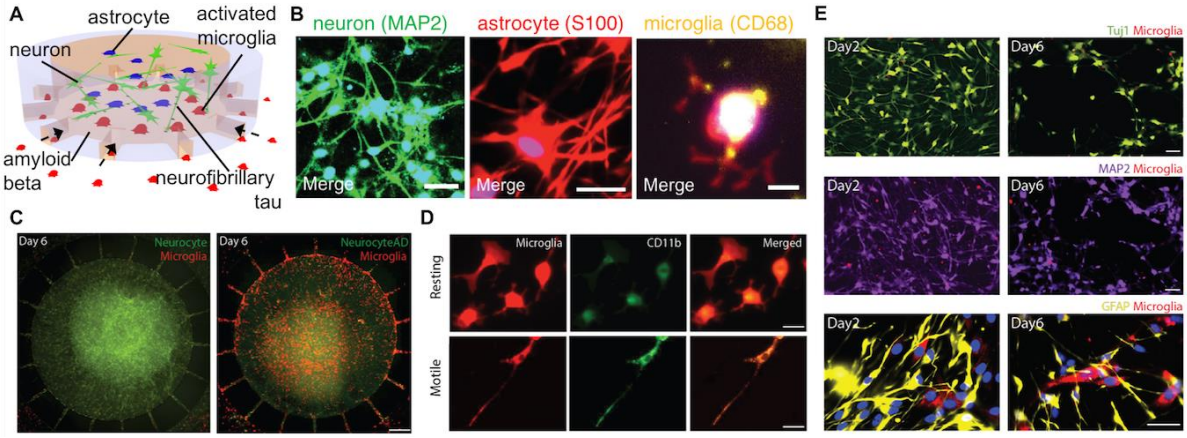
Support: Pioneering Funding Award funded by Cure Alzheimer’s Fund
Duke Energy Special Initiatives funded by Charlotte Research Institute
Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education funded by the Ministry of Education
Bright Focus Foundation
National Institute of Health

Title: Reconstructed neurotoxic microglial activation triggered by reactive astrocytes in a 3d organotypic human Alzheimer’s disease brain model

Authors: *H. CHO[1], J. PARK[1], I. WETZEL[1], I. MARRIOTT[1], D. DRÉAU[1], D. KIM[2], R. E. TANZI[3]
[1]UNC Charlotte, Charlotte, NC; [2]Genet. and Aging Res. Unit, MIND, Massachusetts Gen. Hospital/ Harvard Med. Sch., Charlestown, MA; [3]Massachusetts Gen Hosp, Harvard Med. Sch., Charlestown, MA

Abstract: Alzheimer’s disease (AD) is characterized by beta-amyloid (Abeta) accumulation, phosphorylated tau accumulation, hyper-activation of glial cells, and neuronal loss, which eventually leads to neurodegeneration. The mechanisms of AD pathogenesis, however, remain poorly understood partially due to the lack of relevant human models that can comprehensively recapitulate multistage-intercellular interactions in human AD brains. Here, we present a new 3D organotypic human cellular AD brain model by tri-culturing human AD neurons, astrocytes, and

adult microglia in a 3D microfluidic platform (Figure 1). Our model provided key representative AD features: pathological accumulation of Abeta, p-tau accumulation, microglial proinflammation damaging AD neurons and astrocytes. The relevance of this organotypic brain model lies in the demonstration of physiologically relevant microglial activation: microglial morphogenesis, activation marker expression, recruitment, and the release of proinflammatory cytokines and leukocyte-chemokines regulated by AD neurons and astrocytes in an AD environment, and microglial neurotoxic pro-inflammation, contributing to neuronal damage. In particular, the model mirrored microglial neurotoxic activities such as axonal cleavage and neurotoxic NO release. Abeta mediated TLR4-activation of microglia dependent on astrocyte-derived IFN-γ signaling induces inflammatory neurodegeneration mediated by iNOS-mediated NO release. Our data suggest that the microglia-induced neuronal loss in our model, occurs at least partially *via*IFN-γ and Abeta-dependent mechanisms. In conclusion, our model mimics neuron-glia interactions in neuroinflammation and the hallmarks of human AD brains and may serve as a valid human cellular model for basic mechanistic studies and drug discovery.



Disclosures: H. Cho: None. **J. Park:** None. **I. Wetzel:** None. **I. Marriott:** None. **D. Dréau:** None. **D. Kim:** None. **R.E. Tanzi:** None.

Nanosymposium

267. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: SDCC 24

Time: Monday, November 5, 2018, 8:00 AM - 11:00 AM

Presentation Number: 267.05

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

Title: Reversal of amyloid beta-induced microglial activation through the regulation of metabolism: A novel role for the pro-resolving receptor, Fpr2

Authors: *E. WICKSTEAD[1,2], S. J. GETTING[2], C. BIGGS[2], S. MCARTHUR[1]
[1]Queen Mary, Univ. of London, London, United Kingdom; [2]Univ. of Westminster, London, United Kingdom

Abstract: Background
Microglia are key players in the pathology of Alzheimer's disease (AD), driving the chronic inflammatory and oxidative environment, alongside the altered metabolism seen in the brains of AD patients. Strategies to reduce microglial activation may therefore be a viable therapeutic approach to tackling AD. Formyl peptide receptor 2 (Fpr2), which drives peripheral inflammatory resolution, is expressed in microglia. However, its functional role in neuroinflammation remains unclear.

Aim
Our aim was to determine the effects of the Fpr2 agonist, Quin-C1 on reactive oxygen species (ROS) production and metabolism following the administration of disease-relevant doses of oligomeric $A\beta_{1-42}$.

Methods
Immortalised murine microglia (BV2 cells) were stimulated with 100nM $oA\beta_{1-42}$ 10min (ROS) or 1h (lactate/glucose) prior to the treatment with Quin-C1 (100nM). ROS were monitored with CM-H_2DCFDA and MitoSOX red, with levels detected every 5 min for up to 2h. Cells were fixed at 30min post-$oA\beta_{1-42}$ and immunolabelled for p67phox and gp91phox before being visualised by confocal microscopy to determine NADPH oxidase co-localisation. Lactate content in high (4.5g/L) and low (1g/L) glucose conditions were determined at 24 and 48h post-$oA\beta_{1-42}$ using the YSI 2300 Stat Plus.

Results
$oA\beta_{1-42}$ increased ROS release, an effect significantly attenuated by subsequent Quin-C1 treatment. The ROS inducing capacity of $oA\beta_{1-42}$ was blocked by cellular pre-treatment (10min) with the Rac1 inhibitor, NSC 23766 or DPI, a specific inhibitor of NADPH oxidases. $oA\beta_{1-42}$ treatment resulted in the co-localisation of the NADPH oxidase subunits p67phox and gp91phox in the cell membrane. Quin-C1 was able to completely abolish this response. $oA\beta_{1-42}$ also decreased lactate production when compared to untreated cells. This was similarly inhibited by both NSC 23766 and Quin-C1.

Conclusions
Together, these data highlight the ability of low concentrations of oligomeric Aβ to induce ROS production and modulate the metabolic phenotype of a microglial model. Moreover, these pathological changes could be substantially inhibited by treatment with the Fpr2 agonist, Quin-C1. Given that that these changes are thought to occur in the early stages of AD, our data suggests Fpr2-targeted therapies may be a viable approach to restore homeostasis in AD.

Disclosures: E. Wickstead: None. **S.J. Getting:** None. **C. Biggs:** None. **S. McArthur:** None.

Nanosymposium

267. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: SDCC 24

Time: Monday, November 5, 2018, 8:00 AM - 11:00 AM

Presentation Number: 267.06

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

Support: Life2020 MARBEL
JointLab CrestOptics IIT

Title: The role of microglia in Alzheimer's disease-associated retinal neurodegeneration

Authors: *S. DI ANGELANTONIO[1], A. GRIMALDI[2], C. BRIGHI[2,3], D. RAGOZZINO[4], C. LIMATOLA[4], R. CECCARELLI[5], G. RUOCCO[2]
[1]CLNS@Sapienza, Inst. Italiano Di Tecnologia, Roma, Italy; [2]Ctr. for Life Nanoscience@Sapienza, Inst. Italiano Di Tecnologia IIT, Roma, Italy; [4]Physiol. and Parmacology, [3]Sapienza Univ. di Roma, Roma, Italy; [5]CrestOptics, Roma, Italy

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 central nervous system: Amyloid Beta and hyper-phosphorylated tau. Accumulation of extracellular amyloid beta plaques and intracellular hyper-phosphorylated tau tangles, and consequent neuronal loss begin 10-15 years before any cognitive impairment. In addition to cognitive and behavioral deficits, sensorial abnormalities have been described in AD patients and in some AD transgenic mouse models. Retina can be considered a simple model of the brain, as some pathological changes and therapeutic strategies from the brain may be observed or applicable to the retina. Another important factor in neurodegenerative diseases is the role of neuroinflammation; although neuroinflammatory responses are commonly described in the brain of AD patients and animal models, only few reports describe retinal glia alterations in AD. Retinal glial cells, including astrocytes and microglia, are responsible for the maintenance of the retinal microenvironment, trophic and structural support, regulation of homeostatic functions and an appropriate immune response, fundamental roles for the proper functioning of the retina. We analyzed retinal tissue of triple transgenic AD mouse model (3xTg-AD) for the presence of pathological hallmarks during disease progression. We found in the retinal ganglion cell layer of 3xTg-AD mice amyloid beta plaques, tau tangles, neurodegeneration and astrogliosis, already at pre-symptomatic stage. Moreover, retinal microglia in pre-symptomatic mice showed a ramified, anti-inflammatory phenotype which, during disease progression, switches to a pro-inflammatory, less ramified one, becoming neurotoxic. We hypothesize retina as a window through which monitor AD-related neurodegeneration process.

Disclosures: A. Grimaldi: None. **C. Brighi:** None. **D. Ragozzino:** None. **C. Limatola:** None. **R. Ceccarelli:** None. **G. Ruocco:** None.

Nanosymposium

267. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: SDCC 24

Time: Monday, November 5, 2018, 8:00 AM - 11:00 AM

Presentation Number: 267.07

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

Support: AHA Grant 14SDG20410063

Title: Detrimental effects of endothelial nitric oxide deficiency on microglial phenotype

Authors: *S. A. AUSTIN, Z. S. KATUSIC
Departments of Anesthesiol. and Mol. Pharmacol. and Exp.Therap., Mayo Clin., Rochester, MN

Abstract: People with cardiovascular risk factors have a higher incidence of developing Alzheimer's disease (AD); however, the mechanistic link between cardiovascular risk factors and AD is unknown. A common feature of these risk factors is the decreased bioavailability of endothelial nitric oxide (NO). The close proximity between endothelial cells and cells of the brain parenchyma suggests that endothelial NO may be an important signaling molecule. As the immunocompetent cells of the central nervous system, microglia are constantly contacting other cells to survey and sample the environment. Therefore, we sought to determine the effects of reduced bioavailability of endothelium-derived NO on microglial phenotype. We utilized postnatally-derived microglia isolated from wild type and $eNOS^{-/-}$ P0-P2 pups to characterize the phenotype of microglia. We analyzed protein expression, phagocytic ability, and secretory phenotype. First, we examined protein expression of amyloid precursor protein (APP) and its secretase enzymes. Microglia isolated from $eNOS^{-/-}$ pups had increased expression of APP and β-APP converting enzyme 1 ($n=9$-10, $p<0.05$) while expression of α-secretase enzymes was unchanged. This suggests production of beta amyloid (Aβ) may be increased in $eNOS^{-/-}$ microglia. Next, we examined the protein levels of several key microglia proteins, including: clusters of differentiation (CD)68, major histocompatibility complex (MHC) II, and ionized calcium binding adaptor molecule (Iba)1. No differences were seen in CD68 or MHC II expression ($n=6$, $n=3$, respectively, $p>0.05$). Importantly, Iba-1 expression was significantly lower in $eNOS^{-/-}$ microglia as compared to wild type ($n=9$, $p<0.0001$). Decreased expression of Iba-l could suggest impaired motility and/or phagocytic ability of $eNOS^{-/-}$ microglia. Lastly, we measured the secreted levels of several cytokines. Secreted levels of interleukin (IL) -1β and granulocyte-macrophage colony-stimulating factor were unchanged between wild type and $eNOS^{-/-}$ microglia ($n=2$-3, $p>0.05$). However, secreted levels of IL-10 and tumor necrosis factor α were significantly lower in $eNOS^{-/-}$ microglia as compared to wild type ($n=3$-4, $p<0.05$). These data demonstrate that postnatal microglia isolated from $eNOS^{-/-}$ mice have a dysfunctional phenotype. Thereby, suggesting that loss of endothelial NO may lead to significant detrimental

in vivo consequences. Our findings provide novel mechanistic insight into the link between loss of endothelial NO and dysfunctional microglia.

Disclosures: S.A. Austin: None. **Z.S. Katusic:** None.

Nanosymposium

267. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: SDCC 24

Time: Monday, November 5, 2018, 8:00 AM - 11:00 AM

Presentation Number: 267.08

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

Support: U01AG046139

Title: *Ex vivo* systems to determine the roles of microglia in Alzheimer's disease

Authors: T. E. GOLDE[1], *B. MOORE[2], C. L. CROFT[1], A. M. ROSARIO[1], K. REWIS[1], T. B. LADD[1], C. B. LESSARD[1], P. E. CRUZ[1]
[1]Dept. of Neurosci., Col. of Medicine, Univ. of Florida, Gainesville, FL; [2]Univ. of Florida, Gainesville, FL

Abstract: Recent genome wide association studies have identified rare genetic variants in genes associated with Alzheimer's disease (AD). Rare coding variants in microglial genes, such as, TREM2, PLCG2 and ABI3 have been implicated as risk genes for AD. Recent studies have shown that TREM2 binds amyloid-beta (Aβ) plaques and then causes microglial activation. However, the role of PLCG2 and ABI3 in microglial function and effects on AD pathology remain unclear. Microglia have been difficult to study *in vitro,* in primary microglial cultures or immortalized lines, as they adopt a permanent activated state and are cultured in the absence of other central nervous system cell types. This limits the interpretation of findings in these studies on the relevance to microglial changes in AD in humans. Similarly, microglia in organotypic brain slice cultures (BSCs) at 7 days *in vitro* (DIV) are similar to other *in vitro* cultures of microglia showing an amoeboid activated state. However, by 28 DIV the microglia in BSCs assume the morphology of quiescent *in vivo*-like adult microglia. This lends the opportunity to study microglia in BSCs, a physiologically relevant, three-dimensional system containing the key central nervous system (CNS) cell types enabling the study of cell autonomous and non-autonomous mechanisms.
We have developed assays to assess microglial phenotype and microglial clearance of Aβ in BSCs. We recently showed that a novel modified recombinant adeno-associated virus (rAAV) triple mutant 6 capsid with microglial specific promoters can selectively transduce microglia *in vitro* and *in vivo* and now show widespread transduction of microglia in BSCs. In addition we can use rAAVs in combination with other CNS promoters to target gene expression to the other major CNS cell types in BSCs, including neurons, oligodendrocytes and astrocytes. This rAAV

toolkit enables us to examine microglia in an integrated CNS milieu that BSCs provide. We are determining the roles of microglial genes in AD in this *ex vivo* system through the use of knock out mice, microglia targeted rAAV transduction and pharmacologically to examine the effects on Aβ clearance and phenotype. These studies will provide insight into the role of microglia in AD pathology and potentially highlight therapeutically relevant targets for AD.

Disclosures: T.E. Golde: None. **B. Moore:** None. **C.L. Croft:** None. **A.M. Rosario:** None. **K. Rewis:** None. **T.B. Ladd:** None. **C.B. Lessard:** None. **P.E. Cruz:** None.

Nanosymposium

267. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: SDCC 24

Time: Monday, November 5, 2018, 8:00 AM - 11:00 AM

Presentation Number: 267.09

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

Support: NIH-NIA R01 AG044404

Title: Effects of docosahexaenoic acid and its peroxidation product on Aβ-stimulated microglia

Authors: *X. GENG[1], B. YANG[2], R. LI[3], T. TENG[1], G. Y. SUN[3], C. GREENLIEF[3], J. C. LEE[1]
[1]Bioengineering, Univ. of Illinois at Chicago, Chicago, IL; [2]Chem., [3]Univ. Missouri, Columbia, MO

Abstract: A number of studies have demonstrated that docosahexaenoic acid (DHA) supplementation can improve cognitive performance in different transgenic animal models of Alzheimer's disease (AD). However, the mechanism(s) underlying these beneficial effects are still not fully understood. There is evidence that amyloid-β peptide (Aβ) induces inflammatory responses and production of reactive oxygen species (ROS) in microglia, and these effects are important factors exacerbating the disease. In this regard, we demonstrated that DHA offered protective effects by suppressing Aβ-induced ROS production and nitric oxide synthase (iNOS) in microglia. Since polyunsaturated fatty acids (PUFA) can undergo oxygen free radical reaction to produce alkenal products, such as 4-hydroxyhexenal (4-HHE) from DHA and 4-hydroxynonenal (4-HNE) from arachidonic acid (ARA), our recent studies with LC-MS/MS demonstrated enhanced production of 4-HNE in liposaccharide (LPS)-stimulated microglia through a pathway mediated by activation of cPLA2. In contrast, supplementation of cells with DHA can stimulate an increase in levels of 4-HHE. These results led to the present study to examine effects of Aβ and/or DHA on production of 4-HHE and 4-HNE in microglial cells. In agreement with the inflammatory and oxidative effects of Aβ, Aβ caused an increase in 4-HNE, whereas DHA resulted in an increase in 4-HHE in microglia. More importantly, DHA suppressed the increase in 4-HNE induced by Aβ. In conclusion, results are in agreement with different mechanisms for production of peroxidation products by DHA and ARA, and Aβ-

stimulated microglia through the NF-kB/cPLA2 pathways as well as enhanced 4-HNE, peroxidation product of ARA. Our results also show the ability for DHA to suppress Aβ-induced inflammation and oxidation, as well as the production of 4-HNE in microglia that warrant further investigation.

Disclosures: X. Geng: None. **B. Yang:** None. **R. Li:** None. **T. Teng:** None. **G.Y. Sun:** None. **C. Greenlief:** None. **J.C. Lee:** None.

Nanosymposium

267. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: SDCC 24

Time: Monday, November 5, 2018, 8:00 AM - 11:00 AM

Presentation Number: 267.10

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

Support: NIA U54 AG054345-01

Title: Genetic diversity is a significant driver of amyloid-induced neuroinflammation and neurodegeneration in APP/PS1 mice

Authors: *K. D. ONOS[1], A. UYAR[1], K. J. KEEZER[1], H. M. WILLIAMS[1], C. PREUSS[1], C. ACKLIN[1], R. O'ROURKE[1], R. BUCHANAN[1], T. L. COSSETTE[1], S. J. SUKOFF RIZZO[1], I. SOTO[2], G. W. CARTER[1], G. R. HOWELL[1]
[1]Res., The Jackson Lab., Bar Harbor, ME; [2]Rowan Univ., Glassboro, NJ

Abstract: The majority of mouse strains to study Alzheimer's disease (AD) have been derived from commonly used lab strains (such as C57BL/6J, B6) that have limited genetic diversity. While these strains have given insights into the biology of AD, they do not fully reflect the diversity seen in the human patient population and lack hallmark features of AD including frank neurodegeneration. To maximize genetic diversity we used wild-derived strains, CAST/EiJ, WSB/EiJ and PWK/PhJ, that exhibit natural genetic variation in AD risk genes. These strains harbor a similar degree of genetic and phenotypic variation to that in the human population and vary in AD-associated outcomes such as cardiovascular health, insulin secretion, gut microbiota, telomere length and circadian rhythm. Wild-derived AD mice were generated by backcrossing transgenes carrying two familial AD mutations, amyloid precursor protein, APP^{swe} and presenilin 1, $PS1^{de9}$ (*APP/PS1*) for at least 6 generations. Starting at 6 months, male and female *APP/PS1* and WT mice were assessed for metabolic and cognitive function. At 8 months, tissue was harvested and AD-relevant neuropathology was performed. In contrast to B6.*APP/PS1*, wild derived strains carrying *APP/PS1* showed significant modification of AD-relevant phenotypes including cognitive decline, neurodegeneration, and neuroinflammation. WSB.*APP/PS1* and CAST.*APP/PS1* mice failed to demonstrate preference in a novel spatial recognition task, and exhibited neuronal cell loss in memory-related brain regions. Significant increases in Aβ42 were

accompanied by the presence of cerebral amyloid angiopathy in both CAST.*APP/PS1*, and more prominently, WSB.*APP/PS1*. Additionally, baseline myeloid cell numbers varied across the strains, and differential plaque associated responses were observed. In order to understand drivers of phenotypic differences, transcriptional profiling of brain tissue was employed and data analyzed using Weighted Gene Co-Expression Network Analysis (WGCNA). A myeloid cell-related gene module was significantly associated with *APP/PS1* genotype, and included *Trem2, C1qa* and *Itgb2*. Interestingly, *APP/PS1*-related transcriptomic changes were greater in female compared to male mice. Importantly, neurodegeneration and vascular physiology related pathways were significantly enriched in wild derived *APP/PS1* strains compared to B6.APP/PS1 mice. Although deeper characterization is required, these findings suggest wild-derived AD mice better model the complexity of human AD compared to B6-based models, and support the utility of incorporating genetic diversity in the study of complex diseases.

Disclosures: K.D. Onos: None. **A. Uyar:** None. **K.J. Keezer:** None. **H.M. Williams:** None. **C. Preuss:** None. **C. Acklin:** None. **R. O'Rourke:** None. **R. Buchanan:** None. **T.L. Cossette:** None. **S.J. Sukoff Rizzo:** None. **I. Soto:** None. **G.W. Carter:** None. **G.R. Howell:** None.

Nanosymposium

267. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: SDCC 24

Time: Monday, November 5, 2018, 8:00 AM - 11:00 AM

Presentation Number: 267.11

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

Support: NIH Training Grant 5T326M008151-32
NIH R01AG054517
Lucille P. Markey Pathway Award

Title: The astrocytic circadian clock gates neuroinflammation and neuronal health through regulation of Alzheimer’s disease biomarker Chi3l1 (YKL-40)

Authors: *B. V. LANANNA[1], C. J. NADARAJAH[1], C. A. MCKEE[1], M. R. CEDENO[2], P. GRIFFIN[1], J. DIMITRY[1], E. S. MUSIEK[1]
[1]Washington Univ. in St Louis, Saint Louis, MO; [2]Univ. of Colorado Boulder, Boulder, CO

Abstract: Sleep disruption and circadian dysfunction are common symptoms of several neurodegenerative diseases, including Alzheimer’s Disease (AD). The cell-autonomous circadian rhythms in transcription/translation that govern these behavioral processes are mediated by clock genes and can be abrogated by deletion of the master circadian transcription factor *Bmal1*. We have shown that disruption of clock gene function in the mouse brain causes astrogliosis, synaptic damage, oxidative stress, and exacerbated neurodegeneration. However, the molecular mechanisms linking *Bmal1* to these phenotypes and their implications for AD pathology remain

largely unknown. Here, we report that deletion of *Bmal1* specifically in astrocytes causes a pronounced and unique astrogliosis phenotype both *in vitro* and in mouse cortex and hippocampus *in vivo*. Suppression of glutathione-s-transferase pathways in *Bmal1* deficient cortex and rescue of astrogliosis with supplementation of the glutathione precursor N-acetylcysteine *in vitro* and *in vivo* suggest that loss of astrocytic *Bmal1* induces astrogliosis through disruption of glutathione homeostasis. This clock-controlled astrogliosis is characterized by a robust upregulation of a number of known astrocyte activation markers and a hyperinflammatory phenotype, including almost complete loss of the astrocytic inflammatory regulator and AD biomarker, *Chi3l1* (YKL-40). Conversely, knockout of the *Bmal1* repressors *Per1* and *Per2* increases expression of *Chi3l1*, reinforcing the idea that *Chi3l1* is regulated by the circadian clock. *Chi3l1* deletion exaggerates LPS-induced astrocyte activation and neuroinflammation both *in vitro* and *in vivo* suggesting that BMAL1 may regulate neuroinflammation through regulation of *Chi3l1*. Co-culture of wild-type primary neurons with *Bmal1*-deficient astrocytes impaired neuronal survival and sensitized neurons to oxidative stress. These deficits were rescued by overexpressing *Chi3l1* in the *Bmal1*-deficient astrocytes. These data suggest that *Chi3l1* is an anti-inflammatory, neuroprotective protein regulated by the circadian clock and suggest that BMAL1 could modulate AD-associated inflammation through *Chi3l1*. Additionally, loss of *Bmal1* in a β-amyloidosis AD mouse model disrupts astrocytic plaque clustering and loss of astrocytic *Bmal1* impairs astrocyte Aβ uptake *in vitro*. Taken together, our results demonstrate a novel role for circadian clock genes in the regulation of astrocyte activation and neuroinflammation. Our data also suggest that disruption of astrocyte circadian signaling could exacerbate neuronal injury and Aβ plaque pathogenesis in AD.

Disclosures: C.J. Nadarajah: None. **C.A. McKee:** None. **M.R. Cedeno:** None. **P. Griffin:** None. **J. Dimitry:** None. **E.S. Musiek:** None.

Nanosymposium

267. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: SDCC 24

Time: Monday, November 5, 2018, 8:00 AM - 11:00 AM

Presentation Number: 267.12

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

Support: NIH Grant AG 00538
Alzheimer’s Association #NIRG-15-363477

Title: Complement C5aR1 signaling results in decreased hippocampal neuronal complexity in Alzheimer’s disease mouse models

Authors: P. SELVAN[1], V. AGHAJANYAN[1], S.-H. CHU[1], S. R. BARNAM[4], D. BAGLIETTO-VARGAS[2,4], *A. J. TENNER[3]

[1]Mol. Biol. and Biochem., [2]Inst. for Memory Impairment and Neurolog. Disorders, [3]Univ. California Irvine, Irvine, CA; [4]Microbiology, Univ. of Alabama, Birmingham, AL

Abstract: Alzheimer's disease (AD) is the most common cause of dementia, accounting for between 60 to 80 percent of all reported cases in the elderly. C5aR1 is a receptor of C5a, a proinflammatory cleavage fragment of the complement system. C5aR1 antagonists have been shown to slow pathology and rescue behavioral deficits in AD mice models and thus could be beneficial as a treatment for AD. To provide genetic support for this possibility, Arctic mice, a model of AD, were crossed to either C5aR1 knock-out (KO) mice to create an Arctic C5aR1 KO model or to a transgenic mouse producing the complement activation fragment C5a under the GFAP promoter to create an Arctic C5a overexpression model. At various ages, the mice were perfused (at least 3 mice per genotype per age), brain tissue sections were stained using the Golgi-Cox staining system, and Sholl analysis and/or dendritic spine density analysis was performed. Previously, Sholl analysis demonstrated that in the Arctic mice, neuronal branching complexity was decreased in the CA1 at 10 months of age when object location memory performance was significantly decreased. Further studies here demonstrate a significant difference in the CA3 region of these mice though to a lesser extent than seen in the CA1. Genetic ablation of C5aR1 prevented this loss of neuronal branching in both regions and prevented the behavioral deficits. In addition, overexpressing C5a in Arctic mice resulted in a decrease in CA1 dendritic spine density at an earlier age than in the Arctic mice alone, correlating with the acceleration of behavioral deficits in this C5a overexpressing model. In summary, C5a-C5aR1 signaling leads to a loss of neuronal branching and synapse density which coincides with cognitive deficits, supporting the potential of C5aR1 antagonists as a therapeutic strategy for Alzheimer's disease.

Disclosures: P. Selvan: None. **V. Aghajanyan:** None. **S. Chu:** None. **S.R. Barnam:** None. **D. Baglietto-Vargas:** None. **A.J. Tenner:** None.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.01

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

Support: NIH Grant AG023501
NIH Grant GM105718
NIH Grant AG047270
NIH Grant AG047339
VA Merit Award BX002978

Consortium for Frontotemporal Dementia Research
Gladstone Institutes

Title: A novel murine knock-in model for progranulin-deficient frontotemporal dementia with nonsense-mediated mRNA decay

Authors: *A. D. NGUYEN[1,2], T. A. NGUYEN[2], J. ZHANG[3], S. DEVIREDDY[4], P. ZHOU[5], A. M. KARYDAS[3], X. XU[5], B. L. MILLER[3], F. RIGO[6], S. M. FERGUSON[4], E. J. HUANG[3], T. C. WALTHER[2], R. V. FARESE, Jr.[2]
[1]St. Louis Univ., St Louis, MO; [2]Harvard Sch. of Publ. Hlth., Boston, MA; [3]UCSF, San Francisco, CA; [4]Yale Univ., New Haven, CT; [5]Gladstone Inst., San Francisco, CA; [6]Ionis Pharmaceuticals, Carlsbad, CA

Abstract: Frontotemporal dementia (FTD) is the most common neurodegenerative disorder in individuals under age 60 and has no treatment or cure. Since many cases of FTD result from *GRN* nonsense mutations, an animal model for this type of mutation is highly desirable for understanding pathogenesis and testing therapies. We generated and characterized Grn^{R493X} knock-in mice, which model the most common human *GRN* mutation, a premature stop codon at arginine 493 (R493X). Homozygous Grn^{R493X} mice have markedly reduced *Grn* mRNA levels, lack detectable progranulin protein, and phenocopy *Grn* knockout mice, with CNS microgliosis, cytoplasmic TDP-43 accumulation, reduced synaptic density, lipofuscinosis, hyper-inflammatory macrophages, excessive grooming behavior, and reduced survival. Inhibition of nonsense-mediated mRNA decay (NMD) by genetic, pharmacological, or antisense oligonucleotide-based approaches showed that NMD contributes to the reduced mRNA levels in Grn^{R493X} mice and cell lines and in fibroblasts from patients containing the GRN^{R493X} mutation. The expressed truncated R493X mutant protein was functional in several assays in progranulin-deficient cells. Together, our results suggest that NMD inhibition could be an effective as a therapeutic approach for treating progranulin deficiency caused by the R493X mutation. Additionally, the Grn^{R493X} mice and associated cell lines provide novel model systems to identify therapies for treating FTD resulting from *GRN* nonsense mutations.

Disclosures: A.D. Nguyen: None. **T.A. Nguyen:** None. **J. Zhang:** None. **S. Devireddy:** None. **P. Zhou:** None. **A.M. Karydas:** None. **X. Xu:** None. **B.L. Miller:** None. **F. Rigo:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. **S.M. Ferguson:** None. **E.J. Huang:** None. **T.C. Walther:** None. **R.V. Farese:** None.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.02

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

Support: FWO-Vlaanderen (FWO postdoctoral fellowship to AVdJ and grant G.0327.08 to RD)
Generalitat de Catalunya (FI-DGR predoctoral fellowship 2012 FI_B100198 to RBC
2017 FI_B00326 to CMSF
Ministerio de Economía, Industria y Competitividad of Spain (SAF2016-80027-R and CIBERNED CB06/05/0042; fellowship BES-2011-044405 to APD)
Instituto de Salud Carlos III (AES-PI10/00283)
co-financed by the European Regional Development Fund (ERDF)and the 7FP of the European Commission (MEMOSAD project, Grant FP2007-200611).

Title: Reversal of memory and neuropsychiatric symptoms and reduced taupathology by selenium in 3xTg-AD mice

Authors: *A. VAN DER JEUGD[1], A. J. PARRA-DAMAS[2], R. BAETA-CORRAL3[3], C. M. SOTO-FAGUÁS[4], T. AHMED[5], F. M. LAFERLA[6], L. GIMÉNEZ-LLORT[3], R. D'HOOGE[7], C. A. SAURA[8]
[1]Kuleuven, Leuven, Belgium; [2]Inst. De Neurociencies, UAB, Bellaterra, Spain; [3]Inst. de Neurociències, Departament de Psiquiatria i Medicina Legal, Unitat de Psicologia Mèdica, Univ. Autònoma de Barcelona, Bellaterra, Spain; [4]Inst. de Neurociències, Departament Bioquímica i Biologia Molecular, Ctr. de Investigación Biomédica en Red Enfermedades Neurodegenerativas (CIBERNED), Univ. Autònoma de Barcelona,, Bellaterra, Spain; [5]HBKU, Doha, Qatar; [6]UC Irvine, Univ. California, Irvine, Irvine, CA; [7]KU Leuven (BE0419.052.173), Leuven, Belgium; [8]Inst. Neurociències, Departament de Bioquimica i Biologia Mol., Univ. Autònoma de Barcelona, Bellaterra (Barcelona), Spain

Abstract: Accumulation of amyloid-β plaques and tau contribute to the pathogenesis of Alzheimer's disease (AD), but it is unclear whether targeting tau pathology by antioxidants independently of amyloid-β causes beneficial effects on memory and neuropsychiatric symptoms. Selenium, an essential antioxidant element reduced in the aging brain, prevents development of neuropathology in AD transgenic mice at early disease stages. The therapeutic potential of selenium for ameliorating or reversing neuropsychiatric and cognitive behavioral symptoms at late AD stages is largely unknown.Here, we evaluated the effects of chronic dietary sodium selenate supplementation for 4 months in female 3xTg-AD mice at 12-14 months of age. Chronic sodium selenate treatment efficiently reversed hippocampal-dependent learning and memory impairments, and behavior- and neuropsychiatric-like symptoms in old female 3xTg-AD mice. Selenium significantly decreased aggregated tau-positive neurons and astrocytosis, without globally affecting amyloid plaques, in thehippocampus of 3xTg-AD mice. These results indicate that selenium treatment reverses AD-like memory and neuropsychiatric symptoms by a mechanism involving reduction of aggregated tau and/or reactive astrocytes but not amyloid pathology. These results suggest that sodium selenate could be part of a combined therapeutic approach for the treatment of memory and neuropsychiatric symptoms in advanced AD stages.

Disclosures: A. Van Der Jeugd: None. **A.J. Parra-Damas:** None. **R. Baeta-Corral3:** None. **C.M. Soto-Faguás:** None. **T. Ahmed:** None. **F.M. LaFerla:** None. **L. Giménez-Llort:** None. **R. D'Hooge:** None. **C.A. Saura:** None.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.03

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

Support: VA Merit Award (AD & Gene Therapy)

Title: Neuron-targeted caveolin-1 promotes neuronal plasticity in a mouse model of Alzheimer's disease (AD)

Authors: *S. WANG, K. ZHOU, J. LEEM, P. PATEL, B. HEAD
VA Healthcare System, UCSD, San Diego, CA

Abstract: AD patients develop severe cognitive deficits which closely correlated with decreases in synapses and neuronal loss. Caveolin-1 (Cav-1), a scaffolding protein within membrane/lipid rafts microdomains, organizes signaling complexes that promote dendritic and axonal growth and synapse formation. Our previous work showed that neuron-targeted overexpression of Cav-1(SynCav1) improves memory in adult and aged mice and increases synaptic plasticity *in vivo*. It is therefore conceivable that SynCav1 may serve as a therapy to promote neuroplasticity and improve cognitive function in AD. Wild type (WT) mice received hippocampal injections of SynRFP and APPswe/PS1dE9 (AD) received either SynCav1 or SynRFP at 2.5 months. Learning and memory and general behavior were assessed using fear-conditioning and open field at 9 months of age. There is no difference in anxiety between groups showed by open field test. AD-*SynRFP* mice exhibited *decreased percent freezing (reduced fear learning) on Day 1 compared to other two groups, with no deficit in contextual or cued memory recall on Day 2 or 3, respectively. In contrast, AD-SynCav1 mice exhibited greater percent freezing (i.e., increased fear learning) on Day 1 compared to* AD-*SynRFP* mice *(no difference vs WT-SynRFP), increased contextual and cued memory recall compared to both WT-SynRFP and AD-SynRFP mice on Day 2 and 3, respectively. Immunofluorescence revealed decreased MAP2 and Cav-1 in cortex and hippocampus in AD-SynRFP mice; Cav-1 and MAP2 expression in AD-SynCav1 mice was greater than both WT-SynRFP and AD-SynRFP mice. Immunoblot analysis revealed decreased Cav-1, SMI 31, and TrkB in AD-SynRFP hippocampus, while AD-SynCav1 showed increased Cav-1, TrkB and SMI 31. Electron microscopy of CA1 distal apical dendrites from AD-SynRFP mice showed a reduction in total glutamatergic asymmetric synapses (p = 0.001 vs WT-SynRFP; p = 0.002 vs AD-SynCav1) and decreased* pre-synaptic vesicles(*PSVs)/bouton (p <*

0.0001 vs WT-SynRFP; p < 0.0001 vs AD-SynCav1). G-ratio, an inverse measure of myelination, was increased in Shaffer collateral axons in AD-SynRFP (p = 0.001 vs WT-SynRFP; p = 0.0004 vs AD-SynCav1); AD-SynCav1 mice exhibited decreased G-ratio versus WT-SynRFP. In conclusion, AD mice showed learning deficits and decreased hippocampal Cav-1, TrkB, MAP2, and SMI 31. In addition, AD-SynRFP showed ultrastructural alterations indicative of neurodegeneration (reduced synapses, PSVs and increased G-ratio). AD-SynCav1 exhibited preserved or restored fear learning and increased contextual and cued memory. Furthermore, SynCav1 preserved synaptic plasticity, synaptic ultrastructure and myelination in AD mice.

Disclosures: S. Wang: A. Employment/Salary (full or part-time):; VMRF, UCSD. **K. Zhou:** None. **J. Leem:** A. Employment/Salary (full or part-time):; UCSD. **P. Patel:** A. Employment/Salary (full or part-time):; UCSD. **B. Head:** A. Employment/Salary (full or part-time):; UCSD.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.04

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

Support: NNSFC81601229
NNSFC81441111

Title: The phosphodiesterase-4 inhibitor roflumilast reverses cognition deficits and depression-like effects via cAMP signaling-mediated neuroprotection in APP/PS1 transgenic mice

Authors: H. WANG[1], F. ZHANG[1], Y. XU[1], H.-R. FU[1], X.-D. WANG[1], L. WANG[1], W. CHEN[1], X.-Y. XU[1], Y.-F. GAO[1], J.-G. ZHANG[1], *H. ZHANG[2,1]
[1]Inst. of Pharmacology, Taishan Med. Univ., Tai'an, China; [2]Depts Behav Med. & Psych, Pharm, West Virginia Univ. Hlth. Sci. Ctr., Morgantown, WV

Abstract: Phosphodiesterase-4 (PDE4) has been demonstrated to be a promising target for treatment of Alzheimer’s disease (AD). Roflumilast (Rof), a potent PDE4 inhibitor, has been approved for treatment of chronic obstructive pulmonary disease (COPD) in humans. Recent studies have shown that Rof improves cognition at doses that do not cause an emetic response, the major side-effect of PDE4 inhibitors. However, the effect of Rof on cognition associated with AD remains largely unknown. Here we examined the effects of Rof on behavioral dysfunction and the related mechanisms in APP/PS1 double transgenic mice, a widely used model for AD. Mice at 10 months of age were first tested in novel object recognition for memory. The

recognition index in APP/PS1 mice was decreased compared to WT, which was reversed by Rof at 5 and 10 mg/kg. This was then verified in the Morris water-maze test. The escape latency during acquisition training was significantly longer and the entries into the target quadrant during the probe trial were much less compared to WT controls; these were also reversed by Rof. In the tail-suspension and forced-swimming tests, which measure depression-like behavior, AD mice showed prolonged immobility time, which was reversed by Rof. In addition, the staining of HE and Nissl showed that Rof reduced the loss of neurons and neurocyte apoptosis in AD mice. It also reversed the decreased ratio of Bcl-2/BAX and the increased expression of PDE4D in the cerebral cortex and hippocampus of AD mice. Finally, Rof reversed the decreased levels of cAMP and expression of phosphorylated cAMP response element-binding protein (CREB) and brain derived neurotrophic factor (BDNF) in AD mice. Overall, these results suggest that Rof not only improves learning and memory, but also attenuates depression-like behavior in AD mice, likely via PDE4D/cAMP/CREB/BDNF signaling-mediated neuroprotection. Therefore, Rof can be a therapeutic agent for AD, in particular the comorbidity of memory deficits and depression.

Disclosures: H. Wang: None. **F. Zhang:** None. **Y. Xu:** None. **H. Fu:** None. **X. Wang:** None. **L. Wang:** None. **W. Chen:** None. **X. Xu:** None. **Y. Gao:** None. **J. Zhang:** None. **H. Zhang:** None.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.05

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

Support: p20 gm109098
po1 ag027956
t32 ag052375

Title: Probing late-onset alzheimers disease using 2xtetr-teto-mir-34a transgenic mouse model

Authors: *S. N. SARKAR
Physiol. and Pharmacol., West Virginia Univ., Morgantown, WV

Abstract: In our previous work we have explored the potential for a single miRNA linking synaptic dysfunction and altered bioenergetics in sporadic Alzheimer’s disease (AD). Specifically we have shown that miR-34a in AD brains and primary neurons repressed proteins related to synaptic plasticity and energy metabolism. Our analysis of human genomic sequences from the tentative promoter of miR-34a gene showed the presence of NFκB, STAT1, c-Fos, CREB and p53 response elements. Activation of these transcription factors due to brain

inflammation, metabolic and oxidative stresses, as well as excessive neural activity which occurs during aging will lead to increased miR-34a gene expression and ultimately driving AD progression. The identification of common AD drivers by miR-34a is imperative to establish effective therapeutics, and blocking neuronal metabolic stress at the earliest cognitive symptoms could offer a promising approach to minimize neuronal dysfunction and AD progression. To this end we have generated a conditional miR-34a overexpression mouse (miR-34a$^{+/+}$ 2X (TetR-TetO-miR-34a) **Transgenic Mice**). These mice were used to measure cognitive function with or without doxycycline (2mg/ml) fed in water. We chose Y Maze Spontaneous Alternation behavioral test for measuring the willingness of these mice to explore new environments. Doxycycline treated groups of mice (4-8 weeks) exhibited profound behavioral impairment compared to untreated groups. Cognitive impairment of individual mice in Y-maze task correlated with miR-34a expression in many parts of the brain--including the hippocampus, prefrontal cortex, regions which are known to be involved in this task. Immunocytochemistry of brain sections from mice who poorly performed in y-maze task show high p-tau (AT8 antibody) and amyloid beta (6E10 antibody) specific staining in the hippocampus and entorhinal regions. Western blot analysis for protein samples from these mice revealed that miR34a targets the genes involved in APP metabolism, phosphorylation-dephosphorylation of Tau, and SDHC gene for oxidative phosphorylation. Thus, our results provide insights into polygenetic dysfunction in sporadic AD which is largely idiopathic and disclose miR- 34a as a potential therapeutic target for idiopathic AD.

Disclosures: S.N. Sarkar: None.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.06

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

Support: NIH Grant AG027297
Alzheimer's Drug Discovery Foundation

Title: Novel NFAT inhibitor Q134R ameliorates synaptic deficits in a mouse model of Alzheimer’s disease

Authors: *C. M. NORRIS[1], P. SOMPOL[1], J. L. GOLLIHUE[1], S. D. KRANER[1], I. A. ARTIUSHIN[1], R. CLOYD[1], S. KOREN[1], G. K. NATION[1], J. F. ABISAMBRA[1], O. HUZIAN[2], L. G. PUSKAS[2], *C. M. NORRIS[1]
[1]Sanders-Brown Ctr. Aging, Univ. Kentucky, Lexington, KY; [2]Avidin Biotech., Szeged, Hungary

Abstract: The calcineurin (CN)/Nuclear Factor of Activated T cells (NFAT) transcriptional pathway is hyperactivated at early stages of Alzheimer's disease (AD). Using a common mouse model of AD, we previously reported high levels of activation and/or expression of CN and the NFAT4 isoform in activated astrocytes. Inhibition of CN/NFATs in AD mouse models, using genetic or pharmacologic approaches, typically yields many beneficial effects including reduced neuroinflammation and amyloid pathology, along with greater neuroprotection and improved synapse function. Here, we investigated the effects of Q134R, a novel small chemical compound, developed and tested for human use by Avidin Biotechnology, on NFAT signaling in neural tissue. Similar to the CN inhibitor-cyclosporine, Q134R suppressed IL-1β- or ionomycin-induced NFAT activation in primary rat astrocyte and neuron cultures, but, unlike cyclosporine, did not inhibit CN-dependent dephosphorylation of other non-NFAT substrates. When delivered to 15-month-old APP/PS1 mice (twice daily P.O. for two weeks), Q134R (4 mg/kg) reduced GFAP volume and inhibited the nuclear localization of NFAT4 in hippocampal astrocytes. To investigate long-term treatment effects, we administered Q134R (4mg/kg) or vehicle twice daily (P.O.) for three months to WT and APP/PS1 mice starting at six-months-of-age. Compared to vehicle control, Q134R significantly increased CA3-CA1 synaptic strength and long-term potentiation in brain slices from APP/PS1 mice. Moreover, synaptic indices in Q134R-treated APP/PS1 mice were qualitatively and quantitatively similar to WT mice. The results demonstrate that Q134R inhibits hyperactive NFAT signaling *en route* to protecting synaptic function during the progression of AD-like pathology. The findings offer important proof-of-concept support for the use of small chemical NFAT inhibitors, like Q134R, in the treatment of AD and related neurodegenerative disorders.

Disclosures: P. Sompol: None. **J.L. Gollihue:** None. **S.D. Kraner:** None. **I.A. Artiushin:** None. **R. Cloyd:** None. **S. Koren:** None. **G.K. Nation:** None. **J.F. Abisambra:** None. **O. Huzian:** A. Employment/Salary (full or part-time):; Avidin Biotechnology. **L.G. Puskas:** A. Employment/Salary (full or part-time):; Avidin Biotechnology. **C.M. Norris:** None.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.07

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

Support: University Grants Commission Ph.D. Fellowship

Title: Neuroprotective effect of Carvacrol in Okadiac acid induced tau hyperphosphorylation and cognitive impairment in mice

Authors: *A. JUVEKAR, M. GURSAHANI, N. B. GAWALI, S. MESTRY
Dept. of Pharmaceut. Sci. and Technol., Inst. of Chem. Technol., Mumbai, India

Abstract: Background: Alzheimer`s disease (AD) is a progressive multifactorial neurodegenerative disorder and its major hallmarks are senile amyloid plaques, hyperphosphorylated tau protein and neuroinflammation. There is an urgent need to discover and screen new drugs for anti-Alzheimer`s activity since the currently existing drugs only provide symptomatic relief and do not target the underlying pathophysiology of AD. Okadiac acid (OKA), a potent and selective protein phosphatases (PP2A and PP1) inhibitor is known to induce hyperphosphorylation tau protein. Carvacrol has been known to possess anti-inflammatory and acetylcholinesterase (AChE) inhibitory activity but its effect on cognitive defects and other pathological markers induced by OKA has not been evaluated. Thus the present study was undertaken to evaluate the protective effects of Carvacrol in OKA induced memory impairment, neuroinflammarion and oxidative
stress in mice. Methods: Carvacrol was dosed prophylactically to Swiss Albino mice for 35 days and OKA was administered i.c.v. on the 15th day of the study. Memory was evaluated by novel object recognition task and Y-maze test. After sacrificing the animals, levels of oxidative stress markers (MDA, GSH, SOD and Catalase), inflammatory markers (TNF αand IL-6) and AChE in the brain tissue homogenates.
Results: It was observed that pre-treatment with carvacrol significantly reversed the memory impairment in the behavioural tests. TNF α and IL-6 levels were significantly increased after administration of OKA. Carvacrol treatment significantly mitigated this effect. MDA level was significantly reduced and the levels of GSH, SOD and catalase were significantly increased in carvacrol treatment groups. Significant AChE inhibitory activity was observed in the carvacrol treatment group as compared to the disease control group.
Conclusion: Carvacrol appears to be an excellent candidate for treatment of AD on account of its antioxidant, anti-inflammatory, AChE inhibitory activity and anti-amnesic effects. Its effects should be evaluated further in transgenic animal models in order for the molecule to pave its way to clinical trials.

Disclosures: A. Juvekar: None. **M. Gursahani:** None. **N.B. Gawali:** None. **S. Mestry:** None.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.08

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

Support: NIH/NIA Grant 1R01AG042890

Amon Carter Foundation

Title: Near infrared light treatment reduces synaptic levels of toxic tau oligomers and improves memory in two transgenic mouse models of human tauopathies

Authors: *G. TAGLIALATELA, B. TUMURBAATAR, B. KRISHNAN, R. KAYED, M. COMEROTA
Neurol., Univ. of Texas Med. Br. Dept. of Neurol., Galveston, TX

Abstract: Tau oligomers are emerging as a key contributor to the synaptic dysfunction that drives cognitive decline associated with the clinical manifestation and progression of Alzheimer's disease (AD). Accordingly, there is ample consensus that interventions that target tau oligomers may slow or halt the progression of AD. With this ultimate goal in mind, in the present study we investigated tau oligomer accumulation and its synaptic and behavioral consequences after an *in vivo* treatment with near infrared (NIR) light (600-1000 nm) in two transgenic mouse models, overexpressing human tau alone (hTau mice) or in combination with amyloid beta (Aβ) (3xTgAD mice). We have previously found that a similar NIR light treatment reduced Aβ synaptic accumulation and, most notably, increased synaptic resilience to the dysfunctional binding of Aβ oligomers in Tg2576 mice, thus improving related synaptic and memory deficits. In the present work, we found that a 4-week exposure to NIR light (90 sec/day/5 days a week) significantly reduced levels of endogenous oligomeric tau in both synaptosomes and total protein extracts in the hippocampus and cortex of hTau mice and improved deteriorating memory function. Similar results were observed in the 3xTgAD mice, which further displayed reduced synaptic Aβ after NIR light treatment. On the other hand, ex vivo binding of tau oligomers in isolated synaptosomes as well as tau oligomer-induced depression of long-term-potentiation (LTP) in hippocampal slices from NIR light-treated wt mice were unaffected. Finally, we found that the levels of key proteins involved in two mechanisms associated with clearance of misfolded tau, inducible HSP70 and autophagy, were up-regulated in NIR light treated mice. Collectively, these results show that NIR light decreases levels of endogenous toxic tau oligomers possibly via stimulating their autophagic clearance and alleviates associated memory deficits, thus furthering the development of NIR light as a possible non-invasive therapeutic strategy for AD.

Disclosures: G. Taglialatela: None. **B. Tumurbaatar:** None. **B. Krishnan:** None. **R. Kayed:** None. **M. Comerota:** None.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.09

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

Title: Targeting the eotaxin/CCR3 pathway in aging-associated cognitive decline

Authors: *S. MINAMI, S. REGE, H. HACKBART, E. CZIRR, S. P. BRAITHWAITE
Alkahest, Inc., San Carlos, CA

Abstract: As the population ages, dementia and aging-related diseases are becoming increasingly prevalent, requiring us to develop new therapeutic approaches. We have identified factors in plasma that increase with aging and can negatively affect cognition and inflammation. Among these factors is eotaxin, a chemokine known to induce cognitive deficits in young mice and is implicated in aging-associated diseases such as Alzheimer's disease and Parkinson's disease. Eotaxin signals primarily through the G-protein coupled receptor CCR3; thus we investigated the effect of CCR3 antagonism in animal models. We found that recombinant eotaxin administration, twice daily for 18 days, induced a cognitive deficit in young C57Bl/6 mice in the Y maze and Barnes maze which was prevented by co-administration of a CCR3 antagonist. We also tested whether administration of the CCR3 antagonist in aged mice, a natural model for elevated eotaxin, resulted in similar effects, and found that mice aged 16.5 months and 24 months demonstrated improved cognition in the Y maze, Barnes maze, and T maze when treated with the antagonist systemically. To investigate the central mechanism of action on inflammation resulting from peripheral administration of the antagonist, we treated young C57bl/6 mice with a low dose of LPS chronically for three weeks to induce central inflammation and cognitive deficits, and then treated with the CCR3 antagonist for 4 weeks and found improved cognitive function and decreased neuroinflammation and activated microglia. These results implicate the potential therapeutic utility of CCR3 antagonism for improving neuroinflammation and cognition in aging-associated neurodegenerative diseases.

Disclosures: S. Minami: A. Employment/Salary (full or part-time):; Alkahest, Inc. **S. Rege:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **H. Hackbart:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **E. Czirr:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **S.P. Braithwaite:** A. Employment/Salary (full or part-time):; Alkahest, Inc..

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.10

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

Support: NIH, NIA Grant AG029777
NIH, NIA Grant AG053150

Title: *In vivo* validation of a small molecule inhibitor of tau oligomer formation in htau mice

Authors: *J. G. MOE[1], P. DAVIES[2], E. J. DAVIDOWITZ[1], P. LOPEZ[1], H. JIMENEZ[3], L. ADRIEN[3]
[1]Oligomerix, Inc., Bronx, NY; [2]The Litwin-Zucker Res. Ctr. for the Study of Alzheimer's Dis., [3]The Feinstein Inst. of Med. Research, Northwell Hlth., Manhasset, NY

Abstract: Tau oligomers have been shown to transmit tau pathology from diseased neurons to healthy neurons through seeding, tau misfolding and aggregation that is thought to play a role in the progression of Alzheimer's disease (AD) and related tauopathies. We have also shown that extracellular tau oligomers impair memory formation in mice, inhibit long-term potentiation and are cytotoxic to cultured neuroblastoma cells.
To develop a small molecule therapeutic for AD and related tauopathies we have developed in vitro and cell assays to select molecules inhibiting tau self-association into oligomers and larger aggregates. An optimized lead compound did not exhibit off-target activity in a panel of 47 targets, was not genotoxic in a mini-AMES test, was not a substrate or inhibitor of P-gp, and had little effect on hERG. Pharmacokinetic studies and a 5-day toxicity study in mice were performed showing good exposure in the brain and good tolerability.
In vivo validation studies of an optimized lead compound were independently performed in the htau mouse model of tauopathy that expresses the human isoforms of tau without inherited tauopathy mutations that are irrelevant to AD. Four groups of male and female mice (n=25/group) were treated for four months starting at three months of age with vehicle, 10 mg/kg, 40 mg/kg or 100 mg/kg of the lead compound milled into feed. The compound remained stable in the feed over the course of the study.
Mice did not show any adverse events related to the compound. Total self-associated tau, as measured by mono-antibody ELISA, was reduced with statistical significance. Male htau mice developed significantly more insoluble tau pathology than female mice. The primary endpoint, statistically significant reduction of insoluble tau, was achieved in male mice with a maximum effective dose of 40 mg/kg. Phosphorylated insoluble tau was also significantly reduced at three distinct epitopes. An additional study was performed using only male htau mice using the low and medium doses of compound in feed that showed a statistically significant reduction of phosphorylated tau for the low dose group compared to the control group.
These results demonstrate that our lead compound reduced self-association of tau and inhibited formation of insoluble tau aggregates. The activity translated from in vitro and cellular assays to an in vivo model of tau aggregation validating our screening approach and showing that targeting oligomer formation can inhibit the entire tau aggregation pathway. In vitro safety screens also indicate further advancement of the program.

Disclosures: J.G. Moe: A. Employment/Salary (full or part-time):; Oligomerix, Inc. **P. Davies:** 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.; Oligomerix, Inc. **E.J. Davidowitz:** A. Employment/Salary (full or part-time):; Oligomerix, Inc. **P. Lopez:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. **H. Jimenez:** None. **L. Adrien:** None.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.11

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

Support: P01 AG012411-17A1
VA Merit I01 BX001655

Title: Anti-inflammatory drug prevents and reverses protein aggregation in animal models of Alzheimer's disease

Authors: *S. AYYADEVARA[1,6], S. KAKRABA[8], M. BALASUBRAMANIAM[2], N. R. PENTHALA[3], S. W. BARGER[4,7], S. T. GRIFFIN[1,7], P. A. CROOKS[3], R. J. SHMOOKLER REIS[5,6]
[1]Geriatrics, [2]Gertiatrics, [3]Pharmaceut. sciences, [4]Dept Geriatrics, [5]Dept. of Geriatrics, Reynolds Inst. on Aging 4120, Univ. of Arkansas for Med. Sci., Little Rock, AR; [6]Res., [7]Grecc, Central Arkansas Veterans Healthcare Syst., Little Rock, AR; [8]UAMS/UALR joint Bioinformatics program, Univ. of Arkansas at Little Rock, Little Rock, AR

Abstract: Proper folding and post-synthetic modification of proteins is essential for their evolved functions and activities. However, when certain proteins are misfolded they tend to form pathological, detergent-insoluble aggregates that are the defining neuropathological features of prominent age-related neurodegenerative diseases, including Alzheimer and Huntington neuropathologies and Parkinson's disease. Increasing evidence suggests that neuroinflammation promotes protein aggregation, and is involved in the etiology of neurological diseases. We synthesized and tested analogues of the naturally occurring anti-inflammatory compound combretastatin A-4. One such analogue, PNR502, proved to be effective in reducing (1.) the quantity of Alzheimer-associated protein aggregates in a mouse model of Alzheimer's disease (BRI-Aβ_{1-42}), and (2.) the capacity of the proinflammatory cytokine IL-1β to elevate the steady-state levels of Alzheimer-related protein precursors of Aβ plaques. Moreover, in *C. elegans* strains that express a human Aβ_{1-42} transgene in either neurons or muscles, PNR502 reduced Aβ_{1-42} protein aggregation and concomitantly rescued the Aβ_{1-42}-induced failures in chemotaxis and paralysis in these animals. Importantly, one day after a single dose of PNR502, the average number of Q40::YFP aggregate foci in a *C. elegans* Huntington model was reduced from 96 to 73 ($p \leq 0.0004$) and the lifespan of these animals was extended 15%. Based on this evidence that PNR502 is effective in prevention and treatment of Alzheimer-like aggregation in cellular and animal models, and our identification of PNR502's principal target protein and its predicted

binding site, we suggest that PNR502 has therapeutic potential as an inhibitor of Aβ aggregation in human brain.

Disclosures: S. Ayyadevara: None. **S. Kakraba:** None. **M. Balasubramaniam:** None. **N.R. Penthala:** None. **S.W. Barger:** None. **S.T. Griffin:** None. **P.A. Crooks:** None. **R.J. Shmookler Reis:** None.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.12

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

Support: Alzheimer's Art Quilt Initiative

Title: Gestational high-fat diet attenuates cognitive dysfunction and brain pathology in the offspring of both Alzheimer’s disease and aging mouse models

Authors: *A. DI MECO[1,2], E. LAURETTI[2], D. PRATICO[2]
[1]Philadelphia, PA; [2]Alzheimer's Ctr. at Temple, Lewis Katz Sch. of Med., Philadelphia, PA

Abstract: Background: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder affecting over five million people in US alone. Causes for the most common sporadic form of the disease are still obscure and no therapy is available to halt the progression of AD. Subjects whose mothers were affected by the disease have three times more chance to develop AD later in life compared to subject whose fathers were affected by AD. Lifestyle and nutrition are important risk factor for AD. In fact, saturated fats consumption is positively correlated to AD development later in life. We hypothesized that gestational exposure to high-fat diet would affect AD susceptibility in the offspring later in life. **Methods:** Triple Transgenic (3xTg) and wild type dams were administered high-fat diet or regular chow diet throughout 3 weeks gestation. Offspring were fed regular chow diet and tested for memory, amyloidosis, tau pathology and synaptic dysfunction at 6, 12 and 18 months of age. **Results:** 12 months old 3xTg offspring from mothers exposed to high fat diet had better cognitive performance, lower amyloid burden, reduced tau pathology, improved synaptic function and increased hippocampal neurogenesis compared to controls. Mechanistic studies correlated gestational high fat diet with reduced expression of AD genes (β-secretase, CDK5 and Tau) together with increased levels of CDK6, adult neurogenesis associated kinase, compared to controls. Moreover, gestational high fat diet ameliorated cognitive function and brain pathology in 18 months aged wild type controls through different mechanism involving lower pathogenic tau cleavage by caspase 3 and increased post-synaptic protein 95 (PSD-95). **Conclusion:** High-fat diet exposure during gestation promotes

better cognition and reduces neuropathology in the offspring of both an AD and aging mouse models via different molecular mechanisms respectively. Better understanding the connection between gestational diet and offspring's brain health later in life could help implement new preventive strategy for dementia.

Disclosures: A. Di Meco: None. **E. Lauretti:** None. **D. Pratico:** None.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.13

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

Support: NIH Grant R21AG044682-02
CBC grant HTS-025

Title: Development of a tissue-selective ABCA1 agonist for the treatment of Alzheimer's disease

Authors: *M. BEN AISSA[1], S. H. LEE[2], C. LEWANDOWSKI[3], G. THATCHER[3]
[1]Univ. of Illinois at Chicago. Col. of Phar, Chicago, IL; [2]Medicinal Chem. and Pharmacognosy, [3]Univ. of Illinois At Chicago, Chicago, IL

Abstract: Alzheimer's disease (AD) and related dementia is a multifactorial disease, presenting a challenge to drug discovery. The greatest known risk factor is the APOE4-allele with 50% and 90% risk of developing AD for respectively heterozygotes and homozygotes carriers. In the brain, ABCA1 initiates the assembly of Apolipoprotein E (ApoE) containing lipoprotein-particles, which transport lipids throughout the CNS. ApoE4 particles are less stable and poorly lipidated, contributing to loss of function in AD, which can be mitigated by ABCA1 overexpression. Both amyloid-β (Aβ) related- and non-Aβ mechanisms, contribute to the progression of AD, in APOE4 carriers. Whereas therapeutic approaches solely targeting Aβ, have failed in the clinic, there remains a lack of therapeutic strategies that incorporate APOE4. **Our objective is to restore ApoE function by promoting its lipidation using an effective and well-tolerated tissue-selective ABCA1 agonist (TSAAg) strategy that will address the multifactorial nature of AD and be effective in APOE4 carriers**. Previous agonist approaches that induce ABCA1, ameliorated AD-related pathology, however, induced detrimental lipogenic activation. Therefore, we have taken an innovative functional approach to restore the function of ApoE by screening for TSAAgs, that elevate ABCA1 in astrocytes and counter-screen against SREBP1c activation in hepatocytes to mitigate against a detrimental lipogenic genes activation. Selected hits with neutral lipogenic actions were further profiled based upon multifactorial

properties for cholesterol metabolism; anti-inflammatory and insulin-sensitizing effects. Toxicodynamic and pharmacodynamics (TD/PD) studies were performed in WT and high-fat diet-fed mice. Therapeutic potential of TSAAgs and proof of concept study was performed in EFAD murine model of AD that combines five FAD mutations with human APOE alleles. From initial 25,000-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 for hit-to-lead optimization. TD/PD data 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 for multiple mechanisms of action contributing to AD-like behavior and pathology. A Preclinical Proof-Of-Concept was established. We propose that this functional 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. **C. Lewandowski:** None. **G. Thatcher:** None.

Nanosymposium

268. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models

Location: SDCC 33

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 268.14

Topic: F.02. Behavioral Neuroendocrinology

Title: The aging brain: Long-term effects of environmental and pharmacological neuroprotective factors in male Long-Evans rats

Authors: *M. BARDI, M. GRANGER, J. PERDOMO TREJO, S. SCAROLA, K. GERECKE
Behavioral Neurosci., Randolph-Macon Col., Ashland, VA

Abstract: Despite the recent intensive effort to identify effective ways to shield the brain from the negative effects of aging, neurodegenerative diseases remain one of the most prevalent disorders in the world. Alzheimer’s disease alone was estimated to affect over 30 million people in 2015, with significant associated social and economic costs (Vos et al., 2016). An area of investigation with tremendous potentials that has not been fully developed is the long-term consequences of life-span exposure to known pharmacological (caffeine) and environmental (enrichment and exercise) neuroprotective factors. In the current study, male Long-Evans rats (n=98) were exposed to either low (25mg/kg) or high (50 mg/kg) caffeine treatments, continuous or intermittent environmental enrichment, or volunteer exercise from 21 days of age until they were sacrificed at 11 months of age (n=10 per condition). Twice during this time, animals were also exposed to cognitive (persistence task) and emotional (forced swim task) challenges. Two separate cohort of animals were also exposed to chronic or acute stress for 2 months post-

weaning. Fecal samples were collected throughout the study to assess biomarkers of stress and emotional resilience such as CORT, DHEA, and testosterone. Following the last trial, brains were processed to determine the long-term effects of these treatments on BDNF- and NPY-immunoreactivity, and double-label Cox-2 and Iba1-immunofluorescence in limbic and cortical areas involved in emotional and cognitive responses. Preliminary results indicated the high caffeine dose treatment group showed a significantly higher anxiety than both the control and low dose treatment group. Hormonal assays for CORT and DHEA indicated levels of both hormones were significantly higher in the high dose caffeine treatment group as well. Furthermore, CORT/DHEA ratio, a measure of allostatic load, was significantly higher in the high caffeine dose treatment group at baseline, but was not significantly different after an ecologically relevant stressful task. Surprisingly, both continuous and sporadic exposure to environmental enrichment showed to be effective neuroprotective factors, and they were also able to negate the negative effects of chronic stress. Finally, results indicated that the synergetic effect of environmental enrichment and exercise had the strongest effect on the emotional and neural regulations of rats. In sum, the current findings suggest that long-term exposure to high doses of caffeine and moderate exposure to environmental enrichment coupled with physical exercise are associated with long lasting neurobiological effects.

Disclosures: M. Bardi: None. **M. Granger:** None. **J. Perdomo Trejo:** None. **S. Scarola:** None. **K. Gerecke:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.01

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: Grant-in-Aid for Science Research on Innovation Area “Brain Protein Aging” 26117001 from the Ministry of Education, Culture, Sports, Science and Technology, Japan
Grant-in-Aid for Science Research C, 15K06793 from the Ministry of Education, Culture, Sports, Science and Technology, Japan
the Strategic Research Program for Brain Sciences from Japan Agency for Medical Research and Development

Title: Microglia engulfment of tangle-bearing neurons in a living tauopathy model

Authors: *N. SAHARA[1], H. TAKUWA[1], Y. TAKADO[1], T. URUSHIHARA[1], M. SHIMOJO[1], M. TAKAHASHI[1], M. ONO[1], T. KIMURA[1], C. SEKI[1], J. MAEDA[1], B. JI[1], Y. TOMITA[2], M.-

R. ZHANG[1], T. SUHARA[1], M. HIGUCHI[1]
[1]Natl. Inst. of Radiological Sci., Chiba, Japan; [2]Keio Univ. Sch. of Med., Tokyo, Japan

Abstract: Accumulation of intracellular neurofibrillary tangles (NFTs) consisting of microtubule-associated protein tau is a major hallmark of Alzheimer's disease ad related neurodegenerative diseases referred to as tauopathies, while mechanisms underlying tau-mediated neurodegeneration remain unclear. To elucidate molecular and cellular processes mediating the death of neurons bearing NFTs, we conducted in vivo multimodal imaging studies, consisting of PET, MRI and two-photon microscopy of an inducible transgenic mouse model expressing human 0N4R tau with the P301L mutation,termed rTg4510 mice.Longitudinal PET/MRI studies revealed age-dependent pathological tau accumulation, microglial activation and volume reduction in the cortex and hippocampus. We observed plateaued tau pathology, as there was no significant difference in tau PET signals between rTg4510 mice at 7 and 12-14 months of age. Correspondingly, in vivo two-photon microscopy demonstrated a plateaued total amount of tau inclusions after 7 months of age. This was attributed to equilibrium between emergence of new tau inclusions and disappearance of tangle-bearing neurons, and the rates of these two eventswere significantly reduced by doxycycline-induced suppression of transgenic human P301L tau.Most interestingly, daily two-photon microscopic observations of individual mCherry-expressing neurons and GFP-expressing microglia illustrated engulfment of tangle-burdened neurons by hypertrophic cell bodies or processes of microglia, followed by elimination of these neurons. These data suggest an essential role of phagocytic microglia in tau-induced neuronal death. Further studies are ongoing to search for molecular signals triggering phagocytic microglial activation.

Disclosures: N. Sahara: None. **H. Takuwa:** None. **Y. Takado:** None. **T. Urushihara:** None. **M. Shimojo:** None. **M. Takahashi:** None. **M. Ono:** None. **T. Kimura:** None. **C. Seki:** None. **J. Maeda:** None. **B. Ji:** None. **Y. Tomita:** None. **M. Zhang:** None. **T. Suhara:** None. **M. Higuchi:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.02

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH/NIA Grant RO1 AG054025
NIH/NIDS Grant RO1 NS094557

Title: Immunotherapy targeting tau oligomeric strains in aged transgenic animals of tauopathy

Authors: *R. AL-LAHHAM, A. BITTAR, M. CARRETERO MURILLO, M. MONTALBANO, A. ELLSWORTH, N. BHATT, S. MCALLEN, R. KAYED
Neurol., Univ. of Texas Med. Branch., Galveston, TX

Abstract: Alzheimer`s disease (AD) is characterized by the accumulation of amyloid plaques as well as Neurofibrillary tangles (NFT) of hyperphosphorylated tau. Passive immunotherapy targeting different tau species is a promising approach for developing therapeutic approaches for AD and other neurodegenerative tauopathies. While tauopathies overlap in the presence of tau pathology, each disease has a unique combination of symptoms and pathological features. Recent studies demonstrate that tau aggregates, fibrils and oligomers, are diverse and may represent prion-like strains, displaying different conformations with distinct toxicity profiles. Thus, one antibody may not be sufficient for targeting all toxic tau species in different taupathies. Evaluation of the efficacy of immunotherapy targeting different tau oligomeric strains may, therefore, lead to more efficacious treatment strategies for neurodegenerative diseases The goal of this study is to investigate the potential of passive immunotherapy with different clones of tau oligomer monoclonal antibodies (TOMAs), in two mouse models; Htau, overexpressing WT human tau, and JNPL3 overexpressing the P301L mutant. Previous studies, including ours, used middle aged mice, therefore it is critical to evaluate TauO passive immunotherapy in aged mice, since age is the main risk factor for neurodegenerative diseases and the disease pathology changes with age. Aged mice received a single intravenous injection of 120 µg/animal of different TOMA clones as well as non-specific IgG, and their cognitive functions were assessed one week post-injection using Y-maze and novel object recognition (NOR) tests, and their motor activity assessed using Rotarod test. Brain tissues were homogenized, and analyzed by standard biochemical assays, or cryosectioned and immunostained by immunohistochemical assays. Our preliminary data suggest that certain TOMA clones differentially reverse some of the tauopathy-related cognitive and motor phenotypes in aged animals, parallel to a reduction in the levels of distinct toxic tau aggregates. The effective clones were the ones shown to have strong reactivity with different tau oligomeric species in vitro. This is the first study testing tau passive immunotherapy in aged animals, although it supports our previous reports of oligomeric tau role in disease progression and validate the potential for TOMAs in reversing disease course. Moreover, this study suggests that multiple tau oligomeric strains exist in aged animals, therefore it is of great importance to characterize these strains in aged mouse models as well as human tissues and evaluate antibodies using different tau strains.

Disclosures: R. Al-Lahham: None. **A. Bittar:** None. **M. Carretero Murillo:** None. **M. Montalbano:** None. **A. Ellsworth:** None. **N. Bhatt:** None. **S. McAllen:** None. **R. Kayed:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.03

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Title: An n-terminal motif unique to primate tau enables differential protein-protein interactions

Authors: *K. STEFANOSKA[1], A. VOLKERLING[1], J. BERTZ[1], A. POLJAK[2], Y. D. KE[3], L. M. ITTNER[1,3,4], A. ITTNER[1]
[1]Dementia Res. Unit, Sch. of Med. Sci., The Univ. of New South Wales, Sydney, Australia; [2]Bioanalytical Mass Spectrometry Facility, [3]Motor Neuron Dis. Unit, Univ. of New South Wales, Sydney, Australia; [4]Neurosci. Australia, Sydney, Australia

Abstract: The tau protein is involved in a wide range of progressive neurodegenerative diseases termed Tauopathies. A characteristic feature observed in this group of diseases is the intracellular accumulation of hyperphosphorylated tau. Both the physiological and pathological functions of tau are incompletely understood. Recent studies have suggested that tau function in health and disease are mediated by its differential interactions with other cellular proteins. Primate tau harbors an 11-amino acid motif in its N-terminal region, which is not present in non-primate tau. Given humans are particularly susceptible to tau-mediated neurodegeneration compared to other species, and in an effort to understand the functional relevance of this motif, we used deletion mutagenesis of the longest human tau isoform and investigated protein-protein interactions. In combination with isobaric tags for relative and absolute quantitation (iTRAQ), bioinformatics analysis and co-immunoprecipitation to validate findings, we have identified that the primate-specific N-terminal tau motif (amino acids 18 to 28) differentially mediates interactions with neuronal proteins. Specifically, differential regulation of the binding of vesicle associated machinery, synaptic transmission, signalling and actin-binding proteins. For the first time we have identified an interaction of tau with Annexin A5 that is linked to this 11-amino acid motif. Our work provides novel insight into tau interactions and suggests that human tau has evolved specific residues, which mediate its functions through the differential regulation of protein-protein interactions as compared to other non-primate, mammalian *tau* genes.

Disclosures: K. Stefanoska: None. **A. Volkerling:** None. **J. Bertz:** None. **A. Poljak:** None. **Y.D. Ke:** None. **L.M. Ittner:** None. **A. Ittner:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.04

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH grants U01AG046139, R01AG018454, P50AG047266 to TEG
Florida Department of Health grant 7AZ25 to BIG
Marjorie Thomas Fund
Stop Alzheimer's Now Fund

Title: Insights into tauopathies and tau therapeutic targets utilizing rAAV-based brain slice culture models

Authors: *C. L. CROFT[1], P. E. CRUZ[1], D. H. RYU[1], C. CEBALLOS-DIAZ[1], K. H. STRANG[1], B. M. WOODY[1], K. REWIS[1], M. S. GOODWIN[1], W.-L. LIN[2], M. DETURE[2], E. RODRIGUEZ-LEBRON[3], D. DICKSON[2], P. CHAKRABARTY[1], Y. LEVITES[1], B. I. GIASSON[1], T. E. GOLDE[1]
[1]Univ. of Florida, Dept. of Neurosci., Gainesville, FL; [2]Mayo Clin., Jacksonville, FL; [3]Univ. of Florida, Dept. of Pharmacol. and Therapeut., Gainesville, FL

Abstract: It has been challenging to produce relevant ex vivo models of the inclusion pathologies that are found in many neurodegenerative proteinopathies. Specifically, in the case of tau pathology, such as that observed in Alzheimer's disease (AD), mature neurofibrillary tau inclusions have only been observed in transgenic rodent models. These models restrict throughput, show phenotypic variability and are expensive to maintain and age. This has hindered both therapeutic target identification and mechanistic insight into tau-induced neurodegeneration. We have developed an approach to recapitulate neurofibrillary tau inclusions like those seen in human tauopathies in a three-dimensional, cytoarchitecturally and functionally intact system. We transduced organotypic brain slice cultures (BSCs) from post-natal mice using recombinant adeno-associated viruses (rAAVs) to express human wild-type (WT) or mutant MAPT and maintained them in vitro for several weeks. We found that BSCs transduced with mutant MAPT progressively develop an abundance of sarkosyl-insoluble, filamentous, Thioflavin S positive inclusions between 7 and 28 days *ex vivo* and in extended culture times they also begin to show neuronal loss. More generally, we have developed a rAAV BSC "toolkit" which enables efficient transduction and transgene expression from neurons, microglia, astrocytes and oligodendrocytes, alone or in combination, with transgene expression lasting for several months. These BSCs can be treated with compounds of therapeutic interest and the findings extrapolate to in vivo models. Ongoing screenings of intrabodies, functionalized

intrabodies, novel antibodies and small molecule compounds to target tau in this model will also be presented. These rAAV-based BSC models provide a cost-effective and facile alternative to in vivo studies, and in the future can become a widely adopted methodology to enable the field to determine novel therapeutic strategies against tau inclusions and neurodegeneration in AD and other tauopathies.

Disclosures: C.L. Croft: None. **P.E. Cruz:** None. **D.H. Ryu:** None. **C. Ceballos-Diaz:** None. **K.H. Strang:** None. **B.M. Woody:** None. **K. Rewis:** None. **M.S. Goodwin:** None. **W. Lin:** None. **M. Deture:** None. **E. Rodriguez-Lebron:** None. **D. Dickson:** None. **P. Chakrabarty:** None. **Y. Levites:** None. **B.I. Giasson:** None. **T.E. Golde:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.05

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant K99AG053439
Rainwater Foundation
NIH Grant U54NS100717
NIH Grant R01AG054214

Title: Tau secretion and propagation is regulated by p300/CBP via autophagy-lysosomal pathway

Authors: *X. CHEN[1,2], Y. LI[2], C. WANG[2], Y. TANG[3], S.-A. MOK[3], R. M. TSAI[3], J. C. ROJAS[3], A. KARYDAS[3], B. MILLER[3], A. BOXER[3], J. E. GESTWICKI[3], M. ARKIN[3], A. CUERVO[4], L. GAN[2]
[1]Neurosciences, Univ. of California San Diego, LA Jolla, CA; [2]Gladstone Inst., San Francisco, CA; [3]Univ. of California, San Francisco, San Francisco, CA; [4]Developmental and Mol. Biol., Albert Einstein Col. of Med., Bronx, NY

Abstract: The trans-neuronal propagation of tau has been implicated in the progression of tau-mediated neurodegeneration. Secretion of tau from neurons is the initial step towards tau transmission. However, little is known about the underlying cellular mechanism. Here, we report that p300/CBP - the lysine acetyltransferase that acetylates tau and regulates its homeostasis and toxicity - is a key regulator of tau secretion via modulating the autophagy-lysosomal pathway (ALP). We show that increased p300/CBP is associated with impaired ALP function in tau transgenic mouse model and in HEK293 reconstitution model. p300/CBP hyperactivation increases tau secretion via blockage of the autophagic flux. Conversely, inhibiting p300/CBP

genetically or pharmacologically promotes autophagy, reduces tau accumulation and tau secretion, and ameliorates tau propagation in fibril-induced tau spreading models in vitro and in vivo. Our findings showed that p300/CBP-induced impairment in the ALP underlies excessive unconventional secretion and pathogenic spread of tau. The connections between p300, autophagy and tau secretion underscore the notion that aberrant metabolism might contribute to neurodegeneration.

Disclosures: X. Chen: None. **Y. Li:** None. **C. Wang:** None. **Y. Tang:** None. **S. Mok:** None. **R.M. Tsai:** None. **J.C. Rojas:** None. **A. Karydas:** None. **B. Miller:** None. **A. Boxer:** None. **J.E. Gestwicki:** None. **M. Arkin:** None. **A. Cuervo:** None. **L. Gan:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.06

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH NS091329-01
Alz Association NIRG-14-322441

Title: Pathological tau shifts translation by modifying rpS6 and 5' TOP RNA protein synthesis

Authors: *S. KOREN[1], S. E. MEIER[2], G. K. NATION[1], J. SIMPSON[1], J. RODRIGUEZ-RIVERA[1], S. ESTUS[2], H. ZHU[3], E. M. BLALOCK[4], J. ABISAMBRA[1,2]
[1]Sanders Brown Ctr. on Aging, [2]Dept. of Physiol., [3]Dept. of Biochem., [4]Dept. of Pharmacol., Univ. of Kentucky, Lexington, KY

Abstract: A common symptom in Alzheimer's disease (AD) and related tauopathies is memory impairment, which is based on fundamental molecular mechanisms like translation. Tau interacts with ribosomes in tauopathic brains, but a causative link between tau and protein synthesis was only recently shown. Here, we couple microarray RNA sequencing and a novel nascent proteomic approach based on *in vivo* injections of puromycin to show translational deficits in the (TET/OFF) rTg4510 tau transgenic mouse line. By suppressing tau overexpression at a critical point in cognitive dysfunction in rTg4510 mice, we investigated how reducing tau contributes to rescuing memory loss. Microarray analysis determined that tau overexpression modified an abundance of distinct subsets of transcripts. Many of these transcripts were related to translation suggesting that tau plays a direct role in altering translational dynamics at the transcript level. Nascent proteomics analysis indicated that tau expression suppressed protein synthesis of translation-related peptides, which highly supports the hypothesis that tau impairs inherent mechanisms of translation. We validated these results in human AD brains by focusing on rpS6,

a crucial regulator of translation. When activated, rpS6 promotes the translation of 5' TOP mRNAs, which code for translation-related genes such as ribosomal proteins and elongation factors in response to cell stress and activity. We report tau interacts with rpS6 in human brain and that this interaction occurs more in AD suggesting that tau may be impairing rpS6 function. Strikingly, qPCR and western blot analysis revealed that rpS6 and other 5' TOP mRNAs are increased at the transcript level and decreased at the protein level. Together, these data strongly suggest that pathological tau clogs ribosomal function, potentially through rpS6, and thereby reduces the ability of the ribosome to shift translation in response to cellular stimulus. Since translation is key to neuronal function and complex cognition, these findings suggest a novel role of tau in progressing cognitive decline in disease.

Disclosures: S. Koren: None. **S.E. Meier:** None. **G.K. Nation:** None. **J. Simpson:** None. **J. Rodriguez-Rivera:** None. **S. Estus:** None. **H. Zhu:** None. **E.M. Blalock:** None. **J. Abisambra:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.07

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH R01 NS091329
NIH L32 MD009205-01
Department of Defense GRANT11811993

Title: PERK-Tau coupling causes biphasic consequences to tau pathology and neuronal function *in vitro* and *in vivo*

Authors: *J. F. ABISAMBRA[1,4], S. N. FONTAINE[2], S. KOREN[4], G. NATION[2], B. WEISS[2], R. CLOYD[3], S. MEIER[3], D. POWELL[2]
[1]Sanders-Brown Ctr. on Aging, Univ. of Kentucky, Gainesville, FL; [2]Sanders-Brown Ctr. on Aging, [3]Univ. of Kentucky, Lexington, KY; [4]Univ. of Florida, Gainesville, FL

Abstract: The ER kinase PERK is genetically, biologically, and pathologically linked to tauopathies including Alzheimer's disease. PERK inhibition improves outcomes in several neurodegenerative models including aged tauopathic mice, but the mechanisms behind the tau-PERK association are poorly understood. However, conflicting data and adverse on and off target effects of PERK inhibition substantiate the need to better understand the mechanism of PERK activity in the brain.Using in vitro and in vivo models of tauopathy, we demonstrate that PERK and tau form a complex, and its dynamics and stability dictate positive or negative

tauopathic outcomes. When tau burden is low, the complex is transient, and PERK inhibition is beneficial. Increased tau burden and hyper-activation of PERK result in a stable complex; in this instance, PERK inhibition is neurotoxic. We demonstrate this further in our mouse models of tauopathy and genetic PERK ablation. Finally, we demonstrate that the effects of the PERK-tau complex rely on mechanisms of anti-oxidation and PERK-mediated tau phosphorylation. The dynamic PERK-tau complex promotes positive or negative differential outcomes dependent on complex stability and tau burden. These data suggest that inhibition of PERK early in the disease, when tau burden is low, represents the greatest therapeutic gain. These are important mechanistic insights for future studies with new classes of PERK-targeted small molecules as a therapeutic strategy for Alzheimer's disease and related tauopathies. Our work clarifies the role of PERK activity in the brain, which requires a carefully regulated balance for proper function.

Disclosures: J.F. Abisambra: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; GlaxoSmithKline. **S.N. Fontaine:** None. **S. Koren:** None. **G. Nation:** None. **B. Weiss:** None. **R. Cloyd:** None. **S. Meier:** None. **D. Powell:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.08

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: VA merit
NIH 2P01 AG012411-17A1

Title: Post-translational modifications alter tau structure and impair tubulin binding

Authors: *M. BALASUBRAMANIAM[1], S. AYYADEVARA[2], S. T. GRIFFIN[3], R. SHMOOKLER REIS[2]
[1]Gertiatrics, [3]Geriatrics, [2]Univ. of Arkansas for Med. Sci., Little Rock, AR

Abstract: Neurofibrillary tangles (NFTs), composed of paired helical filaments of hyperphosphorylated tau, are characteristic of neurodegenerative "tau-opathies," including Alzheimer's disease (AD) and frontotemporal dementia. Post-translational modifications can disrupt normal protein folding and thus contribute to aggregation. Numerous toxic species of hyperphosphorylated tau have been identified, including AT8 (pSer202; pThr205), which is enriched in NFTs. Acetylation was recently reported to precede phosphorylation and, in this way, play a critical role in tau aggregation, but it remains unknown how these modifications alter tau

structural dynamics to impact aggregation. We used molecular-dynamic simulations to predict perturbations of tau structure arising from specific patterns of post-translational modification, including novel phosphorylations identified through proteomics of AD-specific aggregates. We first isolated insoluble hypothalamic aggregates by tau immuno-pulldown, differential centrifugation, and detergent insolubility. We identified tau phosphorylation patterns specific to AD or age-matched controls (AMC), and predicted structural fluctuations by modelling full-length tau. Computational protein-protein interaction studies indicate that AMC-tau interacts with tubulin heterodimers at the same interface previously implicated by NMR chemical-shift assays, whereas AD-tau and AT8-tau simulations predict poor binding to tubulin heterodimers. AD-tau shows far less fluctuation than AMC-tau at the microtubule-binding domain, also known as the paired-helical-filament [PHF] core region. AD-tau contains folds within the PHF core region that are absent in AMC-tau. Introducing a K174Q (acetylation-mimetic) substitution in AMC-tau perturbs its dynamic structure substantially (RMSD=11.21 Å); the Ser202 and Thr205 residues are particularly affected, putatively exposing targets of GSK3β kinase and thus allowing conversion to AD-tau.

Disclosures: S. Ayyadevara: None. **S.T. Griffin:** None. **R. Shmookler Reis:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.09

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant R21NS0903771
NIA Grant T32-AG052354
U.S. Department of Veterans Affairs

Title: Constitutive XBP-1s-mediated activation of the endoplasmic reticulum unfolded protein response protects against pathological tau

Authors: *S. M. WALDHERR[1,2,5], B. C. KRAEMER[1,2,5,3,4]
[1]Mol. and Cell. Biol., [2]Div. of Gerontology and Geriatric Med., [3]Psychiatry and Behavioral Sci., [4]Pathology, Univ. of Washington, Seattle, WA; [5]Geriatric Res. Educ. and Clin. Ctr., Veterans Affairs Puget Sound Hlth. Care Syst., Seattle, WA

Abstract: Accurate protein folding and prevention of misfolded protein aggregation in neurons relies on the protein homeostasis network. Cellular stress can increase misfolded proteins in the endoplasmic reticulum (ER), which activates the ER unfolded protein response (UPR^{ER}) to restore homeostasis. Although it is well-characterized in non-neuronal cells, recent studies from

several groups have revealed a key role for the UPR^{ER} in normal neuronal function during aging and neurodegenerative diseases. Neurodegenerative tauopathies are a group of age-related disorders classified by accumulation of cytoplasmic hyperphosphorylated and aggregated tau protein. In cultured mammalian cells and *C. elegans*, we demonstrated the presence of pathological tau can induce the UPR^{ER} via upregulation of the evolutionarily conserved master transcription factor X-box binding protein 1 (XBP1s/XBP-1s). Recent work indicates XBP1s might also play a critical role in tau pathology. We previously generated a transgenic *C. elegans* tauopathy model which recapitulates pathological hallmarks such as neuronal loss and accumulation of abnormal tau species. Our results show loss of *xbp-1* exacerbates tau-related phenotypes, including uncoordinated movement, motor neuron loss, and abnormal tau protein accumulation. Conversely, we found transgenic expression of constitutively active *xbp-1s* ameliorates these pathological tau-induced phenotypes. The UPR^{ER} is composed of three branches which can initiate independent and overlapping stress response pathways. To understand whether the two non-*xbp-1* UPR^{ER} stress sensor branches also participate in tauopathy, we investigated loss of *atf-6* and *pek-1*. Interestingly, we found that *atf-6*, but not *pek-1*, mediates tau toxicity. The ATF-6 branch is also necessary for *xbp-1s*-mediated amelioration of pathological tau-induced movement defects. Additionally, *atf-6* loss of function reverses *xbp-1s* reduction in tau protein levels. Aging is the greatest risk factor for developing neurodegenerative diseases. Others have demonstrated *xbp-1s* activation can also extend lifespan in *C. elegans* via *xbp-1*-mediated neuronal signaling events (Taylor and Dillin, 2013). While the mechanistic nature of *xbp-1s* effects on aging have yet to be dissected, we hypothesize the same *xbp-1s* regulatory target genes mediate both lifespan extension and suppression of tauopathy. Because tau is not an ER-associated cytoplasmic protein, we propose target genes of *xbp-1s* include those involved in protein homeostasis mechanisms outside of the ER, such as ER-associated degradation.

Disclosures: S.M. Waldherr: None. **B.C. Kraemer:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.10

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Title: Effects of USP14 inhibition on proteasomal degradation in mammalian cells

Authors: *Q. WANG[1], J. CHADCHANKAR[2], V. KORBOUKH[4], P. DOIG[4], S. JACOBSEN[5], N. BRANDON[5], S. MOSS[3]
[1]Neurosci., Astrazeneca R&D Boston, Waltham, MA; [2]Tufts Univ., AstraZeneca Tufts

Laboratory for Basic and Transl, MA; [3]Tufts Univ., Boston, MA; [5]Neurosci., [4]AstraZeneca R&D Boston, Waltham, MA

Abstract: USP14 inhibition has been considered a therapeutic strategy for accelerating degradation of aggregation-prone proteins involved in neurodegenerative diseases, but not all published studies support this strategy. Here, we assessed the effects of USP14 inhibition on protein degradation using small molecule inhibitors and a dominant negative mutant USP14 C114A. We tested two published USP14 inhibitors IU1 and b-AP15. We validated that IU1 inhibits proteasome-associated USP14 *in vitro* but surprisingly b-AP15 did not inhibit USP14 in the same assay. Treatment of cells with IU1 did not enhance degradation of Tar DNA-binding protein-43 (TDP-43), microtubule associated protein tau or α-synuclein. Treatment of cells with b-AP15 caused an accumulation of polyubiquitinated proteins and depletion of free ubiquitin, but had no effect on degradation of TDP-43, tau or α-synuclein. Furthermore, neither USP14 WT nor C114A expression changed degradation of TDP-43, tau or α-synuclein co-expressed in HEK293T cells. Interestingly, USP14 C114A expression led to an unexpected robust accumulation of polyubiquitinated proteins in cells, suggesting degradation of these proteins require active USP14.

Disclosures: Q. Wang: None. **J. Chadchankar:** None. **V. Korboukh:** None. **P. Doig:** None. **S. Jacobsen:** None. **N. Brandon:** None. **S. Moss:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.11

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: Rainwater Charitable Foundation

Title: Analysis of tauopathy research funding between 2006 and 2016 reveals critical gaps in research priorities

Authors: *C. M. ALTIMUS[1], P. BRANNELLY[2], K. KELLER[1], E. RILEY[1], L. BRIGGS[1]
[1]Ctr. for Strategic Philanthropy, Milken Inst., Washington, DC; [2]Rainwater Charitable Fndn., Ft. Worth, TX

Abstract: Neurodegenerative diseases encompass a range of diagnoses, such as Alzheimer's and Parkinson's disease. Despite decades of advancements in understanding the neurobiology of individual diseases, this class has few disease-modifying therapeutics and a paucity of biomarkers for diagnosis or progression. However tau protein aggregation has emerged as a

potential unifying factor across several neurodegenerative diseases, which has prompted a rapid growth in tau-related funding. In spite of this growth, research funding in this area is not in line with the immense magnitude of disease burden, and drug discovery and clinical research remains underfunded. Coordinated, collaborative efforts are key to making an impact, which can and should be led by the major funding bodies within the tau space. Here we describe the development and analysis of a tau-focused neurodegeneration funding database, which captures data from 2,040 grants from 2006 to 2016. This database was developed as a public resource to allow funders, researchers and policy makers to better understand tau funding patterns, identify key funders and potential collaborations. This database can be used in conjunction with other neurodegenerative disease databases, such as the International Alzheimer's Disease Research Portfolio (IADRP) to gain specific insight into tau-research funding. Over the study period, overall tau funding rose dramatically; however, changes in capital distribution also changed. Specifically, the field experienced a strong bias toward funding tau in the context of Alzheimer's disease, while at the same time generally decreasing the overall proportion of funding for basic research, treatment development and evaluation. As funding organizations look forward, this resource can both inform future funding strategies and priority areas, and identify potential collaborative efforts with complementary funding organizations.

Disclosures: C.M. Altimus: None. **P. Brannelly:** None. **K. Keller:** None. **E. Riley:** None. **L. Briggs:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.12

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: F31NS103588

Title: The role of the ESCRT pathway in prion disease

Authors: *J. LAWRENCE, C. SIGURDSON, J. TREJO, T. NAM
UCSD, La Jolla, CA

Abstract: Prion diseases are infectious neurodegenerative disorders caused by PrP^{Sc}, a misfolded and aggregated isoform of the cellular prion protein, PrP^{C}. During disease, prion aggregates spread through the CNS, causing neurodegeneration, gliosis, and ultimately death, however the mechanisms of prion transport from cell-to-cell through the brain remain poorly defined. Here we investigated the role of the ESCRT pathway in the intercellular spread of prions. Endosomes mature along the ESCRT pathway with contents degraded in lysosomes or released in exosomes,

extracellular nanovesicles that are important for intercellular communication and transporting proteins. We hypothesize that the endosomal pathway plays a major role in prion spread within the CNS. To further understand how the prion trafficking in endosomes impacts spread, we performed a time course study in prion infected mice, collecting mice from early (20% of the incubation period) to late disease (terminal) and quantifying ESCRT protein levels over time. We found ESCRT-0 and -I protein levels altered, however, transcript levels were unchanged. Ubiquitin levels were elevated by 80% of disease course. In mice terminally infected with various prion strains, levels were also altered. Studies are ongoing to understand the mechanism underlying the dysregulation of the ESCRT pathway and how altered ESCRT protein levels impact neurodegeneration.

Disclosures: J. Lawrence: None. **C. Sigurdson:** None. **J. Trejo:** None. **T. Nam:** None.

Nanosymposium

269. Tauopathies, Tau-Dementias, and Prion Diseases: Cellular and Molecular Mechanisms

Location: SDCC 1

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 269.13

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: National Institutes of Health grant NS069566
National Institutes of Health grant NS076896
Ramón Areces Foundation
Swedish Research Council grant 2015-04521
Swedish Research Council grant 2015-05868
The Göran Gustafsson Foundation

Title: Reducing heparan sulfate chain length increases clearance of fibrillar prions and prolongs survival

Authors: *P. AGUILAR CALVO[1], A. SEVILLANO[2], J. BAPAT[2], K. SOLDAU[2], D. SANDOVAL[3], P. NILSSON[4], J. ESKO[3], C. SIGURDSON[2]
[1]Dept. of Pathology, Sch. of Med., [2]Dept. of Pathology, Sch. of Med, Univ. of California, San Diego (UCSD), La Jolla, CA, [3]Dept. of Cell. and Mol. Medicine, Univ. of California, San Diego (UCSD), La Jolla, CA, Univ. of California, San Diego (UCSD), La Jolla, CA; [4]Dept. of Physics, Chemistry, and Biology, Linköping University, Linköping, Sweden, Linköping Univ., Linköping, Sweden

Abstract: The endogenous co-factors driving prion propagation through the CNS are poorly understood. Heparan sulfate proteoglycans (HSPGs) contain highly heterogenous chains of repeating disaccharide units that promote prion internalization and fibrillation *in vitro*. To test the

hypothesis that HS is a major co-factor involved in prion propagation *in vivo*, we intracerebrally inoculated tg(Ext1)$^{+/-}$ mice, which express short HS chains, and littermate controls with three mouse-adapted prion strains. Strain fidelity was maintained, as prions forming primarily oligomers or fibrils were morphologically and biochemically indistinguishable between tg(Ext1)$^{+/-}$ mice and controls. The disease course was unchanged in the tg(Ext1)$^{+/-}$ mice inoculated with oligomeric prions. In contrast, tg(Ext1)$^{+/-}$ mice exposed to the fibrillar prion strain showed an increase in the survival time and a shift in the brain plaque distribution from the corpus callosum to distant blood vessels. We also found that the fibrillar prions are predominantly formed by extracellularly shed prion protein lacking the glycophosphatidylinositol (GPI)-anchor and that these prions bind approximately 10- to 40-fold more HS than the oligomeric prions. As shortening the HS chains decreases white matter plaques and increases prion accumulation in blood vessels, our results suggest that the longer HS chains trap certain prion fibrils in the HS network, decreasing transit within the interstitial fluid flowing toward blood vessels. This study provides the first *in vivo* evidence that HSPGs enhance the parenchymal plaque deposition of prions, slowing their clearance in the interstitial fluid and accelerating disease progression.

Disclosures: P. Aguilar Calvo: None. **A. Sevillano:** None. **J. Bapat:** None. **K. Soldau:** None. **D. Sandoval:** None. **P. Nilsson:** None. **J. Esko:** None. **C. Sigurdson:** None.

Nanosymposium

270. Vision and Eye Movements

Location: SDCC 4

Time: Monday, November 5, 2018, 8:00 AM - 10:15 AM

Presentation Number: 270.01

Topic: D.08. Visual Sensory-motor Processing

Support: NIH Grant 5T32 EY017271-08
NIH Grant EY022928
NSF-NCS 1734901

Title: Spatial receptive field dynamics in prefrontal cortex

Authors: *S. B. KHANNA[1,2,3], J. A. SCOTT[2], M. A. SMITH[1,2,3]
[1]Dept. of Ophthalmology, [2]Dept. of Bioengineering, [3]Ctr. for Neural Basis of Cognition, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Working memory, the act of maintaining information even when it is absent from the external environment, is a vital process for producing complex behaviors. Active vision, which involves encoding visual stimuli and generating eye movements, necessitates a flexible neural structure as the information to be stored in memory can originate at a wide range of temporal and spatial scales. Prefrontal cortex (PFC) neurons show a wide range of responses during visual

stimulus presentation, eye movement planning and generation, and during the memory period of a working memory task. Early PFC studies proposed that persistent elevated neural activity during the memory period might be the neural mechanism of working memory. More recently, however, population based analyses have suggested a dynamic population code may be the mechanism for working memory. It is thought this dynamic population code could arise from dynamic selectivity (the changing of tuning preferences across time) at the single neuron level, yet few studies have measured the detailed spatial response properties of PFC neurons and how they change over time in an oculomotor task. We used a 96-channel "Utah Array" to record from groups of PFC neurons (area 8ar, near the arcuate sulcus) simultaneously in alert rhesus macaque monkeys performing a conventional memory guided saccade task. We first measured the tuning properties of neurons during the visual and motor epochs of the task to determine if dynamic selectivity was observed at the single neuron level, and whether there was a systematic shift in the tuning preference of these neurons. At the population level, a decoder was trained to discriminate target location and eye movement direction and assess whether there was evidence of a dynamic code during the memory period. Decoding performance of the PFC population was then compared to a population of frontal eye field neurons (FEF) in the same task. A subset of PFC neurons had dynamic selectivity, with some shifts in tuning being as large as 180 degrees, resulting in the preferred directions of particular epochs in the task being in opposite hemifields. Target direction could be reliably decoded from the PFC population, but FEF performance was markedly better. These results confirm the presence of dynamic selectivity at the single neuron level, highlighting the magnitude of the spatial and temporal shifts that must be accounted for to understand how PFC maintains a stable population code, and reaffirm FEF's role in eye movement generation to be more central than that of PFC.

Disclosures: S.B. Khanna: None. **J.A. Scott:** None. **M.A. Smith:** None.

Nanosymposium

270. Vision and Eye Movements

Location: SDCC 4

Time: Monday, November 5, 2018, 8:00 AM - 10:15 AM

Presentation Number: 270.02

Topic: D.08. Visual Sensory-motor Processing

Support: NSF GFRP

Title: Primary visual cortex encodes detailed movement plans

Authors: *G. GUITCHOUNTS[1], J. DAPELLO[1], J. A. MASIS[2], S. B. WOLFF[1], D. D. COX[2]
[2]Mol. and Cell. Biol., [1]Harvard Univ., Cambridge, MA

Abstract: Organisms that move through the world and experience it through sensory organs must coordinate the motor and sensory systems. While rodent primary sensory cortices have

been found to be modulated by movements, with either an increase or decrease in activity during locomotion, it is unclear if early cortical sensory processing encodes detailed plans of upcoming movements. We recorded activity of populations of neurons in V1 of rats freely moving in the dark, and show that a deep neural network can decode detailed information about the animals' head movements using V1 activity. Silencing of secondary motor cortex (M2) abolished the network's decoding ability, suggesting that M2 contributes movement information to V1. Furthermore, V1 activity is suppressed during orienting movements, reminiscent of saccadic suppression reported in subcortical and extrastriate visual areas (but not V1) of cats and monkeys. These results support predictive coding theories of cortical function and suggest that corollary discharge signals in mammalian brains contain detailed movement information.

Disclosures: G. Guitchounts: None. **J. Dapello:** None. **J.A. Masis:** None. **S.B. Wolff:** None. **D.D. Cox:** None.

Nanosymposium

270. Vision and Eye Movements

Location: SDCC 4

Time: Monday, November 5, 2018, 8:00 AM - 10:15 AM

Presentation Number: 270.03

Topic: D.08. Visual Sensory-motor Processing

Support: NSF Grant BCS-1261433

Title: Decoding saccade timing and direction from LFPs associated with corollary discharge in macaque V1

Authors: *S. AKERS-CAMPBELL[1,2], O. RUIZ[4], J. E. NIEMEYER[5], J. LOPER[6], S. GEMAN[1,2,3], M. A. PARADISO[1,2]
[1]Dept. of Neurosci., [2]Carney Inst. for Brain Sci., [3]Div. of Applied Mathematics, Brown Univ., Providence, RI; [4]Vision Ctr. Lab., Salk Inst. for Biol. Studies, La Jolla, CA; [5]Lab. of Neural Dynamics and Cognition, Rockefeller Univ., New York, NY; [6]Ctr. for Theoretical Neurosci., Columbia Univ., Providence, RI

Abstract: Human visual perception takes place primarily during eye fixations that are separated by rapid saccadic eye movements. It is conceivable that perception and the mechanisms that control saccades are entirely independent processes, the saccades simply moving the eyes to objects of interest. However, multiple lines of evidence suggest that saccades influence perception: saccades are associated with perceptual distortions of visual space, perceptual stability and suppression, and the allocation of visual attention. From a neural perspective, a foundation for understanding how perception and saccades interact should be based on establishing two key points. First, it must be shown that signals related to eye movements are present in brain areas involved in perception and, second, there must be information in the

saccade-related signals sufficient to account for any perceptual effects. Numerous physiological studies in animals and humans have established the first point by showing that saccades are associated with changes in EEG, BOLD, single unit activity, and local field potentials. The aim of the present study was to examine the second point above, i.e. what information about saccades and fixations is present in perisaccadic signals? Of particular interest was information about the timing of saccades and fixations and the metrics of saccades (direction). Local field potentials were recorded in macaque primary visual cortex (v1) while animals made saccades between small fixation points in a dimly lit room. No visual stimuli were presented in receptive fields. Recordings were made with Utah electrode arrays so that simultaneous recordings at different cortical locations could be compared. Support vector machines were used to classify epochs of LFP activity. We find that LFPs can be used to reliably distinguish fixations from saccades, precisely estimate the onset time of fixations (i.e. ends of saccades), and infer the directions of saccades. Significant information can be extracted from even 10 ms LFP epochs before, during, and after saccades. These corollary discharge signals may be used by the brain in processes including visual stability, saccadic suppression, receptive field remapping, and trans-saccadic visual perception.

Disclosures: S. Akers-Campbell: None. **O. Ruiz:** None. **J.E. Niemeyer:** None. **J. Loper:** None. **S. Geman:** None. **M.A. Paradiso:** None.

Nanosymposium

270. Vision and Eye Movements

Location: SDCC 4

Time: Monday, November 5, 2018, 8:00 AM - 10:15 AM

Presentation Number: 270.04

Topic: D.08. Visual Sensory-motor Processing

Support: VIDI Grant 452-13-008
ERC-2012-AdG-323413
VU Talentfund
Stichting Talent Support
Jo Kolk Studiefonds

Title: The relationship between fixation duration and saliency coding in superior colliculus during free viewing of natural scenes

Authors: *J. HEEMAN[1], B. J. WHITE[2], S. VAN DER STIGCHEL[3], J. THEEUWES[4], L. ITTI[5], D. P. MUNOZ[2]
[1]Cognitive Psychology, Vrije Univ. Amsterdam/Utrecht Univ., Amsterdam, Netherlands; [2]Queen's Univ., Kingston, ON, Canada; [3]Utrecht Univ., Utrecht, Netherlands; [4]Cognitive Psychology, Vrije Univ., Amsterdam, Netherlands; [5]Dept. of Computer Science,, USC, Los Angeles, CA

Abstract: In the laboratory, free viewing tasks are used as a proxy for real world viewing. Here, we examined the processes that influence when and where to look next by using a computational saliency model to interpret the complex visual input while monkeys freely viewed natural dynamic videos. Simultaneously, we recorded from neurons in the superficial and intermediate layers of the superior colliculus (SCs and SCi respectively), a midbrain area closely associated with gaze, attention and saliency coding. We examined three questions. First, is saliency at the saccade goal a predictor of fixation duration during free viewing? Second, is the neural correlate of saliency at the saccade goal correlated with fixation duration? Third, how is concurrent processing reflected in the SC during free viewing?
During free viewing there is no controlled 'target' onset, so it is not possible to calculate saccade reaction time (SRT) in the traditional sense as is done in controlled experiments. We used fixation duration as a proxy for the available time to process visual input similar to saccade latency. Neuronal activation in the SC as well as eye movements were recorded from three male Rhesus monkeys (Macaca mulatta) while viewing HD video clips. We analyzed only the saccades that were directed into the receptive field (RF) of a given neuron. Model saliency as well as the independent feature outputs were computed at the RF location.
We report four findings. 1) Short fixation durations were associated with higher pre-saccadic saliency in the RF (i.e., when saliency was high in the RF, then gaze was directed there earlier). 2) Saccades following short fixation durations were mostly driven by motion, flicker and edge information. 3) Short fixation durations were associated with higher pre-saccadic SC activity similar to pre-visual activation associated with express saccade production. 4) SCs neurons showed higher post-fixation activity when the current fixation was preceded by a short fixation than a long fixation. SCi neurons did not show this pattern of activation. This suggests a correlate of concurrent visual processing is encoded in the SCs but not in the SCi.
These results suggest a close correlation between fixation duration and saliency coding in the SC, and provide a useful proxy for SRT when investigating real world viewing behavior.
References
1 Itti & Koch. Nature reviews neuroscience 2001
2 Borji, A. & Itti. IEEE Trans. Pattern Anal. Mach. Intell. 2013
3 White et al. Nature Communications 2017
4 White, Kan, Levy, Itti & Munoz. Proc. Natl. Acad. Sci. U. S. A. 2017

Disclosures: J. Heeman: None. **B.J. White:** None. **S. Van Der Stigchel:** None. **J. Theeuwes:** None. **L. Itti:** None. **D.P. Munoz:** None.

Nanosymposium

270. Vision and Eye Movements

Location: SDCC 4

Time: Monday, November 5, 2018, 8:00 AM - 10:15 AM

Presentation Number: 270.05

Topic: D.08. Visual Sensory-motor Processing

Support: NIH R01 EY024831

Title: Functional organization of the presaccadic neural activity in the superior colliculus

Authors: *C. MASSOT, U. K. JAGADISAN, N. J. GANDHI
Eye and Ear Inst., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The superior colliculus (SC) is a central hub for saccade generation. During the epoch immediately preceding saccade onset, SC neurons exhibit varying degrees of ramping or buildup that eventually result in the saccade-generating burst. However, it is not known whether these neural signatures exhibit a systematic organization across depth in the SC. To address this gap in knowledge, we used laminar recordings to analyze the functional organization of the buildup and burst events that precede the saccade onset. We recorded spikes and local field potentials (LFPs) from a 16-channel laminar probe in the SC of two rhesus monkeys performing randomly interleaved delayed, visually-guided and memory-guided saccades. The electrode penetration was orthogonal to the surface of SC and saccade vectors were comparable across all recording contacts. Each session was depth-aligned using a reference channel obtained by Current Source Density (CSD) analysis. We developed an algorithm based on a combination of piecewise linear fits and bootstrapping to reliably detect the onset of buildup and burst events in the neural activity between the 'go' cue and the saccade onset. We found the following: 1. Neurons in the intermediate layers show the earliest onset of buildup activity. Onset times gradually and systematically increase for neurons at more dorsal and ventral sites, suggestive of a propagation of spiking activity in both dorsal and ventral directions within a column. 2. Burst events are present at all depths, suggesting that the putative motor command may be relayed downstream, regardless of the layers from which they originate. Notably, the firing rate at time of burst onset is highest in intermediate layer neurons and decreases gradually for dorsal and ventral channels, implying that the read-out of the motor command may be a function of the laminar position. Burst onset was near simultaneous across the dorsoventral extent of the SC, ~30 ms before saccade onset. 3. Neurons with both buildup and burst activity constitute the majority of units (51% and 56% of recorded units for visually and memory guided saccade tasks, respectively), followed by burst-only units (42% and 31%) and buildup-only units (7% and 13%). Interestingly, the latter are mostly found in the deeper contacts within the SC. In summary, during the pre-saccadic epoch, both buildup and burst activities show a systematic organization across depths, which reflects a principled organization of network processing in SC leading to the production of the motor command.

Disclosures: C. Massot: None. **U.K. Jagadisan:** None. **N.J. Gandhi:** None.

Nanosymposium

270. Vision and Eye Movements

Location: SDCC 4

Time: Monday, November 5, 2018, 8:00 AM - 10:15 AM

Presentation Number: 270.06

Topic: D.08. Visual Sensory-motor Processing

Support: SPEED, ANR SHS2-0006

Title: Modelling the dynamic interactions of spatiotemporal channels during human ocular following

Authors: *A. I. MESO[1], N. GEKAS[2], C. SIMONCINI[3], P. MAMASSIAN[2], G. S. MASSON[4]
[1]Fac. of Sci. and Technol., Bournemouth Univ., Poole, United Kingdom; [2]CNRS & Ecole normale supérieure, Paris, France; [3]CNRS & Aix-Marseille Univ., Marseille, France; [4]Inst. De Neurosciences De La Timone, Marseille, France

Abstract: The human visual system continuously estimates visual motion within viewed scenes using a hierarchical processing architecture which starts with early stage spatio-temporal channels of sensitivity. It is thought that inputs into such early primary visual cortex channels are integrated in subsequent extra striate cortical stages to obtain motion estimates for perceptual judgements or motor action. In this work, we probed this integration process by comparing the relative Ocular Following Responses (OFR) for a range of spatiotemporal stimuli in sessions in which the eye-movement reflexive visual response was measured over a 200ms period from onset. As stimuli, we used dynamic textures called Motion Clouds (MCs) with controlled spatial and temporal frequency mean and bandwidth parameters. In randomised blocks, the MCs were presented either as one of fifteen single components with a range of parameters or as one of nine linearly superimposed triplets of MCs called Compound Motion Clouds (CMCs). The MC parameters were configured to cover a two octave area of the space-time frequencies. The aim was to identify the integration model that best predicted the CMC responses based on the single component responses. The work extended our recent findings based on a similar premise using speed discrimination tasks in which different speed and scale axis interactions were measured (Gekas et al., 2017, Current Biology 27: 1514-1520). With OFR, the continuous probe of eye movements provided a richer output measure, showing a dynamic evolution of the response patterns from onset at about 90ms to a maximum around 150ms. Response averaging did not predict the CMC response under most conditions, with maximum likelihood and interaction models typically making better predictions. The fitted interaction patterns which could be mapped out from participants' data gradually became more elaborate, with stronger inhibition across parts of the channel space arising later in time for most participants. The specific interaction patterns also varied with speed and contrast. We present the range of patterns

empirically estimated and discuss how they elucidate the evolution of excitatory and inhibitory balances during hierarchical pooling of channels.

Disclosures: A.I. Meso: None. **N. Gekas:** None. **C. Simoncini:** None. **P. Mamassian:** None. **G.S. Masson:** None.

Nanosymposium

270. Vision and Eye Movements

Location: SDCC 4

Time: Monday, November 5, 2018, 8:00 AM - 10:15 AM

Presentation Number: 270.07

Topic: D.08. Visual Sensory-motor Processing

Support: ARL/DSO W911-NF-10-2-0022

Title: Natural stimulus evoked visual responses are more reliable when actively engaged with the stimulus

Authors: *J. KI, J. DMOCHOWSKI
Biomed. Engin., City Col. of New York, New York, NY

Abstract: We investigated whether visual processing of natural stimuli differs across passive and active modes. Specifically, we hypothesized that when engaged in a sensorimotor loop with a stimulus, evoked responses are more reliable. To test this, we recorded EEG from subjects (N=18) as they experienced a car race video game in 3 different conditions: active play, “active” viewing without remote control where subjects falsely believed that their EEG was controlling gameplay, and passive free viewing. For each condition, we measured neural reliability by correlating the EEG with time-varying features of the stimulus. We found a significant increase of the stimulus-response correlation for the two active conditions over the passive one. Moreover, the spatial distributions of EEG most correlated with the stimulus differed between active and passive conditions. Our findings suggest that visual responses are more reliable and recruit distinct circuits when actively engaged with a natural stimulus.

Disclosures: J. Ki: None. **J. Dmochowski:** None.

Nanosymposium

270. Vision and Eye Movements

Location: SDCC 4

Time: Monday, November 5, 2018, 8:00 AM - 10:15 AM

Presentation Number: 270.08

Topic: D.08. Visual Sensory-motor Processing

Support: NIH R01NS082046
NIH R01NS38572
CHOP IDF

Title: Eye tracking during virtual reality navigation in a rodent model of epilepsy

Authors: *H. TAKANO[1,2], A. G. BERNHARD[4], S. A. PARK[1], J. B. KAHN[3], D. A. COULTER[1,3]
[1]Pediatrics Div. of Neurol., Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Neurol., [3]Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [4]Biol., Haverford Col., Haverford, PA

Abstract: Cognitive deficit is a prominent feature of temporal lobe epilepsy (TLE). To assess spatial learning and memory function in a rodent model of TLE, we implemented in vivo two-photon calcium imaging of the hippocampal CA1 neurons in a mouse navigating a virtual reality (VR) environment. Our setup allowed us to monitor the activity of CA1 pyramidal cells, which encode spatial information. Our preliminary data suggest that, compared to control animals, animals that had experienced pilocarpine-induced status epilepticus (SE) had CA1 cells with a lower spatial tuning specificity ($p<0.01$, unpaired t-test, n=7 control, n=3 epileptic). The specificity and stability of place fields are modulated by attention. We therefore developed a method to assess levels of engagement in the VR navigation task, through eye tracking and pupillometry. The system consists of an IR camera and a real-time image processing hardware that can measure pupil diameter and pupil position at 200 Hz with only a few millisecond delays. The VR environment we designed was a 5m linear track with distinct four-segment wall patterns with a water reward at the end of the track. After licking the water reward, i.e., a licking task, the subjects would be teleported back to the beginning and would complete several laps. The data were recorded along with the VR track position during the navigation.
We found that pupil diameter gradually increases toward the end of the track in control mice, suggesting recognition and/or expectation of the goal and reward. This finding was supported by the decrease in mice's running speed towards the end of the track. In contrast, the increase in pupil diameter and the change in running speed toward the end of the track were absent in epileptic mice ($p<0.01$, two-way ANOVA, n=10 control, n=3 epileptic). Although the epileptic mice completed the licking task at the goal, thus was teleported back to the beginning and completed several laps, there was no increase in pupil diameter upon receiving the rewards. While the epileptic mice still maintained the ability to change pupil size in response to ambient light, the overall pupil diameter was smaller than the control mice. We found fewer saccades during navigation in epileptic mice. We also found gradual shifts in horizontal pupil position in control, but not epileptic mice. In conclusion, the eye tracking and pupillometry during VR navigation is a potential tool to assess spatial recognition and learning. We discuss the application of this technology to models of other neurological disorders including 22q11.2 DS.

Disclosures: H. Takano: None. **A.G. Bernhard:** None. **S.A. Park:** None. **J.B. Kahn:** None. **D.A. Coulter:** None.

Nanosymposium

270. Vision and Eye Movements

Location: SDCC 4

Time: Monday, November 5, 2018, 8:00 AM - 10:15 AM

Presentation Number: 270.09

Topic: D.08. Visual Sensory-motor Processing

Support: BIAL Foundation Grant 184/14

Title: Hand-selective areas of both dorsal and ventral visual streams represent how to appropriately grasp 3D tools

Authors: *E. KNIGHTS[1], F. W. SMITH[1], C. MANSFIELD[1], D. TONIN[1], H. WEAVER[1], J. GREEN[2], J. SAADA[2], S. ROSSIT[1]
[1]Sch. of Psychology, Univ. Of East Anglia, Norwich, United Kingdom; [2]Dept. of Radiology, Norfolk and Norwich Univ. Hosp. NHS Fndn. Trust, Norwich, United Kingdom

Abstract: Tools are manipulable objects that, unlike other objects in the world (e.g., buildings), are tightly linked to highly predictable action procedures. Neuroimaging has revealed a left-lateralized network of dorsal and ventral visual stream regions for tool-use and tool-knowledge tasks, but the exact role of these regions remains unclear. Moreover, studies involving actual hand actions with real tools are rare as most research to date used proxies for tool-use including presenting visual stimuli (e.g., pictures) or action simulation (e.g., pantomime). Here we investigated with real 3D tools, whether the human brain represents actual object-specific functional grasps, using functional magnetic resonance imaging (fMRI) with multi-voxel pattern analysis (MVPA). Specifically, we tested if patterns of brain activity would differ depending on whether the grasp was consistent or inconsistent with how tools are typically grasped for use (e.g., grasp knife by handle rather than by its serrated edge). In a block-design fMRI paradigm, 19 participants grasped the left or right sides of 3D-printed tools (kitchen utensils) and non-tool objects (bar-shaped objects) with the right-hand. Importantly, and unknown to participants, by varying movement direction (right/left) the tool grasps were performed in either a typical (by the handle) or atypical (by the business end) manner. In addition, for each participant separate perceptual localizer runs were obtained to functionally define regions of interest (ROI). ROI MVPA showed that typical vs. atypical grasping could be decoded significantly higher for tools than non-tools in hand-selective (but not tool-, body- or object-selective) regions of the left lateral occipital temporal cortex (LOTC) and intraparietal sulcus (IPS). Whole-brain searchlight MVPA also identified representations of typicality for tool grasping in bilateral inferior parietal lobule and inferior temporal gyrus, right middle occipital and inferior frontal gyri and left anterior temporal lobe (ATL). Together these findings indicate that representations of how to appropriately grasp tools are automatically evoked (even when irrelevant to task performance)

throughout specific regions within the tool network, left ATL and left hand-selective regions of LOTC and IPS.

Disclosures: E. Knights: None. **F.W. Smith:** None. **C. Mansfield:** None. **D. Tonin:** None. **H. Weaver:** None. **J. Green:** None. **J. Saada:** None. **S. Rossit:** None.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.01

Topic: E.05. Brain-Machine Interface

Title: Advancing hand-grasp neuroprosthetics for spinal cord injury patients: The next step toward clinic-to-home translation

Authors: *G. SHARMA[1], S. COLACHIS, IV[1], M. A. BOCKBRADER[2], D. FRIEDENBERG[1], N. ANNETTA[1], M. ZHANG[1], N. SKOMROCK[1], M. SCHWEMMER[1], J. MYSIW[2], H. BRESLER[1]
[1]Battelle Mem. Inst., Columbus, OH; [2]Physical Med. & Rehabil., Ohio State Univ. Col. of Med., Columbus, OH

Abstract: Individuals with tetraplegia identify restoration of hand function as a critical, unmet need to regain their independence and improve quality of life. Advances in Brain Computer Interface (BCI)-controlled Functional Electrical Stimulation (FES) devices provide a promising approach for meeting this need by bypassing the spinal cord injury (SCI) and directly linking neural activity to a paralyzed limb. However, many of the current BCI-FES systems are far from becoming integrated into the daily lives of individuals with SCIs, in part, due to their inability to provide the user with a sufficient number of functional hand movements. In this study, we demonstrate a critical step in the clinic-to-home translation of BCI-FES neuroprosthetics by demonstrating seven functional, skilled hand functions that can generate adequate force to manipulate everyday objects with high-precision and naturalistic speed.
The investigational system has been demonstrated during an FDA and IRB-approved study. The study participant is a 27-year-old male with C5 quadriplegia from a cervical SCI. Multiunit activity was recorded from an implanted intracortical microelectrode array (Utah Array, Blackrock Microsystems) in the motor cortex, and machine-learning algorithms were used to decode the intent. The decoded signals were used to control activation of the participant's forearm muscles through a high-definition FES system. The participant's functional improvements were evaluated using the standardized Grasp and Release Test (GRT).
The participant was able to perform seven distinct functional hand movements with the system, allowing him to manipulate most GRT objects more efficiently than without BCI-FES. A single Support Vector Machine (SVM)-based decoder was able to reliably decode the seven attempted

movements with individual decoding accuracies of >96% for each movement. The system enabled the participant to select the desired hand movement, out of the seven possible trained movements, and to manipulate objects of different sizes, shapes, and weights with skilled, forceful grasps.
In summary, our BCI-FES hand-grasp neuroprosthetic significantly improves upon the state-of-the-art for assistive devices for restoring multiple, voluntary hand functions in tetraplegia. Our results establish a further step towards translating BCI-FES technologies from research devices to clinical neuroprosthetics, returning hand function to people with paralysis. Our current work includes miniaturizing the hardware to allow portability of the system and integrating deep learning algorithms to minimize training and reaction time.

Disclosures: S. Colachis: A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **M.A. Bockbrader:** None. **D. Friedenberg:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **N. Annetta:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **M. Zhang:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **N. Skomrock:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **M. Schwemmer:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **J. Mysiw:** None. **H. Bresler:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.02

Topic: E.05. Brain-Machine Interface

Support: This work was sponsored by the Defense Advanced Research Projects Agency (DARPA) Biological Technologies Office (BTO) HAPTIX program through the Space and Naval Warfare Systems Center, Pacific Contract No. N66001-15-C-4016

Title: 15-DOF motor decoding based on a high performance PNS interface and deep neural network

Authors: Z. YANG[1], J. XU[1], A. NGUYEN[1], M. JIANG[2], T. WU[1], W.-K. TAM[1], W. ZHAO[1], C. K. OVERSTREET[3], D. LUU[1], C. ZHAO[2], J. J. CHENG[4], *E. W. KEEFER, III[3]
[1]Biomed. Engin., [2]Computer Sci. and Engin., Univ. of Minnesota, Minneapolis, MN; [3]Nerves Inc., Dallas, TX; [4]Plastic Surgery, UT Southwestern Med. Ctr., Dallas, TX

Abstract: As part of the DARPA HAPTIX program, we are developing a prosthetic control/sensory restoration system for upper-limb amputees. Our goal is to provide dexterous control of individual prosthetic fingers using data obtained directly from peripheral nerves. There

are several prosthetic hands on the market with independently actuated digits (Touch Bionics, RL Steeper, Otto Bock), however state-of-art control schemes permit only sequential, not simultaneous control of grasp patterns, and none of the hands have integrated sensors for touch or digit movement. These commercially available robotic hands are controlled by electrical signals recorded through surface electrodes from muscles above the amputation. The most common control scheme uses signals from two muscles to control a specific function - for example, hand opening and closing. Other functions can be controlled by the same signals after switching between grasp patterns, usually through co-contraction of the two muscle sites. These schemes are limited in functionality, unnatural, and unintuitive. For this reason, amputees often do not experience sufficient improvement in their daily activities to make an active prosthesis useful, which consequently results in a large abandonment rate. To overcome these limitations in prosthetic control, we use a novel peripheral nervous system (PNS) interface that selectively removes the large and complex noise artifacts endemic to performing electrophysiology in the PNS while amplifying the small amplitude, high frequency neural signals. Using this hardware solution, combined with an equally novel deep learning based neural decoding strategy where a deep recurrent adversarial autoencoder is first initialized by unlabeled neural data and its knowledge is transferred to a mirrored, 33-layer neural network that is then fine-tuned by labelled data, we can decode 15 degrees-of-freedom from the nerves of amputees performing mirrored task based imagined movements. Having shown the ability to obtain high-content neural data directly from the residual peripheral nerves, and to decode that data into many degrees-of-freedom, we are now implementing real-time control of virtual reality hands and constructing a physical interface to the amputees own prosthetic hands, allowing them to fully utilize the capabilities of their very expensive prosthetics in a natural, intuitive manner.

Disclosures: Z. Yang: None. **J. Xu:** None. **A. Nguyen:** None. **M. Jiang:** None. **T. Wu:** None. **W. Tam:** None. **W. Zhao:** None. **C.K. Overstreet:** None. **D. Luu:** None. **C. Zhao:** None. **J.J. Cheng:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nerves Incorporated. **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.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.03

Topic: E.05. Brain-Machine Interface

Support: DARPA HAPTIX N66001-15C-4017
NSF 1533649

NSF 0903715

Title: Improved long-term performance of utah slanted arrays in clinical studies

Authors: *L. RIETH[1], B. BAKER[2], M. G. STREET[2], R. B. CALDWELL[5], D. CROSLAND[3], D. T. KLUGER[3], J. A. GEORGE[3], A. HARDING[3], R. SHARMA[4]
[1]Ctr. for Bioelectronic Med., Feinstein Inst. for Med. Res., Manhasset, NY; [2]Electrical and Computer Engin., [3]Bioengineering, [4]Electrical and Computer Engin. Dept., Univ. of Utah, Salt Lake City, UT; [5]Halyard Hlth., Alpharetta, GA

Abstract: Utah electrode arrays (UEAs) are currently being used to record and stimulate neurons of human subjects in both the cortex and peripheral nerves, primarily for sensorimotor neural prostheses. For the Utah HAPTIX program, a 1-year take-home trial of a sensorimotor prosthesis will occur in the following year. We report improvements to the IrOx tip metallization and development of a helical lead that are working to increase the functional lifetime of the USEAs for peripheral nerve applications for these studies. Bench studies to test the helical lead developed as part of this program found the leakage currents during 10 day saline soak tests to be stable and much less than the 1 μA criteria. Early testing has found minimal wire breakage during a 470,000 cycle 180° bend test paradigm. Stimulation stability testing and mechanical testing of the electrodes was performed as part of technology translation efforts, and found that the IrOx continues to be stable for billions of stimulation cycles at up to 2,100 μA. Seven USEAs have been used with 3 human subjects, and were in-dwelling for up to 14 months. Arrays had two generations of improvements for leads, and improvements in the metallization. Performance was evaluated by mapping the stimulation thresholds for electrodes. Impedance, SEM, and a 1-way ANOVA were used to evaluate the electrodes and determine if stimulation up to 15.8 mC of injected charge accelerated their failure. Use of helical leads with the USEAs dramatically decreased in the incidence of infection at the percutaneous site, and occurrence of broken wires during the in-dwelling period, as determined by routine medical assessment, and analysis of the threshold and impedance data, respectively. Additional lead improvements implemented for the 3rdHAPTIX subject resulted in a further improvement in the lead lifetime. SEM characterization of electrodes implanted for 14 months found populations of 42, 56, 53, and 39 electrodes with degradation scores of 1 (little), 2 (modest), 3 (significant), and 4 (severe). These results indicate that degradation of the metallization continues to be an important failure mechanism. A 1-way ANOVA with 4 conditions from 2 arrays ($p=0.73$ and 0.44) found that metallization damage did not correlate with amount of stimulation, indicating stimulation did not contribute strongly to electrode degradation for these stimulation doses. Tip metal failure mechanisms continue to be consistent with dissolution of the silicon shank under the tip metal, resulting in mechanical damage to the metal. No systemic damage to the Parylene encapsulation was observed.

Disclosures: L. Rieth: None. **B. Baker:** None. **M.G. Street:** None. **R.B. Caldwell:** A. Employment/Salary (full or part-time):; Halyard Health. **D. Crosland:** None. **D.T. Kluger:** None. **J.A. George:** None. **A. Harding:** None. **R. Sharma:** A. Employment/Salary (full or part-time):; Applied Biosensors.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.04

Topic: E.05. Brain-Machine Interface

Support: NSF Grant No. 1533649
DARPA HAPTIX Contract No. N66001-15-C-4017.

Title: Long-term performance of emg movement decoders trained using dataset aggregation

Authors: *H. CUNHA DANTAS[1], V. MATHEWS[2], S. WENDELKEN[3], G. CLARK[3], D. WARREN[3], T. DAVIS[3]
[2]EECS, [1]Oregon State Univ., Corvallis, OR; [3]Univ. of Utah, Salt Lake City, UT

Abstract: Motor intent decoders extract movement intent from signals such as electromyograms (EMG). Many motor intent decoders have been presented, although their ability to perform well over long periods of time without retraining have not been evaluated in most cases. This work explores the long-term performance of a Kalman Filter (KF), a multilayer perceptron (MLP), and a convolutional neural networks (CNN) decoder; the latter two were trained using the data set aggregation algorithm. The results presented are from two amputee subjects, HS1 and HS2. They were implanted with 32 intramuscular EMG electrodes. The subjects were instructed to mimic a virtual hand using their phantom limb. In each session included in the analysis, the subject performed 10 trials for flexion and extension for each digit. Data from 80 sessions were analyzed offline, containing data over 4 and 11 months for HS1 and HS2 respectively. We compared the performance of the three decoders over multiple time spans between the training and testing data. Figure 1 summarizes the results from 0 to 150 days apart between training and testing. The three decoding methods differed via Repeated Measure ANOVA ($p<0.001$) and the performance in time also differed ($p<0.001$). The system with the best performance was the CNN decoder and the followed by the MLP decoder. Further, the performance of every pair of method statistically differed via Tukey's HSD test ($p<0.001$). We also examined the changes in time via a two-piece linear fit (days 0 to 30 and days 30 to 150). Only the slopes of the first piece of the linear fitting for MLP and CNN were statistically different from the zero-mean slope ($p<0.001$). The slopes for MLP and CNN were 0.0026/day and 0.0025/day, respectively. The statistical tests demonstrated that MLP and CNN decoders outperformed the KF decoders and the CNN decoder outperformed the MLP decoder. Further, it is possible to conclude that the MLP and CNN performance degraded in the first 30 days, but the degradation rate decreased to zero after 30 days. The KF performance degradation rate was no different from zero before or after 30 days.

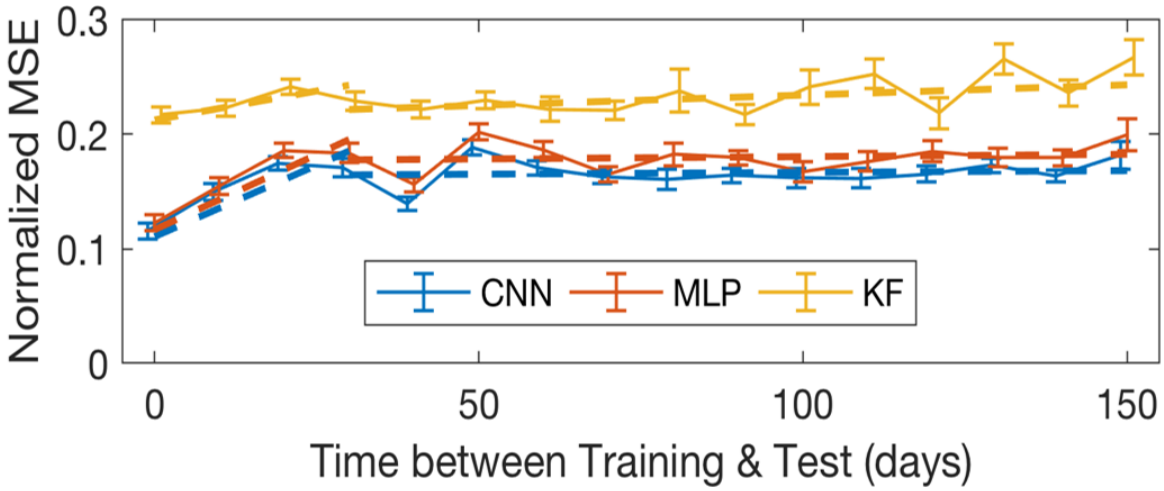


Figure 1: Decoder performance across 150 days separating training and testing sessions. The error bars represent the standard error of the mean (SEM). The dashed lines represent the 2-piece fit for each decoder.

Disclosures: H. Cunha Dantas: A. Employment/Salary (full or part-time):; Oregon State University. **V. Mathews:** A. Employment/Salary (full or part-time):; Oregon State University. **S. Wendelken:** A. Employment/Salary (full or part-time):; University of Utah. **G. Clark:** A. Employment/Salary (full or part-time):; University of Utah. **D. Warren:** A. Employment/Salary (full or part-time):; University of Utah. **T. Davis:** A. Employment/Salary (full or part-time):; University of Utah.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.05

Topic: E.05. Brain-Machine Interface

Support: NIH, 5R01EY01554512
T&C Chen Brain-machine Interface Center at Caltech
Boswell Foundation
Swartz Foundation

Title: Predicting learning performance in a brain-machine interface study with a tetraplegic human

Authors: *S. SAKELLARIDI[1], V. N. CHRISTOPOULOS[1], T. AFLALO[1], K. W. PEJSA[1], E. ROSARIO[2], D. S. OUELLETTE[2], N. POURATIAN[3], R. A. ANDERSEN[1]
[1]Div. of Biol. and Biol. Engin. MC 216-76, Caltech, Pasadena, CA; [2]Res. Inst., Casa Colina Hosp. and Centers for Healthcare, Pomona, CA; [3]Neurosurg., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Recent advances in brain-machine interfaces (BMIs) provide us with the ability to generate precise maps between neural activity and behavioral outputs. By perturbing the BMI mapping, recent studies in non-human primates have explored the neural basis of learning (Sadtler et al. 2014). A BMI mapping is computed by projecting the high dimensional neuronal signals into a lower-dimensional space (intrinsic manifold), which captures the comodulation patterns among the neural units. Then, the mapping from neural activity to kinematics is perturbed either *within* or *outside* the intrinsic manifold, by preserving or altering the relationships among the neural units but altering or preserving the way in which these relationships affected cursor kinematics, respectively. So far, the perturbations were selected in an ad-hoc manner, such that the animals will not be discouraged from performing the task, and not based on how far the perturbation lies from the original mapping. Studying learning mechanisms in humans would represent a significant step forward, as only humans can be instructed, provide verbal reports of how they solve a task, and can be encouraged to continue trying even if the task is difficult or impossible to be solved. In the current study, we explored the mechanisms of learning in a tetraplegic participant who is implanted with a 96 channel microelectrode array in the anterior intraparietal area (AIP). We examined how AIP learns to compensate for errors by perturbing the BMI mapping within the intrinsic manifold, in a 2D cursor center-out control task. We introduced a new measure to formally characterize the degree of difficulty of a perturbation. It is computed as the relative distance between the areas determined by the predicted original and the perturbed open loop velocity vectors at the origin of the center-out movement. It is capable of capturing both the distribution and scaling of the BMI trajectories across space. We showed that this measure is correlated with the participant's performance. Over the course of a session, the participant could regain proficient control of the cursor for short distance perturbations by re-aiming to different directions; however, for long distance perturbations, the performance remained impaired suggesting that learning did not occur. These results suggest that not all within the intrinsic manifold perturbations are 'learnable', at least during the length of a session. The proposed measure reflects the degree of difficulty of a perturbation and predicts the performance of a participant in the time-scale of a session. We are currently testing the capability of this measure for outside the manifold perturbations.

Disclosures: S. Sakellaridi: None. **V.N. Christopoulos:** None. **T. Aflalo:** None. **K.W. Pejsa:** None. **E. Rosario:** None. **D.S. Ouellette:** None. **N. Pouratian:** None. **R.A. Andersen:** None.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.06

Topic: E.05. Brain-Machine Interface

Support: German Research Foundation (DFG) Cluster of Excellence EXC-1086 "Brain-Links BrainTools"
German Ministry of Education and Research (BMBF) 01GQ1510 OptiStim
German Ministry of Education and Research (BMBF) 13GW0053D MotorBic

Title: Neurophysiological recording and stimulation using an off-the-shelf component wireless brain implant

Authors: *C. A. GKOGKIDIS[1], C. BENTLER[2], X. WANG[1], C. SCHEIWE[3], H. CRISTINA SCHMITZ[4], T. STIEGLITZ[2], T. BALL[1]
[1]Translational Neurotechnology Lab, Dept. of Neurosurgery, Med. Ctr., [2]Lab. for Biomed. Microtechnology, Dept. of Microsystems Engin. (IMTEK), [3]Dept. of Neurosurgery, Med. Ctr., [4]CEMT, Med. Ctr., Univ. of Freiburg, Freiburg, Germany

Abstract: Brain implants are increasingly used in neuroscientific research and medical applications. The requirements for such implants are diverse due to different experimental paradigms, scientific problem to address and demands by the researcher or clinician. To overcome these requirements, brain implants that can be built in a customized fashion might be beneficial. We previously introduced such a research grade wireless brain implant, developed exclusively using off-the-shelf components, which allows for quick and customized assembly. To verify the operability of the device during recording and stimulation, we present neurophysiological data obtained in an ovine animal model. During general anesthesia, the 63-channel μECoG electrode array was placed on the cortex of the sheep brain and both auditory and electrical stimuli were used to evoke neurophysiological responses which were recorded at a sampling rate of 4 kHz. Experiments performed in this study were conducted according to EU Directive 2010/63/EU and approved by the Animal Committee of the University of Freiburg and the Regierungspraesidium Freiburg, Germany.
We show that our off-the-shelf research grade brain implant is capable to reliably record neurophysiological brain activity and electrically stimulate, evoking cortico-cortical responses, under *in vivo* conditions. The obtained neurophysiological activity showed clear responses with distinct spatio-temporal patterns to both auditory stimuli and cortical electrical stimulation, the latter with response patterns systematically depending on the exact stimulation site. In addition, spectral analysis revealed a neurophysiological frequency profile of the recorded activity which is in agreement with the well-known frequency power-law, i.e., the frequency-dependent linear

decrease of log-log absolute spectral power.
The presented neurophysiological data are in agreement with previously published recording and stimulation results obtained in sheep using different implantable devices that were not off-the-shelf. The results and their neurobiological implications as presented here highlight that off-the-shelf component brain interfacing devices are feasible and thus open up new avenues for implant-based research, especially when flexible requirements have to be addressed, as it is often the case in basic neuroscientific research. In the future we want to expand our approach to higher channel counts (128-channel high-resolution µECoG electrode arrays), higher recording sampling rate, and functional systems beyond the auditory system, as further use cases of our implant concept in neurotechnological research.

Disclosures: C.A. Gkogkidis: None. **C. Bentler:** None. **X. Wang:** None. **C. Scheiwe:** None. **H. Cristina Schmitz:** None. **T. Stieglitz:** None. **T. Ball:** None.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.07

Topic: E.05. Brain-Machine Interface

Title: Massive-scale dense customizable penetrating silicon electrode array for 3D neural recording and stimulation

Authors: *A. SANDOUGHSAZ[1], V. HETRICK[2], B. ROSTAMI[1], O. J. AHMED[3], K. NAJAFI[1]
[1]Electrical Engin. and Computer Sci. Dept., [2]Dept. of Psychology, [3]Dept. of Psychology, Dept. of Biomed. Engineering, Neurosci. Grad. Program,, Univ. of Michigan, Ann Arbor, MI

Abstract: Accurate mapping and deciphering of neural circuits requires simultaneous high spatiotemporal resolution recordings and stimulation of neurons in multiple layers and areas of the brain. Conventional penetrating multielectrode arrays (MEAs) are limited to a few thousand electrodes at best, with limited volumetric 3D spatial resolution. This is mainly due to the types of fabrication technologies and available designs and materials for making such probes. Many neural applications require a 3D dense array with many electrodes placed in any arbitrary fashion with any arbitrary shape. One such application is comprehensively mapping the rams-horn-shaped 3-dimensional structure of the hippocampus, with important functional differences existing across each dimension. We have developed a new silicon-based microfabrication technology to produce a new generation of large-scale ultra-high-density, large-count, 3D arrays of sharp, long, and narrow microelectrodes with user-defined electrode length, width, density, shape and distribution. To address the shortcomings of current probes, a novel fabrication process based on standard semiconductor additive and subtractive manufacturing technologies in silicon substrates, is developed. Electrode recording sites are defined using a maskless self-

aligned process. Using this technology, we have obtained millimeter-long (1.2mm), narrow (10 to 20µm diameter), sharp (submicron tip size), high-density (400 electrodes/mm^2) high-count (5000+) electrode arrays. There are several aspects of this fabrication technology that are critical for successful neurophysiological studies across three dimensions with high dexterity. First, the length of side-by-side electrodes can be varied from tens of micrometers to several millimeters independently. Second, electrodes spacing can be locally modified to obtain customizable density in the array. Third, electrode widths can be controlled to obtain extremely fine and slender needles, crucial for minimizing tissue damage and improving chronic stability of implanted probes. Any desired distribution of electrodes with customizable length, diameter and pitch across the array can be obtained. These features will enable realization of true 3D access to neurons with high spatiotemporal resolution. Electrode robustness and recording functionality have been demonstrated by *in vivo* LFP recordings in rats under anesthesia. This represents a novel, state-of-the-art, recording technology for understanding how large-scale neural networks control behavior and pathology.

Disclosures: A. Sandoughsaz: None. **V. Hetrick:** None. **B. Rostami:** None. **O.J. Ahmed:** None. **K. Najafi:** None.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.08

Topic: E.05. Brain-Machine Interface

Support: DARPA HAPTIX program, # N66001-15-C-4016

Title: Selective multichannel electrical stimulation of peripheral nerve for sensory prostheses

Authors: *C. K. OVERSTREET[1], J. CHENG[2], E. KEEFER[1]
[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 bidirectional peripheral nerve interface for upper extremity prosthetic devices. Our electrodes are surgically targeted to individual fascicles within the forearm, enabling recording and selective electrical stimulation of the surrounding neural tissue. We have completed several ninety-day implant periods in the forearms of humans with trans-radial or partial hand amputations.
The major focus of our sensory stimulation work has been to develop methods of providing functionally-relevant feedback of interactions between the prosthesis and the external environment. This is a multi-faceted challenge, requiring innovations in stimulation technique, sensorization of prosthetic devices, and understanding of the psychophysics of artificial sensation.

Effective multichannel stimulation will be critical for sensory-capable prosthetic hands with multiple degrees of freedom. The sensations induced by interleaved multichannel stimulation can differ wildly from the sum of the sensations evoked by discrete stimulation on a single electrode; however, little attention has yet been devoted to understanding the sensory effects of multichannel stimulation. We have characterized the changes in evoked sensation due to systematic modification of components of the multichannel stimulation train: the number and distribution of active electrodes, the pattern of stimulation delivered on each electrode, the relative stimulation strength for each channel, and the time separation between stimulation pulses on different electrodes. This information allows us to reliably encode independent contact events for multiple locations on the hand, represent movement, or generate sensations referred to new regions of the hand. These complex sensations provided by multichannel stimulation are intuitive and robust.
Well-designed multichannel electrical stimulation of peripheral nerve can provide a wealth of functionally-relevant sensory information to upper extremity prosthesis users. We have observed improvements in prosthesis embodiment and modifications in grasping strategy in response to sensory stimulation during prosthesis use. We believe that these benefits will be extended by combining this multichannel sensory feedback with intuitive motor control, creating a truly dexterous upper extremity prosthesis.

Disclosures: C.K. Overstreet: None. **J. Cheng:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nerves Incorporated. **E. Keefer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nerves Incorporated.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.09

Topic: E.05. Brain-Machine Interface

Support: NIH NINDS 1R01NS094396

Title: Calcium activation of frequency dependent, phasic, localized, and dense population of cortical neurons by continuous electrical stimulation

Authors: *T. D. KOZAI[1], N. J. MICHELSON[2], R. ISLAM[2], A. VAZQUEZ[3], K. LUDWIG[4]
[1]Bioengineering, [2]Biomed. Engin., [3]Radiology, Univ. of Pittsburgh, Pittsburgh, PA; [4]Neurologic Surgery, Mayo Clin., Rochester, MN

Abstract: Understanding the nervous system requires the ability to readout detailed measurements from controlled inputs. Electrical stimulation remains one of the oldest and most widely used methods for directly interfacing and driving the nervous system. Despite the growing prevalence of neuromodulation therapies and wide use of electrical stimulation as a neuroscience tool, there is only limited understanding of how electric fields generated by a chronically implanted electrode interacts with nearby neuronal and non-neuronal cells. Studies of the interaction between exogenous electric fields and nervous tissue have primarily utilized peripheral nerves, where epineural or intrafascicular electrodes are placed on or into peripheral nerves where the fibers are parallel aligned. In this setting there is limited connectivity between those fibers and the orientation of the electrodes and axon fibers is predictable. In contrast, it is much more difficult to disentangle the complex network of dendrites, axons, and cell bodies of inhibitory and excitatory cells that may be present near the electrode in the brain. A better understanding of the interaction is needed between exogenous electric fields and neuronal and non-neuronal cells local to implanted electrodes. Without this fundamental scientific knowledge, it is difficult to interpret the results of electrical stimulation when used as a tool to probe the circuitry for downstream circuit consequences or understand the mechanism by which targeted electrical stimulation may be creating desired therapeutic outcomes or undesirable side effects. Experiments by Histed et al (Neuron 2009) demonstrated that electrical stimulation activates a much smaller volume of neural processes around the electrode tip, which in turn leads to antidromic neural activation. This led to the conclusion that “it is impossible to activate a set of cells restricted to a small spatial volume”. However, our preliminary in vivo 2photon GCaMP6 results demonstrate that different neural elements (axons, dendrites, somas) in the vicinity of the electrode differ in their responses as a function of time (stimulation onset, during stimulation, after stimulation) and frequency. These data suggest a complex and neural element-specific dose response curve at the point of electrical interface. These experiments are unveiling the local impact of electrical stimulation on nervous tissue and this information can be used to extrapolate the downstream consequences of local activation as well as understanding therapeutic neuromodulation mechanisms of action.
The authors would like to thank James R. Eles for surgical assistance.

Disclosures: T.D. Kozai: None. **N.J. Michelson:** None. **R. Islam:** None. **A. Vazquez:** None. **K. Ludwig:** None.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.10

Topic: E.05. Brain-Machine Interface

Title: Perceptual consequences of changing the frequency of intracortical microstimulation applied to somatosensory cortex

Authors: *T. CALLIER[1], K. KUMARAVELU[3], L. E. MILLER[4], W. M. GRILL[3], S. J. BENSMAIA[2]
[2]Dept. of Organismal Biol. and Anat., [1]Univ. of Chicago, Chicago, IL; [3]Duke Univ., Durham, NC; [4]Physiol., Northwestern Univ., Chicago, IL

Abstract: The use of intracortical microstimulation (ICMS) to convey sensory feedback shows great promise to improve the dexterity and embodiment of upper-limb neuroprostheses for indviduals with spinal cord injury. Two main parameters of stimulation that can be manipulated to sculpt the evoked percept are intensity (charge per pulse) and frequency. We previously characterized the effect of changes in ICMS intensity on discriminability of pulse trains. Here, we seek to understand the degree to which systematic manipulation of frequency can be used to evoke discriminable percepts. Having previously shown that the detectability of ICMS pulse trains depends on frequency, we assumed that supra-threshold changes in ICMS will affect the perceived magnitude of the stimulus. We sought to investigate whether changes in frequency also produce changes in the quality of the evoked percept. To this end, we trained rhesus macaques to discriminate the frequency of ICMS pulse trains delivered to the hand representation in somatosensory cortex through chronically implanted electrode arrays. Frequencies ranged from 50 to 400Hz, and amplitude varied randomly from stimulus to stimulus so that the animals could not rely on intensity cues in making frequency discrimination judgments. The monkeys could distinguish frequency but amplitude had a strong biasing effect on their judgments, and the strength of this bias varied widely across electrodes. To understand the neural correlates of changing ICMS frequency, we simulated, using a detailed neuronal model of a cortical column, the population responses to the stimuli used in the psychophysical experiments and investigated which aspects of the neuronal response might underlie the animals' perceptual judgments. We developed a model that accounts for the ability of monkeys to discriminate ICMS frequency while capturing the biasing effects of intensity.

Disclosures: T. Callier: None. **K. Kumaravelu:** None. **L.E. Miller:** None. **W.M. Grill:** None. **S.J. Bensmaia:** None.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.11

Topic: E.07. Rhythmic Motor Pattern Generation

Support: KU Leuven Research Funding: STG/14/024 and EGM-D2929-C24/17/091
EIT Health Innovation by Ideas, NEURO-WEAR Project

Boateng Asamoah is SB PhD fellow at FWO

Title: tACS effects on the motor system are caused by transcutaneous and not transcranial stimulation

Authors: *M. MC LAUGHLIN, B. ASAMOAH, A. KHATOUN
Neurosci., KU Leuven, Leuven, Belgium

Abstract: *Rationale:* Transcranial alternating current stimulation (tACS) is a noninvasive neuromodulation technique in which electrodes are placed on the scalp and used to deliver sinewave electrical stimulation. The electric field passes through the scalp, skull and CSF before a weak current reaches the brain. tACS has been shown to alter perception, cognition, memory and motor function. It is widely assumed that the weak field in the cortex directly modulates the membrane potential causing neural entrainment which then drives behavioral effects. However, this is controversial, since recent evidence shows that the field in the cortex is too weak to entrain neurons. *Hypothesis:* We hypothesized that reported tACS effects are caused by transcutaneous stimulation of peripheral nerves in the scalp. *Methods:* To test this, we measured the effect of tACS on physiological tremor in healthy volunteers under two experimental conditions and on pathological tremor in essential tremor patients in third experiment. Tremor was measured using an accelerometer. tACS, matched to the tremor frequency, was applied at three peak-amplitudes: 0 mA, 0.5 mA and 2.5 mA. The phase locking value between the tremor and tACS was calculated to quantify entrainment. In Experiment 1 (n=12) tACS was applied using a 4x1 focused montage positioned on the scalp over the motor cortex. The transcutaneous mechanism was blocked by applying topical anesthetic to the scalp. A blinded, randomized, cross-over design was used to test the effects of blocking the transcutaneous mechanism. In Experiment 2 (n=12) we used a non-cephalic placement of the tACS electrodes to effectively block the transcranial mechanism: i.e. electrodes were moved to the arm contralateral to tremor measurement. Stimulation amplitude and frequency was the same as in Experiment 1. In Experiment 3 (n=10) focused tACS was applied on the scalp over the motor cortex in essential tremor patients. In 6 patients topical scalp anesthetic was applied, while in 4 patients no anesthesia was applied. *Results:* In Experiment 1, we found that anesthetizing the scalp caused a significant reduction in physiological tremor entrainment. In Experiment 2, we found that placing the tACS electrode on the contralateral arm still caused significant physiological tremor entrainment. In Experiment 3, the group with anesthesia should less pathological tremor entrainment than the group without anesthesia. *Conclusion:* Our results show that the transcutaneous, and not the transcranial, mechanism cause tACS motor system effects.

Disclosures: M. Mc Laughlin: None. **B. Asamoah:** None. **A. Khatoun:** None.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.12

Topic: E.05. Brain-Machine Interface

Support: NIH BRAIN Grant U01NS099724

Title: Gas vesicles as hemodynamic enhancers for noninvasive functional ultrasound imaging of the mouse brain

Authors: *D. MARESCA[1], T. PAYEN[2], A. LEE-GOSSELIN[1], B. LING[1], D. MALOUNDA[1], C. DEMENÉ[2], T. DEFFIEUX[2], M. TANTER[2], M. SHAPIRO[1]
[1]Caltech, Pasadena, CA; [2]Inserm, Paris, France

Abstract: Functional ultrasound imaging (fUS) is a recent technology that provides a unique combination of spatial coverage (several cm), spatiotemporal resolution (< 100 µm and 10 ms) and compatibility with freely moving animals. However, deep and transcranial monitoring of brain activity over long time spans remains a challenge. Recently, genetically encodable ultrasound contrast agents known as gas vesicles, or GVS, were introduced as ultrasound analogs to green fluorescent proteins [Bourdeau, Nature 2018]. These air-filled proteins can be purified to be used as nanoscale injectables in the blood stream. The analysis of their physical properties revealed that single GVs scatter ultrasound 3 times more strongly than a red blood cells despite being 4000 times smaller. GVs are monodisperse, nanoscale, and inherently stable structures in equilibrium with the surrounding media. Here, we assessed the performance of GVs as smooth hemodynamic enhancers for noninvasive fUS imaging of the brain in mice.
Purified GVs were imaged using a programmable ultrasound system connected to a 15 MHz, 128-element linear array probe. *In vitro* characterization was performed in a flow phantom with flow speeds ranging from 5 mm/s to 50 µm/s comparing GVs to a blood-mimicking fluid. Transcranial fUS was performed in head fixed, anesthetized mice a frame rate of 750Hz over 5 minutes long trials. We recorded visually-evoked activations of deep subcortical structures called the lateral geniculate nuclei using a light stimulation protocol (470 nm blue LED flashing at 3Hz for three periods of 15 seconds over the course of the trials). In each animals, we administered single 50 µL boluses of GVs at a concentration of $6x10^9$ particles per µL via tail-vein injections. GV enhancement of fUS signals was compared to saline and microbubble injections.
In vitro results showed that GVs can endure higher pressures than microbubbles (up to 646 kPa in a 2 mm/s flow), and that GVs stay stable in solution even in flows as slow as 50 µm/s when microbubble sediment below 0.5 mm/s. In addition, our preliminary findings indicate a 30% peak enhancement of fUS activations in the presence of GVs compared to red blood cells alone. Peak correlation scores were increased by 10%. On the contrary, saline injections did not

enhance neural activations, while microbubbles enhanced the signal the most but signal fluctuations hindered correlation scores. These preliminary results demonstrate that GVs can serve as smooth hemodynamic enhancers of transcranial fUS signals and are the most accurate reporters of flow based on our in vitro experiments.

Disclosures: D. Maresca: None. **T. Payen:** None. **A. Lee-Gosselin:** None. **B. Ling:** None. **D. Malounda:** None. **C. Demené:** None. **T. Deffieux:** None. **M. Tanter:** None. **M. Shapiro:** None.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.13

Topic: E.05. Brain-Machine Interface

Support: NIH BRAIN Grant U01NS099724
T&C Chen Brain-machine Interface Center at Caltech
The Boswell Foundation

Title: A functional ultrasound brain-machine interface: Offline proof of concept in non-human primates

Authors: *S. L. NORMAN[1], V. N. CHRISTOPOULOS[1], D. MARESCA[1], C. DEMENÉ[2], T. DEFFIEUX[3], M. TANTER[4], M. G. SHAPIRO[1], R. A. ANDERSEN[1]
[1]Caltech, Pasadena, CA; [2]Inst. Langevin, Paris, France; [3]Inst. Langevin / Inserm U979, Paris, France; [4]INSERM, Paris, France

Abstract: Brain-machine interfaces (BMIs) use neurophysiological signals from the brain to control external devices. Ideally, BMIs have high spatiotemporal resolution, are noninvasive, and portable. Most BMIs rely on neuroelectric methods that are either invasive (e.g. microelectrode arrays) or suffer from poor signal fidelity (e.g. EEG). BMIs based on metabolic activity are either cumbersome, (e.g. fMRI) or sacrifice imaging fidelity for portability (e.g. fNIRS). Recently, functional ultrasound (fUS) was introduced as a revolutionary hemodynamic imaging technique with excellent spatiotemporal resolution (100 μm,10 ms) [Mace et al, Nature Methods, 2011]. In addition, it is both noninvasive and portable: criteria where current techniques fall short. Thus, fUS is an ideal imaging technique for future BMIs.
The goal of this offline BMI study was to classify left-cued vs. right-cued eye and hand movements using changes in fUS hemodynamic signals preceding movement. To this end, a non-human primate was trained to perform memory-guided saccades and reaches (acquired via joystick) to targets presented in left or right visual fields. Each trial started with the animal fixating on a central cue for 6 s. A target was then presented in a lateral peripheral visual field for

300 ms. After target offset, the animal memorized the location of the target for 10 s (saccades) or 5 s (reaches) while maintaining eye fixation. When the fixation cue disappeared ("go signal"), the animal performed a movement to the remembered target location. During the task, we acquired fUS images at 1 Hz over the intraparietal sulcus (IPS) to capture the lateral intraparietal area (LIP) - an area associated with planning eye movements - and the posterior reach region (PRR) - an area associated with planning reaching movements. We used classwise principal component analysis (cPCA) as a feature extraction and dimensionality reduction technique to optimally discard shared information, i.e. noise, between the classes. We then used linear discriminant analysis (LDA) to predict whether the cPCA-transformed images suggested an impending left or right movement. Finally, we used a 10-fold cross validation technique to attain the reported classification accuracies within each run.
We recorded 91 successful saccade trials over two days and 112 successful reach trials on one day. Cross-validated classification accuracies were 67.0% ($p<.001$, binomial test) on day 1 and 63.1% ($p=0.017$) on day 2 for saccade trials and 73.4% ($p<0.001$) for reach trials. These results present, for the first time, a proof-of-concept that fUS is a viable imaging method for BMI control.

Disclosures: V.N. Christopoulos: None. **D. Maresca:** None. **C. Demené:** None. **T. Deffieux:** None. **M. Tanter:** None. **M.G. Shapiro:** None. **R.A. Andersen:** None.

Nanosymposium

271. Brain-Machine Interface

Location: SDCC 7

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 271.14

Topic: C.09.Stroke

Support: H2020 SME Phase II recoveriX

Title: A brain-computer interface group study for motor rehabilitation of chronic stroke patients

Authors: *G. EDLINGER[1], F. CAO[2], S. DIMOV[3], C. GUGER[3]
[1]G.Tec Med. Engin. Gmbh, Schiedlberg, Austria; [2]g.tec neurotechnology GmbH, Albany, NY; [3]g.tec neurotechnology GmbH, Schiedlberg, Austria

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, 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) and level of daily activity (Barthel index, BI). In 27 chronic stroke patients the study showed an average improvement of the UE-FMA of 8 points ($p<0.0001$). Furthermore spasticity and tremor were significantly reduced and the Barthel index increase significantly. Therefore, the BCI based motor rehabilitation is a very effective way of treatment in chronic stroke patients. In future the protocol will be extended to treat lower limb movements with the BCI system.

Disclosures: G. Edlinger: A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **F. Cao:** A. Employment/Salary (full or part-time):; g.tec neurotechnology GmbH. **S. Dimov:** A. Employment/Salary (full or part-time):; g.tec neurotechnology GmbH. **C. Guger:** A. Employment/Salary (full or part-time):; g.tec neurotechnology GmbH.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.01

Topic: G.01. Appetitive and Aversive Learning

Support: F32MH115688 to KAC
R01MH105414 to RLC
R01MH116445 to RLC
R21MH114170 to RLC

Title: Prefrontal somatostatin interneurons promote fear memory expression

Authors: *K. A. CUMMINGS, R. L. CLEM
Mount Sinai Sch. of Med., New York, NY

Abstract: In addition to excitatory projection neurons, prefrontal cortex harbors a network of local inhibitory neurons composed mainly of parvalbumin- (PV-INs) and somatostatin-expressing (SST-INs) interneurons. Intriguingly, *in vivo* electrophysiological recordings have indicated that in contrast to conditioned stimulus (CS)-evoked spiking of projection neurons, fear

memory expression is associated with suppression of activity in prelimbic PV-INs. However, it remains unclear how fear conditioning might drive these dynamic changes in prefrontal population activity. We performed immunohistochemical c-Fos staining and observed that a majority of PL layer 2/3 SST-INs are activated in response to both fear memory acquisition and retrieval. Correspondingly, whole-cell recordings from acute brain slices indicate that fear conditioning leads to a lamina-specific increase excitatory synaptic transmission in excitatory projection cells as well as SST-INs, but not PV-INs. These data suggest that SST-INs may be important for fear learning and/or memory expression. In support of this idea, *in vivo* optogenetic activation or silencing of SST-INs promoted or suppressed fear memory expression, respectively. Optogenetics-assisted electrophysiological recordings in PL revealed that SST-INs provide monosynaptic input onto PV-INs, indicating a potential role for SST-INs in disinhibition of fear-related excitatory projection neurons. In line with this role, c-Fos staining in animals where SST-INs were optogenetically activated revealed that PL is disinhibited and as a result, relevant long-range target structures are engaged. Overall, our results suggest that SST-INs may play a key role in gating fear-related prelimbic circuitry and their expression of synaptic plasticity after fear conditioning could constitute a mechanism for memory storage.

Disclosures: K.A. Cummings: None. **R.L. Clem:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.02

Topic: G.01. Appetitive and Aversive Learning

Support: NIH 2T32MH067563 to DBP
NIH/NIDCD F31DC017062 to DBP
NIH/NIDCD R01DC010014 to JAG

Title: Investigating neural and behavioral mechanisms of olfactory generalization in humans

Authors: *D. B. PORTER[1], L. P. QU[1], E. GJORGIEVA[1], T. KAHNT[1], J. A. GOTTFRIED[2,1]
[1]Neurol., Northwestern Univ., Chicago, IL; [2]Dept. of Neurol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: A critically important feature of the brain is its ability to generalize from previously encountered stimuli to new stimuli. While generalization reduces the need to learn the associative value of every object encountered, discrimination of perceptually related objects that hold different meanings is just as important. Interestingly, when training includes two conditioned stimuli, one paired with a reinforcer (CS+) and another that is not reinforced (CS-), the profile of the gradient is actually not symmetrical about the CS+. A “peak shift” or

displacement is often observed in the direction of the CS+, away from the CS-. Here, we developed a novel functional fMRI paradigm of olfactory aversive conditioning to explore the mechanisms underlying the shift from discrimination learning to generalization. For each subject, a set of 11 odor mixtures was created that systematically varied in perceptually equivalent steps between 100% isoamyl acetate (banana) and 100% beta-pinene (pine). Subjects completed an aversive conditioning task involving repeated stimulus pairings between one of the odor mixtures (the conditioned stimulus, CS+) and mild footshock (US); a closely related odor mixture was paired with no shock, serving as the CS-. Subjects were then exposed to the remaining odor mixtures, in the absence of shock, during fMRI scanning, enabling us to estimate behavioral, physiological, and neural gradients of olfactory generalization. We found that subjects demonstrate robust olfactory behavioral generalization, peaking in the direction of the CS+, away from the CS-. Using multivoxel pattern analysis of fMRI data, we show that odor-evoked activity patterns in orbitofrontal cortex in response to the CS+ increasingly resemble patterns evoked by the "peak shift" odor over the course of the experiment. Understanding how specific brain regions work together to define the boundary between generalization and discrimination has important translational implications for anxiety and post-traumatic stress disorders, where over-generalization can result in maladaptive behaviors.

Disclosures: D.B. Porter: None. **L.P. Qu:** None. **E. Gjorgieva:** None. **T. Kahnt:** None. **J.A. Gottfried:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.03

Topic: G.01. Appetitive and Aversive Learning

Support: NS 22061

Title: Cholinergic signaling in the ventral subiculum modulates neuronal activity and fear conditioning

Authors: *S. WANG[1], L. W. ROLE[2], D. A. TALMAGE[3]
[1]Program In Neuroscience, SUNY At Stony Brook, Stony Brook, NY; [2]Neurobio. & Behavior, [3]Pharmacol. Sci., Stony Brook Univ., Stony Brook, NY

Abstract: The ventral subiculum (vSub) mediates the information exchange between ventral hippocampus(vHipp) and multiple brain regions related to fear conditioning, i.e. basal lateral amygdala(BLA). The vSub function is regulated by cholinergic inputs from the basal forebrain. Previous lesion studies and pharmacological manipulations indicate that cholinergic signaling in vHipp can be crucial to fear learning. However, neither the activity of vSub circuits during

memory acquisition and retrieval, or the mechanism of acetylcholine(ACh) modulating the circuits is well established. In this study we determine how cholinergic signaling specifically in vSub modulates fear conditioning behavior by altering local neuronal activities. To understand the role of cholinergic signaling in vSub, we used chemogenetic methods to manipulate cholinergic signaling. Blocking acetylcholine release specifically in vSub during fear memory retrieval can attenuate fear performance, indicated by decrease in freezing time. Also, fewer numbers of c-fos positive vSub neurons are found in ACh-blocked animals comparing to control animals. This is consistent with ACh modulating fear conditioning via changing the neuronal activity in vSub. To probe the mechanism of how ACh modulates vSub neuronal activity, we monitored local circuit activity using calcium imaging and patch clamp recording. Local application of ACh increases the integrated calcium level in a large population of vSub pyramidal neurons(PYNs), and increases action potential firing rate. ACh also depresses inhibitory synaptic transmission to these PYNs, consistent with a dis-inhibitory mechanism contributing to the increase excitability. The depression of inhibitory input can be blocked by muscarinic ACh receptor (mAChR, likely via M2 or M4 subtype) antagonists. Application of M2/M4 AChR agonists increases integrated calcium level, similar to ACh effect. These data are in consistency with the idea that ACh may modulate fear memory retrieval by alternating the excitability of vSub PYNs, via mechanisms might involve mAChRs signaling.

Disclosures: S. Wang: None. **L.W. Role:** None. **D.A. Talmage:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.04

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant NS021229

Title: Dopaminergic regulation of aversive memory formation

Authors: *T. TSETSENIS, J. K. BADYNA, M. SUBRAMANIYAN, K. YANG, J. A. DANI
Dept. of Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Cognitive impairment and dopaminergic dysfunction commonly accompany mental disorders such as schizophrenia, attention deficit hyperactivity disorder, and Parkinson's disease. Dopamine signaling contributes to the persistence of long-term memories, and dopamine imbalances lead to learning dysfunctions. There is controversy, however, about the intensity and significance of hippocampal dopaminergic innervation and about dopaminergic regulation of synaptic plasticity and memory. Dopamine receptors are highly expressed in the hippocampus, and physiological evidence demonstrates that these receptors are important for controlling

hippocampal synaptic plasticity. Long-term memory consolidation also requires hippocampal dopaminergic signaling at specific time points during the retention interval. Despite this evidence, the circuits, mechanisms and importance of dopaminergic regulation of synaptic plasticity and memory have not been determined. We have recently demonstrated that dopaminergic transmission is necessary for aversive learning and associated synaptic plasticity in the hippocampus. However, the source of the dopamine signal that regulates hippocampal-dependent aversive learning remains unknown. By using a combination of retrograde and anterograde labeling techniques, we have identified and characterized a population of midbrain dopaminergic neurons that directly projects to the hippocampus. Next, we used optogenetics to control dopamine release in the hippocampus originating from midbrain dopaminergic centers. Our data show that optogenetic stimulation of ventral tegmental area (VTA) dopaminergic terminals in the hippocampus facilitates contextual fear conditioning in mice, while suppression of VTA firing attenuates the fear memory. This suggests that midbrain dopaminergic sources targeting the hippocampus are involved in the establishment of aversive memories.

Disclosures: T. Tsetsenis: None. **J.K. Badyna:** None. **M. Subramaniyan:** None. **K. Yang:** None. **J.A. Dani:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.05

Topic: G.01. Appetitive and Aversive Learning

Support: Hong Kong Research Grant Council (RGC-ECS 27104616)
The University of Hong Kong Seed Fund for Basic Research (2016041590006 & 201611159234)

Title: Disrupting consolidation of fear memory through deep brain stimulation of the medial prefrontal cortex

Authors: *S. Z. TAN[1], Y.-S. CHAN[2], L. LIM[3]
[1]The Univ. of Hong Kong, Hong Kong, Hong Kong; [2]Sch. of Biomedic. Sci., Fac. Med., Univ. Hong Kong, Hong Kong, China; [3]Sch. of Biomed. Sciences, Li Ka Shing Fac. of Medicine, The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Anxiety disorder poses one of the biggest threat to mental health in the world, yet current therapeutics have been mostly ineffective due to issues with relapse, efficacy, and toxicity of drugs. Deep brain stimulation (DBS) is a promising therapy for treatment-resistant psychiatric disorders including anxiety, despite this, very little is known about the effects of DBS on fear memories. In this study, we used a modified plus-maze discriminative avoidance task to

model the interaction between innate fear and conditioned fear. We showed that DBS in the medial prefrontal cortex (mPFC) was able to disrupt consolidation, but not acquisition nor retrieval of fear memories. We validated these results using a standard tone-footshock fear paradigm and showed disruption in both tone and contextual fear memory. We further demonstrated short term, but not long term, changes in dopaminergic receptor expression in the ventral, but not dorsal hippocampus. Similarly, we showed a significant decrease in the immediate early gene c-fos in the ventral but not dorsal hippocampus. Based on our results, we propose a model, using a conceptual artificial neural network, on how neuromodulation is able to disrupt memory. Overall, our data suggest that mPFC stimulation is able to alter fear memories, and should be further studied as a potential therapeutic means for anxiety disorders.

Disclosures: S.Z. Tan: None. **Y. Chan:** None. **L. Lim:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.06

Topic: G.01. Appetitive and Aversive Learning

Support: R01 MH074692
T32 MH019524

Title: Brain mechanisms by which emotional learning selectively and retroactively enhances memory for related information

Authors: *D. V. CLEWETT[1], D. YI[2], S. BACHMAN[2], J. E. DUNSMOOR[3], E. A. PHELPS[1], L. DAVACHI[2]
[1]Psychology, [2]New York Univ., New York, NY; [3]Univ. of Texas at Austin, Austin, TX

Abstract: Recent work in humans demonstrates that emotional learning can selectively and retroactively enhance memory for conceptually related neutral information that would otherwise be forgotten (Dunsmoor et al., 2015). However, the mechanisms underlying this retrograde memory enhancement are unclear. Because this effect only emerges after a delay, one possibility is that emotional learning biases post-encoding consolidation processes. Another possibility is that prior representations reactivate during new learning, enabling emotional events to facilitate memory for overlapping past and present information. Here, we tested these possibilities in humans using functional magnetic resonance imaging (fMRI). In a two-phase learning paradigm, participants first viewed images of neutral tools and animals intermixed with neutral scene images (pre-conditioning). Approximately 6 minutes later, participants viewed another stream of neutral tool and animal images, while one of the visual categories was conditioned with shock. Memory for all objects was tested 24 hours later. To examine learning-related changes in

functional connectivity, resting-state scans were collected immediately before and after the conditioning phase. Across participants, learning-related changes in resting connectivity between hippocampus, VTA/SN, and shock-paired category-selective cortex were associated with greater emotion-biased retroactive memory enhancement. During conditioning, individuals who showed greater activity in scene-selective cortex while viewing shocked versus non-shocked objects, an index of pre-conditioning phase context reactivation, also exhibited greater emotion-related retroactive memory enhancement. Furthermore, subsequent memory analyses revealed that increased VTA/SN activity was associated with emotional memory enhancements for conditioning-phase items. This emotional memory effect was also correlated with degree of retroactive memory enhancement for conceptually related information. Together these findings suggest that reinstating prior learning contexts during emotional experiences - along with increased online and offline dopaminergic neuromodulation - can determine the selection and storage of neutral experiences in long-term episodic memory.

Disclosures: D.V. Clewett: None. **D. Yi:** None. **S. Bachman:** None. **J.E. Dunsmoor:** None. **E.A. Phelps:** None. **L. Davachi:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.07

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant MH106719

Title: Mental context tagging reveals deficits of extinction learning in PTSD

Authors: *A. C. HENNINGS[1], J. A. LEWIS-PEACOCK[2], J. E. DUNSMOOR[3]
[1]Inst. for Neurosci., [2]Dept. of Psychology, [3]Dept. of Psychiatry, The Univ. of Texas at Austin, Austin, TX

Abstract: Extinction of conditioned fear is new learning that is contextually specific (Bouton, M. E., 2004). Patients with PTSD show deficits in both learning and retrieval of extinction memories (Hayes et al., 2012). In particular, they show decreased contextual processing during extinction, which may reduce the ability to retrieve extinction memories thereby contributing to the preservation of symptoms (Maren et al., 2013). Recent models of episodic memory in humans highlight the importance of *mental context* for the successful encoding and retrieval of memories (Sederberg et al., 2008). Here, we test the hypothesis that deficits in extinction learning and recall in patients with PTSD are related to an inability to retrieve an extinction mental context, and a decreased ability for episodic encoding during extinction learning. We have previously shown that episodic memories for neutral items from a semantic category

associated with a shock are better remembered than items from another category (Dunsmoor et al., 2015). This selective long term memory enhancement persists during fear extinction in healthy controls (Dunsmoor et al., 2018), but may not in PTSD. We developed an fMRI study in which healthy adults and participants with PTSD received Pavlovian fear conditioning via shocks paired with pictures of tools or animals, followed by standard extinction. Both groups were tested 24 hours later for extinction retrieval by testing contextual renewal of learned fear (i.e., re-introducing the shock apparatus, but without shocks). Critically, we "tagged" the mental context (Gershman et al., 2013) during extinction learning on Day 1 by presenting task-irrelevant scene pictures between trials, and then used multivariate pattern analysis (MVPA) of fMRI data during extinction recall on Day 2 to quantify the reinstatement of the extinction context. After the fear renewal test, we assessed episodic memory for all stimuli with a surprise recognition test. Neural results show significant reinstatement of extinction context in healthy controls (N=19), but not in PTSD patients (N=11). Further, controls showed a selective episodic memory enhancement for conditioned stimuli from fear learning and extinction learning, while PTSD patients showed an enhancement only during fear learning. These results suggest that in humans, the ability to update mental context and encode relevant stimuli during extinction learning is impaired in PTSD.

Disclosures: A.C. Hennings: None. **J.A. Lewis-Peacock:** None. **J.E. Dunsmoor:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.08

Topic: G.01. Appetitive and Aversive Learning

Support: NSF Grant BCS 1460909

Title: Proximity to virtual threats modulates fear learning and extinction networks

Authors: *L. FAUL, J. M. STIVERS, D. STJEPANOVIC, G. W. STEWART, J. L. GRANER, K. S. LABAR
Ctr. for Cognitive Neurosci., Duke Univ., Durham, NC

Abstract: Proximity to a threat is important for configuring defensive behavior, yet few studies have investigated how threats that invade peri-personal space influence fear learning. Here we investigate how the egocentric spatial distance to virtual threats impact the neural mechanisms of fear acquisition, extinction, and reinstatement. Thirty-one healthy adult subjects were presented with four human avatars while passively navigating a 3D virtual environment during functional magnetic resonance imaging. Two characters invaded the peri-personal space of the participant, whereas the other two characters appeared farther away. For each distance, one character was

partially reinforced with aversive shocks ($CS+_{near}$, $CS+_{far}$) during acquisition, and one character at each distance was explicitly unreinforced ($CS-_{near}$, $CS-_{far}$). Participants completed fear acquisition followed by fear extinction in a novel virtual context. The following day, participants returned for extinction recall in the extinction context, followed by fear reinstatement in the acquisition context. Participants provided shock expectancy ratings for each character presentation while skin conductance responses were recorded. The behavioral ratings and arousal responses were higher for CS+ characters than CS- characters during acquisition and reinstatement, especially for threats that invaded peri-personal space, and this difference was reduced following extinction and extinction recall. Neuroimaging results revealed fear-related activation (CS+ > CS-) in the dorsomedial prefrontal cortex (PFC) and insular-opercular cortex during acquisition, which was greater during early trials for CS^{+}_{near} compared to $CS+_{far}$. The right amygdala and hippocampus showed greater fear-related activation for early compared to late acquisition trials. Extinction-related activity was observed in the rostral anterior cingulate cortex, posterior cingulate cortex (PCC), precuneus, and insula. CS^{+}_{near} showed greater operculum activity throughout extinction, whereas $CS+_{far}$ elicited greater activity in the ventral medial PFC and PCC. Similar activation related to fear acquisition and extinction was observed for reinstatement and extinction recall, respectively. Taken together, these results indicate an amplified fear response for proximal than distal threats that impacts extinction learning and recall. These findings have implications for understanding how traumas that invade peri-personal space yield fear persistence.

Disclosures: L. Faul: None. **J.M. Stivers:** None. **D. Stjepanovic:** None. **G.W. Stewart:** None. **J.L. Graner:** None. **K.S. LaBar:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.09

Topic: G.01. Appetitive and Aversive Learning

Support: NIHM 5R01MH097085-03
H2020 Marie Sklodowska- Curie fellowship
Society in Science - Branco Weiss fellowship
NIMH Pathway to Independence Award K99/R00

Title: Identifying neural signatures of reconsolidation in humans

Authors: *M. C. KROES[1], Q. LIN[2], J. E. DUNSMOOR[3], E. A. PHELPS[4]
[1]Donders Inst. for Brain, Cognition, and Behaviour, Radboud Univ. Nijmegen Med. Ctr., Nijmegen, Netherlands; [2]Yale Univ., New Haven, CT; [3]Dept. of Psychiatry, Univ. of Texas at Austin, Austin, TX; [4]Dept Psychol, New York Univ. Dept. of Psychology, New York, NY

Abstract: A reminder can reactive a specific consolidated memory and return it to a labile state requiring re-stabilization processes to be maintained, referred to as reconsolidation. Interventions that interfere with reconsolidation can modify or even eradicate specific memories and reverse neural signatures of memory consolidation. Still unclear is what happens to neural signatures of memory during reactivation that returns a consolidated memory to a labile state and how interventions modify neural representations of memory. We therefore tested human participants on a behavioural reconsolidation intervention study within a Pavlovian threat conditioning paradigm while collecting functional magnetic resonance images. One day following conditioning participants received a reminder to return a threat memory to a labile state (reminder group) or not (no-reminder group) and after a brief break to allow memory to become labile all participants received extinction training. As predicted, extinction following a reminder, that is during the reconsolidation window, diminished the return of threat-related defensive responses on day later. We will present how reactivation of neural representation of memory following a reminder related to the effectiveness of the reminder-extinction procedure to diminish the return of threat responses. And present how the reminder-extinction procedure results in the modification of neural memory representations. The identification of such neural signatures of reconsolidation in humans can be used to optimize reconsolidation-interventions in the future.

Disclosures: M.C. Kroes: None. **Q. Lin:** None. **J.E. Dunsmoor:** None. **E.A. Phelps:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.10

Topic: G.01. Appetitive and Aversive Learning

Support: Wellcome Trust Sir Henry Wellcome Fellowship 206460/Z/17/Z

Title: Aversive learning processes modulate attentional bias to threat

Authors: *T. WISE[1], J. MICHELY[1], P. DAYAN[2], R. DOLAN[1]
[1]Max Planck-UCL Ctr. for Computat. Psychiatry and Ageing Res., [2]Univ. Col. London, London, United Kingdom

Abstract: Attentional bias towards threat is proposed to play a causal role in the development of anxiety disorders. However, the factors underlying this bias remain unclear. Here we examined the influence of aversive learning processes on visual attention, using a reinforcement learning model to identify components of the learning process that may be implicated in pathological attentional bias towards threat. Subjects performed an aversive reinforcement learning task that involved learning to predict the occurrence of mild electric shocks. Eye tracking was used to

monitor gaze fixation locations during the task as an index of visual attention. Computational models of learning were fit to behavioural responses and quantities derived from these models were used to predict gaze position. Results showed that subjects exhibited biased attention towards stimuli when they perceived them to be associated with a high shock probability or when they were uncertain about the probability of receiving a shock. This work highlights the importance of different learning processes underlying the allocation of visual attention, and suggests that the attentional bias towards threat seen in anxiety disorders could result from dysfunctional estimates of aversive value and uncertainty. Future work will apply this computational framework to the study of clinical populations.

Disclosures: T. Wise: None. **J. Michely:** None. **P. Dayan:** None. **R. Dolan:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.11

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant K08-MH104281
NIH Grant R01-MH094536
NIH Grant R01-MH094536-02S1
NIH Grant R21-MH098177

Title: Genetic dissection of catecholaminergic innervation of the cognitive cerebellum

Authors: *E. S. CARLSON[1], S. G. SANDBERG[4], T. M. LOCKE[1], P. E. PHILLIPS[2], L. S. ZWEIFEL[3]
[2]Psychiatry & Behavioral Sci., [3]Psychiatry, [1]Univ. of Washington, Seattle, WA; [4]Unviersity of Washington, Seattle, WA

Abstract: Studies in humans and non-human primates have identified a region of the dentate nucleus of the cerebellum (DCN), or lateral nucleus in rodents (LCN), which is activated during performance of cognitive tasks involving complex spatial and sequential planning. We have previously shown that the dopamine D1 receptor marks a population of neurons in the LCN with similar spatial distribution and regulates cognitive performance on several tasks related to attention and working memory, and has connections with other parts of the brain that are classically involved in these functions. The DCN is implicated in cognitive function in humans with psychiatric illnesses, but virtually nothing is known about its basic anatomical and functional organization. We hypothesized that the locus ceruleus (LC) is the source of both dopamine and norepinephrine release in LCN, catecholamines are required for cerebellar enhancement of attention and working memory tasks, and act on LCN glutamatergic output

neurons. We have mapped projections of the LC to LCN, and analysis has revealed distinct projections from the locus ceruleus, but no other nuclei known for producing catecholamines. When we injected DBH-IRES-Cre mice crossed with TdTomato mice with green retrobeads in LCN, we found overlap of the retrobeads and tomato staining, suggestive of LC projections to LCN. We did not see co-labeling in other noradrenergic or dopaminergic nuclei. When the LC is electrically stimulated, catecholamine release in the LCN is observed with fast scan cyclic voltammetry in anesthetized animals. Deletion of tyrosine hydroxylase (Th) expression in the LCN, results in abnormal performance on working memory behaviors, but not motoric ones. $Th^{lox/lox}$ mice (N = 7) were injected with CAV-Cre (retrograde virus) into LCN coordinates, and trained on an FR1 schedule prior to starting either an impulsivity or a delayed alternation task. Littermate controls (N = 7) were injected with CAV2 encoding the fluorophore zsGreen (Cav2-zsGreen). Viral "hits" were verified by Western blot for Th protein from LCN tissue isolated by hole punch of a section of cerebellum. Tyrosine hydroxylase was reduced by 75% in the LCN with this manipulation. LCN TH knockout mice showed more impulsive pressing after the last press (or more failure to inhibit responses) than littermate controls. LCN TH knockout mice showed a decreased rate of learning delayed alternation, and never achieved the same amount of success on the last day of testing. We found a remarkable parallel in that when we decrease neuronal excitability of glutamatergic LCN output neurons using DREADDs (N = 10 /group), learning of the working memory task is facilitated.

Disclosures: E.S. Carlson: None. **S.G. Sandberg:** None. **T.M. Locke:** None. **P.E. Phillips:** None. **L.S. Zweifel:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.12

Topic: H.01. Animal Cognition and Behavior

Support: R21MH108848

Title: Removal of information from working memory via replacement, suppression, and clearing

Authors: *H. KIM[1], H. SMOLKER[2], L. SMITH[2], M. T. BANICH[2], J. A. LEWIS-PEACOCK[1]
[1]Dept. of Psychology, Univ. of Texas at Austin, Austin, TX; [2]Inst. of Cognitive Sci., Univ. of Colorado Boulder, Boulder, CO

Abstract: Removal is the exclusion of information from working memory (WM) in service of the current goal (Lewis-Peacock et al., 2018). It is one of several processes that control the contents of WM and enable an efficient use of its limited capacity. The neural mechanisms underlying removal are only beginning to be studied. Recent neuroimaging evidence (Banich et

al., 2015) suggests that there are multiple ways to remove an outdated thought: replace it with another thought, suppress that particular thought, or clear all thoughts from mind. A hierarchy of brain regions involved in cognitive control are engaged to varying degrees depending on how thoughts are removed, and their engagement is influenced by individual differences in self-reported difficulty in controlling one's thoughts. However, these results do not address the important question of how removal processes may actually alter the representation of a thought in WM. We addressed this question by using multi-voxel pattern analysis (MVPA) of fMRI data to characterize the representational state of items while retained in WM, and to learn how such representations are altered when removed from WM. Whole-brain pattern classifiers were trained to detect the cognitive operation engaged on each trial (maintain, replace, suppress, or clear), and additional classifiers were trained on ventral visual cortex to track the information content of WM at two levels of specificity: category (faces, fruit, scenes) and subcategory (faces: actors, musicians, politicians; fruit: apples, grapes, pears; scenes: beaches, bridges, mountains). On each trial, participants (N=30) memorized a target picture and then performed one of five mental manipulations: maintain it, replace it with an item from the same category, replace it with an item from a different category, suppress it, or clear all thoughts. Each operation had distinct neural signatures that were successfully decoded, importantly showing that the suppress and clear instructions were not implemented by merely replacing the item. Decoding the trajectory of WM contents during a trial also revealed distinct neural profiles for each cognitive operation. At the end of "maintain" trials, the category- and subcategory-level information of the WM item returned to baseline (i.e., to the level of trial-irrelevant information). In all removal-related trials (replace, suppress, clear), the WM contents dropped *below* baseline. Interestingly, the contents dropped more quickly for clear than for suppress, suggesting a slower removal process for specific thoughts than for all thought. These results demonstrate unique neural processes and consequences of removing information from WM.

Disclosures: H. Kim: None. **H. Smolker:** None. **L. Smith:** None. **M.T. Banich:** None. **J.A. Lewis-Peacock:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.13

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R01-MH097990
NIDA R21-DA035209
Sir Henry Wellcome Fellowship from the Wellcome Trust (098830/Z/12/Z)
NIMH (F32MH081521)
Wellcome Trust New Investigator Award (096689/Z/11/Z)

Middlesex Hospital Medical School General Charitable Trust

Title: Reconciling persistent and dynamic hypotheses of working memory coding in prefrontal cortex

Authors: *S. E. CAVANAGH[1], J. P. TOWERS[1], J. D. WALLIS[2], L. T. HUNT[3], S. KENNERLEY[1]
[1]Univ. Col. London, London, United Kingdom; [2]Univ. of California Berkeley, Berkeley, CA; [3]Univ. of Oxford, London, United Kingdom

Abstract: Competing accounts propose that working memory (WM) is subserved either by persistent activity in single neurons or by dynamic (time-varying) activity across a neural population. To compare these hypotheses, we analysed neuronal data recorded from Prefrontal Cortex (PFC) whilst two monkeys (Macaca mulatta) performed an oculomotor-delayed-response, where the reward amount for successful responses varied across trials (Kennerley and Wallis, 2009). Two cues were sequentially presented (for 500ms apiece), each followed by a 1000ms delay. The spatial cue was shown first, and indicated which of 24 locations the subject had to hold in WM. The reward cue indicated which of five reward magnitudes the subject would receive for a saccade to the remembered location. Single-neuron recordings were taken from four regions of PFC: anterior cingulate cortex, orbitofrontal cortex, dorsolateral PFC and ventrolateral PFC (VLPFC).
Decoding analyses showed that VLPFC WM representations were strongest of any PFC region, and were present throughout the trial. Indexing each neuron's intrinsic temporal stability (time-constant) by fitting an exponential decay to its resting autocorrelation (Cavanagh et al. 2016) demonstrated a large degree of variability in single-neuron time-constants. Within VLPFC, there was a subpopulation of neurons with high time-constants which had the strongest WM representations. Cross-temporal analyses showed that these high time-constant VLPFC neurons reached a stable state during the initial WM delay, consistent with persistent activity theories of WM. However, this stable mnemonic state exhibited a reversed tuning geometry relative to cue-period selectivity, and was disrupted by the subsequent reward cue. Single-neuron analysis revealed many VLPFC neurons switched to coding reward, rather than maintaining task-relevant spatial selectivity until saccade. These results imply WM is fulfilled by dynamic, population-level activity within high time-constant neurons. Rather than persistent activity supporting stable mnemonic representations that bridge distraction, PFC neurons may stabilise a dynamic population-level process that supports WM. Stable activity states in VLPFC may better reflect the locus of the subject's attention, rather the contents of WM.

Disclosures: S.E. Cavanagh: None. **J.P. Towers:** None. **J.D. Wallis:** None. **L.T. Hunt:** None. **S. Kennerley:** None.

Nanosymposium

272. Cortical and Subcortical Mechanisms of Learning and Cognition

Location: SDCC 2

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 272.14

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01-MH55806
NIH P30-EY08126

Title: Microcircuitry of performance monitoring: Laminar origin of outcome monitoring and executive control in supplementary eye field

Authors: *A. SAJAD, J. D. SCHALL
Psychological Sci., Vanderbilt Univ., Nashville, TN

Abstract: We are continuing our investigation of the microcircuitry of supplementary eye field (SEF), an agranular area supporting the monitoring of errors, reward loss, and reward gain. With linear electrode arrays, we sampled neural spiking across all layers of SEF while recording overlying EEG in two monkeys performing the saccade countermanding (stop-signal) task. In this task, monkeys earned fluid reward a constant interval after a secondary tone reinforcement for making the correct response which entailed shifting gaze to a peripheral visual target unless a fixation stop signal appeared. The location of the target cued that either a large or small magnitude of reward could be obtained on the current trial. The assignment of reward magnitude alternated across blocks of ~20 trials. Systematic variation of response time demonstrated monkeys' sensitivity to the reward value. On ~50% of stop signal trials monkeys shifted gaze in spite of the stop signal; these were followed by a distinct tone reinforcement that indicated error and absence of reward. We isolated 293 neurons sampled from all layers. Error neurons were found in all layers with earliest response in L3 and L5. Error responses scaled with magnitude of loss, primarily in L2/3. The magnitude of error response in L2/3 but not L5/6 predicted the magnitude of the error-related negativity (ERN). Secondary and primary reinforcement were signaled by co-modulation of Gain and Loss neurons. Gain neurons, signaling positive cues and outcomes, were concentrated in lower L3 and L5/6 and showed reward value-dependent modulation in the period following the feedback tone, but preceding juice delivery. Loss neurons, signaling negative cues and outcomes in proportion to reward value, were concentrated in L2/3 and in L6. Loss neurons in L2/3 showed sensitivity to reward value by exhibiting lower firing rates upon larger reward gain. The magnitude of slowing of RT following error and speeding of RT following correct trials was predicted by the spike rate of Error neurons and the balanced activation of Gain and Loss neurons in L2/3 but not L5/6. These results guide the formulation of a microcircuit model of executive control and can guide a more accurate interpretation of the ERN.

Disclosures: A. Sajad: None. **J.D. Schall:** None.

Nanosymposium

273. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex I

Location: SDCC 25

Time: Monday, November 5, 2018, 8:00 AM - 10:45 AM

Presentation Number: 273.01

Topic: H.01. Animal Cognition and Behavior

Support: NIMH K01 MH114022

Title: Molecular, anatomical, and behavioral dissection of mPFC projection neuron heterogeneity

Authors: *J. H. LUI[1], N. D. NGUYEN[2], L. LUO[2]
[1]Dept. of Biol. Sci., [2]Stanford Univ., Stanford, CA

Abstract: A highly dissected molecular and anatomical view of neuronal cell types is critical towards understanding how neural circuits function and how cells encode behaviorally relevant information. However, in higher order association areas of neocortex such as prefrontal regions, neurons are particularly multi-purpose and flexibly adapt to changing demands. It is therefore unclear how well cell-type definitions based on stable molecular and anatomical properties match with, or can be predictive of dynamic encoding properties. Here, we first use single-cell RNA sequencing in the mouse medial prefrontal cortex (mPFC) to define multiple distinct excitatory projection neuron subtypes based on gene co-expression. In conjunction with viral-genetic tracing, we find that different long-range projections of mPFC can originate from either unique or combinations of these subtypes. Using the context of a simple learned association task (two-alternative choice) to assay cell-type specific firing patterns with *in vivo* Ca^{2+} imaging, we observe quantitatively different levels of task engagement between different cell types. While all populations assayed have heterogeneous, task-locked firing patterns that tile the experience (cue, choice, and reward periods), pre-reward activity is enriched in a specific subtype of limbic subcortical projection neurons. These results suggest that despite its adaptability, information flow in mPFC can be biased towards or away from specific molecular- and projection-defined cell types.

Disclosures: J.H. Lui: None. **N.D. Nguyen:** None. **L. Luo:** None.

Nanosymposium

273. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex I

Location: SDCC 25

Time: Monday, November 5, 2018, 8:00 AM - 10:45 AM

Presentation Number: 273.02

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01MH095894
NIH R01MH108627
NIH R37MH109728
Simons SFARI 304935

Title: The neural correlates of strategic competition

Authors: *Y. JIANG, M. L. PLATT
Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Primates including humans exhibit complex behaviors when interacting with their conspecifics. Laboratory studies of primate sociality, however, routinely employ choice tasks in restricted, often binary action space and thus afford low external validity. In contrast, we preserved the dynamic nature of live social interactions by examining the continuous behaviors of both humans and rhesus macaque monkeys playing a zero-sum competitive soccer game. To win a point, one player (the kicker) had to maneuver a ball across the screen while the other player (the goalie) attempted to intercept it. We found that in this game the interactions between human pairs (n = 9,000 trials) and monkey pairs (n = 11,600 trials) were profoundly and similarly complex. Upon careful analysis, such complexity can be disentangled and categorized into a set of quantifiable strategies: overall, the kicker's best strategy is unpredictability, whereas the goalie benefits from swift responsiveness to the kicker's actions. Even though it is the interaction between players that dictates the game, gaze patterns and pupil size changes from both players could effectively predict ball position and trial outcome before either player started to move. Additionally, in monkeys we also recorded single unit activity from a subregion of Superior Temporal Sulcus (mSTS), a potential homologue to human Temporal Parietal Junction (TPJ). We found that for both kicker (n = 133) and goalie (n = 125) mSTS neurons signaled the complexity of the strategies used as well as trial outcome. Compared with other conditions, mSTS activity was most strongly modulated when monkeys played against conspecifics, even when they were competing remotely in separate rooms. Finally, simultaneous recordings in both players suggested that changes in cross-brain correlation and synchronization were correlated with strategy changes and trial outcomes as well. These results demonstrate that primate mSTS/TPJ critically contributes to the complex strategies observed in competitive two-player games.

Disclosures: Y. Jiang: None. **M.L. Platt:** None.

Nanosymposium

273. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex I

Location: SDCC 25

Time: Monday, November 5, 2018, 8:00 AM - 10:45 AM

Presentation Number: 273.03

Topic: H.01. Animal Cognition and Behavior

Support: MEXT/JSPS KAKENHI 24220008
MEXT/JSPS KAKENHI 17H06161
MEXT/JSPS KAKENHI 16K18367
MEXT/JSPS KAKENHI 26890007
CREST AMED-JST
JSPS Fellowships for Research Abroad
JSPS Fellowships for Young Scientists 265926

Title: Causally essential neural network for performing metacognitive judgement on experience and ignorance in primates

Authors: *K. MIYAMOTO, R. SETSUIE, T. OSADA, Y. MIYASHITA
Dept Physiol, Univ. Tokyo Sch. Med., Tokyo, Japan

Abstract: Introspection on one's own memory and one's own ignorance is an indispensable ability to achieve highly conceptual reasoning and thought. However, it is unknown how the brain network enables us to perform such metacognitive judgements. In the present study, we designed a behavioural task on metacognition that is applicable to macaque monkeys (macaca fuscata, two female) without verbal report. In the task, the monkeys first performed a memory judgement and then reported confidence on their performance with post-decision wagering paradigm. We confirmed that the monkeys understood the task enough to choose the risky bet option (a large reward is given only after success judgements) more frequently after success judgements than failure as compared with the safe option (a small reward is assured irrespective of performance) ('phi coefficient,' a metacognitive performance index, is significantly positive for both experienced [$p=3.8\times10^{-6}$] and non-experienced [$p=3.8\times10^{-6}$] items). First, by whole-brain searches via functional MRI, we found the neural correlate of metacognition on remotely experienced events, recently experienced events, and unexperienced events at area 9, area 6, and area 10 in the prefrontal cortex, respectively ($p < 0.05$, family-wise error corrected). Next, to test the causal roles of these identified areas, we performed a reversible inactivation with GABA-A receptor agonist (muscimol, 1.33 mg/mL, 1.5μL/site) targeted to either of the localised spots. We found that inactivation at bilateral area 9, area 6, and area 10 selectively impairs metacognitive performance on remotely experienced events, recently experienced events, and unexperienced events, respectively, without impairing recognition performance per se. Control injection with saline did not affect either metacognition nor memory performance. These observations indicate

that brain systems specific to self-evaluation of experience or non-experience, which is independent of memory process per se, are implemented in the prefrontal neural network. Our findings revealed that information from these parallel metacognition systems, which are independent based on cognitive process to be evaluated, would be integrated to assess confidence, and then generate self-awareness of experience and ignorance.

Disclosures: K. Miyamoto: None. **R. Setsuie:** None. **T. Osada:** None. **Y. Miyashita:** None.

Nanosymposium

273. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex I

Location: SDCC 25

Time: Monday, November 5, 2018, 8:00 AM - 10:45 AM

Presentation Number: 273.04

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant EY014924

Title: Representations of dynamic reward in primate prefrontal and visual cortex during value-based learning

Authors: *X. CHEN[1,2], M. ZIRNSAK[1,2], T. MOORE[1,2]
[1]Stanford Univ. Sch. of Med., Stanford, CA; [2]Howard Hughes Med. Inst. - Stanford Univ., Palo Alto, CA

Abstract: Given the stochastic nature of the environment, humans and other animals need to constantly update their behavioral goals adaptively. It is not yet known whether and how visual processing changes during adapting goal-directed behavior. We have begun investigating the dynamics in visual processing by neurons in prefrontal and extrastriate visual cortex during a value-based learning task. In this learning task, monkeys forage via saccadic eye movements, between two identical visual target options at different locations to receive a reward. The reward associated with the two options is varied across blocks of 40-60 trials. In each block, the two options always have the same expected reward outcome, but different reward variance (risk). In each block, the risk of each option is randomly assigned to one of three values (high-risk, medium-risk, no-risk), but not the same value. To maximize the total amount of juice earned in this learning task, monkeys need to identify the risk level associated with the two target locations, and estimate its expected reward magnitude through choices and reward history. While the monkey performs the task, we record simultaneously from populations of neurons within the frontal eye field (FEF) or extrastriate area V4 using linear array electrodes (≥16 channels). Thus far our results show that monkeys exhibit stable risk-seeking behavior during the learning task, consistent with previous studies. More importantly, we observe that in addition to various components of the decision, such as chosen target location and choice probability, the visually driven activity of neurons in the FEF represents reward expectation and risk value. In area V4,

visually driven activity also represents chosen target location and choice probability. But surprisingly, this activity also encodes at least reward expectation.

Disclosures: X. Chen: None. **M. Zirnsak:** None. **T. Moore:** None.

Nanosymposium

273. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex I

Location: SDCC 25

Time: Monday, November 5, 2018, 8:00 AM - 10:45 AM

Presentation Number: 273.05

Topic: H.01. Animal Cognition and Behavior

Support: B.M. was supported by the Fundação para a Ciência e Tecnologia (scholarship SFRH/BD/51711/2011).
N.M was supported by funding from the Astor Foundation, Rosetrees Trust and Middlesex Hospital Medical School General Charitable Trust.
T.E.J.B. was supported by a Wellcome Trust Senior Research Fellowship (WT104765MA) and funding from the James S McDonnell Foundation (JSMF220020372).
P.D. was support by the Gatsby Charitable Foundation.
S.W.K. was supported by a Wellcome Trust New Investigator Award (096689/Z/11/Z).

Title: Neural signatures of model-free and model-based reinforcement learning in striatum and prefrontal cortex

Authors: *B. MIRANDA[1,2], N. MALALASEKERA[2], T. BEHRENS[4,2], P. DAYAN[3], S. W. KENNERLEY[2]
[1]Inst. of Physiol., Fac. of Med. – Univ. of Lisbon, Lisboa, Portugal; [2]Inst. of Neurol., [3]Gatsby Computat. Neurosci. Unit, Univ. Col. London, London, United Kingdom; [4]Wellcome Ctr. for Integrative Neuroimaging, Univ. of Oxford, Oxford, United Kingdom

Abstract: Contemporary reinforcement learning (RL) theory suggests that potential choices can be evaluated either by the model free (MF) strategy of learning their past worth or the model-based (MB) strategy of predicting their likely consequences based on learning how decision states eventually lead to outcomes. Statistical and computational considerations, as well as the trade-off between speed and accuracy, argue that learning agents might advantageously exploit both strategies. Prior lesion and neuroimaging studies in humans implicate the prefrontal cortex (PFC), and its connections to the striatum, in MF- and MB-RL, but little is known about the single-neuron substrates of these systems. This has limited our understanding of how these two RL systems interact to optimize learning in complex environments.
We recorded single-neuron activity from regions in the striatum (caudate and putamen) and PFC

(frontal pole - FP; anterior cingulate cortex - ACC; and dorsolateral PFC) of two monkeys (Macaca mulatta) while they performed a sequential decision task which induced trial-by-trial adjustments in choice that combined both MF and MB-RL control. A descriptive analysis of choice behaviour revealed that the structure of the task (of MB importance) and the reward history (of MF and MB importance) significantly influenced, choice, response vigour and pupil diameter. A detailed, trial-by-trial computational analysis confirmed that choices were made according to a weighted combination of MF and MB-RL, with the influence of the latter approaching 90% across weeks of testing. The residuals from this characterization suggested a new combined RL method, which incorporates a MB credit assignment weighting procedure. Single neuron correlates of key elements for MF and MB learning were observed across both PFC and striatal regions, but with functional dissociations. In striatum, both caudate and putamen showed a reward prediction error (RPE) signal at feedback, resembling midbrain dopaminergic responses. However, at choice, caudate also exhibited a MB signature of action-value. The ACC prominently encoded both reward history and state-transition knowledge. ACC also multiplexed MF and MB action-value, suggesting ACC utilises, and potentially arbitrates between, both RL strategies to optimize choice. Finally, neurons in FP exhibited a unique role in counterfactual processing. These results have important implications in understanding the neural mechanisms that support complex learning-related processes in the primate brain.

Disclosures: B. Miranda: None. **N. Malalasekera:** None. **T. Behrens:** None. **P. Dayan:** None. **S.W. Kennerley:** None.

Nanosymposium

273. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex I

Location: SDCC 25

Time: Monday, November 5, 2018, 8:00 AM - 10:45 AM

Presentation Number: 273.06

Topic: H.01. Animal Cognition and Behavior

Title: Parent-of-origin epigenetics set sleep in mice

Authors: *I. COSENTINI[1], E. BALZANI[2], T. NIEUS[3], V. TUCCI[1]
[1]Neurosci. and Brain Technol., IIT, Genova, Italy; [2]Ctr. for Neural Sci. and Ctr. for Data Sci., New York, NY; [3]Univ. of Milan, Milano, Italy

Abstract: The fundamental properties of sleep are established by developmental mechanisms. Here we investigated how perinatal epigenetics set the structure of sleep and influences adult behavioral/cognitive processes. In a series of recent studies we described the main effects of genomic imprinting in sleep. Imprinting is a parent-of-origin mechanism that influences early developmental behaviors and growth processes. We present new evidence that neurophysiological and cognitive traits are regulated by parent-of-origin effects. We studied reciprocal crosses of AKR/J and DBA/2J inbred strains that show different sleep homeostatic

responses and different mother-pup bonding conditions. We analyzed sleep architecture of two cohorts of mice (F1= AKR/J x DBA/2J, F1r =DBA/2JxAKR/J, mother always reported first) both during baseline condition (24h) and during the 18h following total sleep deprivation. Then, we tested animals in a behavioral timed task (switch task) both before and after sleep deprivation. Moreover, we recorded neuronal activity in the medial prefrontal cortex of mice, an area highly required in cognitive tasks and whose activity is influenced by sleep deprivation. From our study we highlight a set of behavioral and electrophysiological differences that are associated with the parental allelic combination carried by hybrid offspring. In particular, the EEG analysis show that the homeostatic response to sleep deprivation has a different time distribution in our experimental groups. The power density of REM sleep shows different recovery profile: theta power (4-9 Hz) in F1r mice is lower in the first hours of recovery. F1r mice show a delayed behavioral response after sleep deprivation compare to F1 mice, which is then fully recovered after recovery. Single cell activity is also characterized by parent-of-origin differences; in particular, we found that the activity of cells decreases by about 40% following sleep deprivation in F1. Overall, our results demonstrate that parent-of-origin epigenetic processes modulate sleep and sleep-related behaviors by influencing neuronal and network activity. The screening of genetic variants between parental backgrounds identified a number of imprinted genes that can potential refine our understanding of the molecular processes. To this end we carried out initial testing of a few targets and confirmed the link between the molecular processes of REM sleep and the parental modulation.

Disclosures: I. Cosentini: None. **E. Balzani:** None. **T. Nieus:** None. **V. Tucci:** None.

Nanosymposium

273. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex I

Location: SDCC 25

Time: Monday, November 5, 2018, 8:00 AM - 10:45 AM

Presentation Number: 273.07

Topic: H.01. Animal Cognition and Behavior

Support: Howard Hughes Medical Institute
Simons Foundation

Title: A premotor circuit engaged in flexible sensory-action mapping

Authors: *Z. WU, A. LITWIN-KUMAR, P. SHAMASH, A. TAYLOR, R. AXEL, M. SHADLEN
Dept. of Neurosci., Columbia Univ., NEW YORK, NY

Abstract: Cognitive functions in humans build from a capacity to link sensation flexibly to action. Such flexibility allows behavior to be context-dependent and transpire over extended time intervals. We have adapted a simple delayed match to sample (DMS) task in mice to study

flexible decision making. The mice must remember a sample odor over a 1-2 s delay, then compare it to a second test odor to determine if it is a match or non-match, and indicate the decision by licking left or right, respectively.
Multi-neuron population recordings from piriform, orbitofrontal, and anterolateral motor cortices (Pir, OFC, ALM) revealed a graded representation of odor identity and licking across these sensory, associative, and premotor areas. Decoding analysis suggests that sufficient information is present in Pir and OFC to solve the match/non-match decision. We therefore entertained the hypothesis that the lick-left/right neurons in ALM decode this information to command the choice-behavior. If so, participation of ALM might be essential once the test odor is presented, but not before.
To test this, we found that temporally controlled photoinhibition of ALM during sample and delay epochs dramatically impaired performance. Importantly, ALM silencing did not affect licking itself or control tasks that do not require sample memory. The finding was initially surprising because the majority of ALM neurons sampled in our recordings responded in association with licking, leaving at most a sparse representation of sample identity required to solve the task. However, two-photon calcium imaging revealed a population of neurons in Layer 2 of ALM with robust representations of the sample odor during the delay. The diverse time course of their response leads us to infer that they function to configure ALM circuitry to establish the appropriate sensorimotor mapping of the test odor to the lick response. We favor this class of mechanisms because the mice give no indication that they know about match/non-match when challenged with novel odors, whereas they can learn other combinations of flexible test-lick associations, instructed by other sample odors. If so, the simple DMS paradigm could reveal mechanisms of flexible circuit control that are the hallmark of higher cognitive function.

Disclosures: Z. Wu: None. **A. Litwin-Kumar:** None. **P. Shamash:** None. **A. Taylor:** None. **R. Axel:** None. **M. Shadlen:** None.

Nanosymposium

273. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex I

Location: SDCC 25

Time: Monday, November 5, 2018, 8:00 AM - 10:45 AM

Presentation Number: 273.08

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH095894
NIH Grant R01MH108627
NIH Grant R37MH109728
SFARI Grant 304935 MLP

Title: Neural mechanisms mediating cooperation

Authors: *W. S. ONG[1], M. L. PLATT[2]
[1]Dept. of Neurobio., [2]CCN, Univ. of Pennsylvania, Philadelphia, PA

Abstract: We hypothesize that cooperation results from the interaction of neural circuits mediating reward, empathy and theory of mind. fMRI studies in humans have shown that the anterior cingulate cortex (ACC) and temporal parietal junction (TPJ) are activated by vicarious reward and mentalizing respectively. These are two functions that conceivably contribute to cooperation, yet the precise neural processes remain unknown. To address this gap, we developed a new task based on the classic "chicken game". Two monkeys (M1&M2) face each other across a shared screen showing 2 colored annuli and 4 response targets. On some trials, the larger reward (denoted by visual tokens) lies opposite M1 behind the opponent (M2)'s annulus; smaller rewards lie to the left (see figure). To obtain the larger reward, M1 goes straight, but if M2 also goes straight the annuli collide and neither monkey gets reward. On some trials, a "cooperation bar" allows both monkeys to obtain larger rewards if and only if both choose to go left; if only one yields he receives a smaller reward. 4 trained monkeys maximized juice intake by attending to the reward tokens as well as the choices of their opponent. Monkeys' strategies depended on their relative dominance, and the agency of the opponent: Players quickly initiated cooperation for small rewards with an active player, and distinguished between active players and decoy monkeys (computer replay) within 15 trials. We constructed models where M1 uses his beliefs about the strategy of his opponent (M2) to predict M2's action on each trial, which is updated by the strategic prediction error(SPE), the mismatch between M1's expectation about M2's actions and M2's actual actions. To determine the neuronal basis of these behaviors, we recorded 528 neurons from ACC and 448 from the putative monkey TPJ in the middle STS (mTPJ). Elastic net regularisation with 4 model inputs (realized reward, cooperation, SPE and gaze (nuisance variable)) on the firing rate after decision and during reward delivery epochs returned a higher proportion of non-zero estimates for all inputs in STS neurons compared to ACCg neurons (eg 53% in mTPJ for cooperation vs 31% in ACCg). ACCg neurons are minimally modulated and indistinguishable between opponent conditions. mTPJ demonstrates a consistent differentiation between the 3 opponent conditions (no one, decoy, active) from the end of the decision making period to 1.5s after reward delivery in all model inputs. This demonstrates that neurons in mTPJ respond differentially to the presence and behavior of (non-) interactive agents, suggesting it plays a role in the integration of social cues, actions, and outcomes to guide strategic social decisions.

Disclosures: W.S. Ong: None. **M.L. Platt:** None.

Nanosymposium

273. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex I

Location: SDCC 25

Time: Monday, November 5, 2018, 8:00 AM - 10:45 AM

Presentation Number: 273.09

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant U01NS094368-01

Title: Dynamic brain states of the freely-moving monkey

Authors: *R. MILTON, N. SHAHIDI, V. DRAGOI
Neurobio. and Anat., Univ. of Texas Hlth. Sci. Ctr. At Houst, Houston, TX

Abstract: Brain activity must constantly shift to accommodate changing behavioral demands. Studies investigating brain state dynamics have conventionally relied on electrophysiological recordings from primary sensory cortical areas of head-fixed rodents. Here, we sought to extend earlier work to characterize the dynamics of neuronal activity associated with resting and locomotor states. We focused on an executive area of freely moving rhesus macaques using a combination of wireless multi-electrode recordings, wireless eye tracking, and video recordings. We demonstrate strong modulations of population activity in the dorsolateral prefrontal cortex of unrestrained non-human primates during distinct behavioral states. When the monkey is awake and sitting quietly, the cortex is relatively synchronized, but significantly less than during rest. When the monkey is actively exploring its environment, neuronal activity is highly desynchronized and firing rates are elevated. We show that the degree of population synchrony fluctuates during wakefulness, and that desynchronization is correlated with active behavior and pupil dilation. We further demonstrate that these influences impact neural activity in putative excitatory and inhibitory subpopulations. Regardless of behavioral state, putative inhibitory subpopulations tend to be more synchronized than putative excitatory subpopulations. These results demonstrate that brain states dynamically adapt to changes in behavioral context in an executive cortical area of non-human primate, suggesting that these fluctuations are a key characteristic of natural brain activity.

Disclosures: R. Milton: None. **N. Shahidi:** None. **V. Dragoi:** None.

Nanosymposium

273. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex I

Location: SDCC 25

Time: Monday, November 5, 2018, 8:00 AM - 10:45 AM

Presentation Number: 273.10

Topic: H.01. Animal Cognition and Behavior

Support: JSPS KAKENHI Grant Number 15K01843
Ministry of ECSST of Japan

Title: Neural mechanism for information seeking in monkey prefrontal cortex

Authors: *K. NAKAMURA[1], M. KOMATSU[2]
[1]Tokyo Inst. Technol., Yokohama-Shi, Japan; [2]RIKEN Brain Sci. Inst., Saitama, Japan

Abstract: The desire to obtain information is a powerful motivator in daily life, as well as desires for primary rewards such as food and water. Although neural mechanisms for evoking primary rewards have been revealed in detail in homeostasis research, those for information seeking remain poorly understood. Psychological studies have presented several criteria that human subjects use to assess information while they perform information seeking tasks. We examined which criterion the nervous system uses to assess information among the following criteria, the value of information (VOI; Hubbard, 2010), the probability gain (Baron, 1985), and Shannon information, which respectively capture reduction of expected cost, expected improvement of identifying correct response, and reduction in expected entropy. We recorded the activity of 1,126 and 737 neurons from the lateral prefrontal cortex (PFC) of two monkeys while they conducted information seeking tasks. RESULTS: (1) We found that more PFC neurons could encode the information values assessed with the VOI than the values with the other two criteria. (2) Using a principal component analysis, we found that responses of the entire populations of the recorded neurons effectively discriminated between the tasks performed. This suggests that the population responses represent different task variables, including the information values carried in the tasks. (3) Using a "targeted dimensionality reduction" approach (Mante et al., 2013), we found that the population responses could encode the information values of the VOI longer than the values of the other two criteria. CONCLUSION: Our results indicate that the lateral PFC is involved in assessing information according to the criterion of the VOI, which is given by measuring reduction in expected cost.

Disclosures: K. Nakamura: None. **M. Komatsu:** None.

Nanosymposium

273. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex I

Location: SDCC 25

Time: Monday, November 5, 2018, 8:00 AM - 10:45 AM

Presentation Number: 273.11

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R21DA040777

Title: Projections from the claustrum to the PFC regulate impulsive-like behavior

Authors: *J.-F. LIU, R. WU, B. JOHNSON, J. VU, J.-X. LI
Pharmacol. and Toxicology, SUNY At Buffalo, Buffalo, NY

Abstract: The claustrum is a subcortical region located next to the insular cortex. Because of the special shape of the claustrum, the function of the claustrum is obscure. Based on the structure

and connectivity of the claustrum, Crick and Koch proposed that the claustrum plays a critical role in consciousness. However, only a few of studies have investigated the function of the claustrum and the function of projections between the claustrum and other brain areas so far. Here, by using the 5-choice serial reaction time task (5-CSRTT), we explored the role of projections from the claustrum to the prefrontal cortex (PFC) in regulating attention and impulsive-like behavior. Rats were trained to perform the 5-CSRTT until they meet the criteria for test requirements. We then bilaterally microinjected the hM3-mCherry-AVV2/10 virus (0.5 ul/side) into the claustrum, and implanted the cannulae into the PFC. Additional sessions of training were performed after the rats were recovered from the surgery. CNO (1 mM/0.5ul/side) was microinjected into the PFC 10 min before test to activate projections from the claustrum to the PFC. We found that the manipulation had no effect on accuracy or number of omissions during test, but significantly increased premature responses. Perseverative response was not changed by the manipulation. These results suggested that activation of projections from the claustrum to the PFC induced impulsive-like behavior but did not affect attention in the 5-CSTRR task. Our further study is to investigate the effects of inactivation of projections from the claustrum to the PFC by the chemogenetic strategy on the 5-CSTRR task. Our current results suggest that projections from the claustrum to the PFC regulate impulsive-like behavior.

Disclosures: J. Liu: None. **R. Wu:** None. **B. Johnson:** None. **J. Vu:** None. **J. Li:** None.

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.01

Topic: H.02. Human Cognition and Behavior

Support: NIH grant MH061975

Title: A grid cell signal in human entorhinal theta oscillations

Authors: *S. MAIDENBAUM[1], J. MILLER[2], J. JACOBS[2]
[1]Biomed. engineering, [2]Dept. of Biomed. Engin., Columbia Univ., New York, NY

Abstract: Grid cells in the entorhinal cortex are a fundamental part of the brain's spatial system, supporting tasks such as spatial memory and path integration. In rodents, grid cells are thought to rely on large-scale network theta oscillations, but these signals manifest in different ways across species, challenging our understanding of the physiological basis of the grid network.
We analyzed intracranial recordings from neurosurgical patients during virtual navigation to identify the oscillatory characteristics of human grid cells.
The power of entorhinal theta oscillations showed six-fold modulation according to the virtual heading during navigation, which is a key signature of grid cells. This signal was specific to the

theta band, to six-fold symmetry and to the entorhinal cortex. Furthermore, modulation strength during recall correlated with spatial memory performance.
These results are important because they demonstrate a link between theta oscillations and the human grid network and, more broadly, because they show that features of neuronal representations can be identified from population electrophysiological recordings.

Disclosures: S. Maidenbaum: None. **J. Miller:** None. **J. Jacobs:** None.

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.02

Topic: H.02. Human Cognition and Behavior

Title: Spatial modulation of phases of spikes in the human entorhinal cortex

Authors: *Z. NADASDY[1,2,3], Á. TÖRÖK[4], P. NGUYEN[5], J. SHEN[6,8], D. BRIGGS[7,8], P. MODUR[9,8], R. J. BUCHANAN[10,8]
[1]Univ. of Texas At Austin, Austin, TX; [2]HCA Neurosci., Sarah Cannon Res. Inst., Austin, TX; [3]Dept. of Cognitive Psychology, Eötvös Loránd Univ., Budapest, Hungary; [4]Systems and Control Laboratory, Inst. for Computer Sci. and Control, Hungarian Acad. of Sci., Budapest, Hungary; [5]Sch. of Medicine, Baylor Col. of Med., Houston, TX; [6]Dept. of Neurol., Dell Med. School, The Univ. of Texas at Austin, Austin, TX; [7]Dell Med. School, The Univ. of Texas at Austin, Department of Neurology, TX; [8]Seton Brain & Spine Inst., Austin, TX; [9]Dept. of Neurol., Dell Med. School, The Univ. of Texas at Austin, Austin, Austin, TX; [10]Neurosurg., Seton Brain and Spine Inst., Austin, TX

Abstract: The ability to localize objects and ourselves relative to the environment relies on neuronal representations of space in the medial temporal lobe. Entorhinal cortical neurons generate grid-like firing patterns that scale and align with the environment, hence may provide an internal coordinate system for our spatial memory. The same cortical area also generates prominent local field oscillations. Despite the strong correlation of these oscillations with behavioral states, the spatial 2-dimensional relationship between grid-like firing patterns and local field oscillations has not been investigated. We recorded entorhinal cortical neurons in the human brain during spatial memory tasks performed in virtual environments and observed spatially modulated phase-relationship between action potentials and local field potentials. The spatial phase modulation exhibited significant correlations with the movement of the avatar, scaled with the environment, displayed discrete phase tuning at cellular level, rotated phase tuning at electrode level, and expressed spatially coherent phase maps with respect to the environment. Using surrogate data, we demonstrated that phase coherence is dependent on the

spatial phase dynamics of gamma oscillations. We argue that the spatial coordination of spike generation with gamma explains the emergence of grid cell activity in the entorhinal cortex.

Disclosures: Z. Nadasdy: None. **Á. Török:** None. **P. Nguyen:** None. **J. Shen:** None. **D. Briggs:** None. **P. Modur:** None. **R.J. Buchanan:** None.

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.03

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH061975

Title: Decoding spatial information from local field potentials in the human MTL

Authors: *N. A. HERWEG[1], P. A. WANDA[1], A. BRANDT[2], M. R. SPERLING[3], A. D. SHARAN[4], A. SCHULZE-BONHAGE[2], M. J. KAHANA[1]
[1]Dept. of Psychology, Univ. of Pennsylvania, Philadelphia, PA; [2]Epilepsy Ctr., Univ. Med. Ctr., Freiburg, Germany; [3]Neurol., Thomas Jefferson Univ., Philadelphia, PA; [4]Neurosurg., Thomas Jefferson Univ. Hosp., Philadelphia, PA

Abstract: The activity of cell-populations in the MTL represents an animal's trajectory through space. These representations are thought to support spatial navigation as well as memory for the spatial contexts associated with specific events. To characterize spatial representations at different stages of a hybrid spatial-episodic memory task, we recorded local field potentials from micro-wires implanted in the human MTL of 14 patients with medication-resistant epilepsy. Participants navigated through a virtual town consisting of target stores and non-target buildings to deliver objects to a sequence of target stores. We used multinomial logistic regression to decode location information from local field potentials (spectral power in 10 log-spaced frequencies between 3 and 200 Hz). We obtained significant classification of current spatial location in 10 out of 14 participants and at the group level. Classifier output probability for spatial location showed a steep and non-linear drop-off with spatial distance between a given class label and the participants' location, suggesting that a given spatial representation is activated suddenly as opposed to gradually when approaching the respective area in the environment. Furthermore, accuracy of location decoding increased over time, suggesting that classification is based on a representation of the spatial environment that is acquired through experience. In addition to decoding current location, we also obtained significant classification of goal location in 8 out of 14 participants and at the group level. Using classifiers trained on features from different MTL sub-regions yielded no difference in classification performance for current location or goal location. Taken together, these results provide compelling evidence that

neuronal populations throughout the human MTL represent local and distant spatial locations in a reference frame that is acquired through experience to support goal-oriented navigation.

Disclosures: N.A. Herweg: None. **P.A. Wanda:** None. **A. Brandt:** None. **M.R. Sperling:** None. **A.D. Sharan:** None. **A. Schulze-Bonhage:** None. **M.J. Kahana:** None.

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.04

Topic: H.02. Human Cognition and Behavior

Support: NIH R01-MH104606
NSF DGE 16-44869

Title: Intracranial recordings in humans reveal flexible coding of experience in the medial temporal lobe

Authors: *S. E. QASIM[1], J. MILLER[1], C. INMAN[2], R. E. GROSS[2], J. T. WILLIE[2], A. SHARAN[3], C. WU[3], M. SPERLING[3], B. C. LEGA[4], J.-J. LIN[4], S. A. SHETH[5], E. H. SMITH[6], G. MCKHANN[6], C. SCHEVON[7], J. M. STEIN[8], J. JACOBS[1]
[1]Biomed. Engin., Columbia, New York, NY; [2]Dept Neurosurg., Emory Univ. Sch. Med., Atlanta, GA; [3]Neurolog. Surgery, Thomas Jefferson Univ., Philadelphia, PA; [4]Neurosurg., UT Southwestern Med. Ctr., Dallas, TX; [5]Neurosurg., Baylor Col. of Med., Houston, TX; [6]Neurolog. Surgery, [7]Neurol., Columbia Univ., New York, NY; [8]Radiology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: The structures of the medial temporal lobe (MTL) have consistently been linked to spatial cognition and memory processes across species, including humans. However, the manner in which these structures participate in episodic memory retrieval as well as representation of spatial location is unclear. Recording from neurosurgical patients with depth electrodes in the MTL, we sought to untangle the spatial and mnemonic modulation of neural activity as subjects performed a memory task in a virtual environment.
We observed stable and consistent spatially modulated firing indicative of place cell activity in the MTL while subjects moved through the environment, as observed in our prior work. In addition thse stable place cells, we also observed cells that exhibited enhanced spatial firing as subjects approached the retrieval location. These cells, referred to as spatial retrieval cells, thus remapped their spatial fields as a function of the memory retrieval task. They also exhibited a corresponding increase in firing rate during memory maintenance, after the retrieval cue. This is the first evidence of a conjunctive influence of space and memory retrieval on single unit activity, as well as the first evidence in humans for flexible spatial representations at the level of

single cells. This serves as direct evidence that the MTL is involved in representing spatial location with reference to purely internal memory processes.

Disclosures: S.E. Qasim: None. **J. Miller:** None. **C. Inman:** None. **R.E. Gross:** None. **J.T. Willie:** None. **A. Sharan:** None. **C. Wu:** None. **M. Sperling:** None. **B.C. Lega:** None. **J. Lin:** None. **S.A. Sheth:** None. **E.H. Smith:** None. **G. McKhann:** None. **C. Schevon:** None. **J.M. Stein:** None. **J. Jacobs:** None.

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.05

Topic: H.02. Human Cognition and Behavior

Support: BMBF
NIH Grant 563386
DFG grant EXC 1086
SFB 874
SFB 1280
DFG AX82/3
DFG

Title: Cortico-hippocampal communication during goal-directed navigation: Evidence from functional magnetic resonance imaging and intracranial electroencephalography

Authors: *L. KUNZ[1], L. WANG[2], D. LACHNER-PIZA[1], H. ZHANG[3], A. BRANDT[1], M. DÜMPELMANN[1], P. C. REINACHER[4], V. A. COENEN[4], D. CHEN[5], W. WANG[5], W. ZHOU[6], S. LIANG[7], P. GREWE[8], C. BIEN[8], A. BIERBRAUER[3], T. NAVARRO SCHROEDER[9], A. SCHULZE-BONHAGE[1], N. AXMACHER[3]
[1]Dept. of Epileptology, Univ. of Freiburg, Freiburg, Germany; [2]Inst. of Psychology, Chinese Acad. of Sci., Beijing, China; [3]Dept. of Neuropsychology, Inst. of Cognitive Neurosci., Ruhr-University Bochum, Bochum, Germany; [4]Stereotactic and Functional Neurosurg., Univ. Med. Ctr. Freiburg, Freiburg, Germany; [5]Sch. of Systems Sci., Beijing Normal Univ., Beijing, China; [6]Dept. of Epilepsy Ctr., Tsinghua Univ. Yuquan Hosp., Beijing, China; [7]Dept. of Neurosurg., First Affiliated Hosp. of Gen. Hosp. of PLA, Beijing, China; [8]Bethel Epilepsy Ctr., Mara Hosp., Bielefeld, Germany; [9]Kavli Inst. for Systems Neuroscience, Ctr. for Neural Computation, NTNU, Norwegian Univ. of Sci. and Technol., Trondheim, Norway

Abstract: Goal-directed navigation is a complex behavioral capacity (*Chersi & Burgess, 2015*) and requires both a neural representation of the associative cue-location-memory as well as readout mechanisms of the representation during retrieval. Whereas representations of

associative memories are thought to be stored in a distributed fashion across cortical areas (*Josselyn et al., 2015*), the hippocampus may perform readout mechanisms. In the present study, we examined both data from functional magnetic resonance imaging (fMRI) in healthy participants as well as intracranial electroencephalography (iEEG) from presurgical epilepsy patients to further elucidate cortico-hippocampal communication during goal-directed navigation. We hypothesized (i) increased hippocampal blood-oxygenation-level dependent (BOLD) activity during successful cortical reinstatement of cue-location-association-representations in line with recent findings (*Bosch et al., 2014*) and (ii) dynamic reactivation of cortical representations locked to the hippocampal theta phase in line with theoretical models (*Battaglia et al., 2011*; *Watrous et al., 2014*; *Watrous et al., 2015*; *Heusser et al., 2016*). To this end, we employed a cue-location-memory-task requiring subjects to navigate freely in a virtual arena repeatedly asked to retrieve the location of different everyday objects within the arena (*Doeller et al., 2010*; *Kunz et al., 2015*). Applying multivariate pattern analysis on the fMRI data, we decoded cue-location-association-representations from distributed activity patterns primarily engaging visual cortices, lingual gyri, and retrosplenial cortices. Higher temporal stability as well as higher spatial narrowness of the representations were related to better classifier accuracy. Importantly, classifier accuracy correlated with memory performance both across as well as within subjects and decodable trials were accompanied by increased hippocampal activity, which parallels previous findings (*Staresina et al., 2012*; *Bosch et al., 2014*). Then, exploiting the high spatiotemporal resolution of iEEG in combination with representational similarity analysis, we derived temporally confined cue-location-association-representations from multivariate iEEG signals during cue-presentation. Dynamic reactivation of these representations during retrieval were locked to specific hippocampal theta phases. Taken together, our results suggest that the hippocampus coordinates the reactivation of cortical representations during goal-directed navigation and provide further evidence for phase coding in the human brain.

Disclosures: L. Wang: None. **D. Lachner-Piza:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); BrainLinks-BrainTools Cluster of Excellence funded by the German Research Foundation (DFG, grant number EXC CNE1086). **H. Zhang:** None. **A. Brandt:** None. **M. Dümpelmann:** None. **P.C. Reinacher:** 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.; Else Kröner-Fresenius Foundation, Bad Homburg, Germany; German Ministry for Economic Affairs and Energy, Berlin, Germany; Medical Faculty of the University of Freiburg, Freiburg, Germany.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Boston Scientific, Natick, Massachusetts, USA; Brainlab, Munich, Germany; Inomed, Emmendingen, Germany.. **V.A. Coenen:** None. **D. Chen:** None. **W. Wang:** None. **W. Zhou:** None. **S. Liang:** None. **P. Grewe:** None. **C. Bien:** 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.; Deutsche Forschungsgemeinschaft (Bonn, Germany), Gerd-Altenhof-Stiftung (Deutsches Stiftungs-Zentrum, Essen, Germany), diamed (Köln, Germany) and Fresenius Medical Care (Bad Homburg, Germany).. C. Other

Research Support (receipt of drugs, supplies, equipment or other in-kind support); Eisai (Frankfurt, Germany), UCB (Monheim, Germany), Desitin (Hamburg, Germany), Biogen (Ismaning, Germany) and Euroimmun (Lübeck, Germany).. F. Consulting Fees (e.g., advisory boards); Laboratory Krone, Bad Salzuflen, Germany; UCB (Monheim, Germany). **A. Bierbrauer:** None. **T. Navarro Schroeder:** None. **A. Schulze-Bonhage:** 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.; BMBF; NIH Grant 563386; BrainLinks-BrainTools Cluster of Excellence funded by the German Research Foundation (DFG, grant number EXC 1086). **N. Axmacher:** 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.; SFB 874, SFB 1280 und DFG AX82/3..

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.06

Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust Seed Award (204277/Z/16/Z)

Title: Integrating scenes into location-based representations

Authors: *S. BERENS, B. JOENSEN, A. HORNER
Dept. of Psychology, Univ. of York, York, United Kingdom

Abstract: Scene-selective regions of the brain are known to form location-based representations of our environment that are insensitive to heading direction. Given the diverse perceptual input that accompanies differing viewpoints in an environment, the formation of location-based representations is likely to depend on integrating information across multiple viewpoints. Using fMRI in humans, we tracked the emergence of such representations in scene-selective cortical regions for novel environments. We estimated patterns of activity for specific viewpoints before and after a learning phase that required participants to integrate viewpoints from the same location. The learning phase presented two video conditions: a full-panorama video showing two viewpoints at opposite ends of the same location, and an incomplete-panorama video showing two viewpoints from different locations. Representational similarity analysis (RSA) revealed that representations in the right parahippocampal place area (PPA) for viewpoints belonging to the same location became more similar to each after they had been presented in the full-panorama condition. No similar effect was seen in the incomplete-panorama condition. These results

suggest that the PPA plays a role in the rapid formation of location-based representations that generalise across different viewpoints.

Disclosures: S. Berens: None. **B. Joensen:** None. **A. Horner:** None.

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.07

Topic: H.02. Human Cognition and Behavior

Support: Office of Naval Research MURI N00014-10-1-0936
Office of Naval Research MURI N00014-16-1-2832

Title: Theta oscillations during active and passive decision making for human spatial navigation

Authors: *E. R. CHRASTIL[1,2], M. GONCALVES[2], K. MOORE[4,2], C. E. STERN[3], E. NYHUS[5]
[1]Dept. of Geography and Program in Dynamical Neurosci., Univ. of California, Santa Barbara, Santa Barbara, CA; [2]Psychological & Brain Sci., [3]Psychological & Brain Sciences, Ctr. for Memory & Brain, Boston Univ., Boston, MA; [5]Psychology and Program in Neurosci., [4]Bowdoin Col., Brunswick, ME

Abstract: Active navigation seems to yield better spatial knowledge than passive navigation, but it is unclear how active decision making influences learning and memory. We previously found that actively making decisions about where and how to explore a novel environment facilitated learning the path structure of a maze. Here, we tested the relationship between decision making and spatial memory by examining the role of theta oscillations during navigation. Theta rhythm is theorized to play a role in setting the dynamics for encoding and retrieval and is known to contribute to spatial coding in both animals and humans. Theta oscillations in prefrontal cortex could indicate integration of new information into memory and communication with the hippocampus. However, theta is also associated with speed of movement, possibly as a means to explore and encode more information about the environment. To separate the factors of movement speed and exploration, we tested individuals on a maze-learning task in which participants made discrete decisions about where to explore at each choice point in the maze. Half of the participants were free to make decisions at each choice point, and the other half passively explored by selecting a marked choice (matched to active exploration) at each intersection. They were then tested on their knowledge of the maze by traveling from object A to object B within the maze corridors. Exploration and test in this novel environment occurred while undergoing electroencephalography (EEG). Results show an advantage for active decision making during learning and indicate that the active group had greater theta power during choice

points in exploration, particularly in prefrontal cortex. These findings indicate the active exploration, not movement or speed, is important for theta oscillations during human spatial navigation. Finally, large individual differences in performance and theta oscillations were observed. Together, the results of this study suggest that hippocampal-prefrontal interactions are vital for learning and memory during active decision making.

Disclosures: E.R. Chrastil: None. **M. Goncalves:** None. **K. Moore:** None. **C.E. Stern:** None. **E. Nyhus:** None.

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.08

Topic: H.02. Human Cognition and Behavior

Title: Spatiotemporal binding of memories in typical and atypical brain development

Authors: *S. LEE
Daejeon, Korea, Republic of

Abstract: Although we have known for a long time that spatial representation and episodic memory share their hippocampal neural basis, it is still unclear how these processes are related. Using a developmental approach, this study explores the idea that binding of space and time provides a scaffold upon which episodic memory are built. We tested episodic memory in both typical children (2-8 years old) and Williams Syndrome patients (hippocampal abnormalities) using a nonverbal task that required subjects to bind objects and/or locations in a temporal sequence. In typically developing children, we found that the development of episodic memory is preceded by the emergence of the ability to bind together *where* and *when* (space and time) in memory. For instance, around 4 years of age, children began to accurately recall a temporal sequence of locations without being able to recall a temporal sequence of objects (which emerged later). When required to remember *what, where*, and *when* at the same time, children's performance in this full episodic task was predicted by their ability to bind *where* and *when*, but not their ability to bind *what* with *when*, consistent with the claim that the binding of space and time underlies episodic memory. Importantly, this developmental change in binding space-time was not attributable to improvements in spatial memory alone. Williams Syndrome (WS) patients performed significantly worse compared to mental age controls in remembering a sequence of locations, but not in remembering a sequence of objects. Their impairment was not explained by a deficit in spatial coding alone nor by general cognitive abilities. Unlike in typically developing children, however, when required to remember all three components (what, where, when), WS subjects performed even worse than would be predicted by their impairment in spatiotemporal binding. Surprisingly, their ability to remember single components of *what* or

where was intact. These results are consistent with the interpretation that while children first develop space-time binding and then a full episodic memory capacity, WS patients never develop a bounded sense of space-time and are generally impaired in binding elements to support episodic memory. Together, our results add to a growing body of work suggesting that the emergence of episodic recall for events is anticipated by the abrupt development of spatiotemporal binding at 4 years of age, which plays a scaffolding role of memory integration in episodic memory. This development is altered in WS due to the irregularities in their hippocampal function, resulting in the temporally disorganized nature of their episodic memories.

Disclosures: S. Lee: None.

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.09

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant K18 AG048706
Carlson College of Veterinary Medicine, OSU

Title: Age-related differences in spatial learning and neural activations in the early phase of reference memory acquisition in a virtual Morris water maze

Authors: *K. R. MAGNUSSON[1], J. Y. ZHONG[2], N. C. REYNOLDS[1], M. SWARTS[3], C. CLENDINEN[4], S. D. MOFFAT[2]
[1]Dept Biomed Sci, Coll Vet Med. & Linus Pauling Inst., Oregon State Univ., Corvallis, OR; [2]Sch. of Psychology, [3]Sch. of Architecture, Georgia Inst. of Technol., Atlanta, GA; [4]Emory Univ., Atlanta, GA

Abstract: This study applied a virtual Morris water maze (vMWM) task in assessing spatial learning performance differences between 21 young (18-30 years) and 21 older (greater than 60 years) adult men. The participants performed 24 hidden platform (place) trials and 24 visible platform (control) trials across four vMWMs. These trials were randomly mixed over four fMRI runs, each comprised of one vMWM with six place and six control trials. The participants were informed that the hidden platform was kept stationary in each vMWM. Data analysis was performed blinded to age of subject. Young participants and visible trials were used as controls. After controlling for age differences in the mean pathlength in control trials and dividing older adults into good and poor performers with respect to a median split procedure, the older poor performers were found to exhibit greater cumulative proximity to goal (i.e., more searches away from the hidden platform) than both the young ($p = .004$) and good older performers ($p = .027$).

In contrast, the good older performers attained comparable performance as the young ($p = .825$). In the fMRI scans, the group-level [place - control] contrast ($p = .005$) showed that both good and poor older performers exhibited higher activations in the medial frontal gyrus (BA 10), the left superior temporal gyrus (BA 22), and the cerebellum, compared with the young. There were also distinct patterns of neural activation from the comparison between each older performance subgroup and the young: (a) the older poor performers exhibited higher activation in the right precentral gyrus (BA 6/9) and right insula; (b) the older good performers exhibited higher activation in the cuneus, right parahippocampal gyrus (BA 28/34), and right superior parietal lobule (BA 7). Further comparison between the two older performance subgroups showed that good older performers exhibited higher activation in the angular gyrus (BA39) than the poor older performers. These results suggest that elevated engagement of the prefrontal cortex, as well as of other areas pertinent for spatial navigation (i.e., parahippocampal gyrus, parietal cortex), contributed to spatial learning among the good older performers to the same degree as that of the young. In contrast, elevated engagement of the prefrontal cortex did not contribute to successful spatial learning among the poor older performers relative to the young. This could be related to age-related decline in the prefrontal cortical circuits involved in the inhibition of redundant visuospatial information or greater cognitive effort

Disclosures: K.R. Magnusson: None. **J.Y. Zhong:** None. **N.C. Reynolds:** None. **M. Swarts:** None. **C. Clendinen:** None. **S.D. Moffat:** None.

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.10

Topic: H.02. Human Cognition and Behavior

Support: Collaborative Research in Computational Neuroscience Grant (01GQ1303) of the German Ministry of Education and Research (BMBF)
European Research Council Starting Investigator Grant AGESPACE (335090)

Title: Sources and mechanistic explanations for spatial navigation deficits in old age

Authors: *M. STANGL[1], I. KANITSCHEIDER[2], I. R. FIETE[3], T. WOLBERS[4]
[1]German Ctr. for Neurodegenerative Dis. (DZNE), Magdeburg, Germany; [2]Dept. of Neurosci., Univ. of Texas at Austin, Austin, TX; [3]Ctr. for Learning and Memory, UT Austin, Austin, TX; [4]German Ctr. For Neurodegenerative Dis., Magdeburg, Germany

Abstract: Numerous studies have reported a progressive loss of spatial navigation abilities in old age, but our understanding of the underlying sources and neuronal mechanisms is limited at present. One important navigation strategy is path integration, which involves the continuous

integration of self-motion cues to keep track of one's position and orientation. With an interdisciplinary approach, we combined neurophysiological measurements, behavioral path integration tests, and computational modeling of path integration errors. Using fMRI and a virtual reality navigation task in healthy young and older adults, we first investigated the putative firing of grid cells (i.e., grid-like representations), which are known to be a central component of the brain's navigation network. We found that grid-cell-like representations in entorhinal cortex were compromised in old age, and this effect was mainly driven by a reduced stability of grid orientations over time. In a second experiment, we found that individual magnitudes of grid-cell-like representations were predictive of age-related deficits in a behavioral path integration task, in which participants had to navigate based on integrating body-based or visual self-motion cues. Finally, in a third experiment, computational modeling allowed us to assess the influence of different bias-types and noise parameters on path integration performance. We identified internal noise and a bias in estimating velocity magnitude as the main sources of path integration errors in both young and older adults, with internal noise being the major cause of reduced path integration performance in older adults. Together, these results provide insight into sources of path integration deficits in old age, and potential mechanistic explanations for age-related decline of higher-order cognitive functions such as spatial navigation.

Disclosures: M. Stangl: None. **I. Kanitscheider:** None. **I.R. Fiete:** None. **T. Wolbers:** None.

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.11

Topic: H.02. Human Cognition and Behavior

Support: DFG Grant GR2627/8-1
BMBF Grant 01GQ1511

Title: Using mobile brain/body imaging (MoBI) to investigate the role of the retrosplenial complex for natural heading computation

Authors: *K. GRAMANN
Psychology and Ergonomics, Berlin Inst. of Technol., Berlin, Germany

Abstract: Human brain imaging of spatial cognitive processes usually requires stationary setups and immobile participants. Navigating through space, however, makes use of proprioceptive and vestibular information originating from movements and contributing to spatial updating. To overcome the restrictions of established brain imaging modalities, a Mobile Brain/Body Imaging (MoBI, Makeig et al., 2009; Gramann et al., 2011) method was employed to investigate the role of the retrosplenial complex (RSC) in heading computation. We assumed the RSC to be involved

in heading computation with differences in RSC activity for physical movement based on increased idiothetic input as compared to visual flow only. We further expected increased activity in RSC for well-learned as compared to unknown virtual environments.
In two experiments, participants computed heading changes during visual flow or physical rotation on the spot (Exp. I: N=20, female = 9) and while exploring sparse virtual mazes using thrusting gestures to search for walls of the environment (Exp. II: N=32, female = 17). Brain dynamics were recorded using mobile high-density electroencephalography (EEG) synchronized to motion capture and head-mounted virtual reality. EEG data were analyzed using independent component analysis (ICA) with subsequent source localization using equivalent dipole modeling and iterative k-means clustering to optimize a region of interest solution. In Exp. I, band power was computed and compared for different velocities during movement, contrasting physical and visual flow rotations. In Exp. II, spectral perturbations during navigation were computed and contrasted for unknown mazes as compared to well-learned mazes.
The results of Exp. I indicate velocity dependent frequency modulations during physical but not visual flow rotations in the beta frequency range in the RSC and increased activity in a wide frequency range in bilateral inferior parietal cortices. The results from Exp. II demonstrate pronounced and earlier onset activity in the RSC for well-known mazes as compared to unknown mazes in the alpha and beta frequency bands.
Both experiments indicate that the brain dynamics in RSC during physical movement in space differ markedly from visual flow movement even when the visual input is held constant. This points to the modulation of RSC activity based on proprioceptive and vestibular input from movement to compute heading changes. The results from Exp. II further provide evidence that heading can be established in well know environments based on sparse information only providing an important input for the planning of movements.

Disclosures:

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.12

Topic: H.02. Human Cognition and Behavior

Support: CIHR Gant no. 86727, 82638, and 301763
Famille Charron

Title: Different proinflammatory cytokines correlate to hippocampus and caudate nucleus dependent navigation strategies

Authors: *V. D. BOHBOT[1], J. POIRIER[2], J. BREITNER[2]
[1]Dept. of Psychiatry, McGill Univ., [2]Douglas Mental Hlth. Univ. Inst., Verdun, QC, Canada

Abstract: Aging is accompanied by a proinflammatory state that may lead to cognitive impairment and other age-related diseases. There is an increase in the levels of circulating proinflammatory cytokines (PICs) such IL-1, IL-6, and TNFα with age, and IL-6 in negatively correlated to grey matter in the hippocampus (HPC). Atrophy of the HPC is a risk factor for cognitive decline and Alzheimer's disease (AD). Furthermore, IL-1 impairs spatial memory which is a function that requires the critical contribution of the HPC. Therefore, the literature suggests that PICs play a key role in the development of cognitive impairments. Multiple strategies can be used to navigate in an environment. The spatial memory strategy involves forming a cognitive map by learning relationships between landmarks and this process requires the HPC. The stimulus-response strategy involves learning a series of motor responses from given environmental stimuli. The use of spatial, but not the response strategy, is associated with increased HPC grey matter, HPC fMRI activity and better overall cognition. The proportion of spatial strategy users decreases with age in favor of response strategies, and this is paralleled by a decrease in HPC integrity. Given that PIC levels is a marker of systemic inflammation that are negatively correlated with grey matter in the HPC, we wanted to examine the association between PICs and navigation strategies. Results show that TNF-α and IL-6 along with IL-12P40 and GM-CSF are correlated with the use of caudate nucleus dependent response strategies. These results are consistent with the previous literature showing that TNF-α is a predictor of conversion to AD while IL-6 correlates to atrophy of the HPC. On the other hand, INF-α2 and G-CSF correlate to the use of HPC-dependent navigation strategies which is consistent with an emerging literature on the role of certain cytokines in slowing cognitive decline. These results suggest that different cytokines may differentially target separate memory systems. In conclusion, these results suggest that certain PIC levels are favorable to the function of the hippocampus, whereas others are not. This study may contribute to our understanding of the factors involved in predicting cognitive decline in individuals as risk of AD.

Disclosures: V.D. Bohbot: None. **J. Poirier:** None. **J. Breitner:** None.

Nanosymposium

274. Human Cognition and Behavior: Spatial Learning and Navigation

Location: SDCC 23

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 274.13

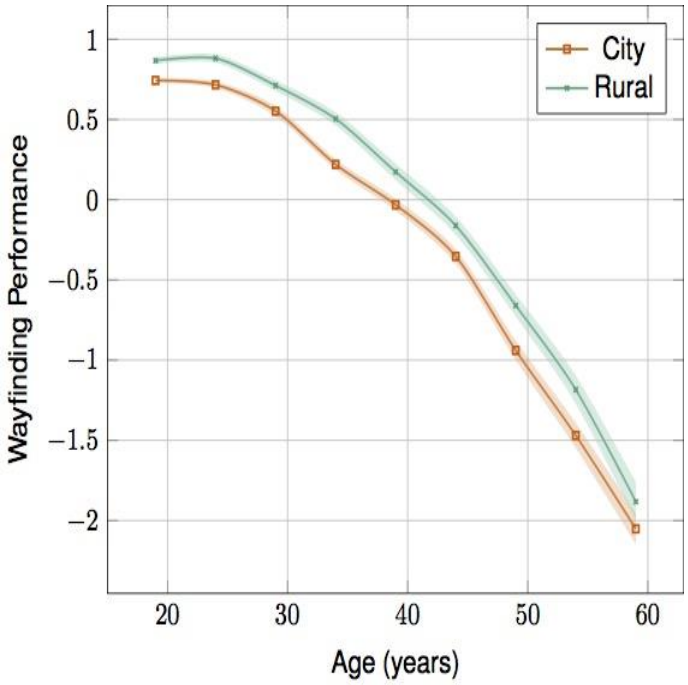
Topic: H.02. Human Cognition and Behavior

Support: ARUK grant
Deutsch Telekom Support

Title: Cities have a negative impact navigation ability: Evidence from mass online assessment via Sea Hero Quest

Authors: A. COUTROT[1], E. PATAI[2], R. SILVA[3], E. MANLEY[4], J. M. WEINER[5], R. C. DALTON[6], C. HOELSCHER[7], M. HORNBERGER[8], *H. J. SPIERS[3]
[1]CNRS, Univ. de Nantes, Nantes, France; [2]Exptl. Psychology, UCL Inst. of Behavioural Neurosci., UCL, United Kingdom; [3]Univ. Col. London, London, United Kingdom; [4]UCL, London, United Kingdom; [5]Univ. of Bournemouth, Bournemouth, United Kingdom; [6]Univ. of Northumbria, Newcastle, United Kingdom; [7]ETH Zurich, Zurich, Switzerland; [8]Univ. of East Anglia, Norwich, United Kingdom

Abstract: Animals display remarkable adaptation to different environments in their navigation abilities. Like other animals humans show an impressive capacity to overcome the challenges of navigating different terrains. These challenges are arguably different in rural and city environments. Cities typically require more discrete decision making on organised street networks, whereas rural environments may require more focus on distal landmarks and travel over greater distances. To examine whether growing up in a rural or a city environment impacts navigation ability we tested people with our virtual navigation test 'Sea Hero Quest' which is an app for mobile and tablet devices that requires participants to navigate a virtual boat to various locations marked on pre-shown map and records position and orientation allowing calculation of navigation skill (which we have shown is predictive of real-world navigation performance). Participants ($n > 200,000$) also reported whether they grew up in a rural, city or a mixed environment, and other demographics (age, gender, country of residence, education, daily commute duration, and handedness). We found that people who report growing up in a city show a consistently a worse level of navigation performance compared to those who report growing up in a rural environment, even when controlling for age, gender and level of education. This result held true in populations from all tested countries, but the effect size varied substantially: the US had the biggest difference (Hedge's $g = 0.23$) while Germany showed only a small difference ($g = 0.08$). While city vs rural environment did not interact with age (see Figure), the superior navigation ability of those with post-high-school education widened with age. Handedness and commute duration had negligible effects on navigation ability. To extend this research further we are exploring the relationship between neuroanatomical data and navigation performance using magnetic resonance imaging and will present preliminary findings.



Disclosures: A. Coutrot: None. **E. Patai:** None. **R. Silva:** None. **E. Manley:** None. **J.M. Weiner:** None. **R.C. Dalton:** None. **C. Hoelscher:** None. **M. Hornberger:** None. **H.J. Spiers:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.01

Topic: H.02. Human Cognition and Behavior

Support: EY016407

Title: Spatial priority in the service of non-spatial working memory

Authors: *M. RAHMATI[1,1], M. PAYTON[2], T. C. SPRAGUE[1], C. E. CURTIS[1], K. K. SREENIVASAN[3]
[1]New York Univ., New York, NY; [2]New York Univ., Madison, WI; [3]New York Univ. Abu Dhabi, Abu Dhabi, United Arab Emirates

Abstract: Previous studies (e.g., Serences et al., 2009; Harrison & Tong, 2009; Rahmati et al., 2018) support a sensory recruitment model of working memory (WM), which posits that the same neural mechanisms that encode sensory information also encode WM content (Postle & D'Esposito, 2015). Persistent activity during WM maintenance in frontal and parietal cortex may

provide top-down feedback signals that sculpt neural population activity in visual cortex during WM, keeping information in an accessible state (Curtis & D'Esposito, 2003; Sreeninvasan et al. 2014). Many of the areas that show robust delay period activity are in topographically organized portions of frontal and parietal cortex, where the topography may coordinate the prioritization of items in WM with retinotopic visual cortex (Jerde et al. 2012). Several studies provide strong evidence for this viewpoint in the context of spatial WM. Here, we extend this idea and test the hypothesis that spatial feedback signals might paradoxically even support WM for non-spatial features. To do so, we scanned subjects while they performed a WM task that required them to maintain the orientation of a Gabor patch presented peripherally in one quadrant of the visual field. After a long 10.5s delay, subjects compared the memorized orientation with the orientation of a second Gabor in the quadrant diagonal to the sample. This allowed us to dissociate the spatial position of the encoded stimulus and the spatial position of the test stimulus. In a pilot psychophysical study, we demonstrate that WM performance was better when the sample and test stimuli were in the same quadrant than when they were diagonal to one another. With fMRI and using an inverted encoding model (IEM; Brouwer & Heeger 2011; Sprague & Serences, 2013) of visual space using the patterns of voxel activity from the delay period activity in visual cortex, we could reconstruct the location of the sample stimulus even though its position was task irrelevant. Additionally, using an IEM of Gabor orientation, we could reconstruct the orientation of the stimulus at both the sample and test locations. Together, these results support the hypothesis that spatial feedback signals may prioritize the representation of even non-spatial features encoded at the prioritized location. Perhaps the shared spatial topographic organization in frontoparietal cortex and visual cortex provides a matched interface for perception and higher-order cognitive functions like WM, even when the relevant content is non-spatial in nature.

Disclosures: M. Rahmati: None. **M. Payton:** None. **T.C. Sprague:** None. **C.E. Curtis:** None. **K.K. Sreenivasan:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.02

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH095984

Title: Reconstructing stimulus identity and context binding from the CDA

Authors: Y. CAI[1,3], J. SAMAHA[4], *B. R. POSTLE[2]
[1]Psychiatry, [2]Univ. Of Wisconsin–Madison, Madison, WI; [3]Sch. of Psychology, Bejing Normal Univ., Bejing, China; [4]Psychology, Univ. of Wisconsin–Madison, Madison, WI

Abstract: A recent fMRI study comparing working-memory activity for one motion patch (1M) vs. 3 motion patches (3M) vs. 1 motion and 2 color patches (1M2C) showed a pattern of parietal delay-period activity of 1M = 1M2C < 3M, suggesting that this activity was sensitive to demands on context binding rather than on stimulus representation per se (Gosseries, Yu, et al., 2018). Might the same be true for the contralateral delay activity (CDA) ERP component? To address this question we applied multivariate inverted encoding modeling (IEM) to EEG data collected while subjects performed a delayed recognition (DR; a.k.a. “change detection”) task. First, to train IEMs, subjects performed a perceptual task that entailed viewing a series of variously oriented black bars. The DR task began with an arrow cuing that trial’s critical hemifield, followed by two balanced arrays of 1 or 3 items, one in each visual field, with trial conditions of 1 orientation (1O), 3 orientations (3O), and 1O + 1 color patch (1C) + 1 luminance patch (1L; i.e., "1O1C1L" trials); 1O vs. 1O1C1L operationalized load, and 1O1C1L vs. 3L operationalized context binding. DR performance followed the pattern 1O > 1O1C1L > 3O, with Cowan’s *k*s of 2.13 (SD=0.32) for 1O1C1L, and of 1.69 (SD=0.42) for 3O. Before computing the CDA, we compared voltages from electrodes contralateral vs. ipsilateral to the cued hemifield, and noted patterns of increasing negativity from 1O < 1O1C1L < 3O from the final 500 msec of the 900 msec delay period, in both sets of electrodes. Subtracting ipsilateral from contralateral signals to compute the CDA removed the 1O1C1L vs. 3O difference, suggesting that this subtraction may remove some signal related to context binding. To assess the informational content of the CDA, we sought to reconstruct representations of stimulus orientation by feeding the subtracted values from contralateral electrodes into the IEM of orientation constructed from the perceptual task (perceptual IEM trained with (unsubtracted) voltages from the same electrodes as contralateral electrodes from DR task). Results revealed successful reconstruction of remembered orientations from the 1O and from 1O1C1L conditions, suggesting that the CDA can contain nonspatial information that is specific to remembered stimuli. Furthermore, the width of the 1O1C1L reconstruction was broader than that from 1O trials, indicating a load-related decline in the precision of the neural representation. Finally, the superior IEM reconstruction of remembered orientation from 1O1C1L than from 3O trials suggests that the CDA contains information about the fidelity of stimulus representation that is not reflected in the first-order index of its magnitude.

Disclosures: Y. Cai: None. **J. Samaha:** None. **B.R. Postle:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.03

Topic: H.02. Human Cognition and Behavior

Title: Oscillations associated with binding errors in visual working memory

Authors: *K. K. SREENIVASAN, A. TEMUDO, V. BABUSHKIN
New York Univ. Abu Dhabi, Abu Dhabi, United Arab Emirates

Abstract: Memory errors are a window into the capacity limits that famously constrain visual working memory (VWM). When subjects maintain multiple items in VWM and are asked to report a feature of one item, they sometimes mistakenly report the feature of another item. This is referred to as a binding error. Understanding the neurophysiology underlying binding errors can provide key insights into how coherent representations are maintained in VWM.
One biophysiological model (Barbosa and Compte, 2015) suggests that object features are stored as bumps in individual attractor networks, and that features are bound together through synchronization between individual bumps. Crucially, this synchronization is mediated by intrinsic low-frequency oscillations in the network. A key prediction of this model is that binding errors should result from disruptions in the low frequency oscillatory pattern of the network. Our aim was to validate this model using magnetoencephalography (MEG) to measure network oscillations in a VWM task designed to induce binding errors.
On each trial, subjects briefly saw 3 circles and had to remember their colors and locations over a memory delay. After the delay, they were sequentially cued to report the location of each circle via a central color cue. Subjects' behavioral reports were analyzed using a maximum likelihood approach that assigned each response a likelihood of being a binding error. Trials with likelihoods greater than 0.7 were considered binding error trials. To examine low frequency network activity associated with binding errors, we computed a phase preservation index (PPI) for each MEG sensor separately for trials with and without binding errors. PPI measures the consistency of the relationship in oscillatory phase across trials. Binding errors were associated with significantly reduced PPI in the upper beta range (25-30 Hz) during the memory delay in frontal sensors. This pattern of reduced phase consistency was specific to binding errors, as opposed to other VWM errors. This finding provides initial support for the idea that object features are bound via low-frequency network oscillations.

Disclosures: K.K. Sreenivasan: None. **A. Temudo:** None. **V. Babushkin:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.04

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH064498

Title: Continuous theta-burst stimulation of parietal cortex alters representational structure of occipital stimulus representations in visual working memory

Authors: *Q. YU[1], O. GOSSERIES[1,2], B. POSTLE[1]
[1]Univ. of Wisconsin-Madison, Madison, WI; [2]Univ. and Univ. Hosp. of Liege, Liege, Belgium

Abstract: Persistent elevated activity in parietal cortex and decodable mnemonic representation in occipital cortex have been consistently observed during working memory maintenance and have thus been a major focus of working memory research. Recent work has suggested that persistent elevated activity in parietal cortex reflects demands of context binding, and that BOLD activity in parietal cortex, multivariate decoding accuracy of stimulus identity in occipital cortex, and behavioral memory precision are all inter-related (Gosseries, Yu, et al., 2018). In the current study, we sought to causally examine the relationship between parietal function and mnemonic representations in occipital cortex using continuous theta-burst stimulation (cTBS). Participants performed a delayed-recall (a.k.a., "-estimation") task on motion directions of load 1, 2, and 3. Each participant underwent a baseline session (no cTBS), two IPS-stimulation sessions (cTBS on IPS), and two MT-stimulation sessions (cTBS on MT). We used multivariate pattern analysis (MVPA) to examine the stimulus representations in occipital voxels with strongest sample-driven activity. Replicating previous findings, the remembered motion direction could be decoded in all three load conditions during the delay period, and decoding accuracy decreased with increasing memory load. This pattern was observed in all conditions, with or without cTBS, except that decoding accuracy for load 3 in the IPS-stimulation condition dramatically dropped to baseline in the middle of the delay period, a result suggesting that perturbation of IPS function impacted stimulus representation in occipital cortex at high loads. Moreover, when the classifier was trained on the baseline condition and tested on the cTBS conditions, or vice versa, most of the decoding performance returned to baseline. This failure in cross-condition decoding suggested a change in representational structure of stimulus representations in occipital cortex when cTBS was applied. These results together suggest a causal role of IPS in controlling stimulus representations in occipital cortex in visual working memory, particularly in conditions that put a heavy demand on context binding, an operation that may be governed by parietal salience maps.

Disclosures: Q. Yu: None. **O. Gosseries:** None. **B. Postle:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.05

Topic: H.02. Human Cognition and Behavior

Support: NSF/SL-CN 1640914
NIH/NEI ROIEY024056

Title: Memory visualization and spatial learning

Authors: *L. T. LIKOVA[1], C. W. TYLER[2]
[2]Smith-Kettlewell Brain Imaging Ctr., [1]Smith-Kettlewell Eye Res. Inst., San Francisco, CA

Abstract: Introduction. To analyze mechanisms of learning and visual working memory, we asked what brain networks are involved in the processes of study through direct viewing, and of visualization from immediate memory, of previously unfamiliar material.
Methods. Functional MRI was run while complex spatial structures in the form of line-drawings were alternately i) shown and viewed to be learned, and ii) mentally visualized on a blank screen in a novel procedure to enhance their memory representations. During every trial, the viewing and visualization blocks were 30 s each, separated by 20 s rest periods, and repeated 3 times. The brain imaging session was followed by testing of comprehension and by reconstruction through memory-guided drawing of the learned material. Results & Conclusions. The first site of particular interest was the primary visual cortex (V1) as our previous studies in the blind have implied that V1 neurally implements - in an amodal form - the 'spatial sketchpad' for working memory (Likova, 2012, 2013). The primary visual cortex was subdivided into foveal, parafoveal, mid- and far-peripheral regions. Remarkably, direct viewing and visualization equally activated the far- and mid-periphery regions, whereas the visualization signal in the parafoveal representation dropped to about half of that of the direct viewing, and surprisingly even inverted into strong suppression throughout the foveal confluence. Stemming from peripheral V1, a distributed visualization network included parietal and frontal regions. Conversely, the classical visual hierarchy beyond V1 was not involved. Granger causality analysis was used to disentangle the interregional interactions within the activated networks and to provide deeper insights into cortical mechanisms of visualization from memory and its involvement in learning.

Disclosures: L.T. Likova: None. **C.W. Tyler:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.06

Topic: H.02. Human Cognition and Behavior

Support: Academy of Finland, grant 298329

Title: A population coding model for simple and complex visual objects in working memory

Authors: *V. SALMELA[1,2], K. ÖLANDER[1], I. MUUKKONEN[1], P. M. BAYS[2]
[1]Dept. of Pychology and Logopedics, Univ. of Helsinki, Helsinki, Finland; [2]Dept. of Psychology, Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Many studies of visual working memory test humans' ability to reproduce primary visual features of simple objects, such as the orientation of a grating or the hue of a color patch, after a delay. A quintessential finding of such studies is that the precision of responses declines continuously with increases in the number of features or objects in memory. This phenomenon, and the specific distributions of error observed at each set size, can be parsimoniously explained in terms of neural population codes. Here we examined visual working memory for high-level objects, images of human faces. We presented participants with memory arrays consisting of oriented gratings, facial expressions (angry, sad, fearful, disgusted or happy), or a mixture of both. Memory precision was measured using a reproduction task in which participants adjusted, after a two second retention interval, the expression (or orientation) of a probe item to match a cued item from the memory array. Precision of reproduction for all five facial expressions declined continuously as the memory load was increased from one to five faces. When both gratings and faces had to be remembered simultaneously, an asymmetry was observed. We found that increasing the number of faces decreased precision of orientation recall, but increasing the number of gratings did not affect recall of facial features. These results suggest that memorizing faces involves the automatic encoding of low-level features, including orientation, in addition to high-level expression information. We adapted the population coding model for circular variables to make it applicable to the non-circular and bounded parameter space used for expression estimation. The model had two free parameters, tuning width and gain constant, that determined the Gaussian tuning and overall response level of neurons encoding expressions of different intensity. Total population activity was held constant as a function of memory load according to the principle of normalization. The intensity of expression was decoded from the population response by drawing samples from the Bayesian posterior distribution. The decreasing activity associated with each item explained the decrease in memory precision with set size, and the differences between expressions were explained primarily by differences in the gain constant. Replacing the uniform prior with a Gaussian further improved the fit to data, by accounting for the bias in participants' responses towards neutral or moderate expressions. Our results show that principles of population coding can be applied to model memory representations at multiple levels of the visual hierarchy.

Disclosures: V. Salmela: None. **K. Ölander:** None. **I. Muukkonen:** None. **P.M. Bays:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.07

Topic: H.02. Human Cognition and Behavior

Title: Retrospectively cuedattention shifts mitigate information loss in human cortex during working memory storage

Authors: *E. F. ESTER, L. RODRIGUEZ, A. NOURI
Psychology, Florida Atlantic Univ., Boca Raton, FL

Abstract: Working memory (WM) performance can be improved by a retrospective cue presented after encoding is complete. Several (non-exclusive) mechanisms may be responsible for this improvement, and the effects of retrospective cues on neural representations of memoranda are poorly understood. To address these issues, we combined EEG and image reconstruction techniques to track cue-driven changes in spatial WM representations over time. Participants encoded the spatial locations of two colored discs (blue and red). During neutral trials, an uninformative color cue presented after the encoding display informed participants to remember the locations of both discs across a 2500 ms blank interval. During valid trials a 100% reliable color cue indicated which disc would be probed at the end of the trial. Valid cues were presented either immediately after offset of the encoding display (valid-early, VE), or at the midpoint (1250 ms) of the subsequent blank interval (valid-late, VL). To examine the effects of retro-cues on spatial WM representations, we computed an estimate of location-specific information for cued and uncued locations by applying an inverted encoding model to spatiotemporal patterns of induced alpha-band activity over occipitoparietal electrode sites during the blank delay period (e.g., Foster et al. J Neurophysiol 2016). During neutral trials we observed a monotonic decrease in location-specific information over the course of the delay period. During valid trials this decrease was eliminated (VE trials) or partially reversed (VL trials) for cued locations and exacerbated for un-cued locations (VE and VL trials). Our findings suggest that retrospectively-cued shifts of attention enhance memory performance by preventing (VE) or partially reversing (VL) information loss during WM storage.

Disclosures: E.F. Ester: None. **L. Rodriguez:** None. **A. Nouri:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.08

Topic: H.02. Human Cognition and Behavior

Support: NIH F32-EY028438
NIH R01-EY027925

Title: Tracking the dynamics and uncertainty of visual spatial working memory representations across human cortex

Authors: *T. C. SPRAGUE[1], A. YOO[1], M. RAHMATI[1], W. MA[1,2], C. E. CURTIS[1,2]
[1]Dept. of Psychology, [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Visual working memory (WM) enables the maintenance and manipulation of information over brief delays. Nearly a decade of neuroimaging studies applying a variety of machine learning techniques have identified neural correlates of WM representations of features like orientation and color in visual (Serences et al, 2009; Harrison & Tong, 2009), parietal (Bettencourt & Xu, 2016), and frontal cortex (Ester et al, 2015; Yu & Shim, 2017). Additionally, when participants must precisely maintain spatial positions in WM, robust decoding of those positions is possible across many retinotopically-organized visual maps (Jerde et al, 2012; Sprague et al, 2014; Rahmati et al, 2018). How do neural representations in each of these visual maps unfold over time to support WM behavior? We applied several multivariate analyses to (1) assay the temporal evolution of WM representations across human cortex and evaluate their stability, (2) decode the uncertainty with which each region represents the remembered feature value and (3) relate these metrics to aspects of behavioral performance. Participants performed a single-item memory-guided saccade task while we measured neural responses using whole-brain fMRI at sub-second temporal resolution (1.33 Hz). We applied a linear inverted encoding model (IEM) to reconstruct the contents of WM as they evolved through each 12-s trial from visual maps in occipital, parietal, and frontal cortex. Despite the sluggishness of the BOLD signal, we observed stark differences in the temporal profile of information content across several visual maps. For example, V3AB representations were observed at earlier timepoints within the trial than those in earlier (V1-V3) or later (IPS0-2) visual maps. Moreover, representations in this map (among several others) were remarkably stable: models estimated at the beginning or end of the delay period enabled reconstruction of nearly identical representations. Next, we extended the linear IEM to a full generative model, which enabled us to recover not just a point estimate of the neural representation, but a full likelihood function over feature space, from which we could estimate uncertainty (van Bergen et al, 2015). Within several posterior parietal and occipital visual maps (including V3AB), we found that increases in decoded uncertainty predict wider memory error distributions, suggesting a critical link between our measure of neural response patterns and the quality of WM representations. Ongoing work aims to extend these methods to larger WM loads and additional task demands, including explicit and implicit judgments about the quality of WM representations (Rademaker et al, 2012; Suchow et al, 2017).

Disclosures: T.C. Sprague: None. **A. Yoo:** None. **M. Rahmati:** None. **W. Ma:** None. **C.E. Curtis:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.09

Topic: H.02. Human Cognition and Behavior

Title: Can TMS to visual cortex reactivate unattended representations held in visual working memory?

Authors: *M. WIDHALM[1], N. S. ROSE[2]
[2]Dept. of Psychology, [1]Univ. of Notre Dame, Notre Dame, IN

Abstract: Recent research on working memory (WM) has shown evidence for activity-silent retention mechanisms and the reactivation of latent representations in WM with transcranial magnetic stimulation (TMS) on simultaneously-recorded EEG (Rose et al., 2016, *Science*). What is unclear is if TMS to sensory cortex can reactivate stimulus-specific features of these representations. Here we used a concurrent TMS-EEG protocol in seven healthy young adults (aged 18-35) to investigate if TMS to primary visual cortex could reactivate stimulus-specific features of latent representations in visual WM. We first applied single pulse TMS (spTMS) to left V1/V2 to localize phosphenes in the lower right visual field for each participant. Then two oriented gratings were presented -- one at the phosphene location for each subject and the other in the opposite (left) hemifield at the same angle and distance from fixation. These gratings were to be retained on a WM task with two retro-cues and two recognition probes, such that one grating would be attended and the other un-attended following each retro-cue. During the delay period following both cue 1 and cue 2, spTMS was applied to the retinotopic location of the target sensory representation in primary visual cortex at 110% of phosphene threshold. We used inverted encoding models to reveal if the specific orientation of the latent memory item could be reconstructed from the TMS-evoked response on simultaneously recorded EEG. Orientation of both the attended and unattended items could be reconstructed from time windows 80-600ms after TMS (ps < .01). TMS also had the effect of reducing recognition memory precision for items presented ipsilateral to TMS that were initially held in an unattended state (p= .03). In sum, TMS to primary visual cortex caused the reactivation of stimulus specific features of latent representations held in visual WM and affected visual WM precision. These results provide causal evidence for a role of sensory recruitment for visual WM.

Disclosures: M. Widhalm: None. **N.S. Rose:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.10

Topic: H.02. Human Cognition and Behavior

Support: NIH grant R01MH076226

Title: Motion perception in 360°: Decoding direction of motion using alpha-band EEG oscillations and sustained ERPs

Authors: *G.-Y. BAE, S. J. LUCK
Psychology, UC Davis, Davis, CA

Abstract: Recent advances in multivariate classification have made it possible to decode neural representations using the topography of human scalp EEG signals. However, it is unclear whether the EEG decoding reflects bona fide stimulus representations or attention-related support mechanisms that underlie task performance. The present study tested the hypothesis that alpha band (8-12 Hz) oscillations primarily reflect attentional mechanisms whereas sustained ERPs reflect both stimulus representations and attentional mechanisms. To test this hypothesis, we recorded the EEG while observers performed a motion direction estimation task. They viewed random dot kinematograms (RDKs; 25.6% or 51.2% coherence) in which the coherent motion could be in any direction from 0°-360°, and they reported their perception of the exact motion direction at the end of the stimulus. In the decoding analyses, the stimulus direction was discretized into 16 direction bins, and a multiclass support vector machine (SVM) was trained to classify the data from a given direction into one of the 16 direction bins. We decoded the direction of motion at each time point during both the stimulus period (during which motion information was being accumulated) and the report period (during which a shift of attention was necessary to make a fine-tuned direction report). For trials with high motion coherence (51.2%), we found that ERP-based decoding was above chance during both the stimulus and the report periods, whereas alpha-based decoding was near chance during the stimulus period but was above chance during the report period. However, both ERP-based and alpha-based decoding were at chance during both the stimulus and the report periods for trials with low motion coherence (25.6%). Because the lack of decodability for the low motion coherence could be due to large variability in the perceived motion direction, we attempted to decode the reported direction instead of the stimulus direction. ERP-based decoding of reported direction for the low motion coherence trials was above chance during both the stimulus and report periods. Alpha-based decoding of the reported direction was only briefly above chance during the stimulus period but well above chance during the report period. Together, these results show that sustained ERP activity reflects both the actual stimulus direction and the reported direction, whereas alpha-band oscillations primarily reflected the process of converting the perceived direction into a report.

Disclosures: G. Bae: None. **S.J. Luck:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.11

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R21EY027703
NIH Grant R01EY022229
NIH Grant R01MH111868
NSF GRFP DGE-1247312

Title: Stimulus-specific visual working memory representations in human cerebellum

Authors: ***J. A. BRISSENDEN**[1], S. M. TOBYNE[2], M. A. HALKO[3], D. C. SOMERS[1]
[1]Psychological and Brain Sci., [2]Grad. Program for Neurosci., Boston Univ., Boston, MA;
[3]Neurol., Harvard Med. Sch. / Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: The question of where working memory (WM) contents are stored in the brain is the subject of ongoing debate. Based on electrophysiological recordings in non-human primates and neuroimaging in humans, it has long been asserted that pre-frontal cortex (PFC) supports WM maintenance (Funahashi et al., 1989; Courtney et al., 1998; Mendoza-Halliday et al., 2014). On the other hand, the sensory recruitment hypothesis posits that WM storage is mediated by the same areas involved in the initial sensory processing of stimuli and that the PFC instead serves as a source of top-down biasing signals (Pasternak & Greenlee, 2005; D'Esposito & Postle, 2015). Recently, it has been suggested that working memory contents are distributed across a number of cortical areas including both sensory and PFC regions (Serences, 2016; Christophel et al., 2017). Despite findings of robust connectivity between cerebellar sub-regions and cortical areas implicated in working memory storage, no one has examined whether any portion of the cerebellum encodes stimulus-specific representations during visual working memory. To investigate WM stimulus specificity in the cerebellum, participants were presented with two circular patches of coherent dot motion followed by a post-cue indicating which motion direction to maintain over a long delay-period (10 s). Participants then adjusted a probe stimulus to match the remembered motion direction. Using a forward encoding model of motion direction, we were able to accurately reconstruct the remembered motion direction from the delay-period multi-voxel activity patterns of cerebellar lobules VIIb/VIIIa. In contrast, non-remembered motion directions could not be reconstructed from cerebellar delay-period activity patterns. These results bolster the notion that a distributed network of brain areas supports WM storage and further show that this network is not limited to cortical structures. Moreover, our findings provide new insight into the function of the cerebellum and its contributions to cognitive processing.

Disclosures: J.A. Brissenden: None. **S.M. Tobyne:** None. **M.A. Halko:** None. **D.C. Somers:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.12

Topic: H.02. Human Cognition and Behavior

Support: NIH R01-EY022229
NSF SMA-0835976
NIH F32-EY026796
NIH F31-NS103306

Title: Sensory-selective and sensory-independent auditory and visual working memory in human cerebral cortex

Authors: *A. L. NOYCE[1], S. M. TOBYNE[2], B. SHINN-CUNNINGHAM[3], D. C. SOMERS[1]
[1]Psychological and Brain Sci., [2]Grad. Program for Neurosci., [3]Biomed. Engin., Boston Univ., Boston, MA

Abstract: Working memory (WM) depends on stimulus-specific sensory representations as well as on more general cognitive processes (e.g. Pasternak & Greenlee 2005; Duncan 2010; D'Esposito & Postle 2015; Ester et al. 2015, Sarma et al. 2016). However, there is still little consensus on the relative contributions of these two systems, or even on which brain structures participate in which. Most prior work has been exclusively within the visual sensory modality, measuring WM specialization for particular visual feature dimensions. Here, we take a broader focus by measuring recruitment in individual subjects during visual WM and auditory WM in order to characterize cortical regions in terms of the degree of sensory selectivity or sensory independence exhibited. Subjects (n=15) performed visual and auditory 2-back while fMRI was collected (TR = 2s, TE = 30ms, 2mm voxels). The magnitude of visual and auditory WM recruitment at each cortical vertex in each subject was used to compute the Multiple Demand Index (Noyce et al. 2017), a continuous measure of shared activation across tasks. We observed sensory-selective activation bilaterally in lateral frontal regions along the precentral sulcus (as previously reported; Michalka et al. 2015; Noyce et al. 2017), as well as in the expected posterior cortical regions. Our previous group-level functional connectivity analysis of Human Connectome Project data suggested the existence of additional sensory-selective regions in more anterior portions of LFC (Tobyne et al., 2017). Here we confirm their existence in individual subjects by revealing sensory-selective WM task recruitment of additional frontal regions (visual: mid inferior frontal sulcus (midIFS); auditory: frontal operculum (FO)). Sensory-independent regions lie immediately adjacent to many of these structures. These include superior & inferior frontal junction and anterior & mid inferior frontal sulcus, as well as anterior insula, medial superior frontal gyrus, lateral/anterior portions of the intraparietal sulcus (IPS), and posterior superior temporal sulcus (STS). The precise organization of sensory-selective and multisensory-selective structures is fine-grained, with regions in close proximity exhibiting different modality preferences; conventional group-average analyses are insufficient to detect organization that can be observed in within-subject analyses. These results demonstrate a new approach to understanding the complex organization of sensory-specific and sensory-independent structures that support human cognition.

Disclosures: A.L. Noyce: None. **S.M. Tobyne:** None. **B. Shinn-Cunningham:** None. **D.C. Somers:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.13

Topic: H.02. Human Cognition and Behavior

Support: ONR AWD1004142

Title: A flexible model of working memory

Authors: *F. BOUCHACOURT[1], T. BUSCHMAN[2]
[1]Princeton Neurosci. Inst., Princeton Neurosci. Inst., Princeton, NJ; [2]Princeton Neurosci. Inst. & Dept of Psychology, Princeton Univ., Princeton, NJ

Abstract: Working memory is fundamental to complex cognition, providing the workspace on which thoughts are held and manipulated. A defining characteristic of working memory is its flexibility: we can hold anything in mind. However, typical models of working memory rely on tightly tuned attractors to maintain a persistent state of activity and therefore do not allow for the flexibility observed in behavior.

Here we present a novel network model that captures the flexibility of working memory. To achieve this, the network uses a two-layer structure. First, a “sensory” layer encodes inputs into several independent pools of selectively tuned neurons. This layer is then randomly, reciprocally connected with a second “random” layer of neurons. The bi-directional recurrent connectivity between the sensory and random layers maintains inputs. Importantly, due to the parameter-free nature of these interactions, the model can maintain any inputs, without tuning, capturing the flexibility of working memory. However, this flexibility comes at a cost: the randomness of connections between the sensory layer and random layer leads to interference between memory representations, resulting in a capacity limitation on the number of items that can be maintained in the network.

Our model provides a mechanistic account for several behavioral and neural hallmarks of working memory. First, the network has a limited capacity, able to maintain only a few items at a time. Second, consistent with electrophysiological and imaging evidence, adding multiple memories leads to divisive-normalization-like interference due to balanced excitation and inhibition in the network. Such interference reproduces experimental observations on the effect of time, load, and their interaction, on memory degradation in analog tasks. Third, neural representations are distributed across the network, as seen in humans and animals. Fourth, neurons in the untuned layer show the high-dimensional, "mixed" selectivity observed in prefrontal cortex. Finally, although neural activity in the model is dynamic, mnemonic representations are separable within a stable subspace, consistent with recent monkey electrophysiology findings for single item working memory tasks. The model makes several

predictions, including that increasing memory load should not change the memory subspace but should reduce the discriminability between memories in this space, making them harder to decode. In summary, we present a simple, parameter-free, network model that uniquely allows for flexible representations while still capturing key behavioral and neural characteristics of working memory.

Disclosures: F. Bouchacourt: None. **T. Buschman:** None.

Nanosymposium

275. Human Cognition and Behavior: Working Memory I

Location: SDCC 5

Time: Monday, November 5, 2018, 8:00 AM - 11:30 AM

Presentation Number: 275.14

Topic: H.02. Human Cognition and Behavior

Support: FP7-HEALTH-2013-INNOVATION-1-602186 BRAINTRAIN
BIGDATIMAGE (CENTRO-01-0145-FEDER-000016)
COMPETE
POCI-01-0145-FEDER-007440
FCT-UID/NEU/04539/2013
UID/NEU/04539/2016
Bial Fellowship Programme Application Numbers 206/ 373/2014

Title: Intracranial recordings within human hippocampus reveal task dependent spectral signatures

Authors: *J. M. CASTELHANO[1], I. C. DUARTE[1], F. PELLE[2], S. FRANCIONE[2], F. SALES[3], M. CASTELO-BRANCO[4]
[1]IBILI/ICNAS, Univ. of Coimbra, Coimbra, Portugal; [2]Claudio Munari Epilepsy Surgery Center, Niguarda Hosp., Milan, Italy; [3]Epilepsy unit, CHUC, Coimbra, Portugal; [4]IBILI - Fac. of Medicine, Univ. of Coimbra, Coimbra, Portugal

Abstract: It is well-known that the hippocampal formation plays a crucial role in memory encoding. However, functional specialization of distinct parts within hippocampus remain unclear. The separation of functions of anterior and posterior regions of the hippocampus is well-recognized. The posterior hippocampus has been shown to be involved in spatial memory and navigation while the anterior hippocampus mediating other complex memory functions. We aimed to clarify the relative role of anterior/posterior human hippocampus in a wide array of memory and non-memory related tasks, through the analysis of task related oscillatory patterns. Patients had been submitted to stereo-electroencephalography (sEEG) with a 3D array of electrodes implanted in different areas of their brain for localization of seizure foci. Many of these patients have implanted depth electrodes with contacts reaching the hippocampus region.

We studied the hippocampus function while subjects were performing distinct neuropsychological tasks, relevant for their assessment. To our knowledge, this is the first study including sEEG analysis of subjects performing distinct neuropsychological tasks for long periods. Invasive data were acquired from 7 subjects who had stereotactically implanted intracranial depth electrodes. Tasks were chosen to assess different cognitive tasks related to memory. Briefly, we divided the data into blocks containing different tasks (Rey Figure, Benton tasks, visuo-spatial memory, face recognition and selective attention) and performed Time-frequency analysis between 5-500Hz [Uhlhaas et al., 2006]. Significant induced oscillations were detected by frequency band of interest (Theta 4-8Hz, Alpha 8-12Hz, Beta 15-25Hz, Gamma, above 30Hz) in the hippocampal contacts. Statistical analysis (Friedman test) comparing the power per frequency band, tasks and hippocampus regions (anterior/posterior) confirmed a main effect of frequency band ($p=0.002$). In the lower frequency bands (theta and alpha), we found mainly differences between high memory load tasks and no memory load tasks ($p=0.002$) in the anterior hippocampus, while power at gamma frequencies was higher for visual attention tasks, in particular in the anterior hippocampus. Furthermore, we found a pattern of activation in alpha and beta bands in posterior hippocampus that show a gradient related to the memory load of the task in hand (lower power for simpler visuoconstructive tasks). The present findings support the critical role of low frequency (human theta and alpha) oscillations in the hippocampus during memory tasks and suggests the presence of task related spectral signatures.

Disclosures: J.M. Castelhano: None. **I.C. Duarte:** None. **F. Pelle:** None. **S. Francione:** None. **F. Sales:** None. **M. Castelo-Branco:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.01

Topic: I.03. Anatomical Methods

Support: NIMH U01MH114829

Title: High throughput anatomical characterization of projection neuron types of the mouse brain

Authors: *H. DONG[1], B. LIM[2], I. R. WICKERSHAM[3], H. HINTIRYAN[1], G. A. ASCOLI[4]
[1]USC Stevens Neuroimaging and Informatics Inst., Keck Sch. of Med. of USC, Los Angeles, CA; [2]Biol. Sci., UCSD, La Jolla, CA; [3]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [4]George Mason Univ., Fairfax, VA

Abstract: Identifying the diversity of neuronal cell types of the nervous system is one of the main objectives of the BRAIN Initiative, with the vision that distinct neuronal identities will allow for their selective manipulation and reveal their functional contributions in health and

disease. However, identifying all the cell types of the mammalian brain is not a trivial undertaking and is hindered by the fact that a satisfactory definition of neuronal cell type is nonexistent, with terms like “class”, “subclass”, “type”, and “subtype” often used interchangeably without proper definition. As part of the BICCN (BRAIN Initiative Cell Census Network), we have developed a practical, robust, and multi-pronged workflow to systematically classify projection neuron types based on their precise anatomical location, long-range connectivity, input/output organization, and detailed neuronal morphology. These connectivity-based neuronal classification strategies can be integrated or validated with other cell type specific information, such as molecular identities (mRNA expression, epigenomics, or genetic labeling), electrophysiological properties, and functional specificities. In addition, we have been developing several informatics databases and online visualization tools (NeuroMorpho.Org; MouseConnectome.org; Hippocampome.org), which allow neuroscientists to view and analyze cell type specific images and maps, serving as foundational open resources for the research community and the general public world-wide. As the first step towards this long term goal, we demonstrate our approach by generating a comprehensive anatomical survey of cell types in the primary motor cortical area upper limb domain of the mouse brain, as a component of the BICCN Mini Atlas project.

Disclosures: H. Dong: None. **B. Lim:** None. **I.R. Wickersham:** None. **H. Hintiryan:** None. **G.A. Ascoli:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.02

Topic: I.03. Anatomical Methods

Support: HHMI (CD, AR and XZ)
NIH R01 4R01DC013087-04 (CD)
5R01HD082131-02 (CD)
1R01MH111502-01 (CD, AR and XZ)
NIH 1R01MH113094-01 (CD and XZ)
NIH 1K99 HD092542-01 (DB-M)
Helen Hay Whitney Fellowship (JRM)

Title: *In situ* Transcriptomics reveals a high resolution spatial and functional atlas of cell types in the mouse preoptic region

Authors: *D. BAMBAH-MUKKU[1,6], J. R. MOFFITT[2], S. EICHHORN[3], E. VAUGHN[4], K. SHEKHAR[7], A. REGEV[7], X. ZHUANG[5], C. DULAC[1]
[1]Dept. of Mol. and Cell. Biol., [2]Chem. and Chem. Biol., [3]Chem. and Chem. Biol., [4]Mol. and

Cell. Biol., [5]Physics, Chem. and Chem. Biol., Harvard Univ., Cambridge, MA; [6]Howard Hughes Med. Inst., Cambridge, MA; [7]Broad Inst., MIT, Cambridge, MA

Abstract: The mammalian brain instantiates behavior through the concerted action of a large number of highly diverse cell types within spatially structured circuits. Recent advances in transcriptional analyses of isolated neurons have helped initiate a systematic classification of neuronal types in various parts of the brain. However, relating these diverse cell-types to function remains a challenging problem. Moreover, the unique cellular architecture of the brain poses complex challenges that can only be addressed at the single cell level and in situ. Instinctive behaviors such as sex, aggression and parenting, and homeostatic functions such as sleep, thermoregulation and osmoregulation are critical for survival and thought to be controlled by genetically identifiable and separable populations of cells in the Hypothalamus. Untangling the neural circuitry underlying these survival functions represents the ideal starting point to understanding how neural organization leads to function.
Our project aims to examine the transcriptome of individual cells still embedded in brain tissue in order to take into account topographical features of individual cells, and their participation in functional circuits. Using a combination of MERFISH (Multiplexed Error Robust Fluorescence In Situ Hybridization - a technique capable of simultaneously imaging hundreds of transcripts in tissue sections) and single cell RNA Sequencing in the mouse hypothalamic preoptic region- a structure critical for several survival functions, we have developed an unbiased experimental approach to classify cell types in situ according to their gene expression profiles. Using this approach, we are working towards a comprehensive cell-type atlas of the preoptic region, which promises to enable us to discover several novel biological principles underlying the organization and function of this important region. We have used our approach to discover a new cell type involved in parenting behavior, providing “cell-type” resolution genetic entry points into the neuronal circuits underlying parenting. This approach promises to transform our ability to analyze and manipulate specific neuronal populations in normal as well as diseased brains.

Disclosures: D. Bambah-Mukku: None. **J.R. Moffitt:** None. **S. Eichhorn:** None. **E. Vaughn:** None. **K. Shekhar:** None. **A. Regev:** None. **X. Zhuang:** None. **C. Dulac:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.03

Topic: I.03. Anatomical Methods

Support: NIH Grant U19MH114830

Title: Whole-brain inputs and outputs of layer and class-specific neurons in mouse cortex

Authors: *J. A. HARRIS[1], Q. WANG[1], K. E. HIROKAWA[1], A. CETIN[1], S. YAO[1], P. BOHN[1], A. WILLIFORD[1], N. GRADDIS[1], L. KUAN[1], R. NICOVICH[1], M. MCGRAW[1], W. WAKEMAN[1], S. M. SUNKIN[1], P. A. GROBLEWSKI[1], L. NG[1], H. ZENG[2]
[2]Structured Sci., [1]Allen Inst. for Brain Sci., Seattle, WA

Abstract: The brain is composed of many cell types interconnected in complex ways that are not yet understood. Systematic large-scale efforts to map the mouse mesoscale connectome provide comprehensive projection data on interareal connections brain-wide, and at the level of specific cell classes or layers within cortical areas. Our Allen Mouse Brain Connectivity Atlas contains maps of long-range axonal projections using Cre driver lines, viral tracers (rAAV), and a high-throughput imaging and informatics platform. Through the BRAIN initiative, we are now generating a complementary dataset of cell class-specific retrograde input maps from target locations in cortical and subcortical locations, using the CVS-N2c rabies system and our brain-wide imaging platform. In the cortex, we inject rabies tracers into ~15 Cre lines at each cortical location. These lines represent classes of excitatory and inhibitory neurons across and within distinct layers. As part of the Brain Initiative Cell Census Network, we started these experiments in primary motor cortex, upper limb region (MOp-ul). Our analyses show that MOp-ul receives input from neurons located in all major brain divisions, most significantly from other isocortical areas; *e.g.,* upper limb region of primary somatosensory, secondary motor, anterior cingulate, lateral orbital, agranular insular, retrosplenial, perirhinal, and ectorhinal cortex. Subcortical areas also provide significant input to most layers in MOp; *e.g.,* dorsal taenia tecta, lateral entorhinal cortex, claustrum, globus pallidus, substantia innominata, dorsal raphe, and locus ceruleus. Several thalamic nuclei also contain cells projecting to neurons in most layers of MOp; *e.g.,* ventral anterior-lateral, ventromedial, posterior complex, anteromedial, lateral dorsal, reunions, and central lateral nuclei. The data so far also reveal potential differential input patterns between cell classes and layers within the same location of MOp. For example, excitatory neurons in L2/3 and L5 seem to receive relatively more amygdalar and callosal cortical input than those in L6. Our goal is to ultimately generate a whole brain, quantitative, connectivity matrix based on monosynaptic retrograde input mapping that is complementary to our existing anterograde (output) mesoscale connectome.

Disclosures: J.A. Harris: None. **Q. Wang:** None. **K.E. Hirokawa:** None. **A. Cetin:** None. **S. Yao:** None. **P. Bohn:** None. **A. Williford:** None. **N. Graddis:** None. **L. Kuan:** None. **R. Nicovich:** None. **M. McGraw:** None. **W. Wakeman:** None. **S.M. Sunkin:** None. **P.A. Groblewski:** None. **L. Ng:** None. **H. Zeng:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.04

Topic: I.03. Anatomical Methods

Support: NIH Grant U19MH114831
NIH Grant U01MH114829

Title: Monosynaptic inputs to connectivity-defined cell types within the upper limb region of mouse primary motor cortex

Authors: *M. S. BIENKOWSKI[1], L. GOU[1], C. CAO[1], M. BECERRA[1], E. M. CALLAWAY[2], J. R. ECKER[3], H. DONG[1]
[1]Mark and Mary Stevens Neuroimaging and Informatics Inst., Keck Sch. of Med. of USC, Los Angeles, CA; [2]Salk Inst., La Jolla, CA; [3]The Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: Neural circuit connectivity within the primary motor cortex (MOp) is critical to coordinated body movements and behavior. Previous macro-connectome level studies in mice have defined the regional connectivity of each MOp body part region, but it remains unclear how different populations of MOp neuronal cell-types are connected at single-cell resolution. As part of the NIH BRAIN Initiative Cell Census Network, we seek to determine a classification of connectivity-defined MOp neuronal cell-types. MOp neuronal cell-types can be classified based on differences in their axonal projection targets and we have found that the MOp upper limb region targets over a dozen other brain regions. To identify the monosynaptic inputs for each class of MOp projection neuron, we used a Cre-dependent G-deleted rabies viral tracing approach with a Cre-expressing AAVretro virus (AAVretro-Cre) to uniquely infect each subpopulation of MOp projection neurons and reveal their direct monosynaptic inputs. In each mouse, AAVretro-Cre was injected into a downstream MOp-targeted brain region to retrogradely express Cre in MOp neurons that send axons to the injection site. Then, we injected EnvA-pseudotyped G-deleted rabies virus and its complementary G glycoprotein- and TVA-expressing Cre-dependent AAV helper virus into the MOp upper limb region. Initial rabies virus infection is restricted to the Cre-expressing subpopulation of MOp projection cell-types and later spreads to upstream monosynaptically-connected input neurons. Using this approach, we have systematically identified the monosynaptic inputs to distinct classes of cortical-projecting and thalamus-projecting MOp neurons and revealed unique characteristics of the neural circuits in the MOp upper limb region.

Disclosures: M.S. Bienkowski: None. **L. Gou:** None. **C. Cao:** None. **M. Becerra:** None. **E.M. Callaway:** None. **J.R. Ecker:** None. **H. Dong:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.05

Topic: I.03. Anatomical Methods

Support: R01 NS39600
R01 NS086082
U01 MH114829

Title: An open repository for single-cell reconstruction of the brain forest

Authors: *G. A. ASCOLI[1], S. NANDA[4], P. MARAVER ABAD[2], M. A. AKRAM, JR[3], K. BIJARI[5], R. ARMANANZAS[2]
[2]Krasnow Inst. for Advanced Study, [1]George Mason Univ., Fairfax, VA; [3]Neurosci., George Mason Univ., Burtonsville, MD; [4]Krasnow Inst. for Advanced Study, Fairfax, VA; [5]GMU, Fairfax, VA

Abstract: NeuroMorpho.Org was launched twelve years ago to provide unhindered access to any and all digitally reconstructed dendritic and axonal morphologies that researchers were willing to share freely upon request. Today this database is the largest public inventory of cellular reconstructions in neuroscience with a content of almost 100,000 neurons and glia from a representative diversity of animal species, anatomical regions, and experimental methods. Datasets continuously contributed by hundreds of laboratories worldwide are centrally curated, converted into a common non-proprietary format, morphometrically quantified, and annotated with comprehensive metadata. Users download digital tracings and corresponding metadata for a variety of scientific applications including visualization, classification, analysis, and simulations. With more than 1000 peer-reviewed publications describing data stored in or utilizing data retrieved from NeuroMorpho.Org, this ever-growing repository also serves as an important bridge between large-scale neuroscience initiatives and the long tail of individual investigators in the research community.

Disclosures: G.A. Ascoli: None. **S. Nanda:** None. **P. Maraver Abad:** None. **M.A. Akram:** None. **K. Bijari:** None. **R. Armananzas:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.06

Topic: I.03. Anatomical Methods

Support: NIH Grant U19MH114830

Title: Pipelined production of 3d full morphology of mouse neurons at whole brain scale

Authors: *H. PENG[1], Z. RUAN[2], L. LIU[2], Z. ZHOU[1], Y. WANG[4], Y. YU[1], J. YANG[5], T. DAIGLE[1], B. TASIC[1], A. LI[6], N. GRADDIS[7], K. HIROKAWA[1], Y. LI[1], Y. WANG[1], S. SORENSEN[1], L. NG[1], R. CAI[3], N. ZHONG[5], Z. GU[2], H. GONG[6], W. XIE[2], J. HARRIS[1], Q. LUO[6], H. ZENG[1]
[1]Allen Inst. for Brain Sci., Seattle, WA; [2]Southeast Univ. - Allen Inst. Joint Res. Ctr. for Neuron Morphology, Southeast Univ., Nanjing, China; [3]Southeast Univ., Nanjing, WA; [4]Shanghai Univ., Nanjing, China; [5]BJUT, Beijing, China; [6]HUST, Suzhou, China; [7]Allen Inst., Seattle, WA

Abstract: Population level brain-wide connectivity patterns have been mapped extensively using bulk injections of anterograde and retrograde tracers. However, intermingled neuron types within a brain region have heterogeneous projection patterns and carry diverse messages. Single neuron reconstructions provide critical information about how neural signals are organized and the routes by which they are transmitted across the brain to their target regions. In addition, the 3D shapes of neurons have an important role in cell type classification, together with other features such as gene expression. So far, generation of a large amount of useable, high quality 3D neuron morphology data has failed to keep pace with the increasing amount of single cell molecular signatures available for correlation analyses. To fill this gap, we are assembling robust tools and practices toward the goal of systematic, coordinated, pipelined production of 3D full morphology for mouse neurons at whole brain scale. We are optimizing labeling, imaging, reconstruction and analysis of neurons. A variety of sparse fluorescent labeling techniques are applied to different neuronal types. Then, images are acquired across the whole brain at high resolution using fMOST systems (x,y: 0.2 to 0.3 um, z: 1.0 um). Following imaging, we utilize two parallel, complementary approaches to reconstruct 3D neuron morphology: (a) complete automation of a 3D reconstruction followed by careful manual correction of any putative errors, and (b) manual and semi-automatic generation of reconstructions based on efficient human-computer interaction software. The produced neuron morphology is checked and finalized using cross-validation. All neuron reconstructions are mapped to the Allen Mouse Brain Common Coordinate Framework (CCFv3), a fully annotated 3D reference space.

Disclosures: H. Peng: None. **Z. Ruan:** None. **L. Liu:** None. **Z. Zhou:** None. **Y. Wang:** None. **Y. Yu:** None. **J. Yang:** None. **T. Daigle:** None. **B. Tasic:** None. **A. li:** None. **N. Graddis:** None. **K. Hirokawa:** None. **Y. Li:** None. **Y. Wang:** None. **S. Sorensen:** None. **L. Ng:** None. **R. Cai:** None. **N. Zhong:** None. **Z. Gu:** None. **H. Gong:** None. **W. Xie:** None. **J. Harris:** None. **Q. Luo:** None. **H. Zeng:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.07

Topic: I.03. Anatomical Methods

Title: Deepneuron + ultratracer automates very large-scale whole-brain full-morphology reconstructions

Authors: *Z. ZHOU[1,2], F. LONG[1], H. PENG[1,2]
[1]Allen Inst. for Brain Sci., Seattle, WA; [2]Southeast Univ. – Allen Inst. Joint Ctr. for Neuron Morphology, Southeast Univ., Nanjing, China

Abstract: Neuron reconstruction at the whole-brain full-morphology level demands processing trillions of voxels in imaging data of a brain in high speed. Traditional manual reconstruction is not able to handle such large-scale data. Automatically reconstructing morphometry of single neurons at the whole brain scale is a necessity yet extremely challenging. *UltraTracer* (Peng, et al., *Nature Methods*, 2017) is our recent solution designed to enable any base neuron-tracing algorithm to trace virtually unlimited data volumes. Here, we extend the *UltraTracer* framework to incorporate machine learning to automate the reconstruction of very large-scale whole-brain full neuron morphology. We have developed an open source tracing toolbox, *DeepNeuron*, which utilizes deep learning networks to trace neurons in light microscopy images. *DeepNeuron* provides a family of modules to solve fundamental yet challenging problems in neuron tracing. These problems include but are not limited to: (1) detecting neuron signal under different image conditions, (2) connecting neuronal signals into tree(s), (3) pruning and refining tree morphology, (4) quantifying the quality of morphology reconstruction, and (5) classifying dendrites and axons in real time. We also combine *DeepNeuron* and *UltraTracer* to reconstruct whole mouse brain neurons. Our preliminary results show that this *DeepNeuron*+*UltraTracer* approach is able to produce robust and useful neuron reconstruction at teravoxel scale.

Disclosures: Z. Zhou: None. **F. Long:** None. **H. Peng:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.08

Topic: I.03. Anatomical Methods

Support: U01 MH114824-01
U19 MH114821-01

Title: Mapping the brain at cellular resolution: Region and gender-specific differences

Authors: *P. OSTEN, A. NARASIMHAN, K. UMADEVI VENKATARAJU
Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: All topics in neuroscience are informed by knowledge of brain cell type anatomy. The distribution and ratios of individual neuronal and glia cell types across the whole brain and the

wiring of neuronal cell types into local and long-range circuits underlie the vast diversity of mammalian behaviors, from the simple startle response of defensive behaviors to the complex neuronal computations during cognitive and emotive processing. Here I will describe our work on systematic atlasing of cell-type distribution and morphology in C57BL/6 female and male mouse brain, including establishing novel microscopy methods for rapid imaging of mouse brains at high spatial resolution, computational methods for mapping cell-type distribution and tracing cellular morphologies, computational methods for registering the whole-brain datasets onto the Allen Common Coordinate Framework (CCF) for postnatal day 56 (P56) mouse brain, statistical methods for rigorous analyses of the generated data, and neuroinformatics methods and an online web portal for integrating and disseminating the whole-brain cell type-based anatomical data.

Disclosures: A. Narasimhan: None. **K. Umadevi Venkataraju:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.09

Topic: I.03. Anatomical Methods

Title: A virtual reality platform for visualization, exploration, and annotation of brain-wide neuronal images

Authors: *Y. WANG[1,2,3], H. PENG[1,2,4]
[1]Southeast Univ. – Allen Inst. Joint Ctr. for Neuron Morphology, Southeast Univ., Nanjing, China; [2]Sch. of Computer Engin. and Sci., [3]Shanghai Inst. for Advanced Communication and Data Sci., Shanghai Univ., Shanghai, China; [4]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Neuron morphometry is a well established yet very challenging procedure in studying neuron types, neuronal connections and circuits, and related applications. Often, this task is further complicated by the very large scale of three-dimensional (3-D) imaging data (often at the scale of terabytes now) for mammalian brains and dense arborization patterns of neurons in these brains. It remains a major bottleneck to visualize and analyze such data, even with the increasingly available data of sparsely labeled and imaged neurons.
In this work, we present the first Virtual Reality (VR)-based morphometry system for the visualization, exploration, and annotation of such very large-scale, multidimensional, brain-wide neuronal volume images in a true 3D environment. We propose several useful features, such as the immersive in-volume data exploration and the 3D virtual finger, to make the system both intuitive and efficient to use. Also, our system is seamlessly integrated with Vaa3D [1,2], which is an open-source and cross-platform software package for image visualization and analysis. Our system supports the smooth switching back and forth between the VR mode and the traditional

desktop mode, enabling a user to flexibly choose the most suitable mode for exploring the current piece of data. Meanwhile, our system has demonstrated strong abilities in tracing weakly labeled axons and discriminating overlapping neurites. Together with other built-in modules of Vaa3D, such as TeraFly [3], our system can easily deal with data at multi-teravoxel scales. With our system, several global collaborating teams at Nanjing (China), Seattle (USA), Wenzhou (China), etc. have started generating valuable new datasets for whole-mouse brain cell morphologies.

[1] Peng, Hanchuan, et al. "V3D enables real-time 3D visualization and quantitative analysis of large-scale biological image data sets." *Nature biotechnology* 28.4 (2010): 348-353.
[2] Peng, Hanchuan, et al. "Extensible visualization and analysis for multidimensional images using Vaa3D." *Nature protocols* 9.1 (2014): 193-208.
[3] Bria, Alessandro, et al. "TeraFly: real-time three-dimensional visualization and annotation of terabytes of multidimensional volumetric images." *Nature methods* 13.3 (2016): 192-194.
Corresponding author: Hanchuan Peng (hanchuanp@alleninstitute.org)

Disclosures: Y. Wang: None. **H. Peng:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.10

Topic: I.03. Anatomical Methods

Title: Annotation and classification of 3d neuron morphology in whole mouse brain

Authors: *L. LIU[1,2], A. LIU[1], J. YUAN[1], S. ZHANG[1], G. HONG[1], Z. MENG[1], J. ZHANG[1], S. PENG[1], Z. MA[1], Y. WANG[3], S. A. SORENSEN[4], W. XIE[6], H. ZENG[5], H. PENG[5]
[1]Southeast Univ., Nanjing, China; [2]Southeast Univ. – Allen Inst. Joint Ctr. for Neuron Morphology, Nanjing, China; [3]Allen Inst., Seattle, WA; [5]Structured Sci., [4]Allen Inst. for Brain Sci., Seattle, WA; [6]Inst. of Life Sciences, Southeast Univ., Jiangsu, China

Abstract: Brain functions are based on communications of neurons located in different regions. The task of characterizing and classifying neuronal types is an essential part of modern neuroscience. However, morphology, projection patterns, and connectivity of neurons are still largely unclear. We used Vaa3D (vaa3d.org) and its new Virtual Reality (VR) modules to reconstruct complex neuron morphology for sparsely labeled neurons in whole mouse brain. VR lets us explore and annotate neuron morphology at an unprecedented precision and efficiency. We have generated neuronal reconstructions in whole mouse brain that exhibit as complete as possible information about the distribution of dendrites, soma location, axonal projections and branches. With such information, one may classify neuronal cell types and even examine their roles in neuronal circuits involved in animal behaviors. We have developed a pipelineable

procedure to produce 3D neuron morphology at the whole brain scale and finished a number of thalamus reconstructions. These neurons exhibit local axonal branches near their soma area and have major secondary branches from their primary axon branches. They have dense axonal terminal branches in their projection areas. Also, major branches coming out from primary axon branches project to different layers of brain. Clearly some neurons are projecting to cortex. In summary, by using several reconstruction tools, we could visualize, annotate and classify neuron morphology in different brain regions and neuronal circuits for brain functions, producing useful data for other related studies as well.

Disclosures: L. Liu: None. **A. Liu:** None. **J. Yuan:** None. **S. Zhang:** None. **G. Hong:** None. **Z. Meng:** None. **J. Zhang:** None. **S. Peng:** None. **Z. Ma:** None. **Y. Wang:** None. **S.A. Sorensen:** None. **W. Xie:** None. **H. Zeng:** None. **H. Peng:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.11

Topic: I.03. Anatomical Methods

Support: the Allen Institute for Brain Science

Title: BigTree: A hierarchical tree construction tool for visualization and processing large brain image data sets

Authors: *Y. YU[1], H. PENG[1,2]
[1]Allen Inst. For Brain Sci., Seattle, WA; [2]Southeast Univ. – Allen Inst. Joint Ctr. for Neuron Morphology, Nanjing, China

Abstract: High resolution and high throughput multidimensional imaging of a whole mammalian brain can easily produce terabyte-scale datasets. To visualize and process such a large dataset, a commonly used strategy is to reformat a raw image dataset into a hierarchical organization of files based on a tree (pyramid) data structure, with which a local volume of interest (VOI) of the image dataset can be extracted for a specified scale quickly. Unfortunately, constructing such a hierarchical tree for teravoxel-sized datasets is a time-consuming task, usually taking many days to complete. To resolve this bottleneck, we introduce a new open source tool, BigTree, which uses an optimized data reformatting strategy to improve the runtime performance based on parallel image decompression and processing. We have tested BigTree on large image datasets such as 30 terabytes per brain. The code is available under MIT license at https://github.com/gnayuy/BigTree.

Disclosures: Y. Yu: None. **H. Peng:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.12

Topic: I.03. Anatomical Methods

Support: NIH Grant U19 MH114821

Title: Genetic dissection of glutamatergic pyramidal neuron subpopulations underlying motor cortex output pathways

Authors: *K. S. MATHO[1], W. GALBAVY[1], H. KONDO[1], K. UMADEVI VENKATARAJU[1], R. PALANISWAMY[1], X. AN[1], J. TUCCIARONE[2], A. NARASIMHAN[1], P. WU[1], M. HE[3], Y. KIM[4], P. OSTEN[1], P. ARLOTTA[5], Z. HUANG[1]
[1]Neurosci., Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Stanford Univ., Stanford, CA; [3]Inst. of Brain Sci., Fudan Univ., Shanghai, China; [4]Col. of Medicine, Penn State Univ., Hershey, PA; [5]Stem Cell and Regenerative Biol., Harvard Univ., Cambridge, MA

Abstract: The motor cortex has been implicated in the volitional control of forelimb movements, a rich set of behavioral skills that allow animals to manipulate the environment according to sensory inputs and internal drive, but the underlying circuitry mechanisms remain largely unexplored. As a first effort to integrate multimodal data generated by the BRAIN Initiative Cell Census Network (BICCN), we have devised a Mini-Atlas project focusing on the primary motor cortex (M1 or MOp), collectively generating single-cell sequencing, anatomical, spatial transcriptomics and Patch-seq data. Specific to the anatomical data, anterograde and retrograde mapping, trans-synaptic tracing, morphology, and cell-type distributions are being generated for multimodal analysis. Glutamatergic pyramidal neurons (PyNs) constitute the vast neural network of the cortex, but the diversity of PyN subpopulations underlying the multiple cortical output channels is poorly understood. Here, we design strategies and generate mouse genetic tools for targeting PyN subpopulations jointly defined by multiple features including laminar location, marker expression, projection targets, input source and developmental origin. We combine genetic and viral labeling and Serial Two Photon Tomography (STP) to characterize and quantify cell distribution and axon projection patterns which are registered to a mouse brain Common Coordinate Framework (CCF) based on the Allen Reference Atlas (v3). This allows to examine with cell-type specific resolution the diversity and connectivity patterns of multiple infragranular layer subpopulations, which comprise the output channels that send their axons to striatal and other subcortical regions. Our systematic genetic strategy provides unprecedented opportunities to reveal motor cortex circuitry and output pathways.

Disclosures: K.S. Matho: None. **W. Galbavy:** None. **H. Kondo:** None. **K. Umadevi Venkataraju:** None. **R. Palaniswamy:** None. **X. An:** None. **J. Tucciarone:** None. **A.**

Narasimhan: None. **P. Wu:** None. **M. He:** None. **Y. Kim:** None. **P. Osten:** None. **P. Arlotta:** None. **Z. Huang:** None.

Nanosymposium

276. The Mouse Brain: Circuitry and Mapping in 3D

Location: SDCC 30B

Time: Monday, November 5, 2018, 8:00 AM - 11:15 AM

Presentation Number: 276.13

Topic: I.03. Anatomical Methods

Title: Whole mouse brain morphology reconstruction using vaa3d

Authors: *S. JIANG[1], Q. OUYANG[1], Y. WANG[2], Z. ZHOU[3], Z. RUAN[1]
[1]Southeast Univ., Jiangsu, China; [2]Sch. of Computer Engin. and Sci., Shanghai Univ., Shanghai, China; [3]Allen Inst. For Brain Sci., Seattle, WA

Abstract: Key words: Vaa3D, Whole Mouse Brain, Neuron Morphology
Reconstructing of neuron morphology at the whole-brain level plays a crucial role in neuroscience field. However, most of the current bioimage-oriented software tools are not powerful enough for the reconstruction of the large-scale (terabyte-level) multidimensional whole-brain data set. As a widely used software system in neuroscience applications, Vaa3D (http://vaa3d.org) has been proved effectively in visualizing and analyzing multidimensional images (Peng, et al., Nature Protocol, 2014), and powered by Terafly (Bria, Alessandro, et al. Nature Methods, 2016) in visualization and annotation on very large-scale volumes. In order to efficiently trace single neuron morphology on the whole mouse brain data, Vaa3D has been further optimized for reconstruction large-scale data set. Particularly, (1) Virtual Reality (VR) module was introduced to visualize/ reconstruct the neuron morphology in a 3D virtual environment which gave incomparable advantage on annotating intricate neuron branches. (2) Enhanced neuron annotation toolbox (e.g. multi-neurons tracing, reference system, morphology related plugins) was developed to improve reconstruction performance on visualizing, annotating, and analyzing interlaced neuron branches. (3) Upgraded functional customization interfaces were developed to tackle diverse complex application scenarios (e.g. the annotation of weak neuron branches).

Disclosures: S. Jiang: None. **Q. Ouyang:** None. **Y. Wang:** None. **Z. Zhou:** None. **Z. Ruan:** None.

Nanosymposium

353. Current Perspectives on Neural Circuit Assembly and Reorganization

Location: SDCC 24

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 353.01

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Knights Templar Eye Foundation to A.R.
R01DA018928 to T.B.
EY023105 to M.C.C.
EY015788 to M.C.C.

Title: Synapse-specific control of circuit maturation and plasticity by SynCAM 1

Authors: *A. RIBIC[1], M. C. CRAIR[2], T. BIEDERER[1]
[1]Dept. of Neurosci., Tufts Univ. Sch. of Med., Boston, MA; [2]Dept. of Neurosci., Yale Univ., New Haven, CT

Abstract: Experience-dependent plasticity of brain circuits tapers off as the brain matures. Maturation of cortical inhibition, as well as a steady increase in the expression of axonal growth inhibitors, is thought to direct circuit maturation and restrict cortical plasticity. However, cell-autonomous synaptic factors that control these processes remain unknown. We here demonstrate that visual activity selectively regulates Synaptic Cell Adhesion Molecule 1 (SynCAM 1/Cadm1) expression during the cortical critical period. Mice deficient in SynCAM 1-mediated synaptic adhesion show increased plasticity at all ages after monocular deprivation, indicating that synaptic adhesion restricts cortical plasticity. SynCAM 1 selectively controls thalamocortical inputs onto Parvalbumin (PV^+) interneurons in the visual cortex and loss of SynCAM 1 in PV^+ interneurons retards the maturation of cortical inhibition and upregulates plasticity in the adult brain. Our work identifies a synaptic locus of critical period closure and the synaptic factors that restrict adult plasticity. These findings further underscore the emerging role of transsynaptic interactions in the wiring and remodeling of functional circuits.

Disclosures: A. Ribic: None. **M.C. Crair:** None. **T. Biederer:** None.

Nanosymposium

353. Current Perspectives on Neural Circuit Assembly and Reorganization

Location: SDCC 24

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 353.02

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant MH071666
Good Ventures Foundation

Title: Unexpected role for neuronal non-classical MHCI Qa-1 in activity-dependent plasticity

Authors: *I. A. MARIN[1], A. Y. WEI[1], K. S. CHEW[1], C. J. SHATZ[1,2]
[1]Dept. of Biol., [2]Dept. of Neurobio., Stanford Univ., Stanford, CA

Abstract: The brain develops with an exuberant number of connections that are gradually pruned with use. This pruning is dependent on neuronal activity and is crucial during developmental critical periods. Our lab has previously discovered a new role for major histocompatibility complex class I (MHCI) molecules in activity-mediated refinement of neural circuits. Initially thought to function solely in the immune system, recent work has revealed that proteins in the histocompatibility locus are expressed in the healthy brain, both in mice and humans. So far, the neuronal function of only two classical MHCI molecules (H2-K^b and H2-D^b, out of 50+) have been studied, demonstrating key roles in synaptic plasticity (Lee et al. Nature 2013). Here we have investigated the function of a novel non-classical MHCI: Qa-1, homologous to the human HLA-E molecule. In the immune system, Qa-1 is known to present antigens to NK cells and T cells. Its expression and function in the healthy brain have been completely unexplored until now. We show that Qa-1 is expressed by a subset of neurons in layer 6 of the cerebral cortex, and its levels are regulated by visually-driven activity. Moreover, we assessed ocular dominance plasticity as a paradigm for activity-dependent circuit remodeling in Qa-1 KO and WT mice. Our data indicate that, following monocular visual deprivation during the critical period, knockout of Qa-1 leads to enhanced strengthening of the open eye both in layer 6 and layer 4, as compared to WT. This and other phenotypes suggest that Qa-1 acts as a break on synaptic plasticity. Our results expand understanding of MHCI function in the healthy brain and point towards a new unexpected role for a non-classical MHCI in CNS neurons.
Supported by NIH Grant MH071666 and the Good Ventures Foundation.

Disclosures: I.A. Marin: None. **A.Y. Wei:** None. **K.S. Chew:** None. **C.J. Shatz:** None.

Nanosymposium

353. Current Perspectives on Neural Circuit Assembly and Reorganization

Location: SDCC 24

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 353.03

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: Diverse developmental trajectories of single identified pyramidal neurons during the critical period in the visual cortex

Authors: *L. TAN[1], S. L. ZIPURSKY[2], J. T. TRACHTENBERG[2], D. L. RINGACH[3]
[1]Biol. Chem., [3]Neurobio. & Psychology, [2]UCLA, Los Angeles, CA

Abstract: Critical period plasticity is a hallmark of mammalian brain development. Behavioral and electrophysiological studies have demonstrated that the cortex acquires the final form and function in an experience-dependent manner during critical periods. The full developmental path taken by individual neurons during development is not known. We performed longitudinal *in vivo* two-photon calcium imaging of single identifiable layer 2/3 pyramidal neurons in the binocular area of the primary visual cortex (V1) in awake mice, and measured their preferences in the joint orientation and spatial frequency domain by separate stimulation of each eye. We discovered that the proportion of cells with similar tuning in the contralateral and ipsilateral eye doubled between the onset (P22/23) and closure (P31/32) of critical period. The developmental trajectories of single neurons during critical period are diverse: (a) most neurons that are binocular throughout the critical period, show an increase in binocular matching of their tuning, (b) most binocular neurons that are well matched at the onset, remain matched during the critical period, (c) most binocular neurons that are not matched at the onset and become well matched, and in over half of them the tuning of ipsilateral eye changes to match the tuning of contralateral eye, (d) binocularly unmatched cells throughout critical period show substantial changes in their tuning (this type of plasticity does not exist in adult), (e) a fraction of binocular neurons become monocular, and (f) a similar number of monocular cells become binocular, and most of them become binocularly matched to the original monocular tuning. In summary, majority of layer 2/3 pyramidal neurons in the mouse binocular V1 exhibit unique plasticity and many of them change tuning or binocularity to achieve binocular matching of both orientation and spatial frequency tuning during the critical period. These data show that multiple mechanisms may be involved in the development of binocular matching.

Disclosures: L. Tan: None. **S.L. Zipursky:** None. **J.T. Trachtenberg:** None. **D.L. Ringach:** None.

Nanosymposium

353. Current Perspectives on Neural Circuit Assembly and Reorganization

Location: SDCC 24

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 353.04

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH grant R01MH105610
Ms. Nancy Lurie Marks
The Besthoff Foundation

Title: Pten signaling regulates apoptosis in cortical GABAergic interneurons during development

Authors: *D. T. PAGE, J. SEJOURNE, O. COHEN, A. ZUCCA
Dept. of Neurosci., The Scripps Res. Inst., Jupiter, FL

Abstract: Cerebral cortical GABAergic interneurons (INs), the primary cell type that mediates inhibitory neurotransmission in the cortex, are over-produced during early development. During early postnatal life a substantial fraction of INs undergo programmed cell death through an unknown mechanism to arrive at a mature population size. Pten encodes a phosphatase that regulates cell death under normal and pathological conditions, and mutations in PTEN are a risk factor for neurodevelopmental disorders associated with imbalanced excitation and inhibition. We hypothesized that intrinsically determined cell death of developing cortical GABAergic INs may occur through a Pten-dependent mechanism. We have generated mice in which a conditional heterozygous mutation in *Pten* is introduced into developing GABAergic cells. Isotropic fractionator, flow cytometry, histology and cell culture were used to assess the impact of perturbations in Pten expression level on cortical interneuron number and apoptosis. We find that mutant animals do not show the approximately 20-30% decrease in cortical GABAergic cells during early postnatal development that occurs in control animals. We also observe reduced markers of apoptosis in Pten mutant cortical GABAergic cells during development and we present evidence that induction of cell death in this cell type is responsive to Pten levels in a bi-directional manner. Mutant animals display altered seizure resistance, social behavior and cortical network activity as indicated by c-Fos, consistent with a net imbalance of excitation and inhibition. Together, our findings indicate a role for Pten in the intrinsic regulation of cell death and population size in developing cortical GABAergic INs.

Disclosures: D.T. Page: None. **J. Sejourne:** None. **O. Cohen:** None. **A. Zucca:** None.

Nanosymposium

353. Current Perspectives on Neural Circuit Assembly and Reorganization

Location: SDCC 24

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 353.05

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Wellcome Trust 103714MA
Sir Henry Wellcome Fellowship
EMBO Postdoctoral Fellowship
Marie Sklodowska-Curie Fellowship

Title: To be, or not to be - Neuronal death during development

Authors: *K. BERCSENYI[1,2], F. K. WONG[1,2], V. SREENIVASAN[1,2], A. PORTALÉS[1,2], M. FERNÁNDEZ-OTERO[1,2], O. MARÍN[1,2]

[1]Ctr. for Developmental Neurobio., [2]Med. Res. Council Ctr. for Neurodevelopmental Disorders, King's Col. London, London, United Kingdom

Abstract: The central nervous system processes information and instructs action based on the balance excitation and inhibition of neuronal networks. The establishment of appropriate numbers for excitatory and inhibitory neurons is essential to this balance; however, our understanding of the regulation of this process is incomplete. In this study we aimed to investigate the regulation of interneuron cell death during early postnatal development in mice. We found that experimental manipulations of the cell death pathway or the activity or cortical pyramidal cells change the survival rate of interneurons during a critical window of postnatal development. We also discovered that PTEN (phosphatase and tensin homolog), a well-known modulator of the Akt (protein kinase B) and mTOR (mammalian target of rapamycin) signaling pathways, is a key regulator of cell death in interneurons. Our results shed light on the mechanisms regulating the ratio of excitatory and inhibitory neurons in the cerebral cortex.

Disclosures: K. Bercsenyi: None. **F.K. Wong:** None. **V. Sreenivasan:** None. **A. Portalés:** None. **M. Fernández-Otero:** None. **O. Marín:** None.

Nanosymposium

353. Current Perspectives on Neural Circuit Assembly and Reorganization

Location: SDCC 24

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 353.06

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: R01 EY025174

Title: GABA transmission necessary for transplantation induced visual plasticity

Authors: *R. PRIYA[1], J. SPATAZZA[2], M. KANEKO[2], M. STRYKER[2], G. J. FISHELL[3], A. A. BUYLLA[2]
[1]Neurosience, Univ. of California, San Francisco, San Francisco, CA; [2]UCSF, San Francisco, CA; [3]Neurobio., Harvard Med. Sch., Boston, MA

Abstract: Survival is essential for the functional integration of transplanted Medial ganglionic eminence (MGE)-derived cortical interneurons (CINs). Previous work has shown that transplanted CINs mimic the developmental milestones of endogenous interneuron populations, including a wave of Bax dependent programmed cell death (Southwell et al. 2012). We have identified the signaling processes governing the survival of endogenous interneurons. Further we explore how newly added transplanted CINs functionally integrate into visual cortex is required to explain how they induce a period of plasticity (Southwell et al. 2010). In reducing seizures, MGE-derived CINs increase inhibition by forming functional inhibitory synapses with native

excitatory neurons in the hippocampus (Hsieh and Baraban, 2017). However the induction of a new period of plasticity is not simply due to increased inhibition. We hypothesized that the transplanted CINs exert their effects on host neurons through tonic GABA release, thus modulating the postsynaptic connections through physically rearranging existing synapses. We show that GABAergic transmission is necessary for ODP induction, suggesting that appropriate synaptic innervation is key.

Disclosures: R. Priya: None. **J. Spatazza:** None. **M. Kaneko:** None. **M. Stryker:** None. **G.J. Fishell:** None. **A.A. Buylla:** None.

Nanosymposium

353. Current Perspectives on Neural Circuit Assembly and Reorganization

Location: SDCC 24

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 353.07

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant NS046579
Nancy Lurie Marks Family Foundation
Simons Foundation Autism Research Initiative

Title: Abnormal corticostriatal development underlies the onset of behavioral deficits in Shank3B$^{-/-}$ mice

Authors: *R. PEIXOTO[1], L. CHANTRANUPONG[1], J. LEVASSEUR[1], W. WANG[1], T. MERCHANT[1], K. GORMAN[1], B. BUDNIK[2], B. L. SABATINI[3]
[1]Harvard Med. Sch., Boston, MA; [2]Harvard Univ., Cambridge, MA; [3]Neurobio., Harvard Med. Sch. Dept. of Neurobio., Boston, MA

Abstract: Autism spectrum disorders (ASD) are characterized by a wide range of cognitive and behavioral deficits including impaired social interactions and repetitive behaviors. Diagnosis of ASD typically occurs during the second year of life often following an apparently normal infancy. This distinct developmental onset and loss of particular cognitive functions suggest that ASD arise from impaired developmental processes in specific brain circuits. Recent genetic and imaging studies point to corticostriatal dysfunction as a converging pathophysiological factor in ASD. We have recently demonstrated that mice with deletions in *Shank3* (Shank3B$^{-/-}$) exhibit a biphasic developmental trajectory of corticostriatal connectivity with precocious and exuberant early maturation followed by posterior arrest or regression later in development. However, the mechanisms underlying these distinct striatal phenotypes and its potential implication in the onset of behavioral abnormalities remain unclear. Here, we performed a longitudinal behavioral characterization of Shank3B$^{-/-}$ mice and found that the onset of behavioral deficits in these animals occurs during early postnatal periods. Using chemogenetic strategies to transiently

manipulate cortical activity we identified a developmental switch in the response of striatal spiny projection neurons (SPN) to cortical hyperactivity that recapitulates the developmental trajectory observed in Shank3B$^{-/-}$ mice. Longitudinal proteomic characterization of striatal synaptic fractions revealed highly dynamic regulation of multiple signaling pathways during this early postnatal period with pronounced enrichment of ASD risk factors and related homologs. Moreover, this study revealed significant expression and synaptic enrichment changes of cAMP dependent protein kinase (PKA) and PKA regulatory proteins suggesting differential regulation of PKA signaling across this developmental period. Reducing PKA activity in striatal SPNs decreased the rate of glutamatergic synaptogenesis and the maturation of intrinsic properties. Importantly, this manipulation normalized corticostriatal activity levels in Shank3B$^{-/-}$ mice and prevented the emergence of behavioral abnormalities in these animals. These results indicate that behavioral deficits in Shank3B$^{-/-}$ mice arise from impaired developmental processes and validate striatal development as a point of convergence of multiple ASD risk factors. Moreover, these results strengthen the validity of Shank3B$^{-/-}$ mice as a model of ASD pathogenesis and suggest that manipulation of striatal maturation via PKA activity might offer significant therapeutic potential.

Disclosures: R. Peixoto: None. **L. Chantranupong:** None. **J. Levasseur:** None. **W. Wang:** None. **T. Merchant:** None. **K. Gorman:** None. **B. Budnik:** None. **B.L. Sabatini:** None.

Nanosymposium

354. Brain Wellness and Aging: Systemic Factors and Brain Function

Location: SDCC 33

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 354.01

Topic: C.01. Brain Wellness and Aging

Support: Chinese '111 Project' (B08020)
US National Institutes of Health (AT009263, MH114233, EB021027 and NS096761)
Natural Science Foundation of Shanghai (17ZR1445300)
Shanghai Jiao Tong University Grants (YG2016ZD06, 14JCRZ05)

Title: Brain-heart interactions underlying traditional tibetan buddhist meditation

Authors: *H. JIANG[1], B. HE[1], X. GUO[2], X. WANG[2], M. GUO[2], Z. WANG[2], T. XUE[2], H. LI[2], T. XU[2], S. YE[1], D. SUMA[1], S. TONG[2], D. CUI[2]
[1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Shanghai Jiao Tong Univ., Shanghai, China

Abstract: ABSTRACT: Despite accumulating evidence which suggests improvement in one's wellbeing as a result of meditation, little is known about if or how the brain and the periphery interact to produce these behavioral and mental changes. It has also been proposed that consciousness is grounded in the neural representations of visceral inputs, such as cardiac

signals, and that meditation, widely accepted as a unique state of consciousness, might influence these features. Here, we investigated the integration of neural and visceral systems and spontaneous whole brain spatiotemporal dynamics underlying traditional Tibetan Buddhist meditation. Through a novel neurovisceral signal analysis method, which specifies and investigates the interactions between the brain and the heart, in combination with advanced EEG source imaging analysis in the simultaneously recorded electroencephalography (EEG) and electrocardiography (ECG) of a large cohort of long-term Tibetan Buddhist monk meditation practitioners, we found distinct transient modulations in the neural response to heartbeats in the default-mode network (DMN), along with instantaneous large-scale network reconfigurations in the EEG gamma and theta bands induced by meditation. Additionally, the temporal-frontal theta network connectivity was negatively correlated with the duration of meditation experience and gamma oscillations were directionally coupled to theta oscillations uniquely during the meditation state. Overall, these data suggest that the neural representation of cardiac signals in the DMN and large-scale spatiotemporal network integrations underlie the fundamental neural mechanisms of meditation, and further imply that meditation may stimulate cortical plasticity and induce both concurrent and long-term lasting changes in the intrinsic organization of brain networks and the neural monitoring of cardiac behavior.

Disclosures: H. Jiang: None. **B. He:** None. **X. Guo:** None. **X. Wang:** None. **M. Guo:** None. **Z. Wang:** None. **T. Xue:** None. **H. Li:** None. **T. Xu:** None. **S. Ye:** None. **D. Suma:** None. **S. Tong:** None. **D. Cui:** None.

Nanosymposium

354. Brain Wellness and Aging: Systemic Factors and Brain Function

Location: SDCC 33

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 354.02

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant AG045571
NIA Grant AG13854

Title: Cognitive SuperAgers are protected from cholinergic axonal abnormalities in prefrontal cortex

Authors: S. JADIDI, G. KIM, A. REZVANIAN, T. GEFEN, *S. WEINTRAUB, E. H. BIGIO, E. ROGALSKI, M.-M. MESULAM, C. GEULA
Cognitive Neurol. and Alzheimer's Dis. Ctr., Northwestern University, Feinberg Sch. of Medici, Chicago, IL

Abstract: Cognitive decline in memory and executive functions has been well documented as a normal phenomenon of 'typical' human aging. We recruited a group of individuals known as

‘SuperAgers’, 80-year-olds who seem to withstand typical age-related cognitive decline, with performance on tests of episodic memory equivalent to healthy 50-65 year-olds or younger. In a previous study, we described the presence of age-related abnormalities in cortical cholinergic axons in cognitively-normal individuals. These axonal abnormalities were found in the form of individual ballooned terminals, terminal swellings in a chandelier arrangement, or thickened axons with no branches. Such abnormalities were sparse in normal young individuals, more prominent in middle-aged participants, and further increased in cognitively-normal elderly. Recently, we demonstrated that the density of these abnormalities in the entorhinal cortex, a limbic region associated with memory function, is significantly less in SuperAgers when compared to cognitively normal elderly ($p<0.05$). The purpose of this study was to further investigate the presence and densities of cortical cholinergic axonal abnormalities in the middle frontal gyrus, a non-memory cortical region associated with executive functions,, including attentional control. Histochemical procedures were used to visualize acetylcholinesterase-rich axons in autopsied specimens of SuperAgers (N = 3) and cognitively normal elderly (N = 4), and the densities of axonal abnormalities were quantified using unbiased stereological methods. The total density of cholinergic axonal abnormalities was found to be significantly less in SuperAgers when compared with cognitively-normal elderly ($p=0.0036$). This result was primarily driven by differences in counts of ballooned terminals ($p=0.0179$). No statistically significant differences were observed in thickened axons and chandelier terminal swellings between the two groups ($p>0.05$). Given the role of cortical cholinergic innervation in memory and attention, as well as SuperAgers’ seeming protection from age-related abnormalities of cortical cholinergic axons across multiple brain regions, it seems likely that this global integrity contributes to the exceptional cognitive status of SuperAgers.

Disclosures: S. Jadidi: None. **G. Kim:** None. **A. Rezvanian:** None. **T. Gefen:** None. **S. Weintraub:** None. **E.H. Bigio:** None. **E. Rogalski:** None. **M. Mesulam:** None. **C. Geula:** None.

Nanosymposium

354. Brain Wellness and Aging: Systemic Factors and Brain Function

Location: SDCC 33

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 354.03

Topic: C.01. Brain Wellness and Aging

Support: Canadian Institutes of Health Research (CIHR) MOP 115011

Title: Selective effects of healthy aging on corpus callosum microstructure: A diffusion tensor imaging tractography study

Authors: *N. V. MALYKHIN[1], W. PIETRASIK[1], I. CRIBBEN[3,2], Y. HUANG[1], F. OLSEN[1]
[1]Biomed. Engin., [2]Neurosci. and Mental Hlth. Inst., Univ. of Alberta, Edmonton, AB, Canada; [3]Finance and Statistical Analysis, Alberta Sch. of Business, Edmonton, AB, Canada

Abstract: ***Introduction*** Previous diffusion tensor imaging (DTI) studies confirmed the vulnerability of the corpus callosum (CC) fibers to normal aging. Most DTI studies in aging employed low order regressions (linear, cubic or quadratic) to study the relationship between age and white matter microstructure. However low-order regressions impose severe shape restrictions on the fitted relationship. The main goal of the present study was to investigate whether higher order regression models (up to power of 10) would better describe the relationship between age white matter microstructure compared to lower order regressions in major subdivisions of the CC across the lifespan using DTI-tractography. ***Methods*** 140 healthy participants (62 men, 78 women; age range:18-85), with no history of psychiatric or neurological disorders, were recruited for this study. Images were acquired on Siemens 1.5T scanner. Tractography was performed using DTI-studio using reliable protocols to segment the CC into its components (genu, body, and splenium). We chose the best model using the Bayesian Information Criterion (BIC). ***Results*** The fractional anisotropy (FA) declined with age, following a quadratic relationship, after the early 20s for the genu and splenium of the CC, and after 50 years of age for the body. Mean diffusivity (MD) rose with age for all CC segments measured, all following a quadratic relationship with the most drastic rise occurring at 50 years. Axial diffusivity (AD) followed a similar trend as the MD, whilst radial diffusivity (RD) followed a cubic relationship with the rise occurring earlier in the 40s. The number of fibers comprising the tract decreased with age in all CC segments, with a more profound age effect in the genu and body compared to the splenium; the average length of the tract decreased in the early 20s for the body and 50s for the genu, with no significant decrease in the splenium. Tract volume decreased with age for all segments of the CC following a quadratic relationship with earlier decrease (after 40 years) for the genu and body, and a later decrease (after 60 years) for the splenium. Higher order regression models were generally similar to lower order models when describing changes in FA, RD, number of fibers, and fiber length for all parts of the CC. However, higher order regressions were better at describing the effects of age on the MD and AD of the body, and volume in the genu and splenium. ***Conclusions*** Our findings demonstrate that the CC is not uniformly affected by aging, with accelerated degradation in anterior sections. Lower order regression models were equally proficient at describing the effects of age compared to higher order models in most cases.

Disclosures: W. Pietrasik: None. **I. Cribben:** None. **Y. Huang:** None. **F. Olsen:** None.

Nanosymposium

354. Brain Wellness and Aging: Systemic Factors and Brain Function

Location: SDCC 33

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 354.04

Topic: C.01. Brain Wellness and Aging

Support: Kunin Professorship in Healthy Brain Aging (LMJ)

Title: Human leukocyte antigen drb1*13 protects against age-related brain changes

Authors: *L. JAMES[1], P. CHRISTOVA[2], A. P. GEORGOPOULOS[3]
[1]Brain Sci. Ctr., Univ. of Minnesota/Minneapolis VAHCS, Minneapolis, MN; [2]Univ. of Minnesota, Minneapolis, MN; [3]Neurosci, Univ. Minnesota, Minneapolis, MN

Abstract: Age-related brain changes are well-documented even among healthy individuals; however, there is considerable individual variability which may be partially attributable to genetic variation. Human Leukocyte Antigen (HLA) alleles play a central role in specific immunity by aiding the elimination of pathogens. Although some HLA variants have been linked to numerous conditions affecting the brain including Alzheimer's disease, other alleles such as those of the DRB1*13 family have been shown to exert protective effects. Here we used structural magnetic resonance imaging and diffusion tensor imaging to investigate brain volume and axonal integrity in seventy-one cognitively healthy (MoCA ≥ 26) women (32-69 years old) characterized according to the presence or absence of DRB1*13. Results demonstrated highly significant age-related decreases in volume and axonal integrity among those lacking DRB1*13. In contrast, no such effects were observed among DRB1*13 carriers. Results of this study provide further evidence of the protective effects of DRB1*13 on age-related brain changes. We hypothesize that the neuroprotection conferred by these alleles may be due to successful elimination of pathogens that could otherwise gradually affect the brain.

Disclosures: L. James: None. **P. Christova:** None. **A.P. Georgopoulos:** None.

Nanosymposium

354. Brain Wellness and Aging: Systemic Factors and Brain Function

Location: SDCC 33

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 354.05

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01 7 RF1 AG057264

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], A. GROMOVA[3], A. R. LA SPADA[2]
[1]Neurol., [2]Duke Univ., Durham, NC; [3]Univ. of California San Diego, San diego, CA

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 in proteostasis 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 muscle proteostasis 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. Analysis of metabolomic profiles shows important age and muscle-TFEB-dependent changes in metabolism pathways in skeletal muscle and brain, suggesting integrated metabolic responses in aging mice can be modulated by maintaining skeletal muscle proteostasis. Proteomics studies also reveal specific TFEB-dependent enrichment of the muscle and brain proteome, highlighting novel muscle-to-brain signaling pathways that regulate the cross-talk between skeletal muscle and CNS. Our current work aims to characterize these targets and validate their therapeutic potential for diseases of the aging CNS.

Disclosures: C.J. Cortes: None. **A. Gromova:** None. **A.R. La Spada:** None.

Nanosymposium

354. Brain Wellness and Aging: Systemic Factors and Brain Function

Location: SDCC 33

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 354.06

Topic: C.01. Brain Wellness and Aging

Title: Multi-modal impact of treatment with a human plasma protein fraction to enhance CNS function

Authors: *E. CZIRR, I. D. GALLAGER, M. K. CAMPBELL, C. TUN, S. REGE, R. R. ALCANTARA-LEE, A. T. LIU, H. HACKBART, M. CASTRO, R. ESTRADA, V. KHEIFETS, S. P. BRAITHWAITE, S. S. MINAMI
Alkahest Inc., San Carlos, CA

Abstract: Age-related disorders are complex with largely unknown aetiology and variable disease course. The impact of these disorders is however increasing as the world's population ages, and therefore new therapeutic approaches are needed to combat them. A promising avenue is the use of young plasma which has been demonstrated to benefit cognition in aging through parabiosis and plasma transfer experiments in mice. However, the need for individual donations, safety risks and logistical considerations make young plasma infusions a complex therapeutic. We have identified a human plasma fraction with superior safety, tolerability and neuroregenerative properties leading to cognitive improvements in both middle aged and old mice. By simplifying the fraction's composition compared to young plasma and by identifying an optimized dosing paradigm, we were able to treat immune-competent C57BL/6 mice for the first time, and investigate the impact of plasma proteins on a wider diversity of mechanisms. In addition to longitudinal effects on neurogenesis, the acute effects of plasma fraction treatment in vivo include decreased microglial activation and enhanced neuronal activation. Together, these data provide the rationale for clinical development of this plasma fraction for the treatment of cognitive decline and the aging milieu in neurodegenerative disorders of aging. The fraction, dosing paradigm, and mechanistic insights identified in animal models have now been translated into design of a clinical trial for mild to moderate Alzheimer's disease patients.

Disclosures: E. Czirr: A. Employment/Salary (full or part-time):; Alkahest Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest Inc. **I.D. Gallager:** A. Employment/Salary (full or part-time):; Alkahest Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest Inc. **M.K. Campbell:** A. Employment/Salary (full or part-time):; Alkahest Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest Inc. **C. Tun:** A. Employment/Salary (full or part-time):; Alkahest Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest Inc. **S. Rege:** A. Employment/Salary (full or part-time):; Alkahest Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest Inc. **R.R. Alcantara-Lee:** A. Employment/Salary (full or part-time):; Alkahest Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest Inc. **A.T. Liu:** A. Employment/Salary (full or part-time):; Alkahest Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest Inc. **H. Hackbart:** A. Employment/Salary (full or part-time):; Alkahest Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest Inc. **M. Castro:** A. Employment/Salary (full or part-time):; Alkahest Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest Inc. **R. Estrada:** A. Employment/Salary (full or part-time):; Alkahest Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest Inc. **V. Kheifets:** A. Employment/Salary (full or part-time):; Alkahest Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

rights/patent holder, excluding diversified mutual funds); Alkahest Inc. **S.P. Braithwaite:** A. Employment/Salary (full or part-time):; sbraithwaite@alkahest.com. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); sbraithwaite@alkahest.com. **S.S. Minami:** A. Employment/Salary (full or part-time):; Alkahest Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alkahest Inc..

Nanosymposium

354. Brain Wellness and Aging: Systemic Factors and Brain Function

Location: SDCC 33

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 354.07

Topic: C.01. Brain Wellness and Aging

Title: Identification and characterization of a beneficial plasma fraction with long term efficacy in the CNS

Authors: *V. KHEIFETS, I. GALLAGER, S. MINAMI, E. CZIRR, N. HUBER, R. ALCANTARA-LEE, M. CASTRO, S. REGE, H. HACKBART, C. TUN, R. ESTRADA, S. P. BRAITHWAITE
Functional Biol., Alkahest, San Carlos, CA

Abstract: Rejuvenating properties of factors present in young murine plasma have been demonstrated through multiple independent heterochronic parabiosis and plasma infusion studies. We confirmed that human plasma from young 18-22 year old donors reverses age-related cognitive decline and enhances hippocampal neurogenesis and cell survival in aged immunocompromised NSG mice, while plasma from aged individuals (62-68 years old) has detrimental effects in young NSG mice. As young human plasma had profound effects on neurogenesis and cell survival, we used cell-based assays that modeled these biological processes to identify a bioactive plasma fraction which demonstrated superior efficacy, safety and tolerability compared to whole plasma. Together with an optimized dosing paradigm, the human plasma fraction enhanced neuroregenerative properties in both middle aged and old mice above the effect observed with whole plasma. We demonstrate a long-lasting effect of this plasma fraction on cell survival and neurogenesis, as well as an acute effect on cell proliferation that promotes neurogenesis by preferentially driving cells towards a neuronal fate. Together, these data provide the rationale for clinical development of this plasma fraction for the treatment of cognitive decline in diseases of aging.

Disclosures: V. Kheifets: A. Employment/Salary (full or part-time):; Alkahest. **I. Gallager:** A. Employment/Salary (full or part-time):; Alkahest. **S. Minami:** A. Employment/Salary (full or part-time):; Alkahest. **E. Czirr:** A. Employment/Salary (full or part-time):; Alkahest. **N. Huber:** A. Employment/Salary (full or part-time):; Alkahest. **R. Alcantara-Lee:** A. Employment/Salary

(full or part-time):; Alkahest. **M. Castro:** A. Employment/Salary (full or part-time):; Alkahest. **S. Rege:** A. Employment/Salary (full or part-time):; Alkahest. **H. Hackbart:** A. Employment/Salary (full or part-time):; Alkahest. **C. Tun:** A. Employment/Salary (full or part-time):; Alkahest. **R. Estrada:** A. Employment/Salary (full or part-time):; Alkahest. **S.P. Braithwaite:** A. Employment/Salary (full or part-time):; Alkahest.

Nanosymposium

355. Motor Neuron and Other Neuromuscular Diseases: *In Vitro* Studies

Location: SDCC 30B

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 355.01

Topic: C.06. Neuromuscular Diseases

Support: Charlotte and Gwenyth Gray Foundation
NIH Grant R01NS082283

Title: From bench to bedside: Gene therapy for Batten (CLN6) disease

Authors: *S. B. LIKHITE[1], J. T. CAIN[3], K. A. WHITE[3], D. J. TIMM[3], S. DAVIS[3], T. JOHNSON[3], C. DENNYS-RIVERS[2], F. RINALDI[2], D. MOTTI[2], S. CORCORAN[2], P. MORALES[4], B. K. KASPAR[2], J. WEIMER[3], K. MEYER[2]
[1]Ctr. for Gene Therapy, [2]Ctr. for gene therapy, Res. Inst. at Nationwide Childrens Hosp., Columbus, OH; [3]Pediatrics and Rare Dis. Group, Sanford Res., Sioux Falls, SD; [4]The Mannheimer Foundation, Inc., Homestead, FL

Abstract: Batten Disease is a fatal, neurodegenerative lysosomal storage disorder with multiple causative genes and a wide range of disease severities. Mutations in ceroid-lipofuscinosis neuronal 6 (CLN6) gene mainly affect children between 18 months and 8 years of age. The disease is characterized by seizures, progressive dementia and loss of visual and motor functions, ultimately leading to death within the first 15 years of life. Unfortunately, there is no cure or therapeutic treatment for CLN6-Batten disease. The disease is caused by mutations causing absence or reduced abundance of CLN6 protein, making gene therapy a promising therapeutic strategy. The objective of this study was to determine the feasibility of adeno-associated vector serotype 9 (AAV9) mediated CLN6 expression as a viable gene therapy for CLN6-Batten disease. We developed a scAAV9 vector expressing the human CLN6 (hCLN6) gene under the control of a chicken β-actin (CB) promoter. To determine the efficacy, scAAV9.CB.CLN6 was administered by a single, postnatal intracerebroventricular injection in CLN6 mice. Mice were assessed for histopathological, behavioral and survival changes. The one-time treatment resulted in drastic reduction of accumulated autofluorescent storage material and ATP synthase subunit C (both hallmarks of the disease) by as early as 1 month of age. There was a significant improvement in motor performance (rotarod assessment) in scAAV9.CB.CLN6 treated animals starting at 8 months of age compared to uninjected CLN6 mice. The treatment also resulted in

significant improvement of learning and memory deficits in CLN6 mice demonstrated by improved performance of scAAV9.CB.CLN6 treated mice in the morris water maze test. Importantly, while all untreated CLN6 mice died between 12-14 months of age, scAAV9.CB.CLN6 administration significantly extended the median survival beyond 22 months of age and all of the histopathological, behavioral and cognitive parameters continued to improve throughout the lifespan of the treated mice. To our knowledge, this is the longest survival extension reported in this mouse model to date. To further translate this approach towards clinic, we dosed three 4-year old Cynomolgus Macaques with scAAV9.CB.CLN6 by intrathecal lumbar injection and monitored them for up to 6 months post injection. No adverse effects or pathology were observed, while high levels of transgene expression were found throughout the brain and spinal cord of all 3 animals. Collectively, this study provided a strong foundation for the currently ongoing first in-human phase I clinical trial for intrathecal administration of scAAV9.CB.CLN6 in CLN6-Batten disease patients.

Disclosures: S.B. Likhite: None. **J.T. Cain:** None. **K.A. White:** None. **D.J. Timm:** None. **S. Davis:** None. **T. Johnson:** None. **C. Dennys-Rivers:** None. **F. Rinaldi:** None. **D. Motti:** None. **S. Corcoran:** None. **P. Morales:** None. **B.K. Kaspar:** None. **J. Weimer:** None. **K. Meyer:** None.

Nanosymposium

355. Motor Neuron and Other Neuromuscular Diseases: *In Vitro* Studies

Location: SDCC 30B

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 355.02

Topic: C.06. Neuromuscular Diseases

Support: CROSS-NEUROD EU

Title: Development of central nervous system 3D *in vitro* models to study molecular mechanisms and develop therapeutic strategies for motor neuron diseases

Authors: *P. RINCHETTI[1], I. FARAVELLI[2], L. MAPELLI[3], S. TAMANINI[2], C. CORDIGLIERI[4], M. RIZZUTI[2], G. FOROTTI[2], N. BRESOLIN[2], G. P. COMI[2], M. NIZZARDO[2], S. CORTI[2]
[1]Univ. of Milan, Milano, Italy; [2]Univ. of Milan, Milan, Italy; [3]Dept of Brain and Behavioral Sci., Univ. of Pavia, Pavia, Italy; [4]Inst. Nazionale Genetica Medica (INGM), Milan, Italy

Abstract: Background: Spinal muscular atrophy (SMA) is the leading genetic cause of death during childhood. SMA is caused in the majority of the cases (up to 95%) by homozygous deletion in the Survival Motor Neuron 1 (SMN1) gene leading to progressive muscular paralysis due to lower motor neurons degeneration. A deeper knowledge of SMN role in different organs/systems would be crucial for the development of efficacious therapeutic approaches and

in vitro novel reliable models of human central nervous system (CNS) are needed. In particular, it would be important to generate a human model able to recapitulate the complexity of the CNS and its development. **Rationale**: In this study, we took advantage of CNS organoid technology, a novel stem cell based three-dimensional (3D) platform that has the potential to address the limitations of human existing bi-dimensional cultures improving preclinical testing. We aim to demonstrate that this approach can recapitulate some of the complexity of whole-organism biology surpassing the conventional use of the iPSCs. The creation of a new model for SMA could lead to a better knowledge of the mechanisms underlying the disorder during the development of the CNS and it might be instrumental in shaping better therapeutic options for affected patients. **Methods:** We obtained iPSCs from human fibroblasts of both control and SMA patients and, using two different protocols, we generated 3D CNS organoids. We performed immunohistochemical and molecular analysis to confirm their differentiation state and electrophysiological analysis to verify their activity. **Results:** CNS organoids derived from healthy subjects and patient have been successfully obtained, as suggested by the protein and gene expression data, by the electrophysiological activity and their ability to respond to stimuli. Preliminary results demonstrated that SMA organoids exhibited alteration in the CNS development and in the proper markers expression. **Conclusion:** We generated and characterized healthy and SMA CNS 3D organoids that recapitulated human CNS development and showed disease-related features.

Disclosures: P. Rinchetti: None. **I. Faravelli:** None. **L. Mapelli:** None. **S. Tamanini:** None. **C. Cordiglieri:** None. **M. Rizzuti:** None. **G. Forotti:** None. **N. Bresolin:** None. **G.P. Comi:** None. **M. Nizzardo:** None. **S. Corti:** None.

Nanosymposium

355. Motor Neuron and Other Neuromuscular Diseases: *In Vitro* Studies

Location: SDCC 30B

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 355.03

Topic: C.06. Neuromuscular Diseases

Title: Phenotypic characterization of human iPSCs-derived SOD1(G93A) motor neurons for identifying and investigating novel ALS targets

Authors: *S. KEILANI[1], P. HUTSON[2], I. REYNOLDS[2], S. RISSO[2]
[1]Small Molecules Discovery Res., [2]Teva Pharmaceuticals, West Chester, PA

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the selective loss of motor neurons (MNs) of cortex, brain stem and spinal cord. The loss of MNs and the subsequent muscular weakness and atrophy lead to paralysis and death within 3-5 years after disease onset with no current effective treatment available to halt or reverse ALS. Treatments that have shown promise in transgenic animals with ALS-like disorders

failed in human clinical trials mostly during phase II and III. Limited disease models that recapitulate the ALS phenotype and the elusive pathophysiology of ALS are the underlying causes of this high rate of failure. Induced Pluripotent Stem Cells (iPSCs) might provide novel approaches to recapitulate in vitro “disease in dish” and thus a valuable tool for identifying novel therapeutics based on the pathophysiology and for predicting the efficacy of drugs, toxicity, and patient-specific drug response. An important pathophysiological biomarker in ALS is hyperexcitability of cortical and motor neurons. Hyperexcitability is an early feature of the disease (reported at embryonic age in SOD1(G93A) motor neurons), precedes neuronal degeneration, and seems to be a final common pathway in both sporadic and familial ALS. Importantly, a recent study demonstrated the broad relevance of motor neuron hyperexcitability for familial ALS across iPSC lines, patients and genotypic etiologies. However, the pathways connecting disease-causing mutations, hyperexcitability and motor neuron death remain to be elucidated. In this study, we utilized motor neurons derived from iPSCs with an engineered mutation in SOD1(G93A) to model hyperexcitability in vitro with the goal to utilize it as an endpoint for phenotypic screening. Our results demonstrate that SOD1(G93A) motor neurons display hyperexcitability starting at 2 weeks when compared to their isogenic controls. In addition, we show that SOD1(G93A) motor neurons display a defect in their spare respiratory capacity, have altered ATP levels, and altered morphometric properties. Finally, SOD1(G93A) motor neurons show altered mitochondrial gene expression particularly in genes involved in mitochondrial membrane polarization and potential, and mitochondrial apoptosis. Taken together, our results clearly demonstrate that SOD1(G93A) motor neurons display several ALS disease-associated phenotypes in vitro. This study sheds a light on the cellular mechanisms that could contribute to the disease state and progression and lays the ground for a phenotypic screen to identify novel ALS targets and drug candidates.

Disclosures: S. Keilani: None. **P. Hutson:** None. **I. Reynolds:** None. **S. Risso:** None.

Nanosymposium

355. Motor Neuron and Other Neuromuscular Diseases: *In Vitro* Studies

Location: SDCC 30B

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 355.04

Topic: C.06. Neuromuscular Diseases

Support: MNDRIA Grant GIA1429
MNDRIA Grant GIA1547

Title: An *in vitro* human neuromuscular connection as a model to study amyotrophic lateral sclerosis

Authors: *Q. DING[1], T. TRACEY[1], P. THAKRE[1], E. WIMBERGER[1], A. RUSSELL[2], R. KANJHAN[1], M. BELLINGHAM[1], L. JEFFEREE[3], M. COLDITZ[3], R. HENDERSON[3], P.

MCCOMBE[3], K. FORREST[3], M. DEVINE[3], M. HILLIARD[1], E. WOLVETANG[1], S. NGO[1], P. G. NOAKES[1]
[1]Univ. of Queensland - St. Lucia Campus, Brisbane, Australia; [2]Deakin Univ., Geelong, Australia; [3]Royal Brisbane & Women's Hosp., Brisbane, Australia

Abstract: Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease, which is characterised by both upper and lower motor neuron (MN) degeneration. A "dying back" hypothesis that the neuromuscular junction (NMJ) degeneration triggers MN loss and precedes the onset of clinical symptoms has been proposed. The NMJ is a specialized synapse between MNs and muscle cells. We have observed NMJ dismantlement in the early stages of disease in ALS patients. These observations have driven us to establish an *in vitro* human neuromuscular circuit, using MNs derived from human induced pluripotent stem cells (hiPSCs) and muscle sourced from muscle biopsies obtained from healthy donors and from ALS patients. So far, we have shown that our hiPSC-MNs express specific MN differentiation markers Hb9, Islet 1, and choline acetylcholine transferase (ChAT). These hiPSC-MNs display typical MN morphology (i.e. one long axon and numerous radiating neurites - likely to be dendrites). Furthermore, these neurons are excitable, namely they can be induced to produce action potentials under current clamp conditions. Using a two chamber micro-fluidic device, we demonstrate that hiPSC-MNs grown in one chamber are able to send their axons to interact with the human muscle cells in the second chamber. Examination of the interaction sites between MN axons and muscle revealed clusters of acetylcholine receptors in the muscle membrane, suggesting the initial induction of postsynaptic specializations. Our next step is to see if such specializations occur between hiPSCs-MNs and muscle cells sourced from ALS patients. The establishment of such human *in vitro* neuromuscular co-culture systems could facilitate investigations into the early loss of NMJs seen in ALS.

Disclosures: Q. Ding: None. **T. Tracey:** None. **P. Thakre:** None. **E. Wimberger:** None. **A. Russell:** None. **R. Kanjhan:** None. **M. Bellingham:** None. **L. Jefferee:** None. **M. Colditz:** None. **R. Henderson:** None. **P. McCombe:** None. **K. Forrest:** None. **M. Devine:** None. **M. Hilliard:** None. **E. Wolvetang:** None. **S. Ngo:** None. **P.G. Noakes:** None.

Nanosymposium

355. Motor Neuron and Other Neuromuscular Diseases: *In Vitro* Studies

Location: SDCC 30B

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 355.05

Topic: C.06. Neuromuscular Diseases

Support: NIH R01 NS644912-1A1
RC2 NS69476-01
Project A.L.S.

Packard Center for ALS Research (P2ALS)
Helping Link Foundation
Young Investigator Development Award from the Muscular Dystrophy Association (MDA
Swiss National Science Foundation Fellowship

Title: Correlation between cellular markers, astrocyte toxicity and disease progression in ALS patients

Authors: *C. N. DENNYS[1], S. B. LIKHITE[3], A. HUFFENBERGER[2], S. J. KOLB[5], B. K. KASPAR[4], K. C. MEYER[6]
[1]Ctr. for Gene Therapy, [2]Nationwide Children's Hosp., Columbus, OH; [3]Ctr. for Gene Therapy, [4]Ohio State Univ., Res. Inst. at Nationwide Childrens Hosp., Columbus, OH; [5]Neurol., The Ohio State Univ. Wexner Med. Ctr., Columbus, OH; [6]Ctr. for Gene Therapy, Res. Inst. Nationwide Childrens Hosp., Columbus, OH

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a severe adult onset neurodegenerative disorder leading to progressive paralysis and death within 2-5 years. Motor neuron death is the most prominent feature of the disease. However, mouse models indicate that oligodendrocytes and astrocytes play a crucial role in disease progression. Studying the role of different cell types in disease advancement is challenging as samples can only be collected when the patient dies, which is usually the end stage. The new and fast reprogramming method we developed allows generating both cell types from skin biopsies of patients at an earlier disease stage. We have previously shown that induced astrocytes and oligodendrocytes from ALS patients are toxic to motor neurons. The degree of astrocyte toxicity is variable with some lines demonstrating a more toxic phenotype than others. Our preliminary data indicates that the severity of astrocyte toxicity might correlate with length of disease progression in the donor. This observation suggests intracellular variation between these cells that renders some patients more vulnerable to rapid disease advancement. We used immunostaining, western blot, and native page to evaluate the relationship between various described cellular ALS markers and astrocyte toxicity in vitro and its correlation to the disease progression rate in patients. Astrocytes with a more aggressive phenotype displayed extreme disruption of the mitochondrial network, whereas mildly aggressive astrocytes had mixed mitochondrial populations containing either normal or fragmented networks. We also evaluated the elevation in ER stress marker (BIP) in addition to aggregate formation (TDP43, p62, and misfolded SOD1) and correlated them to degree of astrocyte toxicity. These findings demonstrate that patients with rapidly progressing disease course have elevated cellular ALS markers present in their induced astrocytes compared to those with a slowly advancing disease. In summary, this model system could be applicable not only to screen for potential therapeutic compounds but also to aid clinicians in assessing disease prognosis of a given patient in the future.

Disclosures: C.N. Dennys: None. **S.B. Likhite:** None. **A. Huffenberger:** None. **S.J. Kolb:** None. **B.K. Kaspar:** None. **K.C. Meyer:** None.

Nanosymposium

355. Motor Neuron and Other Neuromuscular Diseases: *In Vitro* Studies

Location: SDCC 30B

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 355.06

Topic: C.06. Neuromuscular Diseases

Support: Muscular Dystrophy Association
Farber Family Foundation
JCBS Postdoctoral Travel Fellowship

Title: C9orf72 RAN-translated poly-GA dipeptide results in perturbed signaling events and altered machinery required for synaptic transmission

Authors: *B. K. JENSEN[1], X. WEN[1], T. WESTERGARD[1], K. J. MCAVOY[1], K. KRISHNAMURTHY[1], M. H. SCHULDI[2], D. EDBAUER[2], A. HAEUSLER[1], P. PASINELLI[1], D. TROTTI[1]
[1]Jefferson Weinberg ALS Center, Vickie and Jack Farber Inst. for Neurosci., Thomas Jefferson Univ., Philadelphia, PA; [2]German Ctr. for Neurodegenerative Dis. (DZNE), Munich, Germany

Abstract: The most common genetic cause for amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) is a hexanucleotide (GGGGCC) repeat expansion in the C9orf72 gene. From this expanded region, aberrant RNA is generated and dipeptide repeat proteins (DPRs) are produced through the process of RAN-translation. Of the five DPRs, poly-glycine-alanine (poly-GA) is the most abundantly detected in brain and spinal cord samples from patients. In contrast to the robust toxicity invoked by arginine-containing DPRs *in vitro*, we and others have observed a more gradual toxic profile of poly-GA dipeptides. Deficits arising from poly-GA expression in neurons have been documented in two transgenic mouse models. In the first, poly-GA_{50} expression is restricted to the cortex. By six months of age, these animals display cognitive and motor deficits, as well as neuronal loss and brain atrophy. In our model, poly-GA_{149} expression is confined to spinal cord and brainstem, and results in significant motor deficits by four months of age without loss of motor neurons. Our evidence suggests that *in vivo*, motor deficits may occur prior to the death of affected neurons. As such, an understanding of how neurons cope with poly-GA dipeptides and the potential impacts this may have on cellular functions is critical. In cortical and motor neurons, we have seen poly-GA inclusions in axonal and dendritic regions at timepoints greatly preceding cell death. We hypothesized that poly-GA dipeptides may cause disruption of signaling events and impairment of synaptic transmission prior to the loss of neuronal viability.
Fluorescently tagged poly-GA constructs were transfected into primary rat cortical and motor neurons. To approximate the effectiveness of evoked synaptic vesicle release, we employed a dye-unloading assay under conditions of neuronal perfusion with high potassium solution. We

found the ability to successfully release dye greatly diminished in neurons containing poly-GA aggregates. Using GCaMP6f coupled with mCherry-tagged poly-GA constructs, calcium influx was examined under identical perfusion stimulation conditions. In both cortical and motor neurons expressing poly-GA, calcium influx was significantly increased compared with mCherry expressing controls. An examination of synaptic components revealed that synaptic vesicle associated protein 2 (SV2) was reduced in neurites in a poly-GA repeat length dependent manner, while synaptophysin and PSD-95 remained unaffected. Analysis of spinal cord tissue derived from our poly-GA_{149} transgenic mice confirmed this specific reduction of SV2 protein both by western blotting and immunostaining.

Disclosures: B.K. Jensen: None. **X. Wen:** None. **T. Westergard:** None. **K.J. McAvoy:** None. **K. Krishnamurthy:** None. **M.H. Schuldi:** None. **D. Edbauer:** None. **A. Haeusler:** None. **P. Pasinelli:** None. **D. Trotti:** None.

Nanosymposium

355. Motor Neuron and Other Neuromuscular Diseases: *In Vitro* Studies

Location: SDCC 30B

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 355.07

Topic: C.06. Neuromuscular Diseases

Support: NIH R21 NS090912
Farber Family Foundation
Margaret Q. Landenberger Research Foundation
The Professor Fredric Rieders, Ph.D. Scholarship

Title: Poly-GR expression in a novel mouse model of C9orf72-ALS

Authors: *B. A. MORRIS[1,2], X. WEN[2], T. WESTERGARD[2], K. A. RUSSELL[2], A. R. HAEUSLER[2], D. TROTTI[2], P. PASINELLI[2]
[1]Thomas Jefferson Univ., Philadelphia, PA; [2]Dept. of Neurosci., Jefferson Weinberg ALS Ctr., Philadelphia, PA

Abstract: A hexanucleotide repeat expansion mutation in the *C9orf72* gene accounts for the most Amyotrophic Lateral Sclerosis (ALS) cases of known genetic origin. Three potential disease mechanisms result from the expansion: haploinsufficiency of the C9orf72 protein, RNA toxicity from transcription of the expanded region, and RAN translation of the aberrant RNA to form various species of dipeptide repeat proteins (DPRs). While human post-mortem tissue presents strong evidence of the presence of sense-encoded DPRs, it is debated whether DPRs are causative or passenger gene products in the pathogenesis of C9orf72-ALS. Arginine-containing DPRs have a particularly toxic profile and have been implicated in nucleocytoplasmic transport defects, nucleolar stress, inhibition of splicing, and membraneless organelle dysfunction,

resulting in competing theories as to their site of inflicted toxicity: nucleus or cytoplasm. Human post-mortem tissue suggests a cytoplasmic role for the glycine-arginine (GR) DPR as it uniquely colocalizes with cytosolic phospho-TDP-43 in clinically relevant areas.
We have developed a novel Cre-inducible C57BL/6 mouse model expressing the DPR glycine-arginine with 50 repeats (GR_{50}-GFP) at a ubiquitous promoter site as well as a comparable GFP control line. This model uses a randomized codon strategy and is ATG driven, allowing us to study the role of the DPR independent of any RAN-translation or RNA effects. Initial immunochemistry of clinically relevant regions (frontomotor cortex and spinal cord) detects GR_{50} diffusely expressed in the cytosol of NeuN-positive neurons with evidence of perinuclear accumulation. Current motor assessments include grip strength, rotarod, body weight, and quantitative gait analysis. Both male and female rodents are included in the study and assessments are performed blinded to the genotype of the mice. GR_{50}-GFP mice are compared to age and gender-matched GFP and wild type controls. Initial analyses of GR50-GFP expressing mice up to 9 months of age do not suggest a discernable motor phenotype. Assessments are ongoing to determine if a role exists for GR_{50}-GFP in any emergent motor phenotypes.

Disclosures: B.A. Morris: None. **X. Wen:** None. **T. Westergard:** None. **K.A. Russell:** None. **A.R. Haeusler:** None. **D. Trotti:** None. **P. Pasinelli:** None.

Nanosymposium

355. Motor Neuron and Other Neuromuscular Diseases: *In Vitro* Studies

Location: SDCC 30B

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 355.08

Topic: C.06. Neuromuscular Diseases

Support: Grant from The Packard Center for ALS Research at Johns Hopkins

Title: tRNA requirements for C9orf72 RAN translation

Authors: *A. NELSON[1,2], H. GAMPER[2,3], S. MAHARJAN[2,3], A. LOWE[2], A. R. HAEUSLER[1,2], Y.-M. HOU[2,3], D. TROTTI[4,2]
[1]Neurosci., [3]Biochem. and Mol. Biol., [2]Thomas Jefferson Univ., Philadelphia, PA; [4]Neurosci., Dept. of Neurosci., Philadelphia, PA

Abstract: The *C9orf72* $(GGGGCC)_n$ repeat expansion leads to the production of neurotoxic dipeptide repeat proteins by a non-canonical mechanism known as repeat-associated non-AUG (RAN) translation. The molecular requirements for this mechanism are just beginning to be understood (PMC5722904, PMC5764992 and PMC5754368). All forms of translation are intimately dependent on transfer RNAs (tRNAs), which shuttle amino acids to the ribosome for protein synthesis. tRNA pool composition and distribution are species- and tissue-specific (PMC1713254). Moreover, the depletion of glutaminyl-tRNA has been shown to increase the

propensity of -1 frameshifting during RAN translation of CAG repeats linked to other neurological disorders (23352662). Dysfunction in tRNAs themselves has also been demonstrated to cause translational defects and result in neurodegeneration (PMC5693308). Therefore, the tRNA availability, function, and usage are of high relevance in pathogenic processes, possibly including *C9orf72*-linked RAN translation. Here, we describe a custom *in vitro* translation system, in which we derive all translational machinery from rodent nervous system tissue, and supplement it with 1.) AUG-driven mRNA transcripts encoding the C9 repeat sequence (sense and antisense) tagged in all three reading frames with a reporter sequence (nLuc/FLAG) and 2.) tRNA pools derived from various species/tissue types. This system allows us to monitor translation by reporter expression, giving us a tractable model we can use to rapidly and consistently assess the efficiency of translation in the presence of different tRNA pools. We demonstrate that the efficiency of translation of the C9 repeat is dependent on tissue-specific tRNA pools and appears to be enhanced in the presence of human-derived tRNA. More studies are underway to determine the specific tRNA requirements for *C9orf72* RAN translation.

Disclosures: A. Nelson: None. **H. Gamper:** None. **S. Maharjan:** None. **A. Lowe:** None. **A.R. Haeusler:** None. **Y. Hou:** None. **D. Trotti:** None.

Nanosymposium

355. Motor Neuron and Other Neuromuscular Diseases: *In Vitro* Studies

Location: SDCC 30B

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 355.09

Topic: C.06. Neuromuscular Diseases

Support: National Key R&D Program of China (2016YFA0501902)

Title: The structural basis of reversible fibril involved in phase separation and neurodegenerative diseases

Authors: *D. LI[1], X. GUI[2], Y. LI[1], F. LUO[2], C. LIU[2]
[1]Bio-X Institutes, Key Lab. For the Genet., Shanghai, China; [2]Chinese Acad. of Sci., Shanghai City, China

Abstract: Pathological amyloid fibrils are characteristic of highly thermostable cross-β structure. However, the stable cross-β architecture cannot explain the reversible amyloid fibrils formed by RNA-binding proteins such as hnRNPA1 and FUS that is involved in the dynamic assembly of stress granules. Here we found that the reversible amyloid cores (RACs) of FUS and hnRNPA1 that can form reversible amyloid fibrils under the regulation of temperature and phosphorylation. We determined the atomic structures of the RACs in fibrillar forms by micro-electron diffraction and X-ray diffraction. Combined with biochemical and cellular experiments, we reveal the structural basis of reversible amyloid formation regulated by phosphorylation, and explains how

ALS disease-associated mutation abolishes reversibility of RACs which results in abnormal aggregation observed in the brain of ALS patients. Our study sheds light on understanding not only the dynamic amyloid formation in RNA granules but also how the dysregulation of reversible amyloid leads to diseases.

Disclosures: D. Li: None. **X. Gui:** None. **Y. Li:** None. **F. Luo:** None. **C. Liu:** None.

Nanosymposium

355. Motor Neuron and Other Neuromuscular Diseases: *In Vitro* Studies

Location: SDCC 30B

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 355.10

Topic: C.06. Neuromuscular Diseases

Support: R01 NS090335
R01 NS076919-01
R03 NS103060-02
Kennedy's Disease Association

Title: Role of USP7 in the pathogenicity of spinal and bulbar muscular atrophy

Authors: *A. PLUCIENNIK[1], D. MERRY[1], G. MARSH[2], S. TODI[2]
[1]Thomas Jefferson Univ., Philadelphia, PA; [2]Wayne State Univ. Sch. of Med., Detroit, MI

Abstract: Spinal and bulbar muscular atrophy (SBMA) is characterized by a loss of brainstem and spinal cord motor neurons, and of the associated innervated muscles. This toxicity to the neuromuscular system is caused by the expansion of a CAG repeat-encoded polyQ segment within the androgen receptor protein, a transcription factor that requires activation by its cognate ligands, testosterone or dihydrotestosterone, to produce the symptoms of SBMA. Although the molecular events that mediate expanded-polyQ-dependent toxicity remain largely obscure, such long polyQ tracts have been suggested to cause cellular dysfunction and ultimately cell death by dysregulating protein-protein interactions that sustain normal cellular function. Therefore, to understand this dysregulation, we have employed a quantitative proteomics approach involving stable isotope labeling of amino acids in cell culture (SILAC) to identify changes in the AR protein interaction network caused by polyQ expansion. One of the top hits identified was the ubiquitin-specific protease USP7, which we have validated as a preferential interactor with polyQ-expanded AR. This protein preferentially interacts with soluble AR, and does not colocalize with AR nuclear inclusions. Moreover, reduction of USP7 levels by shRNA-mediated gene silencing in polyQ-expanded AR-expressing cells decreases the frequency of nuclear inclusions and cytotoxicity. Using the proximity ligation assay, we show that partial knockdown of USP7 results in an increase in ubiquitination of polyQ-expanded AR, suggesting the direct action of USP7 on AR. Consistent with these findings, overexpression of wild-type, but not

catalytically inactive, USP7 results in a dramatic increase in polyQ-expanded AR aggregation as well as cytotoxicity. Biochemical analysis revealed that overexpression of USP7 decreases the levels of ubiquitinated polyQ-expanded AR. Knockdown of USP7 in a fly model of SBMA results in suppression of DHT- and polyQ expansion-dependent eye phenotype. In summary, our results demonstrate a functional role for USP7 in polyQ-expanded AR aggregation and toxicity *in vitro* and *in vivo*, revealing new mechanistic insights into SBMA pathogenesis and suggesting that USP7 may be an attractive target for disease modification in SBMA.

Disclosures: A. Pluciennik: None. **D. Merry:** None. **G. Marsh:** None. **S. Todi:** None.

Nanosymposium

355. Motor Neuron and Other Neuromuscular Diseases: *In Vitro* Studies

Location: SDCC 30B

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 355.11

Topic: C.06. Neuromuscular Diseases

Support: NIH R01 NS090335

Title: Impaired nuclear export of polyglutamine-expanded androgen receptor contributes to toxicity in spinal and bulbar muscular atrophy

Authors: *F. ARNOLD, A. PLUCIENNIK, D. E. MERRY
Thomas Jefferson Univ., Philadelphia, PA

Abstract: Spinal and bulbar muscular atrophy (SBMA) is a neuromuscular disease caused by a polyglutamine (polyQ) expansion in the androgen receptor (AR). Prior studies have highlighted the importance of nuclear AR in SBMA pathogenesis, as both the presence of hormone and an intact nuclear localization signal (NLS) are required for the toxicity of polyQ-expanded AR in cell and animal models of SBMA. Given the requirement of nuclear localization for mutant AR toxicity, we sought to determine if the nuclear export of polyQ-expanded AR is disrupted, and, if so, whether enhancing the nuclear export of polyQ-expanded AR is protective in models of SBMA. We demonstrate here that the nuclear export of polyQ-expanded AR is impaired, even prior to the formation of intranuclear inclusions of aggregated AR. Additionally, we find that promoting AR export with an exogenous nuclear export signal (NES) substantially reduces its aggregation and blocks hormone-induced toxicity in PC12 cells. Moreover, we show that these protective effects are conferred by destabilization of the mutant protein due to an increase in cytoplasmic AR proteasomal degradation. Despite a growing body of evidence that global disruption of nucleo/cytoplasmic transport occurs in ALS and HD, our data suggest that no such global disruption occurs in models of SBMA; rather, an AR-specific mechanism is responsible for the impaired nuclear export of polyQ-expanded AR. Notably, we also find that previously described mechanisms for AR nuclear export, including phosphorylation at Serine 650 (S650)

fail to regulate AR nuclear export in our cell models of SBMA, underlining the need for future research to determine the mechanism for AR nuclear export in neuronal cells.

Disclosures: F. Arnold: None. **A. Pluciennik:** None. **D.E. Merry:** None.

Nanosymposium

355. Motor Neuron and Other Neuromuscular Diseases: *In Vitro* Studies

Location: SDCC 30B

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 355.12

Topic: C.06. Neuromuscular Diseases

Title: Tmem184b loss causes motor and sensory impairment

Authors: *M. R. BHATTACHARYA[1], J. FENG[2], C. JARVIS[1], E. M. FRENCH[1], H. HU[2]
[1]Univ. of Arizona, Tucson, AZ; [2]Anesthesiol., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Sensory detection and motor function are both mediated by specialized nerve terminal endings that detect or transmit signals to and from the central nervous system. The 7-pass transmembrane protein TMEM184b participates in maintaining both motor and sensory nerve terminal morphology, suggesting that its loss may compromise functions of both of these systems, but very little is known about its role. We performed a series of tests to probe motor, sensory, and cognitive functions in TMEM184b mutant mice, including rotarod, gait analysis, grip strength, paw withdrawal threshold, hot plate sensitivity, tail flick latency, anxiety, and depression. We find that both motor and sensory behavior is abnormal in mice lacking TMEM184b. We hope to explore the molecular explanation for these phenotypes in future work.

Disclosures: M.R. Bhattacharya: None. **J. Feng:** None. **C. Jarvis:** None. **E.M. French:** None. **H. Hu:** None.

Nanosymposium

356. Spinal Cord Injury: Factors Influencing Recovery

Location: SDCC 7

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 356.01

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation
Cordula and Gunter Paetzold Fellowship

Title: Ketogenic diet reduces inflammation after spinal cord injury

Authors: *K. L. KOLEHMAINEN[1,2], O. SEIRA[1,2], I. BEATTIE[1], R. PATEL[1], N. ALAEIILKHCHI[1,2], T. MATZINGER[3], J. LIU[2], W. TETZLAFF[1,2]
[1]Univ. of British Columbia, Vancouver, BC, Canada; [2]ICORD, Vancouver, BC, Canada; [3]Franzens Univ. Innsbruck, Innsbruck, Austria

Abstract: Spinal cord injury (SCI) is a physically, emotionally, and financially debilitating disorder that has a significant lifelong impact. Previous findings in our lab demonstrated that the ketogenic diet (KD) may be a promising SCI treatment as rats fed with KD acutely after cervical SCI showed behavioural improvement in forelimb function. KD is a high fat, low carbohydrate diet and is clinically used in drug-resistant epilepsy in children. We hypothesize that KD can improve recovery after acute SCI by reducing inflammation. Using C57BL/6 mice, we performed a cervical dorsolateral funiculus crush and assessed behavioural function for 8 weeks following injury in mice fed a standard diet (SD) or KD. We saw modest improvements in behaviour with KD including favoring of the injured paw in a rearing exercise at 3 days after injury and fewer errors on a horizontal ladder at 2 weeks after injury. At 7 days post-injury, we assessed inflammation at the injury site by imaging phosphorylated p38 MAPK, an upstream mediator of inflammation. KD-fed mice showed significant reduction of phosphorylated p38 fluorescence intensity. Together these results suggest that KD could be modulating inflammation to improve recovery from SCI. Given the modest results overall, we decided to move to a more severe injury model: a thoracic midline contusion. Cytokine production is a more direct indicator of increased inflammation. Therefore, we assessed production of inflammatory cytokines at 48 hours and 7 days following the T9 contusion. Cytokine production did not differ between SD and KD at 48 hours post-injury but levels of MIP1alpha and MIP1beta, two pro-inflammatory cytokines involved in immune cell recruitment and activation, were reduced at 7 days post-injury for KD-fed mice. Similarly, we assessed cytokine production after cervical hemi-contusion in Sprague-Dawley rats and saw an increase in anti-inflammatory cytokine production, specifically IL-10 and IL-4, as soon as 48 hours post-injury for KD-fed rats. Together our results suggest that KD reduces the inflammatory response in the injured spinal cord if administered directly after injury. Further research will look at the mechanism behind this modulation of cytokine production with an emphasis on macrophage subtypes present in the injured spinal cord.

Disclosures: K.L. Kolehmainen: None. **O. Seira:** None. **I. Beattie:** None. **R. Patel:** None. **N. Alaeiilkhchi:** None. **T. Matzinger:** None. **J. Liu:** None. **W. Tetzlaff:** None.

Nanosymposium

356. Spinal Cord Injury: Factors Influencing Recovery

Location: SDCC 7

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 356.02

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NSF GRFP
Wings for Life
Craig H Neilsen Foundation
NIH NS099872

Title: Cortical spinal tract stimulation induces white matter remodeling in spinal cord injured rats

Authors: *B. KONDILES[1], R. ROBINSON[1], A. ZHANG[2], T. LEE[2], S. I. PERLMUTTER[1], P. J. HORNER[2]
[1]Univ. of Washington, Seattle, WA; [2]Houston Methodist Res. Inst., Houston, TX

Abstract: Spinal cord injury (SCI) causes the disruption of ascending and descending signals due to neuronal death, axonal loss, and demyelination. These morphological disruptions cause long-term functional deficits. For decades, electrical stimulation has shown potential as a means to improve recovery following SCI, although the mechanisms remain unknown; it may increase neuronal excitability, promote neural plasticity, encourage synaptogenesis, and promote remyelination. To explore candidate mechanisms, we quantified transcriptional and morphological changes induced by cortical stimulation. Female Long-Evans rats (275-350g) received a hemi-contusion injury at cervical level four on their dominant side. Penetrating electrodes were implanted into the contralateral forelimb motor cortex to deliver electrical stimulation to corticospinal tract (CST) neurons. An anterograde tracer was injected at the site of the electrodes to label surviving, stimulated CST axons. Animals were stimulated for 5 hours a day with current at 80% of the amplitude needed to evoke forelimb movements; control animals had injuries, tracer injections, and implants but no stimulation. After one week, total RNA was purified from regions across the central nervous system from of a subset of stimulated (n=2) and non-stimulated animals (n=2). RNA strands were sequenced, aligned to a rat genome, and analyzed using DeSeq2. Stimulation-induced differential expression was statistically compared in all examined regions. A number of genes related to Node of Ranvier maintenance, assembly, and function were significantly down regulated in the subcortical white matter of the stimulated motor cortex. In addition, mRNAs involved in early myelination were upregulated at the lesion site, implying stimulation promotes remyelination. A second group of animals (n=9) were stimulated for 3 weeks and spinal cords were studied with immunohistochemistry. A preliminary analysis of blinded counts of Nodes of Ranvier indicates that stimulated animals (n=5) had CST axons with fewer nodes rostral to the injury than axons in unstimulated controls (n=4). Further analysis will confirm whether stimulation does induce the formation of longer internodes, which would account for the decrease in nodal density. Future work is necessary to determine how longer myelin sheaths would alter signal conduction and subsequently affect behavior.

Disclosures: B. Kondiles: None. **R. Robinson:** None. **A. Zhang:** None. **T. Lee:** None. **S.I. Perlmutter:** None. **P.J. Horner:** None.

Nanosymposium

356. Spinal Cord Injury: Factors Influencing Recovery

Location: SDCC 7

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 356.03

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIBIB-NIH R21EB020318
Travis Roy Foundation to Cure Spinal Cord injury

Title: Paired brain and spinal cord stimulation strengthens spared spinal circuits after injury

Authors: *A. PAL[1], A. GARCIA-SANDOVAL[2], S. RATNADURAI-GIRIDHARAN[1], Q. YANG[1], T. BETHEA[1], A. RAMAMURTHY[1], T.-C. WEN[1], W. VOIT[2], J. B. CARMEL[1,3]
[1]Burke Neurolog. Inst., White Plains, NY; [2]Dept. of Mechanical Engineering, Departments of Materials Sci. and Engin. and Bioengine, The Univ. of Texas at Dallas, Richardson, TX; [3]Brain Mind Res. Inst. and Departments of Neurol. and Pediatrics, Weill Cornell Medicine, New York, New York, NY

Abstract: Using the principles of associative learning, we have developed a neuromodulation paradigm that augments sensorimotor excitability in the spinal cord. We pair supra-threshold motor cortex stimulation with sub-threshold spinal cord stimulation using a timing that causes the stimuli to arrive synchronously in the spinal cord. This paired stimulation strongly augments motor evoked potentials (MEPs) at the time that they are delivered. When pairing is performed repeatedly for 5 minutes, there is lasting and robust increase in MEPs. The present study tests the efficacy of paired stimulation in rats with injury of the sensorimotor system. We hypothesized that the tissue spared by spinal cord injury (SCI) would be sufficient to enable the lasting effects of paired stimulation. We further hypothesized that repeated sessions of paired stimulation would produce cumulative effects on spinal excitability. To test paired stimulation, we implanted three sets of electrodes: epidural screw electrodes over each motor cortex, EMG electrodes in each biceps muscle, and spinal epidural electrodes. The spinal electrodes are printed using photolithography, allowing them to be very thin (<100μm). In addition, the electrodes are patterned on a softening polymer which is stiff at room temperature making them easy to insert into the epidural space. It becomes supple after implantation, which protects the cervical spinal cord. A moderate C4 contusion injury was performed, and electrode arrays were inserted over C5-C6. Two weeks later, repetitive stimulation was performed. We measured biceps MEPs produced by cortical and spinal cord stimulation. Both cortical and spinal MEPs were augmented by ~75% and this lasted for over 60 minutes. We also measured H-reflexes in the forelimb. Rats with SCI were hyperreflexic, as demonstrated by the rate-dependent suppression of the H-reflex. Paired stimulation restored the measure of hyperreflexia close to the values of uninjured rats. Finally, we measured the effects of paired stimulation 5 minutes every day for 10 days in rats

with a cut injury to the corticospinal tract from one hemisphere. Over the 10 days of pairing, the effects increased from ~75% change to more than 250%. This suggests that there can be a cumulative effect of repeated pairing after injury. Thus, the circuits spared by CST lesions were sufficient to augment MEPs with paired stimulation, which enhanced spinal excitability while decreasing hyperreflexia.

Disclosures: A. Pal: None. **A. Garcia-Sandoval:** None. **S. Ratnadurai-Giridharan:** None. **Q. Yang:** None. **T. Bethea:** None. **A. Ramamurthy:** None. **T. Wen:** None. **W. Voit:** None. **J.B. Carmel:** None.

Nanosymposium

356. Spinal Cord Injury: Factors Influencing Recovery

Location: SDCC 7

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 356.04

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH 5R01NS064004 (JHM)
NYS SCIRB C30606GG, C31291GG (JHM)

Title: Motor cortex and cervical spinal cord electrical stimulation promotes forelimb motor function after spinal cord injury in rats

Authors: *Q. YANG[1], A. RAMAMURTHY[1], S. LALL[1], J. SANTOS[1], N. ZAREEN[2], H. ALEXANDER[2], D. F. RYAN[2], J. H. MARTIN[2], J. B. CARMEL[1]
[1]Burke Neurolog. Inst. Weill Cornell Med., White Plains, NY; [2]Physiology, Pharmacol. and Neurosci., The City Col. of the City Univ. of NY, New York, NY

Abstract: Cervical spinal cord injury impairs arm and hand function largely by interrupting descending tracts. Most spinal cord injuries spare some axons at the lesion, including the corticospinal tract (CST), which is critical for voluntary movement. We targeted spared CST connections using paired stimulation of motor cortex and spinal cord. We hypothesized that electrical stimulation would improve forelimb function and CST axon sprouting below the injury site. We adopted a stimulation approach developed in the John Martin laboratory that combines intermittent theta burst stimulation of forelimb motor cortex with trans-spinal direct current stimulation placed on the skin over the neck. This paradigm promotes plasticity and can be easily and non-invasively applied. While cortical stimulation is applied epidurally via implanted screw electrodes in rats, this can be done using transcranial magnetic stimulation in people. The spinal stimulation is delivered through skin electrodes that produce current flow through the cervical spinal cord. Before injury, rats were trained and tested on skilled horizontal ladder walking and food manipulation (IBB) tasks. All animals received a moderate C4 spinal cord contusion injury (200 kDyn), which ablates the main CST. We randomized injured rats into stimulation and sham

groups. The stimulated rats received paired cortical and spinal cord stimulation for 10 consecutive days, starting 11 days post injury. Sham group rats were connected to the stimulator through head stage and neck surface electrodes but no stimulation was delivered. All rats were assessed on the same behavior tasks weekly from weeks 4-7 after injury. CST axons were traced by injecting biotinylated dextran amine (BDA) in forelimb area of motor cortex and quantified in the spinal cord bilaterally above and below the lesion site. All assessments were performed by experimenters blinded to the treatment allocation. Rats with paired cortical and spinal stimulation achieved significantly better forelimb motor function recovery, as measured by fewer stepping errors on the horizontal ladder task and higher scores on the food manipulation (IBB) task. The change in axon outgrowth in rats with stimulation versus sham is being tested. This study replicates a previous positive study using paired stimulation after spinal cord injury from the Martin laboratory. The large effect size and the replication in independent laboratories validates this approach, which will be trialed in cats before being tested in people.

Disclosures: Q. Yang: None. **A. Ramamurthy:** None. **S. Lall:** None. **J. Santos:** None. **N. Zareen:** None. **H. Alexander:** None. **D.F. Ryan:** None. **J.H. Martin:** None. **J.B. Carmel:** None.

Nanosymposium

356. Spinal Cord Injury: Factors Influencing Recovery

Location: SDCC 7

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 356.05

Topic: C.11. Spinal Cord Injury and Plasticity

Support: the Leona M. and Harry B. Helmsley Charitable Trust
Christopher and Dana Reeve Foundation
Kessler Foundation
National Institutes of Health
Medtronic plc

Title: Characteristics of lower limb EMG activity and standing ability in individuals with motor complete spinal cord injury using spinal cord epidural stimulation

Authors: *E. REJC[1], F. GONNELLI[2], S. MESBAH[2], C. A. ANGELI[3], S. J. HARKEMA[4]
[1]Univ. of Louisville, Louisville, KY; [2]Kentucky Spinal Cord Injury Res. Ctr., Louisville, KY; [3]Frazier Rehab Inst., Louisville, KY; [4]Dept Neurol Surgery, Univ. Louisville, Frazier Rehab Inst, KSCIRC, Louisville, KY

Abstract: Previous studies showed that the combination of spinal cord epidural stimulation (scES) and activity-based training progressively improved standing ability in individuals with chronic motor complete spinal cord injury (SCI). In particular, scES optimized for standing

modulated the excitability of spinal circuitry so that little EMG activity and no leg movements were observed in sitting; on the other hand, the sensory information related to the change in body position from sitting to standing promoted the generation of lower limb EMG patterns that, most frequently, coincided with either the participant's ability to stand with independence of hip and knees extension, with independence of knees extension, or with the inability to maintain independently the upright posture. The primary aim of this study is to identify EMG activity features that can characterize different standing abilities. Ten individuals with chronic motor complete SCI, who were implanted with a spinal cord epidural stimulation unit and were enrolled in different activity-based training interventions, performed several experimental sessions that included standing overgound. EMG activity was recorded from 8 muscles of the right and left lower limb. EMG data collected during standing periods in which external assistance at hip and knees, as well as scES parameters, were consistent for 30 to 60 seconds was considered for further analysis. Continuous Wavelet Transform was used for frequency analysis of the EMG signals. After transforming the signal to the time-frequency domain, we calculated the average power for each frequency component, and from this power-frequency curve we extracted: *i)* the maximum power and *ii)* total power of the signal; *iii)* the dominant frequency at which the maximum power occurred; *iv)* the median frequency. In addition, the variability of EMG activity was assessed by calculating the coefficient of variation for the linear envelope of the raw EMG signals. Paired comparisons showed that better standing ability generally coincided with higher EMG signal power of primary extensor muscles (~ +76%), higher dominant and median frequency of primary extensor muscles (~ +13%), and lower variability of the EMG linear envelope of all muscles (~ -24%). Determining the characteristics of muscle activation related to improved standing performance may enhance the selection of scES parameters for promoting standing in individuals with severe SCI, as EMG patterns recorded during experimental sessions may be quantified and compared, possibly in real-time, with the features that generally result in better standing.

Disclosures: E. Rejc: None. **F. Gonnelli:** None. **S. Mesbah:** None. **C.A. Angeli:** None. **S.J. Harkema:** None.

Nanosymposium

356. Spinal Cord Injury: Factors Influencing Recovery

Location: SDCC 7

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 356.06

Topic: C.11. Spinal Cord Injury and Plasticity

Support: International Research in Paraplegia
Conquer Paralysis Now Challenge award
Walkabout Foundation
Broccoli Foundation

the Christopher & Dana Reeve Foundation,

Title: Tessla: Transcutaneous electrical spinal stimulation for lower urinary tract functional augmentation

Authors: *P. GAD[1], E. KREYDIN[2], H. ZHONG[3], K. LATACK[2], V. EDGERTON[4]
[1]Univ. Of California Los Angeles, Woodland Hills, CA; [2]USC, Los Angeles, CA; [3]Integrative Biol. and Physiol., UCLA, Los Angeles, CA; [4]Dept Integrative Biol. & Physiol., Univ. of California Los Angeles, Los Angeles, CA

Abstract: It is commonly assumed that restoration of locomotion is the ultimate goal after spinal cord injury (SCI). However, lower urinary tract (LUT) dysfunction is universal among SCI patients and significantly impacts their health and quality of life. Micturition is a neurologically complex behavior that depends on intact sensory and motor innervation. SCI disrupts both motor and sensory function and leads to marked abnormalities in urine storage and emptying. Current therapies for LUT dysfunction after SCI focus on preventing complications and managing symptoms rather than restoring function. In this study, we demonstrate that Transcutaneous Electrical Spinal Stimulation for Lower urinary tract functional Augmentation (TESSLA), a noninvasive neuromodulatory technique, can reengage the spinal circuits' active in LUT function and normalize bladder and urethral sphincter function in individuals with SCI. TESSLA may represent a novel approach to transform the intrinsic spinal networks to a more functionally physiological state. The present study shows that in 7 SCI subjects, TESSLA can be used to stimulate the neural circuitries in the spinal cord to facilitate LUT function by reducing detrusor overactivity (DO), decreasing detrusor-sphincter dyssynergia (DSD), increasing bladder capacity and enabling voiding. Each of these features has significant clinical and functional implications. Controlling DO and increasing bladder capacity lead to fewer incontinence episodes, thus benefitting patients' health and self-confidence. Decreasing DSD lowers the risks of high pressure voiding, loss of bladder compliance and kidney injury. Additionally, our finding that TESSLA mediates recovery of bladder-sphincter synergy suggests that coordination between the detrusor and the external urethral sphincter can occur at the spinal level, thus challenging the dogma that bladder-sphincter coordination is facilitated solely by the brainstem. Finally, TESSLA directly addresses one of the primary dysfunctions caused by SCI, i.e. the inability to void on command. The ability to void at predetermined intervals, increased bladder capacity, reduced detrusor overactivity and improved bladder-sphincter synergy stand to significantly benefit SCI patients by improving their quality of life and reducing the risk of incontinence, kidney injury and urinary tract infection, all the while lowering healthcare costs.

Disclosures: E. Kreydin: None. **H. Zhong:** None. **K. Latack:** None. **V. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurorecovery Technologies.

Nanosymposium

356. Spinal Cord Injury: Factors Influencing Recovery

Location: SDCC 7

Time: Monday, November 5, 2018, 1:00 PM - 2:45 PM

Presentation Number: 356.07

Topic: C.11. Spinal Cord Injury and Plasticity

Support: The Leona M. and Harry B. Helmsley Charitable Trust
The Christopher and Dana Reeve Foundation
University of Louisville Hospital
Medtronic plc
NIH NIBIB R01EB007615
Kessler Foundation
NIH NIGMS P30 GM103507

Title: Recovery of walking overground after chronic motor complete spinal cord injury

Authors: *C. A. ANGELI[1,2], M. BOAKYE[3,2], R. MORTON[2,1], J. VOGT[2,1], K. BENTON[2,1], Y. CHEN[2], C. FERREIRA[2], S. J. HARKEMA[2,1]
[1]Frazier Rehab Inst., Louisville, KY; [2]Kentucky Spinal Cord Injury Ctr., [3]Neurolog. Surgery, Univ. of Louisville, Louisville, KY

Abstract: Individuals diagnosed with motor complete spinal cord injury (SCI) have not responded to therapies or rehabilitation strategies for the recovery of walking or standing and receive rehabilitation that primarily focuses on compensation, without expectation of recovery. We have previously shown that spinal cord epidural stimulation (scES) the combined with task specific training improved standing ability in individuals with chronic motor complete SCI. Eight individuals with a chronic motor complete SCI, received a surgically implanted epidural spinal cord stimulator approximately 2-4 years post-injury. They received intense locomotor training with constant scES. Two out of eight individuals achieved overground walking following intense locomotor training with stepping scES (Step-scES) Outcomes for independent overground walking were speed, distance, and electromyography (EMG). Secondary measures included independent standing and trunk mobility with and without scES. One individual (AIS B C5) has been able to achieve overground walking (maximum speed 0.19 m/s, distance 362 meters) with balance assist generated by a rhythmic, alternating flexor and extensor EMG locomotor pattern. This occurred after 275 sessions of locomotor training where we combined synergistically customized stepping scES (Step-scES) with intent by the individual to step and manually assisted stepping. The second individual (AIS B T1) was able to achieve walking overground after only 81 sessions. Independent standing and trunk mobility also were observed with task-specific scES. Individuals diagnosed with complete chronic motor paralysis can recover the ability to intentionally walk overground and stand with intense rehabilitation. This

supports that human spinal circuitry is sufficiently plastic and with the appropriate excitability state can integrate weak residual supraspinal input originating from above the injury. Clinically these observations should challenge the current view that individuals with a diagnosed clinically complete injury cannot recover motor behavior below their injury level.

Disclosures: C.A. Angeli: None. **M. Boakye:** None. **R. Morton:** None. **J. Vogt:** None. **K. Benton:** None. **Y. Chen:** None. **C. Ferreira:** None. **S.J. Harkema:** None.

Nanosymposium

357. Cerebellum: Local and Long-Range Functions

Location: SDCC 4

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 357.01

Topic: E.02. Cerebellum

Support: NIH Grant EY022788

Title: Adaptive behavior in the face of uncertainty: Predictive timing activity in dentate nucleus

Authors: *V. PREVOSTO[1], M. A. SOMMER[2,1]
[1]Neurobio. Dept., [2]Biomed. Engin., Duke Univ., Durham, NC

Abstract: A growing body of evidence implicates the cerebellum in predictive operations that extend beyond purely motor functions to more general adaptive behavior. In particular, lateral and posterior cerebellar regions that are reciprocally connected with associative cerebral cortical regions may share their higher-level functions. Lateral cerebellum neurons have been reported to participate in an internal model of hidden target dynamics (Cerminara et al., 2009), encode abstract temporal rules to execute a saccade (Ashmore & Sommer, 2013), and anticipate periodic sensory signals (Ohmae et al., 2013). Here we asked how lateral cerebellar neurons adapt to the uncertainty of less predictable events. We recorded from single neurons in the dentate nucleus, the exit pathway for the lateral cerebellum. Neurons in the caudal pole of the dentate nucleus (cDN) are linked to eye movement areas such as the frontal eye field (FEF). Three rhesus macaques were trained to perform a saccadic countermanding task. Each trial started with an initial fixation period, followed by the extinction of the fixation point and the appearance of a peripheral visual target, to which the animals were required to make a saccade. In a minority of randomly interleaved “stop signal” trials, the fixation point reappeared after a variable delay. Upon appearance of this stop signal, the monkeys were required to withhold their saccade and maintain fixation for reward. Recorded cells (n=100) were classified into four different response profiles aligned with saccade initiation (n=86 clustered). Unlike in other areas tested on countermanding, such as the FEF, few cDN cells had responses compatible with a role in the execution, or cancellation, of saccades. Rather, the cDN responses were typically best aligned to the expected time of the stop signal (ETSS), even in the majority of trials when there was no stop

signal. Re-clustering the neurons in alignment with the ETSS revealed three distinct population response profiles: sustained activity that declines at the ETSS, U-curved activity with a trough at ETSS, and activity that plateaus at ETSS before increasing further. Additionally, analysis of latent variables in the pooled population's trial-averaged responses, using dimensionality reduction techniques, showed a strong inflection of latent variables' temporal profiles around the ETSS and early divergence between cancelled and non-cancelled saccade trials. Preparatory activity leading to the ETSS, therefore, may have the biggest impact on the trial outcome. Taken together, these data suggest that cDN neurons adapt to task constraints in order to predict behaviorally relevant sensory or motor events.

Disclosures: V. Prevosto: None. **M.A. Sommer:** None.

Nanosymposium

357. Cerebellum: Local and Long-Range Functions

Location: SDCC 4

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 357.02

Topic: E.02. Cerebellum

Support: HBP Grant 720270
HBP Grant 785907
University of Pavia BSR77992

Title: Low-frequency oscillations correlate with plastic changes in deep cerebellar nuclei induced by theta-patterned tactile stimulation *in vivo*

Authors: *I. MONTAGNA[1], L. MOSCATO[1], L. DE PROPRIS[2], S. TRITTO[1], L. MAPELLI[1], E. D'ANGELO[1]
[1]Univ. of Pavia, Pavia, Italy; [2]Inst. Neurologico IRCCS Fondazione C. Mondino, Pavia, Italy

Abstract: Deep cerebellar nuclei (DCN) are thought to play a pivotal role in cerebellar learning and memory. Plasticity of DCN neurons activity has been widely studied *in vitro*, while it is still unknown whether it can be observed *in vivo*, following theta-sensory stimulation (TSS).
It has been previously demonstrated that TSS is able to drive long-term plasticity in the cerebellar granular and molecular layers, in urethane anesthetized rodents. Herein, we characterized DCN neurons single unit responses to orofacial stimulation and changes in neuronal activity after TSS in the fastigial nucleus of urethane-anesthetized mice.
DCN neurons discharge patterns showed autorhythmic activity and responded to tactile stimulation with a combination of bursts (excitation) and/or pauses (inhibition) in the peri-stimulus time histogram (PSTH), often followed by stimulation-induced low frequency oscillations. Following the TSS, DCN neurons responses to sensory stimulation showed plastic changes, expressed in terms of protracted spike-related potentiation (SR-P) or suppression (SR-

S) of the response. Interestingly, the units showing stimulus-induced low-frequency oscillations showed plastic changes that followed resonant functions peaking between 5 and 9 Hz. More precisely, the units with an initial burst in burst-pause response showed an SR-P peak at 9 Hz, while the initial pause in pause-burst units showed an SR-S peak at 5 Hz. The existence of different type of responses in DCN neurons, as burst and pauses, suggested the activation of excitatory inputs from mossy fibers entering the cerebellar cortex and of inhibitory inputs sent by Purkinje cells.
Local injection of selective blockers of glutamatergic transmission (NBQX and APV) suppressed the burst responses, confirming their excitatory origin, while not affecting stimulus-induced oscillations nor the expected changes after TSS, following the above-mentioned resonant function. Our results support the hypothesis that the sign and intensity of persistent changes in neuronal synaptic responsiveness in DCN following TSS *in vivo* correlate with the stimulus-induced oscillations, apparently not affected by burst behavior. Since low-frequency oscillations were observed only in those units showing at least a pause, and they were not affected by blockade of excitatory transmission, ongoing investigation is devoted to determine whether modifying pauses behavior (e.g. by optogenetic tools) might modify DCN units oscillatory behavior and the predicted activity changes after TSS.

Disclosures: I. Montagna: None. **L. Moscato:** None. **L. De Propris:** None. **S. Tritto:** None. **L. Mapelli:** None. **E. D'Angelo:** None.

Nanosymposium

357. Cerebellum: Local and Long-Range Functions

Location: SDCC 4

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 357.03

Topic: E.02. Cerebellum

Support: NIH (NS62771) to C.H.
National Ataxia Foundation (YI-SCA Award) to G.G.
Institute for Translational Medicine at The University of Chicago (Core Subsidies Mini-Awards) to G.G. and C.H.
Dutch Organization for Medical Sciences (ZonMw) to C.I.D.Z.
Life Sciences (ALW) to M.S. and C.I.D.Z.
Erasmus University Fellowship to M.S.
Senter (Neuro-Bsik) to M.S.

Title: Learning deficit associated with a selective and cell-type specific impairment of intrinsic plasticity in cerebellar Purkinje cells

Authors: *G. GRASSELLI[1], H.-J. BOELE[2], H. K. TITLEY[1], N. BRADFORD[1], L. VAN BEERS[2], L. JAY[1], C. I. DE ZEEUW[2,3], M. SCHONEWILLE[2], C. HANSEL[1]

[1]Dept. of Neurobio., Univ. of Chicago, Chicago, IL; [2]Dept. of Neurosci., Erasmus MC, Rotterdam, Netherlands; [3]Netherlands Inst. for Neurosci., Amsterdam, Netherlands

Abstract: Currently, prevailing theories of learning and memory are based on synaptic plasticity as the main underlying cellular mechanism (long-term potentiation and depression, i.e. LTP and LTD, respectively). However, a growing body of evidence suggests that synaptic plasticity might be complemented by other forms of neuronal plasticity, such as activity-dependent changes in membrane excitability ('intrinsic plasticity'). What remains controversial is the question whether intrinsic plasticity actually plays a relevant role in learning and memory independent from synaptic plasticity. In order to directly test this hypothesis, we report a new conditional knock-out mouse for SK2, the calcium-gated potassium channel that mediates intrinsic plasticity in cerebellar Purkinje cells (its downregulation is responsible for their activity-dependent increase of excitability). We used this new mouse line to generate a Purkinje cell-specific SK2 knock-out mouse (L7-SK2). These mice show Purkinje cell morphology and density comparable to control littermates. Intrinsic plasticity is absent from these mice, but no alterations were found in synaptic transmission and plasticity at parallel fiber-to-Purkinje cell synapses (both LTD and LTP). We observed a selective impairment in delay eyeblink conditioning, an associative learning paradigm known to require an intact cerebellum and modulation of the simple spike activity. We also found a moderate alteration in the pattern of locomotion of these mice, namely a significant increase in step length and, accordingly, a decrease in frequency. However, we did not find signs of general ataxia, or changes in other types of motor behaviors, such as motor performance on the rotarod, or eye movement-related motor behaviors as tested in the optokinetic response (OKR), the vestibulo-ocular reflex (VOR), or the visually enhanced vestibulo-ocular reflex (VVOR). Importantly, we also did not find significant alterations in VOR gain-increase adaptation, which is another major paradigm for testing cerebellar learning. These results indicate that a purely non-synaptic, SK2-dependent mechanism of neuronal plasticity is necessary for specific forms of cerebellar learning by contributing to the encoding of memories.

Disclosures: G. Grasselli: None. **H. Boele:** None. **H.K. Titley:** None. **N. Bradford:** None. **L. van Beers:** None. **L. Jay:** None. **C.I. De Zeeuw:** None. **M. Schonewille:** None. **C. Hansel:** None.

Nanosymposium

357. Cerebellum: Local and Long-Range Functions

Location: SDCC 4

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 357.04

Topic: E.02. Cerebellum

Support: NRF-Korean Government 2012R1A5A2A44671346
NRF-Korean Government 2017M3C7A1029611

NRF-Korean Government 2013H1A2A1034318

Title: Intrinsic plasticity of the cerebellar Purkinje cells is required for cerebellar-dependent motor memory formation

Authors: H. SHIM, D. JANG, C. RYU, *S. KIM
Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: A long-standing question in the neuroscience field is how the brain stores the information and subsequently modifies the weight of input and output signals to adjust behaviour. To answer this, activity-dependent changes in synaptic transmission such as long-term potentiation and depression (LTP, LTD, respectively) and non-synaptic intrinsic plasticity have been regarded as the cellular mechanisms of this phenomenon. A classical view of the cerebellum-dependent motor learning has been focused on the synaptic plasticity between parallel fiber (PF) and the cerebellar Purkinje cells (PCs). This study suggests the other forms of the plasticity for the eye movement adaption (vestibule-ocular reflex, VOR) beyond the PF-PC LTD: the intrinsic plasticity. We observed that the long-lasting reduction of intrinsic excitability (LTD-IE) was accompanied by PF-PC LTD induction, suggesting that the the neuronal net output might be synergistically determined by both forms of plasticity. Interestingly, cooccurrence of PF-PC LTD and LTD-IE was found after VOR gain-up training. In order to elucidate the role of the LTD-IE in VOR memory formation, we assessed the neural plasticity including synaptic and intrinsic plasticity and behavioral feature by using memory consolidation deficit mice model, PC-specific STIM1 knockout mice, $STIM1^{PKO.}$ Surprisingly, $STIM1^{PKO}$ showed impairment of the LTD-IE whereas PF-PC LTD was normal, implying that the intrinsic plasticity in PCs might derive the memory consolidation. These results led us to hypothesize that intrinsic plasticity might provide instructive signal into neurons in the vestibular nuclei (VN) in order to induce appropriate neuronal plasticity resulting in long-term memory storage over a day. Notably, the VOR gain-increase training elicited the potentiation of the excitatory synaptic transmission and excitability in VN neurons in wild-type animal, however, the synaptic and intrinsic plasticity were absent in the $STIM1^{PKO}$ mice. Therefore, we conclude that the synergistic modulation of the intrinsic excitability with the synaptic plasticity may play a role in the memory transfer from the cerebellar cortex into sub-cortical area, VN for cerebellar-dependent long-term memory formation.

Disclosures: H. Shim: None. **D. Jang:** None. **C. Ryu:** None. **S. Kim:** None.

Nanosymposium

357. Cerebellum: Local and Long-Range Functions

Location: SDCC 4

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 357.05

Topic: E.02. Cerebellum

Support: HBP Grant 720270
HBP Grant 785907

Title: The richness of cerebellar granule cell firing properties captured by modeling optimization procedures

Authors: *M. TOGNOLINA[1], S. MASOLI[1], E. D'ANGELO[1,2]
[1]Dept Of Brain and Behavioral Sci., Univ. of Pavia, Pavia, Italy; [2]Brain Connectivity Ctr., C. Mondino, Pavia, Italy

Abstract: The cerebellar granule cells (GrCs) are thought to form a highly homogeneous neuronal population, all having the same channel complement. This concept led to the represent all GrCs through a canonical description of their firing properties. However, such a stereotyped description contrasts with the potential richness of functional states that could emerge from differential engagement of the membrane conductances involved.
To assess the hypothesis of different functional states, patch-clamp whole-cell recordings were carried out in current-clamp configuration while delivering 2-sec current steps at different intensities from the holding potential of -70 mV. Notably, this protocol is longer than the usual 500-800 ms steps (D'Angelo et al., 1995, 1998; Brickley et al., 1996). While initial GrCs responses (0-500 ms) corresponded to the classical description, at longer times (e.g. 1500-2000 ms) the responses showed a richness of different properties. A *k*-mean analysis of frequency changes *vs*. initial firing frequency uncovered the existence of four independent data clusters showing regular firing (n=3), moderate firing adaptation (n=9), marked firing adaptation (n=9), firing acceleration (n=4), suggesting that four GrCs prototypes could be distinguished based on firing adaptation properties. These different firing properties impacted on synaptic excitation when the mossy fiber bundle was stimulated at different frequencies (between 1 and 100 Hz). Interestingly, a range of different filtering properties emerged, with some cells showing one-to-one responses while others responding faster or slower than the input.
In order to assess if these different discharge modalities could be explained by the same ionic channel complement, we generated a family of GrCs models in which the maximum ionic conductances are automatically determined using a genetic algorithm. Interestingly, given a common set of ionic channels, a rich repertoire of GrCs functional states emerged into the model, in good agreement with the experimental results. The model also showed that the different patterns derived from the fine tuning of ionic conductances, especially the Ca and Ca-dependent K conductances.
While the mechanisms controlling the differentiation of GrC discharge remain to be elucidated, these results suggest that the richness of GrC adaptation and bursting properties may lead to generate information channels with differential filtering properties.

Disclosures: M. Tognolina: None. **S. Masoli:** None. **E. D'Angelo:** None.

Nanosymposium

357. Cerebellum: Local and Long-Range Functions

Location: SDCC 4

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 357.06

Topic: E.02. Cerebellum

Support: Alexander von Humboldt Foundation (LDK)
Carl von Siemens Foundation (LDK)
Fonds de recherche du Québec - Santé (LDK)
Joachim-Herz Stiftung (AMK)

Title: Motor context shapes output from Purkinje cell functional regions to establish cerebellar internal models

Authors: *L. D. KNOGLER, A. M. KIST, R. PORTUGUES
Max Planck Inst. of Neurobio., Planegg, Germany

Abstract: Animals use sensory input and information about their current motor actions to dynamically update their behavior. The cerebellum is believed to be the site of internal models that enable motor coordination and learning. Nevertheless, the mapping between model elements and cerebellar networks is still under debate.
Aims/Methods: Here, we use imaging and electrophysiology during behavior to find physiological evidence of internal models related to sensorimotor behaviors across the cerebellar Purkinje cell population in larval zebrafish.
Results: We show that Purkinje cells are functionally clustered into three regions along the rostrocaudal axis that each receive similarly tuned, sensory climbing fiber input relating to distinct behaviors. In contrast, we observe that simple spike activity is similar across the cerebellum and predominantly modulated by motor efference signals relayed by granule cells. The interaction between sensory complex spikes and motor efference simple spikes is heterogeneous across cells, and during behavior, excitatory motor efference inputs increase baseline simple spike rates in a way that changes the modulation by a complex spike and could alter subsequent plasticity between parallel fibers and Purkinje cells. Finally, we perform a pharmacological perturbation and find that complex spikes occur in response to a previously neutral stimulus.
Conclusions: Our findings suggest that Purkinje cells receive efference related inputs that can be transformed into sensory predictions as in a forward model. The altered sensory climbing fiber activity following a behavioral perturbation also suggests that sensory error signals can be used to recalibrate the motor to sensory assignations performed by Purkinje cells.

Disclosures: L.D. Knogler: None. **A.M. Kist:** None. **R. Portugues:** None.

Nanosymposium

357. Cerebellum: Local and Long-Range Functions

Location: SDCC 4

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 357.07

Topic: E.02. Cerebellum

Support: NIH NRSA NS103328
McKnight Foundation
Klingenstein Foundation
NSF 1749568

Title: Graded and bidirectional control of real-time reach kinematics by the cerebellum

Authors: *M. I. BECKER[1], A. L. PERSON[2]
[2]Physiol. and Biophysics, [1]Univ. of Colorado Sch. of Med., Aurora, CO

Abstract: The rules governing the relationship between cerebellar output and movement production remain unknown despite the well-recognized importance of the cerebellum in motor learning and precision. Previous functional studies of cerebellar contributions to purposive behavior were limited by temporal imprecision and lack of control over the acute behavioral context of neural manipulation. In this study, we investigated how cerebellar output sculpts reach behavior in mice by manipulating neural activity in the anterior interposed nucleus (IntA) in closed-loop with ongoing behavior. By tracking mouse reach kinematics in real time, we were able to modulate cerebellar output from IntA at precise kinematic landmarks throughout the reaching movement. Optogenetic modulation of IntA activity revealed monotonically graded and bidirectional control of real-time reach velocity. The directionality of the kinematic effect was consistent across all animals tested; excitation of IntA decreased outward and upward velocity, while inhibition of IntA increased outward and upward velocity. Moreover, the pattern of kinematic effect was maintained during decreasing magnitudes of stimulation, as the amplitude of the effect concomitantly decreased. Furthermore, kinematic effects were relatively context invariant, suggesting that cerebellar output summates with ongoing motor commands generated elsewhere throughout the reaching movement. Preliminary experiments in which the stimulation was limited to IntA premotor output neurons revealed similar kinematic effects, implying a specific role for these neurons in ongoing motor control. These results characterize the relationship between cerebellar output modulation and reach behavior as a bidirectional and scalable kinematic command signal. Our findings illustrate how learned, predictive coding in the cerebellar cortex could be actuated through the cerebellar nuclei to contribute in real time to purposive motor control.

Disclosures: M.I. Becker: None. **A.L. Person:** None.

Nanosymposium

357. Cerebellum: Local and Long-Range Functions

Location: SDCC 4

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 357.08

Topic: E.02. Cerebellum

Support: HBP SGA1 Grant Agreement 720270
HBP SGA2 Grant Agreement 785907

Title: Reconstructing and simulating functional cerebellar network

Authors: *C. MEDINI[1], C. CASELLATO[2], S. CASALI[3], E. MARENZI[1], S. MASOLI[1], E. D'ANGELO[4]
[1]Dept. of Brain and Behavioural Sci., [2]Dept. of Brain and Behavioral Sci., [3]Brain and Behavioral Sci., Univ. of Pavia, Pavia, Italy; [4]Dept. of Brain and Behavioural Sci., Univ. of Pavia, 27100 Pavia, Italy

Abstract: Reconstructing local microcircuits is a fundamental step toward the understanding of how local neuronal computation propagate into large-scale brain networks. There is a need for a general development framework representing the three main properties of microcircuits: neuronal location, synaptic connectivity, subcellular/cellular mechanisms. Here, we propose a "scaffold" microcircuit model that (i) can account for synaptic connectivity data provided in different formats, (ii) can be easily updated once novel information becomes available, (ii) can host different neuronal and synaptic models, and (iv) can be easily tuned in order to test different structural and functional hypotheses. As a test bench for this framework we choose the cerebellar microcircuit. Cerebellum is long known to participate in cognitive functions along with the autonomic and motor processes, through its highly compartmentalized microzone organization, in which neuronal location is clearly segregated with dendritic and axonal processes strictly organized along specific planes. The cerebellar scaffold integrates the granular layer, molecular layer and deep cerebellar nuclei (DCN), including the following cell types: Golgi cells, granule cells, Purkinje cells, stellate cells, basket cells and DCN glutamatergic neurons. In order to account for available data, in some cases neuronal connectivity was represented using spatially confined convergence/divergence ratios (e.g. in the granular layer), while in others a touch-detector proved more appropriate (e.g. in Purkinje cells). Once generated the placement and connectivity of all neurons in a defined cerebellar sub-volume, insertion of active neuron models was hybrid as well, mono-compartment simplified but specifically tuned models together with multi-compartment morphology-based Purkinje neurons. The whole network was built and simulated in pyNEURON. Preliminary results show that the network model can reproduce realistic network dynamics, e.g. the well-known granular layer electroresponsive behavior, the center-surround activation. Moreover, the PCs show complex responses integrating excitatory

synaptic inputs from ascending axons and from parallel fibers of granule cells, and inhibitory synaptic inputs from molecular interneurons, with temporal-spatial patterns matching the real dynamics. The scaffold is a versatile multi-scale tool, powerful to investigate functionality and to generate predictions about functional and dysfunctional cerebellar network states, even in large-scale networks challenged in multiple repetitions of task during which adaptive behaviors can emerge.

Disclosures: C. Medini: None. **C. Casellato:** None. **S. Casali:** None. **E. Marenzi:** None. **S. Masoli:** None. **E. D'Angelo:** None.

Nanosymposium

357. Cerebellum: Local and Long-Range Functions

Location: SDCC 4

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 357.09

Topic: E.02. Cerebellum

Title: A computational model of the cortico-cerebello-thalamo-cortical pathway under essential tremor and cerebellar stimulation

Authors: *S. SANTANIELLO[1,2], X. ZHANG[1]
[1]BIOMEDICAL ENGINEERING, [2]CT Inst. for the Brain and Cognitive Sci., UNIVERSITY OF CONNECTICUT, Storrs, CT

Abstract: Recent studies suggest that the neuromodulation of the cortico-cerebello-thalamo-cortical (CCTC) pathway in patients with essential tremor (ET) and Parkinson's disease may ameliorate debilitating movement disorders like freezing of gait and tremor, thus providing a potential alternative to deep brain stimulation (DBS) of the basal ganglia and thalamus. Despite the interest in electrical stimulation of the cerebellar structures, though, the cellular mechanisms of cerebellar neural stimulation still require investigation. Similarly, while exaggerated low-frequency oscillations have been reported in the neuronal activity of the cerebellar-recipient portion of the thalamus (i.e., the ventral intermediate, VIM) under ET and Parkinson's disease and correlated with movement disorders like tremor, it remains unclear whether these oscillations depend on the presynaptic activity of the cerebellar afferents or rather stem from distributed network effects that involve the activation of reentrant loops along the CCTC pathway. To address these questions, we developed a computational model of the reentrant circuits forming the CCTC pathway. This model includes single compartment representations of the major cell types involved in this pathway, including Purkinje, Golgi, and granular cells, deep cerebellar nuclei cells, and afferent fibers from the inferior olive. Validated against single unit recordings from mice, the model was used to assess the role of the inferior olive and the cerebellar cortex in the formation of exaggerated tremor-band (4-7 Hz) oscillations in the VIM under ET. Furthermore, the model was used to study the circuit effects of electrical stimulation

of the Purkinje cells, which is used as a proxy for transcranial direct current stimulation, and deep brain stimulation of the deep cerebellar nucleus cells. Results indicate that a disruption of tremor-band oscillations in the VIM can be achieved by stimulating cerebellar structures, thus suggesting that cerebellar stimulation may be an alternative to VIM DBS for the treatment of ET. The proposed model is the first known computational platform to test the circuit effects of cerebellar stimulation for movement disorders. In the proposed simulation study, we report that cerebellar stimulation, both of cerebellar and deep structures, may facilitate the disruption of tremor-related oscillations in the thalamocortical subsystem.

Disclosures: S. Santaniello: None. **X. Zhang:** None.

Nanosymposium

357. Cerebellum: Local and Long-Range Functions

Location: SDCC 4

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 357.10

Topic: E.02. Cerebellum

Support: Royal Society Leverhulme SRF
BBSRC
Wellcome Trust

Title: Detection of eye-blink conditioning signals in the human cerebellum with optically-pumped magnetometers

Authors: *R. C. MIALL[1], C.-H. LIN[2], T. M. TIERNEY[2], N. HOLMES[4], E. BOTO[4], J. LEGGETT[4], S. BESTMANN[3], R. BOWTELL[4], M. BROOKES[4], G. R. BARNES[2]
[1]Sch. of Psychology, Univ. of Birmingham, Birmingham, United Kingdom; [2]Wellcome Ctr. for Human Neuroimaging, [3]Inst. for Neurol., Univ. Col. London, London, United Kingdom; [4]Sir Peter Mansfield Imaging Ctr., Univ. of Nottingham, Nottingham, United Kingdom

Abstract: Growing evidence suggests the human cerebellum contributes to cognitive functions beyond sensorimotor control. Its electrophysiology in these domains is largely unexplored. Conventional M/EEG systems have poor coverage. Optically pumped magnetometers (OPMs) individually positioned around the posterior cranium can significantly reduce source-to-sensor distance and increase signal magnitudes.
As a test case, we recorded evoked responses in an eye-blink conditioning paradigm. Randomly timed non-noxious air-puff stimulation was applied to the left eye, known to elicit simple and complex spike responses in ipsilateral Purkinje cells in untrained animals. Participants undertook 4 sessions of 200 trials, each comprising 70% air-puff trials, 20% bleeps and 5% paired air-puffs/bleeps in a pseudorandom sequence. This design is intended as the baseline phase of classical conditioning. Each trial began with a random wait of 1-2.5 seconds, followed by either

a 30 ms air-puff to the left cornea, a 550 ms binaural tone, or a tone co-terminated with an air-puff. Between 17-24 OPMs were housed in 3D-printed head-casts individualized for three participants, based on anatomical MRIs, covering bilateral cerebellum and contralateral somatosensory cortex. OPM data were filtered between 5-80 Hz, and cut into 500 ms epochs, 200 ms before air puff-onset. Outliers were removed and epochs were averaged over 548-588 air-puff trials, baseline corrected to a 50 ms time window prior to stimulus onset.
Within-subject average data showed bipolar evoked responses with an early peak at around 50 to 60 ms in the posterior sensors, and later components. Bayesian dipole fitting, with a single-shell forward model, was performed to explain the earliest evoked field in each subject. A single dipole in left cerebellar cortex or paired left cortical/nuclear dipoles best fitted the data, consistent with the location expected from previous animal experiments and human fMRI. Our next step in identifying the sources will be to study them during acquisition and extinction of the conditioning.
With high sensitivity from the targeted positioning of OPM sensors, we expect this technology to enable investigation of the electrophysiological basis of human cerebellar function in motor and cognitive tasks.

Disclosures: R.C. Miall: None. **C. Lin:** None. **T.M. Tierney:** None. **N. Holmes:** None. **E. Boto:** None. **J. Leggett:** None. **S. Bestmann:** None. **R. Bowtell:** None. **M. Brookes:** None. **G.R. Barnes:** None.

Nanosymposium

357. Cerebellum: Local and Long-Range Functions

Location: SDCC 4

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 357.11

Topic: E.02. Cerebellum

Support: HBP Grant 720270
HBP Grant 785907
Centro Fermi 7(17)

Title: Modeling of NMDAr-dependent mechanism of cerebellar granular layer hyperfunctioning in the IB2 KO mouse model of autism

Authors: *T. SODA[1], L. MAPELLI[1], F. LOCATELLI[1], S. CASALI[1], L. BOTTA[1], M. GOLDFARB[2], F. PRESTORI[1], E. D'ANGELO[1]
[1]Univ. of Pavia, Pavia, Italy; [2]Biol. Sci., Hunter Col., New York, USA, MA

Abstract: Autism spectrum disorders (ASD) are pervasive neurodevelopmental conditions that often involve mutations affecting synaptic mechanisms. Recently, the involvement of cerebellum in ASD has been suggested but the underlying functional alterations remained obscure. Here we

exploited a combination of whole-cell patch-clamp recordings with voltage sensitive dye imaging (VSDi) in acute cerebellar slices to investigate single-neuron and microcircuit properties of autistic IB2 KO mice. The granule cell of IB2 KO mice revealed a 2.5-times larger NMDAR - mediated current in and enhanced synaptic plasticity (WT = 20.4 ± 4.2 %, n=12 vs. IB2 KO = 107.7 ± 44.4, n=9; $p<0.05$). Moreover, the granular layer showed enhanced excitatory/inhibitory (E/I) balance (WT = 0.98 ± 0.27, n=6vs. IB2 KO = 2.78 ± 0.32, n=7; $p<0.01$) and the spatial organization in response to mossy fiber inputs shifted from a "Mexican hat" to a "stovepipe hat" profile, with stronger excitation in the core (WT = 12.9 ± 1.7 μm vs. IB2 KO = 29.5 ± 4.9 μm, n=5 for both; $p<0.01$) but limited inhibition in the surround (WT/KO ratio $I_{WT/KO}$ = 2.83 ± 0.17, n=5). In order to determine whether NMDA receptor hyperfunctioning was indeed necessary and sufficient to explain neuronal and micorcircuit alterations, we used a realistic computational model. According to experimental determinations, the NMDAR conductance in the model was increased by three-times with respect to its normal value. As a consequence, the E/I balance map changed from its normal shape to that typical of IB2 KO mice.The model confirms therefore that a complex set of alterations generated in the cerebellar microcircuit by a single gene mutation can be fully explained by the alteration of NMDA currents, which control the E/I balance and the *center-surround* (C/S) organization of responses.This implies that the IB2 KO mouse model therefore configures a complex cerebellar *synaptopathy* centered on *NMDA receptor gain of function*, that in several respects resembles alterations also observed in cortical minicolumns. The profound changes of signal processing at the cerebellar input stage unveil a possible new mechanism contributing to the pathogenesis of autistic-like behavior.

Disclosures: T. Soda: None. **L. Mapelli:** None. **F. Locatelli:** None. **S. Casali:** None. **L. Botta:** None. **M. Goldfarb:** None. **F. Prestori:** None. **E. D'Angelo:** None.

Nanosymposium

358. Emotion: Circuits and Mechanisms

Location: SDCC 5

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

Presentation Number: 358.01

Topic: F.04. Stress and the Brain

Support: Howard Hughes Medical Institute
NIH RO1DC015032
NIH 1R01DC016442

Title: Odor blocking effects on stress

Authors: *E. LEE[1], L. R. SARAIVA[1,2], L. B. BUCK[1]
[1]Div. of Basic Sci., Fred Hutchinson Cancer Res. Ctr., Seattle, WA; [2]Sidra Med., Doha, Qatar

Abstract: Mammals can discriminate a multitude of environmental chemicals sensed as odors as well as social cues that elicit innate responses. In mice, predator odors cause not only behavioral aversion but also increases in blood stress hormones, which are controlled by corticotropin releasing hormone (CRH) neurons in the hypothalamus. Interestingly, we found two common odorants that can block aversion to a predator odor and also stress hormone responses to both a predator odor and a non-olfactory stressor, physical restraint. Using a retrograde viral tracer, we found that both blocking odorants activated neurons upstream of CRH neurons in the ventromedial hypothalamus (VMH). Some of those VMH neurons were GABAergic. Moreover, GABAergic neurons in the VMH showed significant activation by a blocking odorant. Chemogenetic activation of VMH GABAergic neurons decreased the stress hormone response to restraint. Furthermore, chemogenetic silencing of VMH GABAergic neurons decreased the ability of a blocking odorant to inhibit the stress hormone response to restraint. Taken together, these results suggest that GABAergic inhibitory neurons in the VMH are important for odor blocking of the stress hormone response to physical restraint. The findings are consistent with a model in which signals from stress blocking odorants directly suppress CRH neurons and thereby prevent their activation by stressors.

Disclosures: E. Lee: None. **L.R. Saraiva:** None. **L.B. Buck:** None.

Nanosymposium

358. Emotion: Circuits and Mechanisms

Location: SDCC 5

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

Presentation Number: 358.02

Topic: F.04. Stress and the Brain

Support: JSPS KAKENHI Grant 17K08559
JSPS KAKENHI Grant 17H05540
JSPS KAKENHI Grant 26460311

Title: Neural pathway supposedly mediating the descending autonomic information from the dorsomedial hypothalamus to the ventral medullary cardiorespiratory regions

Authors: *Y. OKADA[1], Y. KONO[2,1], Y. ARIMA[3], S. YOKOTA[3], H. ONIMARU[4], I. FUKUSHI[1], K. KOIZUMI[2], Y. HASEBE[2,1], M. YOSHIZAWA[2,1], H. KISE[2], T. TODA[2]
[1]Murayama Med. Ctr., Tokyo, Japan; [2]Dept. of Pediatrics, Fac. of Med., Univ. of Yamanashi, Kofu, Yamanashi, Japan; [3]Dept. of Anat. and Morphological Neurosci., Shimane Univ. Sch. of Med., Shimane, Japan; [4]Showa Univ. Sch. of Med., Tokyo, Japan

Abstract: Psychological stress induces excitation of the cardiorespiratory autonomic neuronal networks, which increases ventilation and elevates blood pressure. It has been reported that regions in the hypothalamus, in particular the dorsomedial hypothalamus (DMH), play crucial

roles in this information processing. Thus, there should be anatomical and functional connections from the DMH to the medullary cardiorespiratory regions. Our functional mapping analysis by voltage imaging has demonstrated that electrical stimulation of the DMH evokes excitation in the ventral medullary cardiorespiratory regions, i.e., in the rostral ventrolateral medulla (RVLM), rostral ventromedial medulla (RVMM), caudal ventrolateral medulla (CVLM) and nucleus raphe pallidus (RP). On the basis of our functional study, we aimed in the present study to investigate the anatomical connectivity from the DMH to the ventral medullary cardiorespiratory regions. For this purpose we conducted retrograde and anterograde tract-tracing analyses in young adult rats. In retrograde tracing, iontophoretic injection of fluoro-gold (FG) was made stereotaxically into the unilateral RVLM (n=3). After 7-10-day survival, FG-labeled neurons in the hypothalamus were explored. In anterograde tracing, biotinylated dextran amine (BDA) was stereotaxically injected into the unilateral DMH (n=5). After one week survival, BDA-labeled axons and terminals were detected in the ventral medulla. We also investigated the projection of axon fibers from the DMH to tyrosine hydroxylase (TH)-immunoreactive neurons in the ventral medulla. Retrogradely FG-labeled neurons were found in the ipsilateral DMH. Axon fibers anterogradely BDA-labeled from the DMH were detected in the RVLM, CVLM and RVMM as well as in the RP. In addition, some axon terminals from the DMH were in contiguity with TH-immunoreactive neurons in the RVLM and RVMM, indicating that DMH neurons send axons directly to catecholaminergic neurons in the ventral medullary regions. These descending pathways from the DMH to the ventral medullary cardiorespiratory regions (RVLM, RVMM, CVLM and RP) may play important roles in conveying the stress-related information. Our study would be the basis to understand the physiology of the cardiorespiratory responses to stress.

Disclosures: Y. Okada: None. **Y. Kono:** None. **Y. Arima:** None. **S. Yokota:** None. **H. Onimaru:** None. **I. Fukushi:** None. **K. Koizumi:** None. **Y. Hasebe:** None. **M. Yoshizawa:** None. **H. Kise:** None. **T. Toda:** None.

Nanosymposium

358. Emotion: Circuits and Mechanisms

Location: SDCC 5

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

Presentation Number: 358.03

Topic: G.03. Emotion

Support: TIFR intramural grant, VAV

Title: Chronic chemogenetic activation of forebrain excitatory neurons in postnatal life evokes long-lasting changes in mood-related behavior

Authors: *S. PATI[1], S. SALVI[1], P. TIWARI[1], T. BANERJEE[1], S. MUKHOPADHYAY[2], V. A. VAIDYA[1]

[1]Tata Inst. of Fundamental Res., Mumbai, India; [2]Dept. of Neurosci., The Scripps Res. Inst., San Diego, CA

Abstract: Early life adverse experience is associated with increased risk of psychopathology in humans. Several rodent models phenocopy the persistent behavioral effects observed in humans in addition to enhanced serotonin 2A (5-HT_{2A}) function in adulthood. The emergence of anxiety and depressive-like behavior in the models of early-life stress are blocked by co-administering a $5HT_{2A/2C}$ receptor antagonist. Further, administration of selective $5HT_{2A/2C}$ receptor agonist (±)-2,5-Dimethoxy-4-iodoamphetamine hydrochloride (DOI) in postnatal life is sufficient to evoke a persistent increase in anxiety. Consistent with the pharmacological studies, the developmental knockout of $5HT_{2A}$ receptor reduces anxiety-like behavior, which can be restored to normal levels by the forebrain-specific rescue of the receptor. The $5HT_{2A}$ receptor is a G-protein coupled receptor that is coupled to Gqα mediated downstream signaling and causes neuronal depolarization. Other Gq-coupled receptors like M1/M5 muscarinic acetylcholine receptors and α1-adrenergic receptors also show altered function in animals with a history of early life stress. We hypothesized that increased activation of cortical excitatory neurons by activating Gqα mediated signaling during the postnatal critical window is sufficient to bring about the long-lasting increase in anxiety and depressive-like behavior in adulthood. We used a chemogenetic approach where we expressed the excitatory Designer Receptors Exclusively Activated by Designer Drugs (DREADD) hM3Dq in CamKIIα-positive cortical excitatory neurons using a bigenic mouse line (CamKIIα-tTA:: tetO hM3Dq). We fed the pups the hM3Dq ligand, clozapine-N-oxide (CNO; 1 mg/kg) from postnatal day 2 to 14 (PNCNO) and performed various behavioral tests in adulthood. The PNCNO-treated animals displayed significantly enhanced anxiety-like behavior in open-field test, elevated plus maze and light-dark avoidance test. These animals also showed increased depressive-like behavior in the forced swim test and impaired sensory-motor gating in pre-pulse inhibition. Chronic CNO (1 mg/kg) administration in adulthood, however, did not result in any significant alteration in anxiety and depressive-like behavior or sensory-motor gating. Further, we did not observe any significant alterations in anxiety-like behavior in adulthood following postnatal activation of Gq signaling in PV-positive inhibitory neurons. Taken together, these results indicate that chronic activation of Gq-signalling in cortical excitatory neurons in first two weeks of postnatal life, but not in adulthood is sufficient to evoke long-lasting changes in emotional behavior.

Disclosures: S. Pati: None. **S. Salvi:** None. **P. Tiwari:** None. **T. Banerjee:** None. **S. Mukhopadhyay:** None. **V.A. Vaidya:** None.

Nanosymposium

358. Emotion: Circuits and Mechanisms

Location: SDCC 5

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

Presentation Number: 358.04

Topic: G.03. Emotion

Support: YNPRC Office of Research Infrastructure Programs ODP51OD11132
CIFAR Azrieli Global Scholar Award
Brain Health Institute Award

Title: Zona incerta modulates fear responses in mice

Authors: *A. VENKATARAMAN[1], N. BRODY[2], P. REDDI[3], B. G. DIAS[1,4,5]
[1]Div. of Behavioral Neurosci. & Psychiatric Disorders, [2]Neurosci. & Behavioral Biol. Undergraduate Program, [3]Emory Univ. Biol. Undergraduate Program, Emory Univ., Atlanta, GA; [4]Yerkes Natl. Primate Res. Ctr., Atlanta, GA; [5]Dept. of Psychiatry and Behavioral Sci., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: The ability to inhibit fear in neutral, non-threatening conditions is crucial for adaptive functioning of an organism. Dysregulation of fear inhibition is associated with a wide range of psychopathological conditions. In the mammalian brain, the sub-thalamic zona incerta, typically considered a sensorimotor relay, is gaining attention for its role in modulating behavioral responses in a state-dependent manner. However, very little is known about its role in modulating fear.

In this study, we used differing shock intensities (low-shock and high-shock) in an auditory discrimination paradigm in mice to study the role of ZI in fear inhibition. Animals trained in low-shock conditions expressed intact fear inhibition, while animals trained in high-shock conditions expressed impaired fear inhibition. C-FOS immunohistochemistry revealed higher neuronal activity in the rZI of animals that showed intact fear inhibition (low-shock training group) compared to the animals that showed impaired fear inhibition (high-shock training group). To establish the functional role of rZI in fear inhibition, we used designer receptors exclusively activated by designed drugs (DREADD) technology. Reducing activity of rZI using inhibitory DREADDs in wild-type animals, trained in low shock conditions, resulted in decreased fear inhibition. Increasing activity of cells in the rZI using excitatory DREADDs in wild-type animals, trained in high shock conditions, restored fear inhibition.

Immunohistochemical staining indicated strong vGAT expression in the rZI and therefore, we hypothesized that stimulation of GABAergic cells within the rZI would be sufficient to rescue impairments in fear inhibition observed in animals trained in high shock conditions. Targeted manipulation of GABAergic cells using Cre-dependent excitatory DREADDs in vGAT-Cre animals (high-shock trained) robustly restored appropriate fear inhibition.

Taken together, we found that the rZI bidirectionally modulates fear inhibition. In particular, stimulation of GABAergic cells in the rZI was sufficient to rescue impaired fear inhibition. In summary, our data suggest a previously unappreciated role for the ZI in modulating fear responses.

Disclosures: A. Venkataraman: None. **N. Brody:** None. **P. Reddi:** None. **B.G. Dias:** None.

Nanosymposium

358. Emotion: Circuits and Mechanisms

Location: SDCC 5

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

Presentation Number: 358.05

Topic: F.04. Stress and the Brain

Support: NIH Grant 1F30NS105408-01
NIH U01AG046139
R01AG018454
P50AG047266

Title: CTRND05 is a high affinity corticotropin releasing hormone antibody that blocks the metabolic, immunologic, and neural sequelae of chronic stress

Authors: *H. S. FUTCH[1], M. Z. KUHN[1], B. D. MOORE[1], Y. LEVITES[2], C. G. JANUS[3], P. CHAKRABARTY[2], M. R. SHAPIRO[4], T. M. BRUSKO[4], E. G. KRAUSE[5], T. E. GOLDE[6]
[2]Neurosci., [3]CTRND and Dept. of Neurosci., [4]Diabetes, [5]Dept Pharmacodynamics, [1]Univ. of Florida, Gainesville, FL; [6]Dept. of Neurosci., Col. of Medicine, Univ. of Florida, Gainesville, FL

Abstract: Epidemiologic studies have posited associations between experience of chronic stress or early life stress and an increased incidence of a multitude of health issues such as stroke, myocardial infarction, neuropsychiatric disorders, and dementias including Alzheimer's disease. Corticotropin-releasing hormone (CRH) is a central coordinator of the neuroendocrine and behavioral response to stressful stimuli, and single nucleotide polymorphisms (SNP's) in the CRH receptor (CRHR1) and the CRH-binding protein (CRHBP) genes are associated with several neuropsychiatric disorders. These data coupled with extensive investigation into animal models have implicated CRH and Hypothalamic-Pituitary-Adrenal (HPA) Axis dysfunction as the biological link between early-life or chronic stress and a plethora of diseases. Unfortunately, CRHR1 antagonists have variable efficacy in animal models and have historically failed in clinical trials for alcoholism, major depression, and post-traumatic stress disorder (PTSD). In addition, glucocorticoid synthesis inhibitors and receptor antagonists have undesirable pharmacokinetic or pharmacodynamic profiles and off-target effects. Therefore, while there is an immense amount of potential to alleviate disease burden through successful modulation of the HPA axis, the field lacks efficacious tools to investigate and target the axis therapeutically. Considering this information, we aimed to create active and passive vaccination approaches to directly neutralize CRH as a novel therapeutic strategy that may offer enhanced efficacy over receptor-based approaches. We have generated a high affinity (K_d<1.0E-12) monoclonal CRH antibody (CTRND05) that is able to reduce the glucocorticoid response to acute restraint stress by greater than 85% in mice, with an in-vivo half life of one week. CTRND05 is able to provide long term HPA axis suppression with only weekly dosing, and is a completely novel tool and

potential therapeutic ready to implement into HPA axis, early-life stress, and chronic stress research. When applied as a therapeutic, this antibody is able to reverse the metabolic, immunologic, and neural sequelae of chronic variable stress in mice. Humanization of the antibody, central target engagement, and behavioral studies are ongoing. These studies have broad implications for both basic research on the HPA axis and for the treatment of stress-related disorders, and could possibly herald a new class of therapeutics that target hypothalamic neuropeptides using high affinity antibodies.

Disclosures: M.Z. Kuhn: None. **B.D. Moore:** None. **Y. Levites:** None. **C.G. Janus:** None. **P. Chakrabarty:** None. **M.R. Shapiro:** None. **T.M. Brusko:** None. **E.G. Krause:** None. **T.E. Golde:** None.

Nanosymposium

358. Emotion: Circuits and Mechanisms

Location: SDCC 5

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

Presentation Number: 358.06

Topic: F.04. Stress and the Brain

Support: Howard Hughes Medical Institute
NIH RO1DC015032
NIH 1R01DC016442

Title: Virus-assisted single-cell transcriptomics for the genetic dissection of neural circuits

Authors: *N. K. HANCHATE[1], E. LEE[1], A. ELLIS[3], K. KONDOH[4], X. YE[1], R. BASOM[2], C. TRAPNELL[3], L. BUCK[1]
[1]Basic Sci. Div., [2]Genomics and Bioinformatics Shared Resources, Fred Hutchinson Cancer Reserach Ctr., Seattle, WA; [3]Dept. of Genome Sci., Univ. of Washington, Seattle, WA; [4]Div. of Endocrinol. and Metabolism, Natl. Inst. for Physiological Sci., Okazaki, Japan

Abstract: Animals employ instinctive behavioral and physiological responses to a variety of stressors to overcome danger and restore homeostasis. Hypothalamic corticotropin-releasing hormone (CRH) neurons govern the physiological response to stress by regulating the hypothalamic-pituitary-adrenal axis, which controls circulating levels of stress hormones. At present, the neural circuits and molecular mechanisms that convey different stress signals to CRH neurons are poorly understood. Here, we developed a novel strategy, termed “Connect-Seq,” which uses single-cell RNA sequencing of virus-infected cells upstream of specific neurons in neural circuits to define their molecular identities. As a proof of concept, using Connect-Seq, we profiled single-cell transcriptomes of ~150 brain neurons and identified subpopulations of neurons that are likely to communicate stress-related signals to CRH neurons. Analyses of single-cell transcriptomes for ‘fast-acting’ neurotransmitters revealed a large

population of cells expressing markers of inhibitory GABAergic neurons and a minor population of cells expressing markers of excitatory glutamatergic neurons. Further analyses showed a number of other neuromodulators/neurotransmitters in upstream neurons, including acetylcholine, dopamine, histamine, norepinephrine, and, altogether, ~35 different neuropeptides, each expressed in individual neurons or subsets of neurons. These findings reveal extreme molecular heterogeneity among the upstream neurons and suggest they use diverse neurochemical messengers to transmit signals to CRH neurons. Many neurons coexpressed different neurotransmitters/neuromodulators, suggesting co-release of neurochemical messengers. Dual labeling of brain sections verified expression of specific neuropeptides in virus-infected neurons upstream of CRH neurons in selected brain areas. Our results indicate that Connect-Seq can be applied to genetically dissect neural circuits and uncover molecular identities of neurons upstream of specific neuronal types of known function. Molecular markers identified in those neurons lay a foundation for the application of cell-specific genetic tools to investigate the functions and physiological significance of diverse neuronal subsets within complex neural circuits.

Disclosures: N.K. Hanchate: None. **E. Lee:** None. **A. Ellis:** None. **K. Kondoh:** None. **X. Ye:** None. **R. Basom:** None. **C. Trapnell:** None. **L. Buck:** None.

Nanosymposium

358. Emotion: Circuits and Mechanisms

Location: SDCC 5

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

Presentation Number: 358.07

Topic: H.01. Animal Cognition and Behavior

Support: NIH 1R01MH106568

Title: Projections from medial prefrontal cortex to amygdala are involved in social familiarity induced anxiolysis (sofia)

Authors: *S. MAJUMDAR, A. ABREU, E. A. LUNGWITZ, N. BHARADWAJ, A. D. DIETRICH, K. D. ANDREWS, W. A. TRUITT
Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Mental health is crucially linked to social behavior. Healthy social behavior involves learning to adapt emotional responses to social cues, for example learning to suppress anxiety through social familiarity, or *social familiarity-induced anxiolysis (SoFiA).* SoFiA is well documented and forms the basis for interpersonal therapy, however, the neural mechanisms of SoFiA are unclear. SoFiA is modeled in rats by employing social interaction habituation (SI-hab) protocol. Using SI-hab protocol it has been determined that SoFiA represents social safety learning, which requires both anxiogenic stimulus (Anx) and social familiarity (SF) during

training sessions (5-6 daily social interaction sessions), and SoFiA expression is dependent on infralimbic cortex (IL). Based on these findings we hypothesize that Anx and SF are processed by unique neural systems, and repeated convergence of these signals interact within IL to induce plasticity resulting in social safety learning and anxiolysis. Here we investigated the role of IL in SoFiA acquisition and expression, using hM4D(Gi) recombinant adeno-associated virus AAV5-CAMKIIa-hM4D(Gi)-mCherry and CNO (exogenous ligand for Gi-DREADDs) to inhibit IL neurons and/or axons. Rats (n=7/group) received bilateral viral injections (200nL) targeting IL and after viral expression (6 week), we found that i.p. injections (30 min prior to testing) of CNO (0.25 & 0.5mg/kg), but not vehicle, completely blocked SoFiA acquisition. In order to target IL efferents to amygdala, we employed combined use of a CRE-recombinase expressing canine adenovirus-2 (CAV2) with adeno-associated virus [pAAV5-hsyn-DIO-hM4D(Gi)-mCherry] in amygdala and IL respectively. CAV cre induces expression of Gi-DREADDs in IL neurons projecting to amygdala. Rats receiving this combined viral injection, but not rats receiving control virus injections, bilaterally, exhibited inhibition of SoFiA expression following CNO injection (30 min prior to testing). Post CNO injection, Gi-DREADDs and DIO-CAV group exhibit comparable inhibition in SoFiA expression suggesting the inhibition of IL neurons expressing Gi-DREADDs is due to involvement of IL efferents to amygdala in SoFiA expression. This observation validates our data from intracranial study, where intracranial CNO injections into BLA of IL-Gi-DREADD expressing rats inhibited SoFiA expression.

Disclosures: S. Majumdar: None. **A. Abreu:** None. **E.A. Lungwitz:** None. **N. Bharadwaj:** None. **A.D. Dietrich:** None. **K.D. Andrews:** None. **W.A. Truitt:** None.

Nanosymposium

358. Emotion: Circuits and Mechanisms

Location: SDCC 5

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

Presentation Number: 358.08

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01 MH095810

Title: 2510002D24Rik, a 22q11 deletion syndrome gene candidate for CA2-dependent social memory deficit

Authors: *P. DEVARAJU[1], J. YU[1], D. EDDINS[1], S. HAN[1], K. KAVDIA[1], D. KAMINSKI[1], J. PENG[2], S. ZAKHARENKO[1]
[1]Developmental Neurobio., [2]Structural Biol., St. Jude Children's Res. Hosp., Memphis, TN

Abstract: Altered social behavior is a feature of several neuropsychiatric disorders including schizophrenia and autism spectrum disorders (ASDs). One of the major genetic predispositions for schizophrenia and ASDs is 22q11.2 deletion syndrome (22q11DS), the most common human

microdeletion syndrome. Using mouse models, we identified *2510002D24Rik*, a nuclear gene encoding mitochondrial protein as a culprit for hippocampal CA2-dependent social memory deficits associated with 22q11DS. Both homozygous and hemizygous deletion of *2510002D24Rik* affects social recognition in a 1-chamber 2-trial social memory task. Similar observations were reported in the *Df(16)1A*$^{+/-}$ mice, which harbor a hemizygous 1.3-Mb chromosomal deletion syntenic to the human 22q11.2 critical region. Though the CA2 circuitry was implicated in the social memory deficit in *Df(16)A*$^{+/-}$ mice, the gene(s) responsible and the molecular mechanism are unknown. In this study we have dissected the cellular and molecular mechanisms by which *2510002D24Rik* deficiency gives rise to CA2-dependent social memory deficit. *2510002D24Rik* deficiency reduces the firing rate of GABAergic interneurons in the hippocampal CA2 region and gives rise to imbalance of excitation-inhibition in the CA3-CA2 circuit but not the entorhinal cortex-CA2 circuit. *2510002D24Rik* deficiency also affects long-term plasticity of inhibitory post-synaptic currents and disinhibition-mediated potentiation of excitatory potentials in the CA3-CA2. Consistent with its association to mitochondria, *2510002D24Rik* is enriched in the mitochondrial fraction. Proteomic analyses of *2510002D24Rik*-deficient hippocampus reveal that Atp23, involved in the processing of subunit 6 of ATP synthase, is the most downregulated target. Using the recently developed ATP/ADP fluorescent sensor, PercevalHR, we determined that *2510002D24Rik* deficient fast-spiking interneurons but not pyramidal neurons displayed reduced interconversion of ATP and ADP during an evoked train of action potentials. Overexpression of Atp23 in interneurons in vivo rescues the firing rate of CA2 fast-spiking interneurons and partially rescues the social memory deficit. Our results suggest that *2510002D24Rik* deficiency contributes to social memory deficits of 22q11DS mice by affecting ATP-ADP interconversion in the fast-spiking interneurons and altering excitation-inhibition balance in the hippocampal CA2.

Disclosures: P. Devaraju: None. **J. Yu:** None. **D. Eddins:** None. **S. Han:** None. **K. Kavdia:** None. **D. Kaminski:** None. **J. Peng:** None. **S. Zakharenko:** None.

Nanosymposium

359. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex II

Location: SDCC 25

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 359.01

Topic: H.01. Animal Cognition and Behavior

Support: HHMI
NIH U01

Title: Imaging cortical dynamics from millimeter to micron scale during evidence based decision making in rats

Authors: *B. B. SCOTT[1], S. THIBERGE[2], C. GUO[3], D. G. TERVO[4], C. BRODY[2], A. Y. KARPOVA[5], D. W. TANK[2]
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]Princeton Univ., Princeton, NJ; [3]Janelia Res. Campus, Ashburn, VA; [4]Howard Hughes Med. Inst. Janelia Farm Res. Campus, Ashburn, VA; [5]HHMI/ Janelia Res. Campus, Ashburn, VA

Abstract: Evidence-based decision making is thought to require the activity of large populations of neurons distributed throughout the cerebral cortex. While most studies focus on the activity of a few neurons selected from one or more candidate brain regions, the emergence of widefield calcium imaging tools offer the ability to record dynamics across many regions simultaneously. We recently developed a head-mounted macroscope, cScope, that extends the domain of widefield calcium imaging to freely moving behaviors. We used cScope to record dynamics from multiple cortical regions in transgenic GCAMP6f-expressing rats, during a visual accumulation of evidence task. In this task rats view a sequence of brief (10ms) flashes presented from two LEDs. The number and timing of flashes was independent between the two LEDs and rats oriented to the LED with the greater number of flashes to obtain a reward. Analysis of task-related calcium dynamics recorded with cScope revealed multiple regions in occipital and parietal cortex which had neural signals that encode behavioral choice and sensory evidence. Comparison of cScope imaging data with calcium dynamics recorded at cellular resolution with two-photon microscopy revealed that local neurons with heterogeneous dynamics contribute to widefield signals. These results extend the domain of head-mounted microscopes to larger scale neural dynamics and suggest cortical locations as new candidates for future cellular resolution imaging studies.

Disclosures: B.B. Scott: None. **S. Thiberge:** None. **C. Guo:** None. **D.G. Tervo:** None. **C. Brody:** None. **A.Y. Karpova:** None. **D.W. Tank:** None.

Nanosymposium

359. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex II

Location: SDCC 25

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 359.02

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NINDS K99NS092972
NIH Director's Pioneer Award 8DP1HD075623
Defense Advanced Research Projects Agency (DARPA) Biological Technology Office (BTO) ''NeuroFAST'' award W911NF-14-2-0013
the Simons Foundation Collaboration on the Global Brain awards 325380 and 543045
Howard Hughes Medical Institute

Title: Urgency-related neural population dynamics in the dorsal premotor cortex during a reach reaction time decision-making task

Authors: *C. CHANDRASEKARAN[1], K. V. SHENOY[2]
[1]Electrical Engin., Stanford Univ., Stanford, CA; [2]EE, BioE & Neurobio., Howard Hughes Med. Inst. - Stanford Univers, Stanford, CA

Abstract: When driving, encountering a car ahead of you increases the urge to act: either to brake or to make a lane change. This choice-independent urge to act as time elapses has been termed "urgency." Some studies suggest urgency is a critical factor in decisions while others posit that decisions are primarily driven by the deliberation on sensory evidence (e.g., the diffusion decision model (DDM)). Here, we combine behavioral modeling and analysis of neural populations in PMd, a brain region thought to be involved in perceptual decisions (Thura and Cisek, 2014, Chandrasekaran et al., Nat. Comm, 2017), to understand if and how urgency affects decision-making dynamics.

We trained two male rhesus macaques to perform a visual reach reaction time (RT) discrimination task. The task was to discriminate the dominant color of a visual checkerboard and report the decision with an arm movement. We fit the choice and RT distributions using cognitive process models. Urgency and collapsing boundary models, two models with urgency, provided better fits to the behavior of the monkeys than the simple DDM (Akaike Information Criterion differences > 100). However, a DDM with variable non-decision time performed nearly as well as models with urgency.

While monkeys performed the task, we recorded single neurons and multiunits in PMd (n=996). We tested if neural population dynamics in PMd were more consistent with urgency or these alternative non-urgency models. We found a lawful relationship between the pre-stimulus neural state and eventual RT, but not the choice. This result supports an urgency model and not a DDM with start points biased towards one or other choice for different trials. Neural state ~100ms before movement onset did not vary across RT ruling out urgency being implemented through collapsing boundaries, which predicts that bounds decrease with time leading to lower bounds for longer RTs. Finally, for the easiest stimulus difficulty, choice selectivity emerged at different rates for fast and slow RTs. This result argues against the non-decision model, which predicts the same rate of choice selectivity for fast and slow RTs.

The correlation between RT and pre-stimulus neural state in PMd leads to the hypothesis that urgency manifests as a change in initial condition for decision-related dynamics. Future work should involve understanding how urgency exerts effects on the structure (e.g., speed or network trajectory) of the stimulus-induced decision-related dynamics in PMd. Together, our results suggest that the decision-making behavior of monkeys and neural dynamics in PMd may be understood through the lens of decision-making models that involve urgency.

Disclosures: C. Chandrasekaran: None. **K.V. Shenoy:** None.

Nanosymposium

359. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex II

Location: SDCC 25

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 359.03

Topic: H.01. Animal Cognition and Behavior

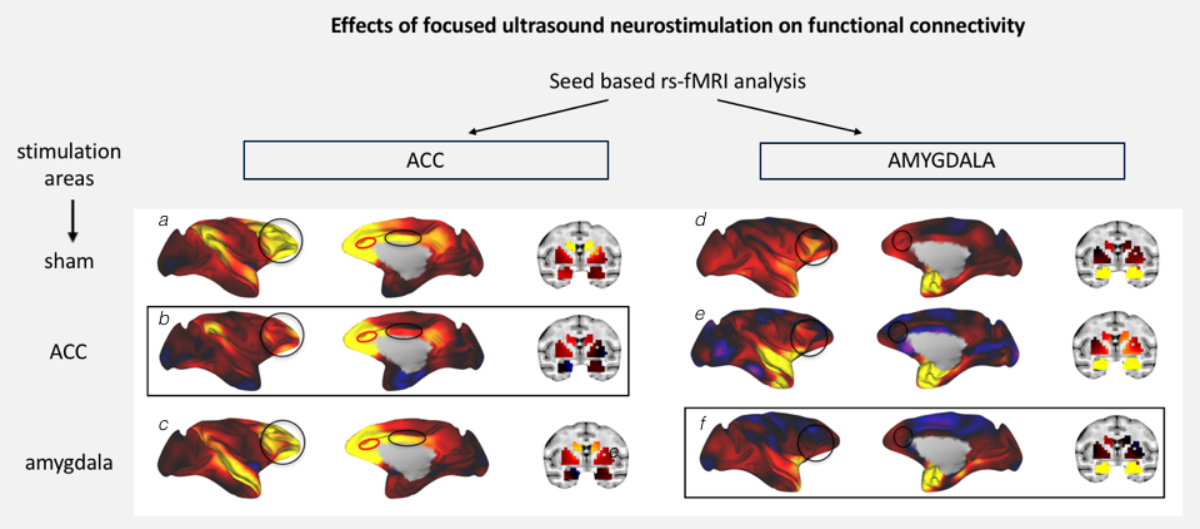
Support: Wellcome Senior Investigator Award WT100973AIA
MRC programme grant MR/P024955/1
MRC programme grant G0902373
Wellcome Trust UK Grant 105651/Z/14/Z
Wellcome Trust UK Grant 105238/Z/14/Z

Title: Reversible and non-invasive manipulation of activity in deep and subcortical brain structures using focused ultrasound neuromodulation

Authors: *D. FOLLONI[1], L. VERHAGEN[1], R. B. MARS[2,3], E. FOURAGNAN[1], J.-F. AUBRY[4,5], M. F. S. RUSHWORTH[1], J. SALLET[1]
[1]WIN, Dept. of Exptl. Psychology, [2]WIN, Ctr. for Functional MRI of the Brain (FMRIB), Nuffield Dept. of Clin. Neurosciences, Univ. of Oxford, Oxford, United Kingdom; [3]Donders Inst. for Brain, Cognition and Behaviour, Radboud Univ. Nijmegen, Nijmegen, Netherlands; [4]UMRS, INSERM, CNRS, UMPC, Inst. du Cerveau et de la Moelle épinière, Paris, France; [5]Dept. of Radiation Oncology, Univ. of Virginia, Charlottesville, VA

Abstract: Introduction: Using focused ultrasound neuromodulation (FUN) combined with resting-state fMRI (rs-fMRI) we show that is possible to transcranially and reversibly modulate neural activity with high spatial resolution and high inter-subject reproducibility in deep and subcortical areas such as the anterior cingulate cortex (ACC) and amygdala in the Macaca mulatta. **Methods:** A single-element ultrasound (US) transducer, focused at ~5cm, was used with region-specific coupling cones for stimulation of either ACC (n=3) or amygdala (n=4). The transducer resonance frequency was set to 250 kHz and 100 ms bursts of US waves were generated. Registration of animals' structural images to a neuronavigation system was used for targeting of the US to each region. Rs-fMRI data were acquired for up to 90 minutes at 3T under isoflurane anesthesia for each subject. **Results:** We investigated the off-line focal effects of FUN targeted at ACC and amygdala by measuring changes in their whole-brain functional connectivity. We found dissociable and spatially focused effects of FUN in both cases. Primarily, FUN induced a region-specific change of coupling with the effects being most prominent in regions strongly interconnected with the stimulated area. Compared to controls, FUN applied bilaterally to the amygdala decreased transiently and reversibly its connectivity with ventrolateral, orbital and medial prefrontal cortices (PFC). Consistently, FUN targeted at ACC markedly reduced short- and long-range connectivity with middle and posterior cingulate, and

lateral PFC. Notably, ACC FUN resulted in a disruption of ACC connectivity sub-cortically with the amygdala. This change was mirrored by FUN targeted at the amygdala. Together, the results show the high spatial focality of FUN and its capacity to transiently and non-invasively modulate deep brain areas such as amygdala and ACC. **Conclusion:** In summary, we have shown the potential of FUN as a novel technique to non-invasively modulate deep cortical and subcortical regions activity with high spatial specificity in a transient and reversible fashion.



Whole-brain functional connectivity between stimulated areas and the rest of the brain. Panels a, b, and c on the left side of the figure show activity coupling between ACC (seed highlighted in red) and the rest of the brain in sham/no stimulation (**a**), after ACC FUN (**b**), and after amygdala FUN (**c**). Hot colours indicate positive coupling (Fisher's z). Panels d, e, f show activity coupling between amygdala (seed masked in yellow) and the rest of the brain in sham/no stimulation (**d**), after ACC FUN (**e**), and after amygdala FUN (**f**). Functional connectivity from FUN-targeted regions are highlighted by black boxes (**b**,**f**). Each type of FUN had a selective effect on the stimulated area: ACC coupling was strongly changed by ACC FUN only (**b**) and amygdala coupling was strongly changed by amygdala FUN only (**f**). Areas showing changes in coupling with FUN-targeted regions after FUN are circled in black and compared with the other 2 control conditions.

Disclosures: D. Folloni: None. **L. Verhagen:** None. **R.B. Mars:** None. **E. Fouragnan:** None. **J. Aubry:** None. **M.F.S. Rushworth:** None. **J. Sallet:** None.

Nanosymposium

359. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex II

Location: SDCC 25

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 359.04

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01EY11378
HHMI

Title: A population code in area LIP for decisions spanning several eye movements

Authors: *N. SO[1], M. N. SHADLEN[2,3]
[1]Neurosci., Columbia Univ. Zuckerman Inst., New York, NY; [2]Neurosci., Howard Hughes Med. Inst. - Columbia Univ., New York, NY; [3]Zuckerman Insitute, New York, NY

Abstract: Cognitive operations such as decision-making and working memory can persist not only over time, but also across intervening activities. Although the neurons in the lateral intraparietal area (LIP) are known to represent neural computations in flexible timescales, LIP neurons are also known to reset their activity after each saccade, which raises the question whether they can carry out computations that span multiple oculomotor actions. Two monkeys made perceptual decisions that were interrupted by intervening eye movements. In each trial, the monkey viewed random dot motion, but before reporting the direction, it carried out an intervening eye movement task: a saccade to a choice-neutral upper target, fixation there, and pursuit of a target to the original fixation. The task then continued with a delay period and a saccadic choice. Despite the interruption, monkeys performed the task well. We recorded simultaneously from multiple LIP neurons (V-probe, Plexon Inc.) while the monkey performed the task. Before the intervention, LIP neurons reflected decision formation if a choice target was in the response field (RF), even though the next eye movement was never to the RF. During the intervening task, however, these neurons no longer represented the decision, presumably because the choice target was no longer in their RF, but they recovered the choice information when the pursuit eye movement returned the gaze to the original point of fixation. Simultaneous neural recordings show that other LIP neurons represented the choice information during the intervening task. The RFs of these neurons overlapped the choice target relative to the gaze during all phases of the intervening task. We analyzed the trial-by-trial variability of choice-related neural responses across time and neurons using a graph theoretical approach. The pattern suggests that LIP neurons represent a common signal, and moreover, it appears to be passed from the neurons representing the decision before the intervening task, and ultimately back to these neurons. Although individual LIP neurons represent space in an oculocentric coordinate frame, our results suggest that the population of neurons in LIP can represent a decision in a head-, ego- or allo-centric coordinate frames by passing information to appropriate members of the population. Such message passing could achieve invariance (e.g., to direction of gaze) without explicit representation.

Disclosures: N. So: None. **M.N. Shadlen:** None.

Nanosymposium

359. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex II

Location: SDCC 25

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 359.05

Topic: H.01. Animal Cognition and Behavior

Support: Champalimaud Foundation
Howard Hughes Medical Institute
Simons Collaboration on the Global Brain grant 542997
Pew Scholarship in Biomedical Sciences
NIH Award R01MH109180
McKnight Scholars Award
NIH/NINDS K99/R00 grant NS092972

Title: Population dynamics of choice representation in dorsal premotor and primary motor cortex

Authors: *D. PEIXOTO[1,2], R. KIANI[3], C. CHANDRASEKARAN[4], S. RYU[5], K. V. SHENOY[6], W. T. NEWSOME III[7]
[1]Stanford Univ. Sch. of Med., Stanford, CA; [2]Champalimaud Neurosci. Programme, Lisbon, Portugal; [3]Ctr. for Neural Sci., New York Univ., New York, NY; [4]Electrical Engin., Stanford Univ., Stanford, CA; [5]Dept Neurosurg, Palo Alto Med. Fndn., Palo Alto, CA; [6]EE, BioE & Neurobio., Howard Hughes Med. Inst. - Stanford Univers, Stanford, CA; [7]Dept Neurobiol, Stanford Univ. Sch. Med., Stanford, CA

Abstract: Studies in multiple species have revealed the existence of neural signals that lawfully co-vary with different aspects of the decision-making process, including choice, sensory evidence that supports the choice, and reaction time. These signals have been identified in several motor preparation circuits and have often been interpreted as the representation of a decision variable (DV). While they provide insight about mechanisms underlying the decision-making process, the single-trial dynamics of DVs and their representation at the neural population level remain poorly understood. Here, we examine the representation of the DV in simultaneously recorded neural populations of dorsal premotor (PMd) and primary motor (M1) cortices of monkeys performing a random dots direction discrimination task with arm movements as the behavioral report. We show that single-trial DVs covary with stimulus difficulty in both areas but are stronger and appear earlier in PMd compared to M1 when the stimulus duration is fixed and predictable. When temporal uncertainty is introduced by making the stimulus duration variable, single-trial DV dynamics are accelerated across the board and the two areas become largely indistinguishable throughout the entire trial. These effects are not trivially explained by the faster emergence of motor kinematic signals in PMd and M1. All key aspects of the data were replicated by a computational model that relies on progressive recruitment of units with stable choice-related modulation of neural population activity. In contrast with several recent results in rodents, decision signals in PMd and M1 are not carried by short sequences of activity in non-overlapping groups of neurons but are instead distributed across many neurons, which once recruited, represent the decision stably during individual behavioral epochs of the trial.

Disclosures: D. Peixoto: None. **R. Kiani:** None. **C. Chandrasekaran:** None. **S. Ryu:** None. **K.V. Shenoy:** None. **W.T. Newsome III:** None.

Nanosymposium

359. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex II

Location: SDCC 25

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 359.06

Topic: H.01. Animal Cognition and Behavior

Support: CIHR MOP-102662
CFI
FRSQ
FYSSEN foundation
GRSNC

Title: A cortico-basal ganglia network for dynamic decision-making

Authors: *D. THURA, P. CISEK
Dept Neurosci., Univ. Montreal, Montreal, QC, Canada

Abstract: Computational studies often propose that decision-making recruits multiple interconnected brain structures encoding specific aspects of the choice process. However, neurophysiological data in support of such mechanisms emerging from network-based operations is lacking. Here we investigate the respective role of five areas of the cortico-basal ganglia sensorimotor circuit during dynamic decision-making between actions. We recorded neurons in the dorsal premotor cortex (PMd), the primary motor cortex (M1), the dorsolateral prefrontal cortex (dlPFC) and in the external (GPe) and internal (GPi) segments of the globus pallidus of two monkeys trained to perform a probabilistic reach decision task in which sensory evidence continuously evolves within each trial. The task allowed us to dissociate the process of deliberation from the moment of commitment, and to induce adjustments of the monkeys' speed-accuracy trade-off (SAT). With single-neuron and "state-space" analyses of the neural responses, we found that while animals deliberate between the two reach targets, dlPFC, PMd and M1 neurons continuously reflect the evolving sensory evidence guiding the decision. By contrast, the effect of sensory evidence is much weaker in GPe and virtually absent in GPi. Instead, GPe and GPi cells exhibit build-up and decreasing activities consistent with a time-varying signal reflecting the growing urgency to commit, which is adjusted to control the SAT. This urgency signal influences activity in PMd and M1, but less so in dlPFC. About 280ms before movement onset, we see what appears to be a neural correlate of the moment of commitment, consisting of a prominent peak in PMd activity accompanied by an increase of tuned activity in GPe/GPi. Interestingly, we do not observe any signature of commitment in dlPFC. These results are captured by a dynamical attractor model in which cortical activity reflects a biased competition between actions, which is gradually amplified by an urgency signal from the basal ganglia that effectively controls the amount of evidence needed before the animal commits to the currently

favored reach choice. As the cortical bias grows in favor of one of the targets, it begins to influence activity in the GPe, producing a gradual emergence of tuning before commitment. When that contrast becomes strong enough to engage tuning in the GPi, the basal ganglia output activity leads to a positive feedback that constitutes commitment to the action choice. The model simulates the main features of our data, including effects of microstimulation, and makes specific predictions for future experiments aimed at elucidating the mechanisms of dynamic decision-making.

Disclosures: D. Thura: None. **P. Cisek:** None.

Nanosymposium

359. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex II

Location: SDCC 25

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 359.07

Topic: H.01. Animal Cognition and Behavior

Support: K99MH111926

Title: Cortical computation of an economic reference point

Authors: *C. M. CONSTANTINOPLE[1], A. PIET[2], P. BIBAWI[1], C. D. KOPEC[1], C. D. BRODY[3]
[2]Neurosci., [1]Princeton Univ., Princeton, NJ; [3]Princeton Neurosci. Inst. and Dept of Mol. Biol., HHMI / Princeton Univ., Princeton, NJ

Abstract: Behavioral economic theories of choice have sought to describe the ways in which people make decisions when choosing between probabilistic (i.e., risky) options. These theories have provided compelling evidence for systematic cognitive biases that influence choice in most individuals. Here, we present a behavioral paradigm for studying the neural basis of these cognitive biases in rodents. Rats were trained to choose between explicitly cued probabilistic gambles on each trial. High-throughput behavioral training yielded tens of thousands of choices per rat in more than two dozen well-trained subjects. Subjects consistently maximized rewards, and exhibited cognitive biases observed in humans: nearly all rats exhibited diminishing sensitivity to larger rewards as well as probability distortion, typically overweighting most, but especially low, probabilities. Rats also exhibited reference dependence, in which the valence of outcomes (gain or loss) was determined by an internal reference point that reflected recent reward history. Optogenetic perturbations revealed that orbitofrontal cortex (OFC), but not posterior parietal cortex (PPC), was causally involved in representing the reference point during the trial. In contrast, perturbations of PPC during the inter-trial interval improved behavioral performance by suppressing suboptimal sequential effects across trials. Electrophysiological recordings from OFC demonstrated strong encoding of rats' subjective reference points. This

demonstrates that an economic reference point, a cognitive variable hypothesized from behavioral economics, can be observed and manipulated at the level of individual neurons in orbitofrontal cortex.

Disclosures: C.M. Constantinople: None. **A. Piet:** None. **P. Bibawi:** None. **C.D. Kopec:** None. **C.D. Brody:** None.

Nanosymposium

359. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex II

Location: SDCC 25

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 359.08

Topic: H.01. Animal Cognition and Behavior

Support: Human Frontier Sciences Program
Wellcome Trust 205093
Wellcome Trust 102264
Simons Foundation 325512
Gatsby Charitable Foundation GAT3531
European Research Council 694401
EU Horizon 2020 Marie Curie 656528

Title: Local and global neural correlates of a decision-making task in the mouse brain

Authors: *N. A. STEINMETZ, P. ZATKA-HAAS, M. CARANDINI, K. D. HARRIS
Univ. Col. London, London, United Kingdom

Abstract: Behavior arises from neuronal activity patterns, but whether the relevant activity is concentrated in a small number of brain regions or distributed across many regions remains unknown. We studied mice performing a visually-guided perceptual decision task (Burgess et al, 2017). Mice were trained to give one of three responses (choose left, right, or neither) depending on the relative contrast of two visual stimuli, presented simultaneously on the left and right. Widefield imaging of dorsal cortex revealed that after stimulus presentation, activity progressed from primary visual cortex to secondary visual areas, secondary motor cortex, and finally primary motor cortex. Using scanning optogenetic inactivation, we determined that visual cortex and secondary motor cortex inactivation impaired performance, in distinct ways and in sequentially offset time periods of the task. However, we did not find any performance deficits when inactivating primary motor cortex. To explore the additional roles of subcortical structures, we recorded the activity of >20,000 neurons during task performance using multiple acutely-inserted Neuropixels probes. These electrode arrays span ~4 mm of tissue and thus record simultaneously across diverse brain regions, including: sensory, parietal, frontal, and motor isocortex; thalamic nuclei; hippocampus; striatum; superior colliculus (SC); and multiple

midbrain structures. Neurons with responses that correlated with visual stimuli or upcoming choice were localized to specific brain regions, but neurons with correlates of ongoing movement or recent reward were widespread. Visually-responsive neurons were found in superficial SC, visual cortex, and striatum. Neurons that predicted the animal's choice earliest (~100 ms prior to movement) were found in deep SC and the mesencephalic reticular formation. However, activity concurrent with action execution and following reward delivery were observed in nearly every region we recorded. We suggest that when mice perform this task, visual information flows through visual and secondary motor cortices and striatum, to the midbrain where a behavioral choice is selected. By contrast, corollary information about ongoing movements and rewards is represented globally including in primary motor cortex, but this activity is not required for task execution.

Disclosures: N.A. Steinmetz: None. **P. Zatka-Haas:** None. **M. Carandini:** None. **K.D. Harris:** None.

Nanosymposium

359. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex II

Location: SDCC 25

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 359.09

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant K99NS092972

Title: Recapitulating decision-related neural activity in premotor cortex using recurrent neural networks

Authors: *J. C. KAO[1], C. CHANDRASEKARAN[2]
[1]Electrical Engin., UCLA, Los Angeles, CA; [2]Electrical Engin., Stanford Univ., Stanford, CA

Abstract: Recurrent neural networks (RNNs) are increasingly being used for deriving hypothetical circuit and computational mechanisms for behavior. In this setting, RNNs replicate the behavior of animals performing tasks with artificial neurons that resemble cortical activity. The trained RNN is viewed as an in-silico dynamical model of a brain area and is analyzed for putative computational mechanisms underlying the behavior.
Here, we sought to use RNNs to understand dorsal premotor cortex (PMd) neurons recorded from monkeys performing a perceptual decision-making task. The monkeys discriminated the dominant color of a central static red-green checkerboard and reported their decision with an arm movement to the corresponding colored target. The red and green targets, presented before the checkerboard stimulus, were different from trial-to-trial, thus decoupling color and action choice. PMd neurons show hallmarks of a candidate decision-variable —— covarying with action choice, stimulus difficulty and reaction time (RT), but not the color choice.

We trained RNNs to perform this task. The inputs to the RNN were the identity of the targets and the checkerboard stimulus (summarized as the number of red and green squares). The RNN output represented the decision to the left or right target. The trained RNN reproduced the psychometric curve and RT trends of animals. In an architecture with only one "vanilla" RNN, neurons demonstrated both color and direction selectivity—— a result at odds with the observation that PMd neurons lack significant color selectivity. Thus, we imposed an additional architectural constraint to the model. We reasoned that upstream cortical areas process the visual stimulus and provide input to PMd. We, therefore, used as a starting point, an architecture with separate RNNs connected in a feedforward chain. In this model, RNNs later in the chain showed significantly less color selectivity and were a better representation of decision-related neural activity in PMd.
Accounting for processing in other cortical areas may be necessary when using RNNs to model decision making tasks. More generally, neural data in addition to behavior may help constrain the design of RNNs and, in turn, lead to better dynamical models of neural activity.

Disclosures: J.C. Kao: None. **C. Chandrasekaran:** None.

Nanosymposium

359. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex II

Location: SDCC 25

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 359.10

Topic: H.01. Animal Cognition and Behavior

Support: Simons Collaboration on the global brain award: Jonathan Pillow: SCGB AWD1004351
NSF CAREER Award: Jonathan Pillow: (IIS-1150186)
Swiss National Science Foundation: Valerio Mante, SNSF Professorship PP00P3_157539
Simons Foundation: William T Newsome, Valerio Mante, Award 328189
Swiss Primate Competence Center in Research: Valerio Mante
Howard Hughes Medical Institute (HHMI): William T Newsome, Investigator
OD | USAF | AFMC | Air Force Research Laboratory (AFRL): William T Newsome, agreement number FA9550-07-1-0537

Title: Multi-dimensional, dynamic encoding, decoding, and decision making in prefrontal cortex

Authors: *M. C. AOI[1], V. MANTE[2], J. W. PILLOW[3]
[1]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]Inst. of Neuroinformatics, Zurich, Switzerland; [3]Psychology, Princeton Neurosci. Inst., Princeton, NJ

Abstract: A growing body of experimental and theoretical evidence in mice, rats and monkeys is pointing to a role for prefrontal cortex (PFC) that is important for decision formation and memory in perceptual decision making tasks. A number of recent studies have also attempted to characterize neuronal population activity in PFC during such tasks in order to identify its computational primitives and generate hypotheses about its function.
However, a good description of how population activity covaries with different combinations of task variables requires that dimensionality reduction methods permit investigators to parse the influence of stimuli, context cues, and behavioral outcomes on multi-neuron dynamics. To this end we describe a method of model-based dimensionality reduction and demonstrate its use in identifying multi-dimensional dynamics in dorsolateral PFC. Our analysis reveals that monkey PFC has a multidimensional, dynamic code for decisions, context, and relevant (as well as irrelevant) stimulus information during decision-making. We show that there are distinct dynamic phases of activity characterized by a early phase, where activity lies on a 1D, linear subspace, followed by later/rotational phase through a higher-dimensional subspace.
We also perform model-based decoding of PFC activity, allowing for simultaneous estimation of all relevant task variables. Our results demonstrate that the optimal readout rule is time-dependent, requiring the readout rule change throughout the stimulus presentation. We also show that the time a which decoding becomes accurate is consistent with the transition between dynamic phases. We further demonstrate that much of the information that is available about the animal's decision is available in the early moments of stimulus presentation but that a dynamic encoding of the stimulus persists throughout the trial. This suggests that while the animal maintains an accurate perception of the stimulus throughout the trial, it may have made its decision well before the end of the stimulus presentation.Finally, we discuss generalizations of our model-based dimensionality reduction framework to cutting-edge data recording modalities and demonstrate the utility of our method when applied to these modalities.

Disclosures: M.C. Aoi: None. **V. Mante:** None. **J.W. Pillow:** None.

Nanosymposium

359. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex II

Location: SDCC 25

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 359.11

Topic: H.01. Animal Cognition and Behavior

Support: R01DA038063-04
R01MH104251-04

Title: Adaptive choice stochasticity is a function of adapting value sensitivity in monkey orbitofrontal cortex

Authors: *J. ZIMMERMANN[1], P. W. GLIMCHER[3], K. LOUIE[2]
[2]Ctr. Neural Sci., [1]New York Univ., New York, NY; [3]Ctr. Neural Sci., New York Univ. Ctr. for Neural Sci., New York, NY

Abstract: Variability in decision making can arise from many factors. Noise in the value coding choice architecture, idiosyncratically changing preferences, or context dependent value signal representation can lead to stochasticity in simple choice. Here we explore how temporal changes in the composition of available value options influence choice stochasticity as well as neural sensitivity in monkey orbitofrontal cortex. We propose that mechanisms akin to sensory adaptation - following principles of efficient information coding within finite constraints - influence value encoding of simple options that in turn change choice behavior. We recorded single-unit activity in orbitofrontal cortex (OFC; area 13) while monkeys performed a saccadic choice task between two options differing systematically in reward magnitude and juice type. Blocks of trials comprised a mixture of adaptor and measurement trials. In measurement trials (identical across blocks), monkeys chose between an unvarying reference reward and one of five variable rewards, providing a quantification of probabilistic preference between rewards (a *choice curve*). Across blocks, we systematically varied the structure of the adaptor trials to induce a narrow or wide background reward environment. Overall adaptor variability had a significant effect on both choice behavior and OFC value coding ($p<0.05$). Consistent with an adapting decision mechanism, monkeys exhibited steeper measurement trial choice curves in narrow vs. wide background environments. Of 620 OFC neurons, 288 exhibited a significant ($p<0.05$) modulation by value in the measurement trials (cue or reward period). Consistent with neural adaptation, the strength of value coding was on average stronger in narrow vs. wide blocks ($p<0.05$). Notably, the extent of this coding difference (narrow-wide) corresponded to the behavioral difference in the choice curve slopes (narrow-wide) across sessions. In the cue interval, cells significantly coding value exhibited a strong correlation between neural and behavioral adaptation (M1: $r=0.57$, $p=0.009$, M2: $r=0.39$, $p=0.035$). Interestingly this correspondence was absent in the reward period. These results indicate a link between choice stochasticity and value coding in OFC neurons, suggesting a neural mechanism for adaptive decision making. Importantly these results also suggest that choice stochasticity results from value sensitivity in the value encoding architecture and is not simply a result of noise or changing preferences. Current work aims to uncover the extent of this adaptation on different subtypes of value coding cells as well as model the dynamics of the value adaptation process.

Disclosures: J. Zimmermann: None. **P.W. Glimcher:** None. **K. Louie:** None.

Nanosymposium

360. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC 31C

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 360.01

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 DA037229
Klingenstein-Simons Foundation

Title: Prospective goal state representation in monkey OFC and RSC in a 3D virtual reality foraging task

Authors: *M. WANG[1], B. Y. HAYDEN[2]
[1]Brain and Cognitive Sci., Univ. of Rochester, Rochester, NY; [2]Univ. of Minnesota, Minneapolis, MN

Abstract: During natural foraging, animals exhibit goal-directed behavior to learn the structure of the environment and obtain reward. Prospective goal state representation and navigation planning are essential to this process. Although neural activities for route planning have been shown in hippocampus, the neural underpinnings for the learning and use of goal state encoding, which potentially informs hippocampal route-planning activities, is still unknown. We hypothesized that OFC11 (orbitofrontal area 11) and RSC (restrosplenial area 29/30) are key to the learning and use of goal state encoding, based on previous functional and anatomical findings. To test this hypothesis, we developed a novel 3D virtual reality foraging task for monkeys and simultaneously recorded populations of neurons in OFC11 and RSC. In each session, a jackpot reward is hidden at a random location in the virtual maze (goal location) while other maze configurations stay the same across all sessions. On each trial, the subject is teleported to a random location (start location) during the inter-trial interval (ITI). The subject then navigates through the virtual maze with a joystick to forage for the hidden jackpot reward. Subjects took significantly longer search time (from start location to goal location) and less efficient travelled paths during pre-learning than during post-learning trials (even while controlling for Euclidean distance from start to goal locations.) In one example session, we simultaneously recorded 74 neurons in OFC11 and 51 neurons in RSC across 66 trials. We defined goal, start, and current states as population activity pattern containing averaged firing rates across 1500 ms at goal, start, and current locations, respectively, from each neuron. Representational similarity analysis reveals that on each trial, start state representation significantly resembles goal state activities of the previous trial and this pattern shows up earlier during a session in OFC11 than in RSC. During navigation in pre-learning trials, current state representation in neither OFC11 nor RSC reflects goal state encoding. In contrast, during post-learning trials, current state representation shows brief bursts of reactivation of goal state of the previous trial in OFC11 but shows sustained reactivation of goal state in RSC. Goal state encodings across trials are more stable in OFC11 but show a gradient of higher stabilization across trials in RSC. These results suggest that both OFC11 and RSC are involved in learning and prospective representation of goal state, which possibly guides goal-directed planning and navigation behavior in monkeys.

Disclosures: M. Wang: None. **B.Y. Hayden:** None.

Nanosymposium

360. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC 31C

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 360.02

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 1R01MH109177
NIH Grant 1F31MH110111
John Templeton Foundation

Title: FMRI evidence for the successor representation in human value computation

Authors: *E. RUSSEK[1], I. MOMENNEJAD[2], M. M. BOTVINICK[3,4], S. J. GERSHMAN[5], N. D. DAW[2]
[1]New York Univ., New York, NY; [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [3]DeepMind, London, United Kingdom; [4]Gatsby Computat. Neurosci. Unit, Univ. Col. London, Lonson, United Kingdom; [5]Dept. of Psychology and Ctr. for Brain Sci., Harvard, Cambridge, MA

Abstract: Computing multi-step reward expectations requires simulating the sequence of expected upcoming states and summing their rewards. We hypothesized that the brain simplifies this computation by storing long-run state predictions, aggregated over multiple steps; a strategy referred to as the successor representation (SR). The SR predicts a specific difficulty in updating expectancies for multi-step state transitions, and thus cumulative rewards, following changes in a task's state transitions. Recent behavioral evidence has found that humans make more errors in updating their preferences following changes in state transitions compared to changes in state rewards, consistent with the SR. We sought neural evidence that such behavioral errors are accompanied by inaccurate multi-step state expectancies predicted by the SR. We used an MVPA approach to measure multi-step state expectances during evaluation and compared them across trials to see if SR predicted expectancies tended to accompany behavioral errors following transition changes. In order to control for nuisance effects not related to the SR, we also examined this relationship for reward changes. Each trial of the FMRI task (N = 40) consisted of two phases. In a training phase, subjects were exposed to two three-state sequences, composed of visual stimuli, whose final states contained rewards of different magnitude. Stimuli were organized so that each final state was from a different decodable category that was also different from the category for starting states. In a revaluation phase, subjects learned that the final state to which each middle state transitioned (transition condition) or the reward in each final state (reward condition) had been switched. Before and after revaluation, subjects successively viewed the first image of each sequence and rated their preference for starting a sequence from that state.

During each rating, we measured relative classifier evidence for each final state category (not present on the screen) and treated this as a neural measure of multi-step state expectation. As predicted by the SR, subjects made more errors in updating preferences following revaluation on transition trials than reward trials ($p < .001$). Additionally, on transition trials, neural measures of the final state erroneously expected by the SR following revaluation were stronger when subjects made larger errors ($p = .023$). This effect itself was stronger on transition than on reward trials ($p = .005$) demonstrating that it was specific to the SR. This provides neural evidence for use of the SR in value computation. Ongoing work aims to localize SR state predictions using additional multivariate methods.

Disclosures: E. Russek: None. **I. Momennejad:** None. **M.M. Botvinick:** None. **S.J. Gershman:** None. **N.D. Daw:** None.

Nanosymposium

360. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC 31C

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 360.03

Topic: H.01. Animal Cognition and Behavior

Support: NIDA 1R01DA038891
Deepmind

Title: The role of episodic memory in model-based planning

Authors: *O. M. VIKBLADH[1], D. SHOHAMY[2], N. DAW[3]
[1]Neural Sci., New York Univ., New york, NY; [2]Columbia Univ., New york, NY; [3]Princeton Univ., Princeton, NJ

Abstract: Prominent theories view choices as arising from a combination of model-free (MF) habit learning and model-based (MB) planning. Recent evidence suggests a third possibility: in addition to the incrementally learned summaries that guide MB and MF choice, behavior may also be informed by episodic memories of individual experiences. In sequential decision tasks, this “third way” may provide an alternative explanation for apparently MB choices, because episodic memories (e.g. spatial trajectories) can collectively embody the same information as summarized in a world model (e.g. maps). This suggestion is supported by recent evidence that damage to the hippocampus (a key site for episodic memories) specifically impairs behavioral signatures of MB but not MF evaluation.
Here we sought to evaluate the contribution of episodic memory to MB and MF strategies by creating a behavioral task that combines multi-step choice dynamics with trial-unique images that also predict reward. By later presenting these images as memory retrieval cues, we probe

subjects' capacity to perform MB and MF evaluation, drawing on episodic memories for the rewards received in a cued episode. Comparing trials with and without valid cues, we also test how reliance on individual episodes trades off against choice effects that have previously been interpreted as depending on MB or MF incremental learning about recent rewards. To the extent these trade off, it supports the possibility that even these choices are driven by covert episodic retrieval, which might be redirected toward a specific episode when cued.
We examined choice data from two datasets: one involving 80 subjects recruited via Amazon's Mechanical Turk, and another with 30 subjects tested while scanned using fMRI. In both datasets, regressing cued and recent rewards on choices demonstrates that in addition to standard MB and MF strategies, subjects' choices are also sensitive to MB, but not MF, evaluations based on individual cued episodes. Furthermore, these cueing effects were accompanied by reduced reliance on recent rewards for MB, but not MF, evaluation (compared to uncued trials). These results suggest a specific role for episodic memories in MB, rather than the MF, reinforcement learning strategies. Furthermore, they indicate that choice behaviors that are widely assumed to reflect an incrementally learned, semantic map or model of the environment may actually reflect, in whole or part, covert retrieval of individual episodes. Ongoing analysis of the fMRI data seeks direct neural evidence for such retrieval

Disclosures: O.M. Vikbladh: None. **D. Shohamy:** None. **N. Daw:** None.

Nanosymposium

360. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC 31C

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 360.04

Topic: H.01. Animal Cognition and Behavior

Support: WT101261/Z/13/Z

Title: The hippocampal formation facilitates social decision-making by transforming reference frames

Authors: *R. KAPLAN[1], K. J. FRISTON[2]
[1]Univ. Col. London, London, United Kingdom; [2]UCL Wellcome Ctr. for Human Neuroimaging, London, United Kingdom

Abstract: Knowing how other people's preferences relate to our own is a central aspect of social cognition, yet how the brain performs this transformation is unclear. Here we ask whether the putative role of the hippocampal formation in transforming first person and extra-personal spatial cues during navigation also extends to social learning. In our functional MRI experiment, subjects learn a stranger's preference for an everyday activity relative to a personally familiar

individual and subsequently decide how the stranger's preference relates to two additional familiar people. We observe hippocampal and retrosplenial cortex responses when evaluating choices that require fine-grained social knowledge. Finding reference frame sensitive responses in the hippocampal formation, we isolate an entorhinal/subicular region responding to fine-grained choices involving self-comparisons, but more discretized choices otherwise. We also find that striatal responses precede accurate choices, which were partially driven by decisions involving which individual is highest or lowest. Our data highlight a potential division of labor within the hippocampal formation that helps relate newly gathered information about others to our prior knowledge of the world.

Disclosures: R. Kaplan: None. **K.J. Friston:** None.

Nanosymposium

360. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC 31C

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 360.05

Topic: H.01. Animal Cognition and Behavior

Support: NSERC
CIHR

Title: Single-neuron and population encoding of objects and space in hippocampus and dorsolateral prefrontal cortex during virtual navigation

Authors: *R. A. GULLI[1,2], L. DUONG[1], B. W. CORRIGAN[1], G. DOUCET[3], J. C. MARTINEZ-TRUJILLO[4]
[1]Dept. of Pharmacol. and Physiol., Western Univ., London, ON, Canada; [2]Integrated Program in Neurosci., [3]McGill Univ., Montreal, QC, Canada; [4]Physiol. and Pharmacol., Univ. of Western Ontario, London, ON, Canada

Abstract: It is accepted that the hippocampus (Hc) is critical for memory formation and consolidation in functionally associated neocortex. The Hc mediates many forms of memory, including associative memory and spatial memory. Dorsolateral prefrontal cortex (DLPFC) is also implicated in similar types of memory formation, and it is known to encode attention, space, and objects. The relative extent to which both areas encode space and non-spatial elements of the environment is not clear. Moreover, the differences in how and when these are represented across areas have important implications for our understanding of the brain-wide dynamics that govern learning and guide behaviour in space.
To compare and contrast spatial and mnemonic encoding across these regions we trained four macaque monkeys to perform an associative memory task that required spatial navigation using a

joystick in a three-dimensional virtual maze. We recorded activity from 183 single neurons in the Hc and 139 neurons in the DLPFC (area 8a) while measuring eye positions and spatial trajectories. All animals learned and correctly performed the task. Neurons in both the Hc and DLPFC encoded information about the animals' position, which could be used by a linear classifier to decode subjects' location in the virtual maze. However, the proportion of recorded neurons that encoded spatial position, and the amount of spatial information encoded by a single neuron differed considerably between the two areas. In the Hc, 55% of neurons contained significant spatial information content, with a median of 0.48 bits per spike. Under the same conditions, 96% of neurons in DLPFC showed significant spatial information content. However, the median prefrontal neuron contained <0.1 bits per spike. In both cases, spatial activity was confounded, and better explained by non-spatial components of the associative memory task. Our data support the view that the Hc and the DLPFC contain high dimensional representations of objects and space that guide goal directed behavior during virtual navigation tasks. Whereas DLPFC strongly encoded information available in the sensory environment during active viewing and decision making, the Hc strongly encoded mnemonic information related to previous experiences.

Disclosures: R.A. Gulli: None. **L. Duong:** None. **B.W. Corrigan:** None. **G. Doucet:** None. **J.C. Martinez-Trujillo:** None.

Nanosymposium

360. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC 31C

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 360.06

Topic: H.01. Animal Cognition and Behavior

Support: NIDA IRP

Title: Examining outcome and location representations in orbitofrontal cortex

Authors: *A. M. WIKENHEISER[1], M. P. GARDNER[1], L. E. MUELLER[1], G. SCHOENBAUM[2]
[1]Natl. Inst. on Drug Abuse, Baltimore, MD; [2]Natl. Inst. on Drug Abuse Intramural Res. Program, Baltimore, MD

Abstract: Convergent work has suggested striking functional similarities between the orbitofrontal cortex (OFC) and the hippocampus. However, it is unclear to what extent spatial coding, one of the hallmarks of hippocampal function, occurs in the OFC. To test whether OFC neurons share any coding strategies with the hippocampal/entorhinal system, we modified a task used to study spatial representations in rodents.

Male rats (n=4) searched for sucrose pellets scattered by dispensers mounted above a large, square arena with stable local and distal visual cues. Pellets were scattered with equal density throughout the arena. However, unlike studies of grid or place cells, four discriminable flavors of pellets were distributed in distinct "flavor zones" aligned with the walls of the arena. Thus, rats most commonly encountered each flavor along one of the walls of the arena, and with decreasing likelihood as they moved toward the center of the arena, where all flavors were equally likely. We hypothesized that creating such place-flavor contingencies would engage the OFC, which encodes features of appetitive outcomes such as flavor.
Electrodes were implanted bilaterally in OFC, and we recorded single-unit activity on three variants of the task. In the *stable* condition, pellets were delivered in the flavor gradients as described above. In the *neutral* condition, the standard flavor gradients were in effect for half of the session, and unflavored pellets were distributed uniformly across the area for the other half of the session. In the *novel* condition, rats foraged under the standard gradients in the first half of the session, and then foraged with one of the usual flavors swapped for a flavor that rats had never experienced on the task previously.
Rats spent more time in the flavor zone that was altered in the second half of *novel* task sessions. This indicates that rats formed flavor-place associations, and modified their search patterns in response to violations of flavor expectancy. We will use analyses developed to study spatial representations to examine whether OFC neurons show spatially-consistent firing patterns, whether OFC firing patterns are related to flavor-location pairings, and whether violations in flavor-location expectancies influence neural representations in the OFC.

Disclosures: A.M. Wikenheiser: None. **M.P. Gardner:** None. **L.E. Mueller:** None. **G. Schoenbaum:** None.

Nanosymposium

360. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC 31C

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 360.07

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant ZIA-DA000587

Title: Representation of environmental structure by the orbitofrontal cortex and hippocampus within an odor sequence task

Authors: *J. ZHOU[1], M. GARDNER[1], T. STALNAKER[1], S. RAMUS[2], A. WIKENHEISER[1], M. MONTESINOS-CARTAGENA[1], Y. NIV[3], G. SCHOENBAUM[1]
[1]Natl. Inst. on Drug Abuse, IRP, Baltimore, MD; [2]Bowdoin Col., Bowdoin, ME; [3]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: The orbitofrontal cortex (OFC) has long been implicated in signaling information about expected outcomes to facilitate adaptive or flexible behavior. Current proposals focus on signaling of scalar values versus the representation of a cognitive map of the task. We suggest a framework that views these two ideas as two ends of a continuum determined by experience, rather than fundamentally opposed. As learning proceeds, an initial cognitive map might be acquired, based largely on external information. With more experience, this hypothesized map can then be tailored to include relevant abstract hidden cognitive constructs, perhaps becoming equivalent to a scalar value in simple situations. If this is true, how does the map in the OFC differ from maps in other brain regions, like the hippocampus? We suggest that the cognitive map represented by the OFC is more distorted by task goals, while that represented by the hippocampus more faithfully reflects the structure of the environment . We tested these predictions by recording single unit activity from the OFC and hippocampus in rats navigating an odor sequence task analogous to a spatial maze. Rats sampled one of 16 odors on each trial and made a “go” or “no-go” response to obtain reward or to avoid a prolonged ITI. The 16 odors were organized into two pairs of 6-trial odor sequences (S1a vs. S1b and S2a vs. S2b). In sequences S1a and S1b, the shared odors made identical reward predictions, whereas in sequences S2a and S2b, some made opposing predictions, depending on the context (i.e., on previous odors in the sequence). The odor sequences provided a mappable state space, with 24 unique “positions” defined by sensory information, likelihood of reward, or both. Consistent with the hypothesis that the OFC represents a cognitive map tailored to the subjects’ task, we found a close correspondence between how subjects’ behavior suggested they were mapping the sequences, and the neural representations of the sequences in OFC ensembles. Specifically, although OFC ensembles showed stable representation of positions defined by unique odor cues even when that information was not necessary for prediction of reward, the representation of positions defined by the odor sequences was profoundly dependent on the subjects’ use of that information. Importantly, these representations were robust to the removal of neural activity related to value, consistent with the idea that value, while not dissociable, is embedded within a richer task structure represented by OFC. However, contrary to our prediction, our preliminary analyses have shown that the cognitive map represented by the hippocampus is more likely to be generalized according to value.

Disclosures: J. Zhou: None. **M. Gardner:** None. **T. Stalnaker:** None. **S. Ramus:** None. **A. Wikenheiser:** None. **M. Montesinos-Cartagena:** None. **Y. Niv:** None. **G. Schoenbaum:** None.

Nanosymposium

360. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC 31C

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 360.08

Topic: H.01. Animal Cognition and Behavior

Support: Brain Canada
NSERC

Title: Hippocampal and neocortical correlates of goal-directed activity in freely-behaving macaques

Authors: O. TALAKOUB[1], P. SAYEGH[1], *T. WOMELSDORF[2], P. FRIES[4], C. M. LEWIS[5], K. L. HOFFMAN[3]
[1]Psychology, York Univ., North York, ON, Canada; [2]Dept. of Psychology, [3]Vanderbilt Univ., Nashville, TN; [4]Ernst Struengmann Inst. (ESI), Frankfurt, Germany; [5]Ernst Strüngmann Inst. (ESI), Frankfurt Am Main, Germany

Abstract: Rats engaged in goal-directed behaviors show increased theta-band (4-10 Hz) oscillations in the hippocampus (Buzsaki et al., 2002). In macaque hippocampus, however, theta activity is generally decreased during goal-directed visual search, despite the preservation of another hippocampal oscillation: the sharp-wave ripple (Leonard et al., 2015, 2017). The latter experiments differed from rodent studies not only in species, but also the immobility of animals during the task. Here, we sought to measure the hippocampal correlates of goal-directed activity under freely-behaving conditions, and to determine whether or not the activity was specific to the hippocampus. We recorded wirelessly from the hippocampus in three macaques and in additional neocortical areas in two of those animals, as they displayed goal-directed and volitional behaviors, consummatory/repetitive behaviors, and during sleep. Unlike the activity described in the rodent, we found that theta-band activity was strongest as the animals entered the early stages of sleep, and seldom occurred during walking and goal-directed behaviors, for hippocampal sites as well as in medial prefrontal cortex and retrosplenial/posterior-cingulate cortex. In contrast, goal-directed, foraging and walking behaviors were associated with increases in beta and gamma band power (>20 Hz). We will discuss these findings in the context of freely-moving rat recordings and, more recently, recordings in freely-moving humans (Bohbot et al., 2017; Aghajan et al., 2017).

Disclosures: O. Talakoub: None. **P. Sayegh:** None. **T. Womelsdorf:** None. **P. Fries:** None. **C.M. Lewis:** None. **K.L. Hoffman:** None.

Nanosymposium

360. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC 31C

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 360.09

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust

Title: Role of hippocampal place cells and reactivation/replay in optimal path-finding

Authors: É. DUVELLE, E. HEW, N. ATEşYAKAR, W. PARRY-JONES, R. M. GRIEVES, A. RAWSON, G. MAKDAH, *K. J. JEFFERY
Inst. of Behavioural Neurosci., Univ. Col. London, London, United Kingdom

Abstract: Finding one's way in complex environments is a crucial skill. While the hippocampus is believed to support spatial memory, little is known about its role in path-planning. We postulate that rats can find shortest path in a complex environment and that hippocampal place cells could be involved in this. Combining behaviour and electrophysiology, the present work asks 1) whether rats can flexibly plan the shortest path to a goal and 2) whether place cell activity and reactivation could reflect this planning.
Our maze, similar to the "Star maze" of Rondi-Reig *et al.*, 2006, comprises a central hexagon-shaped ring with 6 radiating arms, one of which is food-rewarded. Between any pair of arms, two paths around the ring are available. Rats discover the day's designated goal arm during an initial exploratory trial and then subsequently find the optimal (shorter) path leading to the goal from any of the 5 other arms, ordered randomly. To assess if rats can dynamically re-plan paths and if the hippocampus reflects this, a transparent barrier is placed on the central hexagon on some sessions, forcing detours. Control foraging sessions preceded goal-directed training, to allow place field determination.
15/16 rats learned the task. From day 5 (± 4), these rats' performance was above chance level (goal reached in more than 20% of trials) and they mainly used optimal paths. The performance reached 75% correct in 15 (± 6) days. Rats were insensitive to local-cue disruption, suggesting the use of a place strategy. Performance dropped on the first barrier session (54%) but recovered quickly.
Place cells were then recorded from a subset of these rats. Preliminary observations suggest that the goal location is not overrepresented and that there is no remapping depending on task demands (navigation vs. foraging). Place cell reactivations were frequently observed, especially at the end of trials.
So far, we conclude that rats can plan optimal routes to their goal, while place cells' unit activity mainly encodes spatial information and does not overrepresent the goal, nor reflect task parameters (foraging vs. goal-directed). The barrier's effect on place cell activity will be discussed as well as the contents of place cell reactivations and whether they mostly represent optimal paths. Overall, this paradigm allows us to study flexible goal-directed navigation in rats and to offer insights into the role of the hippocampus in flexible path optimisation, beyond purely spatial memory.
Rondi-Reig et al (2006) J Neurosci. 12;26(15):4071-81

Disclosures: É. Duvelle: None. **E. Hew:** None. **N. Ateşyakar:** None. **W. Parry-Jones:** None. **R.M. Grieves:** None. **A. Rawson:** None. **G. Makdah:** None. **K.J. Jeffery:** None.

Nanosymposium

360. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC 31C

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 360.10

Topic: H.01. Animal Cognition and Behavior

Support: National Science Foundation of China 31671101

Title: Characterization of exploration patterns and hippocampal-prefrontal network oscillations during emergence of free exploration

Authors: B. SI[1], H. CHEN[2], T. SIT[2], C. T. GROSS[3], *Y. ZHAN[2]
[1]Shenyang Inst. of Automation, Chinese Acad. of Sci., Liaoning, China; [2]Brain Cognition and Brain Dis. Inst., Shenzhen Inst. of Advanced Technology, CAS, Guangdong, China; [3]EMBL, Monterotondo (RM), Italy

Abstract: During free exploration, emergence of patterned and sequential behavioral responses in the unexplored environment reflects the exploration traits and adaptation strategy. However, the neural substrates underlying exploratory behavior is poorly understood. We quantified the exploration pattern by computing occupancy entropy of the trajectories, and found that theta activity in dorsal hippocampus (dHPC) was highly correlated with the exploration pattern. Perturbation of exploration by diazepam only affected the exploration in the familiar areas but not in the unexplored areas. Specifically, diazepam increased the conditional Granger causality from the prefrontal cortex (PFC) to the ventral hippocampus (vHPC) while decreased the other hippocampal-prefrontal network directionality. Individual dHPC and PFC oscillations could faithfully classify various dimensions of the exploration among a combination of power, coherence and causality oscillatory predictors. Initiation of exploration was accompanied by a coordinated decrease and increase in theta activity in PFC and dHPC, respectively. Our results indicate that dHPC and PFC work synergistically in shaping exploratory behavior by modulation of exploratory traits during emergence and visits to unknown environments.

Disclosures: B. Si: None. **H. Chen:** None. **T. Sit:** None. **C.T. Gross:** None. **Y. Zhan:** None.

Nanosymposium

360. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC 31C

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 360.11

Topic: H.01. Animal Cognition and Behavior

Support: NSERC RGPIN-2014-04947
Google 2016 Faculty Research Award
CIFAR Learning in Machines and Brains Fellowship

Title: Episodic caching assists model free control in reinforcement learning tasks with changing reward contingencies

Authors: *A. CARSON, B. A. RICHARDS
Cell & Systems Biol., Univ. of Toronto Scarborough, Scarborough, ON, Canada

Abstract: Biological agents must learn to navigate a complex world in order to find rewards such as food -- a highly non-trivial task involving parsing and correctly weighting contributions of task-relevant stimuli to the decision making process, and generating a probabilistic distribution over actions likely to lead to rewarded states. Comptutational reinforcement learning (RL) models provide a normative framework in which to study the mechanisms the brain employs to approach optimal behaviour. Current state-of-the-art model systems successfully solve RL tasks in stationary environments - i.e. where the underlying statistics remain stable over time - but fail when non-stationarity is introduced. It has been suggested that hippocampal-dependent rapid encoding of single episodes can provide a “one-shot” learning system that can be used to guide behaviour even in the absence of up-to-date information about changes in environmental statistics. This representation of episodic memory comes at relatively low computational cost while maintaining flexibility in rapidly changing environments, key features in any representation the brain may utilize to bootstrap for successful on-line learning in non-stationary conditions. We develop a model-free controller (MFC) with an auxiliary episodic caching (EC) system. When environmental statistics change, the MFC utilizes cached episodes to formulate a policy for how to act. Preliminary results indicate that the MFC is unable to solve a reward task with changes in either reward contingencies or state transition statistics. We predict that the use of the EC module will improve success with non-stationary reward contingencies. Moreover, the relative success on such tasks will be conditional on the nature of the representations stored to memory. While conventionally the hippocampus has been thought to encode an explicit model of space, recent work has shown that its activity may be more likely described in terms of a predictive map or “successor representation,” wherein space is represented in terms of the likelihood of future occupancy of states. We aim to explore the

relative success of EC systems storing successor representations over conventional state representations of Euclidean space.

Disclosures: A. Carson: None. **B.A. Richards:** None.

Nanosymposium

360. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC 31C

Time: Monday, November 5, 2018, 1:00 PM - 4:00 PM

Presentation Number: 360.12

Topic: B.07. Synaptic Plasticity

Support: R01 NS052819
NARSAD Young Investigator grant to Joanna Giza

Title: BDNF Met66 prodomain eliminates spines and synapses in developing fear extinction circuitry thus changing circuit adaptation abilities and consequently the behavior

Authors: *J. GIZA[1], F. S. LEE[2], B. L. HEMPSTEAD[2], J. KIM[2]
[1]Weill Cornell Med. Col., New York, NY; [2]Weill Cornell Med., New York, NY

Abstract: Val66Met polymorphism is associated with higher risk of developing anxiety disorders and in particular post-traumatic stress disorder (PTSD). We find that BDNF Met prodomain gains new function and develops the ability to eliminate spines and synapses in mature hippocampal neurons in vitro . We pinpointed the spatiotemporal ability of the BDNF Met prodomain to perform this action in vivo to be limited to vCA1 neurons projecting to the prefrontal cortex (PFC) in the fear extinction circuitry during its development in adolescence. Using fiber photometry, we discovered that vCA1 neurons adapt during fear extinction trials and predict the stimulus that signals a threat subsequently attenuating their responses while the neurons with knocked-in BDNF Met allele fail to adapt. We propose molecular mechanism responsible for extinction failure in the BDNF Met carriers, which may be particularly important to cognitive therapies based on elevation of endogenous BDNF levels that may also raise the levels of detrimental BDNF Met prodomain. The Val66Met is present in more than 25% of human population.

Disclosures: J. Giza: None. **F.S. Lee:** None. **B.L. Hempstead:** None. **J. Kim:** None.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.01

Topic: H.02. Human Cognition and Behavior

Support: Basque Government PhD fellowship from Department of Education, University and Research from the Basque Government to J. A-T.
PSI2015-65696 from the Spanish Ministry of Economy and Competitiveness (MINECO) to P.M.P-A.
RYC-2014-15440 from the Spanish Ministry of Economy and Competitiveness (MINECO) to P.M.P-A.
BCBL acknowledges funding from Ayuda Centro de Excelencia Severo Ochoa SEV-2015-0490 MINECO.

Title: Neurodevelopmental correlates of the testing effect

Authors: *J. ARNAEZ-TELLERIA[1], M. CARREIRAS[1,2], P. M. PAZ-ALONSO[1]
[1]Basque Ctr. On Cognition, Brain and Language, Donostia-San Sebastian, Spain;
[2]IKERBASQUE, Basque Fndn. for Sci., Bilbao, Spain

Abstract: The use of testing during encoding is highly beneficial for long-term memory retention relative to classical repeated study strategies. This facilitation is known as the testing effect, and has been extensively demonstrated in behavioral research. However, there is limited neuroimaging data regarding the neural mechanisms underlying this effect. Also, to date few studies have looked at the developmental trajectories of the ability to benefit from testing. Here we present data from behavioral and magnetic resonance imaging (MRI) studies with 8- to 12-years-old children and young adults, aimed at investigating 1) age-related changes in the ability to benefit from testing effects; 2) functional and structural differences in the involvement of the hippocampus while retrieving information encoded under repeated study or repeated retrieval conditions; and 3) differences in the pattern of functional connectivity between regions within the hippocampus and other cortical regions known to be engaged during successful memory encoding and retrieval (i.e. parietal cortex and prefrontal cortex, PFC).
Participants encoded 100 Swahili-Spanish word pairs (e.g. rafiki-amigo) under repeated retrieval or repeated study conditions and underwent MRI scanning 2 days later. At the scanner, participants performed a cued-recall task on studied and non-studied items. Behavioral results confirmed long-term memory benefits from repeated retrieval compared to repeated study, and revealed that the ability to benefit from testing increased with age from early to late middle childhood.

MRI data showed stronger hippocampal engagement for successfully remembered items studied under repeated study vs. repeated retrieval. For the repeated study group, strong association between the volume of the dentate gyrus, CA3 and CA4 and the number of correctly remembered items were observed. In contrast, no associations emerged in the repeated retrieval group. Differential functional coupling was observed between repeated retrieval and repeated study conditions. Whereas repeated retrieval vs. repeated study showed tighter coupling among distributed hippocampal-PFC regions, repeated study vs. repeated retrieval only revealed stronger connectivity among hippocampal regions.
Altogether, our results showed that testing effects are subjected to changes during development, with increases in the ability to benefit from testing across middle childhood years. Also, retrieval practice appears to facilitate the creation of additional routes to trace back information from long-term memory, making this information less hippocampal dependent compared to repeated study.

Disclosures: J. Arnaez-Telleria: None. **M. Carreiras:** None. **P.M. Paz-Alonso:** None.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.02

Topic: H.02. Human Cognition and Behavior

Support: EU-H2020-FET 1564

Title: Fundamental scaling law of memory recall

Authors: *M. V. TSODYKS, M. KATKOV
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Recall is a challenging task that often fails even when information to be recalled is still available in memory. When probed in the lab with randomly assembled lists of words, the number of recalled words tend to increase with the list length, but the fraction of words that are recalled is decreasing, such that most of the words cannot be recalled even for moderate list lengths. Many of models were put forward to explain this behaviour, but none of them can predict the recall performance without fitting a large number of parameters. We recently proposed a phenomenological description of recall process based on two simple assumptions on memory neural representations and transitions between them. We found that if the memory representations are random and sparse, the average recall performance approaches the fundamental power-law scaling dependence on the list length and cannot exceed it if no structure is present in the list. We compiled the experimental results on free recall obtained in several labs

over the course of many decades of studies, and found that recall performance indeed never exceeds the predicted one, approaching it for presentation rates that are slow enough. We develop general considerations that could account for the observed scaling law.

Disclosures: M.V. Tsodyks: None. **M. Katkov:** None.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.03

Topic: H.02. Human Cognition and Behavior

Support: NSF DGE 16-44869
NIH UL1 TR000040

Title: Dopaminergic enhancement of associative memory in healthy humans

Authors: *E. K. BRAUN[1], K. D. DUNCAN[3], R. GIRGIS[2,4], S. WOOD[3], M. SHARP[5], C. VAN GEEN[1], A. ABI-DARGHAM[6], D. SHOHAMY[1]
[1]Psychology, [2]Psychiatry, Columbia Univ., New York, NY; [3]Psychology, Univ. of Toronto, Toronto, ON, Canada; [4]New York State Psychiatric Inst., New York, NY; [5]Neurol., McGill Univ., Montreal, QC, Canada; [6]Psychiatry, Stony Brook Univ., New York, NY

Abstract: For memory to be adaptive the brain must prioritize memory for events that are motivationally relevant; however, questions persist about the brain mechanisms that support this prioritization. Since the neurotransmitter dopamine signals motivationally relevant information, it may also facilitate the selection of adaptively important memories to be consolidated for future use. Indeed, research from animal and cellular models has shown that dopamine in the hippocampus improves memory, and these findings make the specific predictions that: 1. The enhancing effects of dopamine on memory will emerge only after consolidation, and 2. Dopamine will potentiate memories when present at encoding but not at retrieval. Yet, questions remain about whether dopamine modulates memory in humans and when these effects emerge. We sought to answer these questions using a pharmacological manipulation in healthy humans by testing the effect of a dopamine agonist (d-amphetamine) on associative memory, which is known to depend on the hippocampus. Using a double-blind design, we administered either drug (n=40) or placebo (n=20) to participants, before they encoded novel pairs of objects. Memory was tested either immediately (on drug or placebo) or a week later (no drug). At test, participants indicated whether object pairs were intact (a pair of objects studied together), rearranged (a pair of objects studied in different combinations), or new (at least one object was new). Associative memory performance was measured as participants' ability to correctly discriminate between the

intact and rearranged pairs. We also interleaved a brief working memory task with the long-term memory task, so that we could identify how d-amphetamine influenced long-term memory beyond its impact on working memory and attention. We found that increased levels of dopamine agonist (mg d-amphetamine/kg body weight) improved associative memory performance when memory was tested either immediately or after a delay. Next, we tested whether these drug-induced effects on memory were better explained by the drug itself or by the separate effect of drug on working memory. We found that only delayed memory performance was uniquely predicted by drug level, whereas immediate performance was more strongly linked to working memory performance during encoding. These findings suggest that dopamine promotes long-term memory through multiple mechanisms: it indirectly supports memories that last for minutes by enhancing working memory and attention, and as predicted by cellular and physiological data, it also directly supports the formation of memories that last for days.

Disclosures: E.K. Braun: None. **K.D. Duncan:** None. **R. Girgis:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Allergan, Genentech, BioAdvantex. **S. Wood:** None. **M. Sharp:** None. **C. Van Geen:** None. **A. Abi-Dargham:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Forest, Pfizer, Pierre-Fabre. F. Consulting Fees (e.g., advisory boards); Otsuka, Roche, Forum, Lundbeck. **D. Shohamy:** None.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.04

Topic: H.02. Human Cognition and Behavior

Support: DARPA Restoring Active Memory (RAM) program (Cooperative Agreement N66001-14-2-4032)

Title: Distinct cortical systems reinstate content and context information during memory search

Authors: *J. E. KRAGEL[1], G. A. WORRELL[2], M. R. SPERLING[3], R. E. GROSS[5], B. C. LEGA[6], B. C. JOBST[7], S. A. SHETH[8], K. A. ZAGHLOUL[9], J. M. STEIN[10], R. GORNIAK[4], M. J. KAHANA[1]
[1]Psychology, Univ. of Pennsylvania, Philadelphia, PA; [2]Mayo Clin., Rochester, MN; [3]Neurol., [4]Radiology, Thomas Jefferson Univ., Philadelphia, PA; [5]Neurosurg., Emory Univ. Sch. of Med., Atlanta, GA; [6]Neurosurg., UT Southwestern Med. Ctr., Dallas, TX; [7]Neurol., Dartmouth-Hitchcock Med. Ctr., Lebanon, NH; [8]Neurosurg., Baylor Col. of Med., Houston, TX; [9]Surgical Neurol. Br., Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD; [10]Radiology, Hosp. of the Univ. of Pennsylvania, Philadelphia, PA

Abstract: Episodic recall depends upon the reinstatement of cortical activity present during the formation of a memory, encoding the content of an event and the context in which it occurred. Reinstatement of neural activity across prefrontal and temporal structures has been shown to predict either contextual attributes or semantic contents of retrieval. However, because prior studies typically focused on one form of mnemonic information in isolation, little is known about the relation between these two forms of reinstatement. Here, we used intracranial recordings from 67 neurosurgical patients as they performed categorized free recall to examine content and context reinstatement. First, we used resting state functional MRI to localize implanted electrodes within anterior temporal (AT) or posterior medial (PM) networks of interest, given their hypothesized roles in the representation of content and context information. We found respective increases in functional connectivity within the AT and PM networks in the theta (3-10 Hz) and beta (17 Hz) bands, validating our assignment of electrodes to each network. Next, we constructed encoding models tuned to predict brain activity from either the semantic content or temporal context of presented stimuli. Using these models, we found that context reinstatement was specific to the PM network, whereas content reinstatement was significantly stronger within the AT network. Our work demonstrates distinct neural pathways involved in the recall of episodic memories, providing evidence for the role of large-scale cortical networks in allowing individuals to remember what happened when.

Disclosures: J.E. Kragel: None. **G.A. Worrell:** None. **M.R. Sperling:** None. **R.E. Gross:** None. **B.C. Lega:** None. **B.C. Jobst:** None. **S.A. Sheth:** None. **K.A. Zaghloul:** None. **J.M. Stein:** None. **R. Gorniak:** None. **M.J. Kahana:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); M.J.K. has started a company, Nia Therapeutics, LLC (``Nia''), intended to develop and commercialize brain stimulation therapies for memory restoration. He holds more than 5% equity interest in Nia.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.05

Topic: H.02. Human Cognition and Behavior

Support: DARPA Cooperative Agreement N66001-14-2-4032
NIH T32NS091006
NIH MH55687

Title: Connectivity-guided choice of intracranial stimulation targets for optimal cognitive enhancement

Authors: *E. A. SOLOMON[1], R. E. GROSS[5], B. C. LEGA[6], M. R. SPERLING[7], G. A. WORRELL[9], S. A. SHETH[10], K. A. ZAGHLOUL[11], B. C. JOBST[12], J. M. STEIN[2], S. DAS[3], R. GORNIAK[8], C. S. INMAN[13], S. E. SEGER[14], J. E. KRAGEL[1], D. S. RIZZUTO[4], M. J. KAHANA[1]
[1]Psychology, [2]Radiology, [3]Dept. of Neurol., [4]Univ. of Pennsylvania, Philadelphia, PA; [5]Dept Neurosurg., Emory Univ. Sch. Med., Atlanta, GA; [6]Neurosurg., UT Southwestern Med. Ctr., Dallas, TX; [7]Neurol., [8]Radiology, Thomas Jefferson Univ. Hosp., Philadelphia, PA; [9]Mayo Clin., Rochester, MN; [10]Neurosurg., Baylor Col. of Med., Houston, TX; [11]Surgical Neurol. Br., Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD; [12]Neurol., Dartmouth-Hitchcock Med. Ctr., Lebanon, NH; [13]Neurosurg., Emory Univ., Atlanta, GA; [14]Neurosurg., Univ. of Texas Southwestern, Dallas, TX

Abstract: Focal electrical stimulation of the brain incites a cascade of neural activity that propagates from the stimulated region to nearby and remote areas, offering the potential to control the behavior of large-scale brain networks. Clinicians and scientists increasingly view these artificial brain perturbations as a means to a therapeutic end, but little is known about how stimulation evokes change in neural activity, and how such changes manifest in behavior. To investigate how intracranial stimulation can be used to modulate episodic memory, we asked 74 neurosurgical patients to complete verbal free-recall tasks and concurrently stimulated regions of the frontal, temporal, and medial temporal lobes. First, to determine how stimulation interacted with the intrinsic connectivity of a targeted region, we assessed whether downstream changes in spectral power were correlated with the strength of baseline functional connectivity. We observed that long-range functional connections were predictive of increases in theta (5-8 Hz) power at downstream sites ($t(70) = 4.0$, $P = 0.0002$), while recording sites near stimulation saw modest increases in high-frequency activity (HFA, 75-100 Hz). Furthermore, proximity to white matter tracts was positively correlated with network-related change in low-frequency power ($r(69) = 0.33$, $P = 0.005$). Next, we asked whether stimulation-related changes in neurophysiology were linked to stimulation-related changes in behavior, as measured through performance on the free-recall task. In a closed-loop stimulation paradigm, we measured recall performance on word lists when stimulation was applied relative to control lists with no stimulation (Ezzyat, et al. 2018). While some subjects saw marked enhancement in memory with stimulation, the effects were highly variable. We hypothesized that placement of the stimulation electrode - and its corresponding ability to modulate network-wide spectral power - explained some of that variance. Change in memory performance was significantly inversely correlated ($r = -0.33$, $P = 0.014$) with the theta modulation index, or the degree to which connectivity predicts changes in theta power. These results suggest that targeting “live zones” of the brain - or areas where functional connections yield maximal change in network-wide spectral activity - may provide more meaningful control of a desired behavioral outcome.

Disclosures: E.A. Solomon: None. **R.E. Gross:** None. **B.C. Lega:** None. **M.R. Sperling:** None. **G.A. Worrell:** None. **S.A. Sheth:** None. **K.A. Zaghloul:** None. **B.C. Jobst:** None. **J.M. Stein:** None. **S. Das:** None. **R. Gorniak:** None. **C.S. Inman:** None. **S.E. Seger:** None. **J.E. Kragel:** None. **D.S. Rizzuto:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nia Therapeutics.

M.J. Kahana: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nia Therapeutics.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.06

Topic: H.02. Human Cognition and Behavior

Support: DARPA Restoring Active Memory (RAM) N66001-14-2-4032
NSF EPSCoR Award Number 1632738

Title: Fast timescale network dynamics underlying episodic encoding and retrieval

Authors: *L. L. OWEN[1], M. SPERLING[2], B. C. LEGA[4], G. A. WORRELL[5], R. E. GROSS[6], B. C. JOBST[7], K. DAVIS[8], K. A. ZAGHLOUL[11], S. SHETH[12], J. STEIN[9], S. DAS[10], R. GORNIAK[3], J. R. MANNING[1]
[1]Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [2]Dept. of Neurol., [3]Dept. of Radiology, Thomas Jefferson Univ. Hosp., Philadelphia, PA; [4]Neurosurg., UT Southwestern Med. Ctr., Dallas, TX; [5]Mayo Clin., Rochester, MN; [6]Dept Neurosurg., Emory Univ. Sch. Med., Atlanta, GA; [7]Neurol., Dartmouth-Hitchcock Med. Ctr., Lebanon, NH; [9]Dept. of Radiology, [10]Dept. of Neurol., [8]Hosp. of the Univ. of Pennsylvania, Philadelphia, PA; [11]Surgical Neurol. Br., Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD; [12]Dept. of Neurolog. Surgery, Columbia Univ., New York City, NY

Abstract: There is increasing evidence from human and animal studies that memory encoding and retrieval is supported by fast timescale network dynamics involving the coordinated activities of widespread brain structures. However, measuring these network dynamics directly in the human brain poses a substantial methodological challenge. In prior work, we developed a method for inferring high spatiotemporal resolution activity patterns throughout the brain, using recordings taken at only a small number of ECoG electrodes (Owen and Manning, 2017). The method, which we call SuperEEG, builds up a covariance model that describes how the activity patterns throughout the brain are related, as a function of their spatial location. We train the model by stitching together recordings taken from a large number of patients, each with electrodes implanted in a different set of locations. Once the covariance model has been fit, we can apply the model to ECoG recordings from a small number of locations to estimate activity patterns throughout the rest of the brain.
In our prior work, we evaluated our approach using a cross-validation method applied to a single ECoG dataset comprising hundreds of hours of recordings taken from 88 neurosurgical patients. We showed that the activity patterns we estimated at held-out electrode locations were reliably

correlated with the true (observed) activity recorded from those electrodes. Here we apply this same approach to two new large ECoG datasets, using an open source Python toolbox that we recently released. We first replicate our prior results, showing that we can reliably estimate activity patterns from held-out electrodes. We also examined the extent to which recordings taken within versus across patients, or within versus across experimental task affected the quality of the reconstructions. We found that the approach performs best when we incorporated data from other patients and tasks-- in other words, the properties our approach leverages to predict activity patterns appear to be person-general and task-general.
Finally, we leverage SuperEEG to explore fast-timescale full-brain network dynamics during memory encoding and retrieval, in individual patients. Whereas prior ECoG studies of the network dynamics underlying memory encoding and retrieval have required studying these patterns across patients, our approach allows us to explore individual differences in full-brain network dynamics and relate those dynamics to memory behaviors.

Disclosures: L.L. Owen: None. **M. Sperling:** None. **B.C. Lega:** None. **G.A. Worrell:** None. **R.E. Gross:** None. **B.C. Jobst:** None. **K. Davis:** None. **K.A. Zaghloul:** None. **S. Sheth:** None. **J. Stein:** None. **S. Das:** None. **R. Gorniak:** None. **J.R. Manning:** None.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.07

Topic: H.02. Human Cognition and Behavior

Support: DARPA Restoring Active Memory (RAM) program (Cooperative Agreement N66001-14-2-4032)
NINDS Intramural Research program

Title: Separable oscillatory state in human temporal lobe underlies cued but not free recall

Authors: *M. M. EL-KALLINY[1], T. SHEEHAN[2], V. SREEKUMAR[1], J. H. WITTIG, JR[1], M. SPERLING[3], B. C. LEGA[4], G. A. WORRELL[5], R. E. GROSS[6], B. C. JOBST[7], K. DAVIS[8], Y. EZZYAT[9], J. STEIN[10], S. DAS[8], R. GORNIAK[11], S. INATI[12], M. J. KAHANA[9], K. A. ZAGHLOUL[1]
[1]Surgical Neurol. Br., NINDS, Natl. Inst. of Hlth., Bethesda, MD; [2]UCSD, San Diego, CA; [3]Dept. of Neurology, Thomas Jefferson Univ. Hosp., Philadelphia, PA; [4]Neurosurg., UT Southwestern Med. Ctr., Dallas, TX; [5]Mayo Clin., Rochester, MN; [6]Dept Neurosurg., Emory Univ. Sch. Med., Atlanta, GA; [7]Neurol., Dartmouth-Hitchcock Med. Ctr., Lebanon, NH; [8]Dept. of Neurol., Hosp. of the Univ. of Pennsylvania, Philadelphia, PA; [9]Psychology, Univ. of Pennsylvania, Philadelphia, PA; [10]Dept. of Radiology, Hosp. of the Univ. of Pennsylvania,

Philadelphia, PA; [11]Dept. of Radiology, Thomas Jefferson Univ. Hosp., Philadelphia, PA; [12]Office of the Clin. Director, NINDS, Bethesda, MD

Abstract: Episodes that are experienced nearby in time are thought to be bound together in memory via their shared temporal context. However, this binding may be disadvantageous in tasks that demand a clear separation between these episodes in memory. To investigate the neural mechanisms underlying the separation of episodic memories, we evaluated behavioral and electrophysiological responses during two verbal memory tasks which call for differing degrees of separation between memories. In paired associates learning, separation of word pairs is critical to the success of recall, which is cued. In contrast, during free recall, the linking together of sequential words may be a beneficial strategy, since no external memory cue is provided during retrieval. Using intracranial EEG recordings from 78 participants with electrodes placed for seizure monitoring, we demonstrate that the rate of change in patterns of low-frequency (3-12 Hz) power across the temporal lobe directly predicts increased performance during cued but not free recall. In a subset of participants, we applied direct cortical stimulation and found that stimulation sometimes enhanced memory performance and sometimes impaired memory performance. Interestingly, we found that observed changes in memory performance were predicted by modulation of the rate of change in low frequency patterns of power. These findings provide evidence that the rate of change in patterns of low-frequency power reflects processes that underlie the cognitive separation of memories, and may be an important factor in the therapeutic treatment of memory dysfunction.

Disclosures: M.M. El-Kalliny: None. **T. Sheehan:** None. **V. Sreekumar:** None. **J.H. Wittig:** None. **M. Sperling:** None. **B.C. Lega:** None. **G.A. Worrell:** None. **R.E. Gross:** None. **B.C. Jobst:** None. **K. Davis:** None. **Y. Ezzyat:** None. **J. Stein:** None. **S. Das:** None. **R. Gorniak:** None. **S. Inati:** None. **M.J. Kahana:** None. **K.A. Zaghloul:** None.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.08

Topic: H.02. Human Cognition and Behavior

Support: DFG grant SFB 654 (Plasticity and Sleep)

Title: Sleep consolidates emotional meaning through diverging effects on automatic and cognitive emotional responses in children

Authors: *K. ZINKE[1], E. M. BOLINGER[1], J. BORN[1,2]
[1]Inst. of Med. Psychology and Behavioural Neurobio., Univ. of Tübingen, Tübingen, Germany; [2]Ctr. for Integrative Neurosci., Tübingen, Germany

Abstract: Emotional experiences elicit both physiological and behavioral responses that are subject to differing amounts of cognitive control. Sleep after emotional experiences enhances memory for these experiences, but sleep's influence on the emotional response associated with these memories is elusive. Children are an excellent model to investigate this question because they tend to have more emotional incidents during sleep (e.g. nightmares) and show heightened levels of emotional memory-related sleep EEG features (e.g. REM theta power, spindles). Here, in a sample of 16 children (8-11 yrs, 8 females), we compared the influence of nocturnal sleep (vs. daytime wakefulness) on the emotional response towards pictures in a within-subject cross-over design. During the encoding sessions, children encoded emotionally negative and neutral pictures and then either slept or stayed awake during a 10-h retention interval. During recognition, participants saw the original together with new pictures and were asked to report whether they had seen each picture during encoding. In all encoding and recognition sessions, subjective ratings (valence, arousal), as well as response measures of the central nervous (late positive potential, LPP, of the EEG) and autonomic nervous system(heart rate deceleration, HRD) were collected for each picture. Sleep enhanced picture memory, with the degree to which emotional pictures were preferentially recognized (over neutral pictures) being correlated with REM sleep theta power during post-encoding sleep. Compared to the dynamics across wakefulness emotional response (defined as the difference in response to negative minus neutral pictures) in subjective valence ratings and the LPP decreased across sleep. In contrast, compared to dynamics across wakefulness, the emotional HRD response increased across sleep, with this effect again being correlated to REM sleep theta activity. Sleep, compared to wakefulness, therefore appears to consolidate the immediate emotional meaning by enhancing more automatic emotional responses (HRD) while promoting top-down control of emotional responses (leading to down regulation of subjective ratings and LPP), perhaps through strengthening respective neocortical representations.

Disclosures: K. Zinke: None. **E.M. Bolinger:** None. **J. Born:** None.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.09

Topic: H.02. Human Cognition and Behavior

Support: IBS R015-D1

Title: The dynamic changes in narrative understanding represented in the regional- and network-level state of the human brain

Authors: *H. SONG[1,2], B.-Y. PARK[1,3], J. HAN[1,2], H. PARK[1,4], W. SHIM[1,2]
[1]Ctr. for Neurosci. Imaging Research, IBS, Suwon, Korea, Republic of; [2]Dept. of Biomed. Engineering, Sungkyunkwan Univ. (SKKU), Suwon, Korea, Republic of; [3]Dept. of Electronic, Electrical and Computer Engineering, Sungkyunkwan Univ. (SKKU), Suwon, Korea, Republic of; [4]Sch. of Electronic and Electrical Engineering, Sungkyunkwan Univ. (SKKU), Suwon, Korea, Republic of

Abstract: When comprehending narratives of temporally extending stimuli, the human brain constantly integrates incoming information to make a cohesive representation of event structures. Here, we investigate how the dynamic changes in cognitive states relating to the process of narrative understanding are represented in the whole brain. In a behavioral experiment, subjects reported moments when they thought to have understood the narratives while watching a scrambled version of the silent films. The moments of each film were separated into when the reported frequency of narrative understanding was low and when the frequency of narrative understanding was high. Using fMRI, we examined moment-to-moment regional- and network-level changes while a separate group of subjects were viewing the same set of scrambled films. First, we found that the BOLD activity in the default mode network (DMN) was increased during times of high narrative understanding, whereas activity in the regions within high-level visual network and dorsal attention network was increased during times of low narrative understanding. Next, we asked if such changes in the cognitive states modulate the dynamic reconfiguration of the brain networks (Shine et al. 2016). Whole brain time-resolved functional connectivities (FCs) were measured, and the graph indices were compared between the time points of high and low understanding. The modular structure of the brain was tightly integrated when the understanding was high, indicated by the decreased modularity and clustering coefficient scores. The brain temporarily entered into integrated states by strengthening the across-modular FCs, which were not only specific to the regions of the DMN or visual network, but spanning other functional networks as well. Similar patterns of changes were not shown when subjects repeatedly watched the same film, indicating that these state changes were not driven by the physical characteristics of the visual stimuli but resulted from subjects' narrative comprehension. Furthermore, decoding analysis was performed to examine whether the dynamics of cortical activity can predict the degree of narrative understanding of each moment. The selective FCs of the whole brain were able to predict the degree of understanding at a specific time point of a novel subject, and even for a novel film. While consistent with the previous studies on the role of DMN in the process of comprehending the narratives (Simony et al. 2016), our findings suggest that the time-resolved FCs and large-scale network states contain information on the dynamic changes in the cognitive states when engaging in narrative comprehension.

Disclosures: H. Song: None. **B. Park:** None. **J. Han:** None. **H. Park:** None. **W. Shim:** None.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.10

Topic: H.02. Human Cognition and Behavior

Support: DARPA Restoring Active Memory (RAM) program (Cooperative Agreement N66001-14-2-4032)

Title: Low-frequency memory-related oscillations in the human neocortex

Authors: J. MILLER[1], H. ZHANG[1], M. SPERLING[2], B. C. LEGA[3], G. A. WORRELL[4], R. E. GROSS[5], B. C. JOBST[6], K. DAVIS[7], K. A. ZAGHLOUL[8], S. A. SHETH[9], J. STEIN[7], S. DAS[10], R. GORNIAK[2], *J. JACOBS[1]
[1]Dept. of Biomed. Engin., Columbia Univ., New York, NY; [2]Thomas Jefferson Univ., Philadelphia, PA; [3]Neurosurg., UT Southwestern Med. Ctr., Dallas, TX; [4]Mayo Clin., Rochester, MN; [5]Dept Neurosurg., Emory Univ. Sch. Med., Atlanta, GA; [6]Neurol., Dartmouth-Hitchcock Med. Ctr., Lebanon, NH; [7]Hosp. of the Univ. of Pennsylvania, Philadelphia, PA; [8]Surgical Neurol. Br., Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD; [9]Neurosurg., Baylor Col. of Med., Houston, TX; [10]Dept. of Neurol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: A key issue for understanding the neural basis of cognition is identifying the brain signals that distinguish successful memory encoding. At the group level, episodic memory encoding has often been characterized by increases in the power of high-frequency neuronal activity in concert with decreases in low frequency power. This finding might be considered surprising based on the large body of animal studies that emphasized the role of theta oscillations (4-8 Hz) in memory encoding and synaptic plasticity. Using a large dataset of direct brain recordings from neurosurgical patients, we show that many individual sites in patients do in fact show low-frequency (1-10 Hz) oscillations that increase in power for successful memory encoding, consistent with animal model systems. This phenomenon was present in spatial memory, where it was prevalent in both the left hippocampus and across the entire neocortex. Further, in verbal episodic memory, the subset of sites that showed memory-related power increases were the ones that showed slower intrinsic oscillation frequencies. These findings suggest that the human brain contains at least two types of memory-related signals, in part differing from simpler animals: a pattern of low-frequency oscillations that positively correlate with memory, consistent rodent models, as well as a broader network of cortical sites that reliably show the opposite pattern.

Disclosures: J. Miller: None. **H. Zhang:** None. **M. Sperling:** None. **B.C. Lega:** None. **G.A. Worrell:** None. **R.E. Gross:** None. **B.C. Jobst:** None. **K. Davis:** None. **K.A. Zaghloul:** None. **S.A. Sheth:** None. **J. Stein:** None. **S. das:** None. **R. Gorniak:** None. **J. Jacobs:** None.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.11

Topic: H.02. Human Cognition and Behavior

Support: NIH R21 NS095094
UT Brain Seed Grant #366582

Title: Hippocampal functional distinctions in memory processing

Authors: *J.-J. LIN, S. E. SEGER, B. C. LEGA
Neurosurg., Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Functional differences along the longitudinal hippocampal axis have been well described and supported in animal literature. Along with differences in gene expression, anatomical connectivity, and emotional/cognitive processing, meta-analysis of human noninvasive data has proposed that the relevant functional difference in terms of memory along the hippocampal axis is between encoding and retrieval. Specifically, greater activation in the anterior hippocampus during encoding, and greater activation in the posterior hippocampus during retrieval. Greater anatomical connectivity with parietal regions implicated in attention towards internal (rather than external) representations was postulated to support this distinction, mapping onto proposed anterior versus posterior attentional systems in the brain. To further investigate this question of anterior versus posterior specialization during mnemonic processing we present a follow-up to a previously published analysis utilizing an expanded intracranial EEG dataset of 32 subjects performing a free recall task who has simultaneous sampling from both the anterior and posterior hippocampus from separate electrodes, which allowed for matched-pair statistical comparison between the encoding and retrieval epoch. Our findings help corroborate existing evidence showing greater posterior hippocampal activation during item retrieval. We also present them in the context of groundbreaking animal study that demonstrated a shift in gamma oscillation during memory processing by examining gamma differences between the encoding and retrieval conditions.

Disclosures: J. Lin: None. **S.E. Seger:** None. **B.C. Lega:** None.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.12

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant NS095094-02

Title: Comparison of fMRI and intracranial EEG metrics of successful memory encoding

Authors: *P. F. HILL[1], S. E. SEGER[2], D. R. KING[1], B. C. LEGA[2], M. D. RUGG[1]
[1]Ctr. for Vital Longevity, Univ. of Texas at Dallas, Dallas, TX; [2]UT Southwestern Med. Ctr., Dallas, TX

Abstract: Functional magnetic resonance imaging (fMRI) and intracranial electroencephalography (iEEG) are widely used methods for studying the neurophysiological basis of episodic memory. The aim of the current study was to clarify the relationship between hemodynamic and electrophysiological correlates of memory formation. Participants (N=19) underwent fMRI scanning as they completed a verbal free-recall task. Subsequent memory effects (SMEs) were defined as the difference in encoding-related BOLD activity for subsequently recalled vs. forgotten study items. For each participant, we extracted the mean SME parameter estimates across all voxels within each of 264 spherical ROIs (7.5 mm radius). We compared fMRI SME values to iEEG SMEs from the same ROIs in a publicly available sample of 153 pre-surgical epilepsy patients as they completed a similar free-recall task. For the iEEG sample, single electrode SMEs were defined at the group level as the average difference (*t*-score) in power for subsequently recalled vs. forgotten study items in the delta (2-4 Hz), theta (4-8 Hz), alpha (8-16 Hz), beta (16-30 Hz), gamma (30-70 Hz), and high gamma (70-150 Hz) frequency bands. Data from 81 ROIs contained electrodes from fewer than 15 patients and were dropped from subsequent analyses, resulting in a total of 183 ROIs. For each fMRI participant, we determined the correlation between the subject-specific fMRI SMEs and the corresponding group-level iEEG SMEs. Fisher transformed correlation coefficients for each frequency band were submitted to a random effects one sample *t*-test (two-tailed) against a zero null. Mean transformed fMRI-iEEG SME correlations were significantly different from zero in the alpha and high gamma frequency bands (both $p < .001$). The across-ROI correlations between the fMRI SMEs averaged over subjects and the iEEG SMEs were $r = -.19$ and $r = .37$ for the alpha and high gamma bands, respectively. Behavioral memory performance was greater for initial list items. Despite this primacy effect, across-subject SME correlations in the alpha and high-gamma bands were more robust for words occurring in the body of the list. Across-subjects correlations in the delta, theta, beta, and gamma frequency bands did not significantly differ from zero after

correcting for multiple comparisons. The findings are consistent with prior evidence suggesting that fMRI BOLD activity is positively correlated with neural activity in the high gamma range, but negatively correlated with activity in the alpha band.

Disclosures: P.F. Hill: None. **S.E. Seger:** None. **D.R. King:** None. **B.C. Lega:** None. **M.D. Rugg:** None.

Nanosymposium

361. Human Cognition and Behavior: Human Long-Term Memory: Encoding and Retrieval

Location: SDCC 32

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 361.13

Topic: H.02. Human Cognition and Behavior

Title: Deep brain stimulation of the human posterior cingulate cortex during episodic memory processing

Authors: *V. S. NATU[1], J.-J. LIN[1], A. BURKS[1], A. ARORA[1], M. D. RUGG[2], B. LEGA[1]
[1]Dept. of Neurolog. Surgery, Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [2]Ctr. for Vital Longevity, Univ. of Texas at Dallas Ctr. for Vital Longevity, Dallas, TX

Abstract: Human fMRI and iEEG experiments suggest that the posterior cingulate cortex (PCC) supports mnemonic processes preferentially during episodic memory retrieval. However, lesion studies are equivocal and direct causal evidence for PCC's role in episodic and associative memory processes is lacking. With deep brain stimulation and intracrannial electrophysiology measurements in epileptic patients (*N*=18), we tested whether stimulating the PCC would affect behavioral recall performance or temporal/semantic clustering, or both. In a free recall experiment, participants learned 20 word lists with 10 words each. We stimulated the PCC during 50% of the encoding trials of 10 lists and compared the effect of stimulation during the remaining 50% of encoding trials when no stimulation was present. Stimulation was applied throughout the encoding period (25s of continuous 100 Hz stimulation). Our data revealed the following findings. Recall performance was lower when PCC was stimulated during encoding than when no stimulation was applied during encoding. This decrement in performance was driven by a reduction in primacy effect (i.e., greater ability to remember first two items in a list than the remaining items) when stimulation was present than when stimulation was absent. Next, measuring theta and gamma power in hippocampus during encoding of correctly remembered words versus incorrectly remembered words (subsequent memory effect, SME), elucidated that, larger the difference in gamma SME during no stimulation versus stimulation conditions, larger the stimulation effect on recall memory. We also asked if stimulation had a preferential impact on associative encoding processes, namely temporal and semantic clustering. Temporal clustering score was larger in stimulation than in no stimulation condition, but semantic

clustering scores were comparable, and these measures were not correlated with oscillatory changes. A subset of participants (*N*=12) had performed baseline free recall (without stimulation) and we evaluated functional hippocampal—PCC connectivity during memory encoding (gamma phase coherence) and correlated connectivity with behavioral effect of stimulation. This revealed that participants with higher connectivity have stronger (negative) effect of stimulation on memory. Thus, our results suggest that stimulation of PCC might preferentially disrupt non-associative encoding strategies (based on the impact on primacy items) but not contextually mediated processing. Our data provide the first direct causal evidence implicating PCC in episodic memory encoding and have important implications for theories of human memory processing.

Disclosures: V.S. Natu: None. **J. Lin:** None. **A. Burks:** None. **A. Arora:** None. **M.D. Rugg:** None. **B. Lega:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.01

Topic: H.02. Human Cognition and Behavior

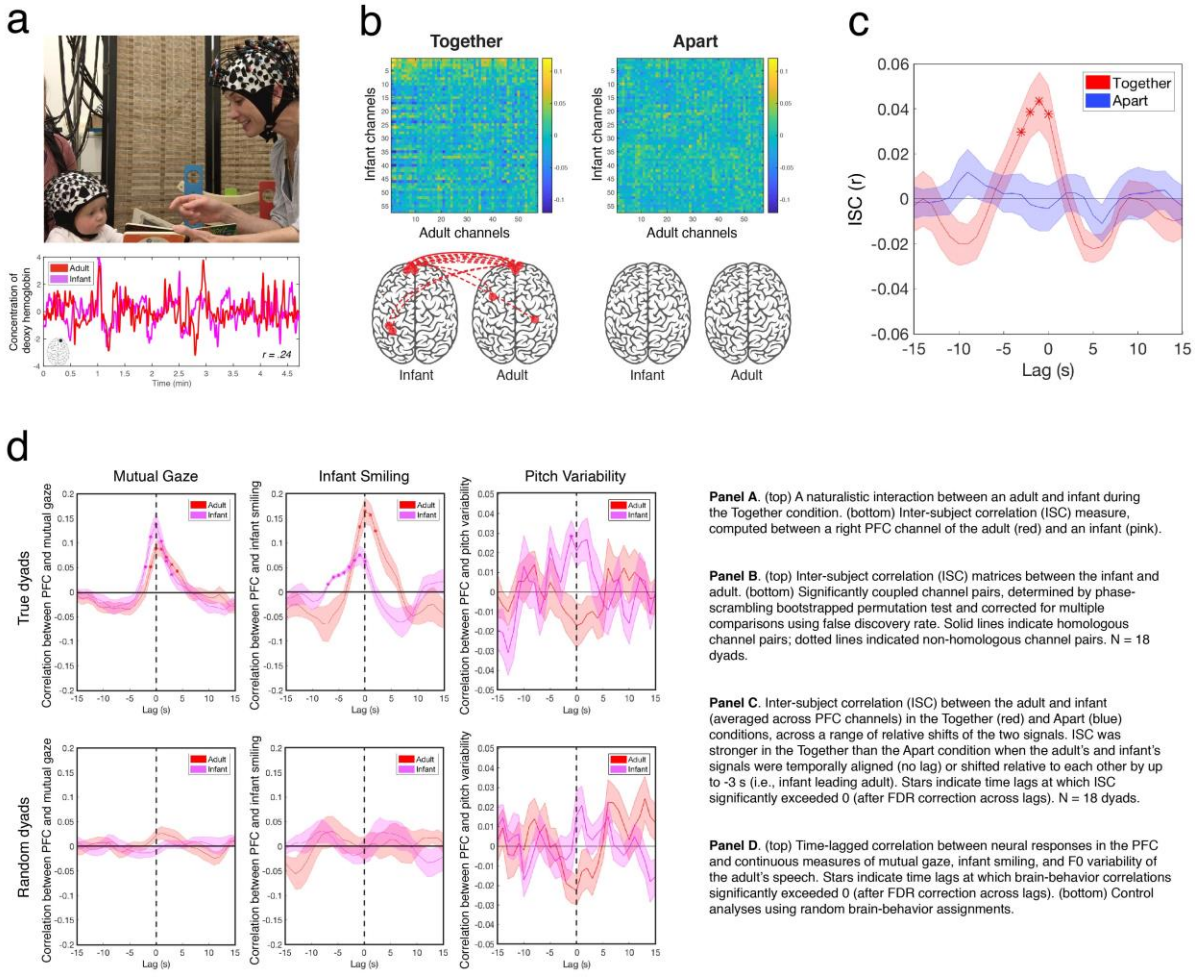
Support: C. V. Starr Postdoctoral Fellowship
NIH 1DP1HD091948
NIH HD079779

Title: Infant and adult brains are coupled to the dynamics of social behavior during real-life communication

Authors: *E. A. PIAZZA, L. HASENFRATZ, U. HASSON, C. LEW-WILLIAMS
Princeton Univ., Princeton, NJ

Abstract: Infancy is the foundational period of learning from adults, and the dynamics of the social environment have long been proposed as central to children's development. Here, we reveal a novel, naturalistic approach for studying live interactions between infants and adults. Using functional near-infrared spectroscopy (fNIRS), we simultaneously and continuously measured the brains of infants (9-15 months) and an adult while they communicated and played with each other in real time. We found that time-locked neural synchrony within dyads was significantly greater when they interacted with each other ("Together") than with control individuals ("Apart" condition). Surprisingly, we also found that prefrontal activation in the infant brain preceded and drove similar activation in the adult brain, which crucially advances our understanding of children's influence over the accommodative behaviors of the caregivers around them. Furthermore, we found that both infant and adult brains continuously tracked the

moment-to-moment fluctuations of mutual gaze, infant emotion (smiling), and adult speech prosody with high temporal precision. The specific temporal pattern of tracking was unique to each dyadic interaction and could not be explained by large-scale fluctuations (e.g., task-related changes in arousal). These findings represent a critical step toward understanding how children's brains begin to extract the most important structure from adults' input, and how adults, in turn, represent infants' emotional feedback as they strive to engage them. Our approach marks a new way to investigate how the brains and behaviors of infants both shape and reflect those of their caregivers during real-life communication.



Panel A. (top) A naturalistic interaction between an adult and infant during the Together condition. (bottom) Inter-subject correlation (ISC) measure, computed between a right PFC channel of the adult (red) and an infant (pink).

Panel B. (top) Inter-subject correlation (ISC) matrices between the infant and adult. (bottom) Significantly coupled channel pairs, determined by phase-scrambling bootstrapped permutation test and corrected for multiple comparisons using false discovery rate. Solid lines indicate homologous channel pairs; dotted lines indicated non-homologous channel pairs. N = 18 dyads.

Panel C. Inter-subject correlation (ISC) between the adult and infant (averaged across PFC channels) in the Together (red) and Apart (blue) conditions, across a range of relative shifts of the two signals. ISC was stronger in the Together than the Apart condition when the adult's and infant's signals were temporally aligned (no lag) or shifted relative to each other by up to -3 s (i.e., infant leading adult). Stars indicate time lags at which ISC significantly exceeded 0 (after FDR correction across lags). N = 18 dyads.

Panel D. (top) Time-lagged correlation between neural responses in the PFC and continuous measures of mutual gaze, infant smiling, and F0 variability of the adult's speech. Stars indicate time lags at which brain-behavior correlations significantly exceeded 0 (after FDR correction across lags). (bottom) Control analyses using random brain-behavior assignments.

Disclosures: E.A. Piazza: None. **L. Hasenfratz:** None. **U. Hasson:** None. **C. Lew-Williams:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.02

Topic: H.02. Human Cognition and Behavior

Title: Intersubject correlation for social and non-social videos in the default mode network

Authors: *M. STRACCIA[1,2], A. GORDON[2], M. LIEBERMAN[2]
[1]Psychology, [2]UCLA, Los Angeles, CA

Abstract: The default mode network is known to be involved when reasoning about others, mind wandering, self-referential processes, imagining the future, and remembering past episodic events. Using intersubject correlation, previous research have shown the default mode network is also involved while participants watch videos and listen to narratives. From this research, however, it is not clear which part of narratives involves the default mode network since the videos have mostly been social in nature. We ran 30 participants in an fMRI scanner while they watched social (e.g. short story, interviews, reality TV, storytelling) and non-social videos (e.g. documentaries, how it's made, science videos). Social videos required participants to hold information about others and reason about their actions while non-social videos required participants hold information about physical objects and reason about the processes involved with these objects. Using intersubject correlations, we see differences within the default mode network depending on the social and non-social nature of the videos.

Disclosures: M. Straccia: None. **A. Gordon:** None. **M. Lieberman:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.03

Topic: H.02. Human Cognition and Behavior

Support: R01MH116026
R56MH080716

Title: Endogenous variation in ventromedial prefrontal cortex state dynamics

Authors: *L. CHANG[1], J. CHEONG[1], P.-H. CHEN[1], K. RAPUANO[2], E. JOLLY[1]
[1]Dartmouth Col., Hanover, NH; [2]Yale Univ., New Haven, CT

Abstract: The brain has a remarkable capacity for simultaneously processing exogenous information about the external world, while continuously generating endogenous evaluations about the meaning of events that reflect our internal states and goals. The ventromedial prefrontal cortex (vmPFC) has been implicated as a key region in this process based on its role in generating affective meaning via self-relevant appraisals. Because internal states and goals differ both between and within individuals across time, responses to external cues in the vmPFC are

likely to be highly variable with long temporal durations, which is in stark contrast to sensory processing areas (e.g visual cortex). This provides a unique challenge for studying brain responses that reflect such variability. In this study, we investigate the role of the vmPFC in processing endogenous information in the context of watching a naturalistic character driven television drama. Thirty-five participants watched the first episode of the television show Friday Night Lights. We calculate the temporal recurrence of spatial patterns of activation for every sample of time (2sec) across the 45-minute episode. We find evidence suggesting that the vmPFC may have a longer temporal receptive window compared to sensory regions. On average the temporal autocorrelation of the spatial patterns in the vmPFC was considerably longer than patterns in early visual cortex. In addition, within a single participant, we find that these patterns can persist for long periods of time (i.e., on the order of minutes). Interestingly, these spatial patterns appear to be highly variable across participants and show low levels of spatial synchronization. Finally, we find that the scenes in which most participants exhibit a sustained spatial pattern were associated the strongest affective experiences measured via facial expressions and emotional ratings in a separate group of participants. Overall, this work demonstrates that the vmPFC has fundamentally different functional properties than other areas of cortex that is consistent with its role in integrating information about self-relevant internal states, past experiences, and future goals.

Disclosures: L. Chang: None. **J. Cheong:** None. **P. Chen:** None. **K. Rapuano:** None. **E. Jolly:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.04

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant HD091948

Title: Thinking ahead: Using ECoG to map the spatiotemporal dynamics of prediction during natural language comprehension

Authors: *A. R. PRICE[1], L. HASENFRATZ[1], A. ZADBOOD[1], D. FRIEDMAN[2], P. DUGAN[2], W. DOYLE[2], O. DEVINSKY[2], L. MELLONI[3], A. FLINKER[2], U. HASSON[1]
[1]Princeton Univ., Princeton, NJ; [2]Neurol., NYU, New York, NY; [3]Neurosci., Max Planck For Empirical Aesthetics, Frankfurt Am Main, Germany

Abstract: A key property of language is that we continuously generate predictions for upcoming words when listening to a speaker. This process facilitates rapid comprehension and allows us to exchange information quickly in dialogues. How does the brain generate such predictions? In

previous work, investigators often developed sets of isolated sentences in which the cloze probability of the final word was high or low. However, in natural comprehension (e.g. listening to a story), predictions for upcoming words may be influenced by information accumulated over multiple timescales, ranging from the recent words in a sentence to information gathered over multiple paragraphs as a story unfolds. To obtain a continuous measure of prediction over multiple timescales, we developed a novel sliding-window behavioral paradigm, where 50 healthy participants attempted to predict each upcoming word in a real-life spoken story as it unfolded over time (~1000 words). Cloze probabilities varied across words in the story, ranging from 0 to 100% predictability with a mean of 28%. To assess whether word predictions depended on information gathered over long timescales, we also collected prediction data in new groups of subjects (50 per group) using temporally scrambled versions of the story at the level of paragraphs, sentences, or phrases. We found that behavioral prediction accuracies parametrically decreased as the story was scrambled at finer timescales. Next, we recorded electrocorticography signals from ~1000 surface electrodes in 10 epileptic patients who listened to the same story. We used the average cloze probability for each word from the behavioral data to gain insights into the neural mechanisms underlying the word prediction in our story. We found that changes in high-frequency broadband power (HFB; 70-200 Hz) tracked the cloze probability of each word in electrodes over superior temporal gyrus (STG) and inferior frontal gyrus (IFG). Relative to word onset, the timing of the HFB response significantly differed as a function of cloze probability, with peak responses to highly predicted words preceding those for poorly predicted words by ~250ms. For the most predictable words, significant effects were detected even before word onset in STG and IFG. Furthermore, HFB responses were best modeled by cloze probabilities for the intact story, and they decreased for predictions generated from progressively shorter timescales. Together, these results provide insights into the dynamic neural processes by which, in real-life contexts, we use information accumulated over many seconds to generate expectations for the semantic content of upcoming stimuli.

Disclosures: A.R. Price: None. **L. Hasenfratz:** None. **A. Zadbood:** None. **D. Friedman:** None. **P. Dugan:** None. **W. Doyle:** None. **O. Devinsky:** None. **L. Melloni:** None. **A. Flinker:** None. **U. Hasson:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.05

Topic: H.02. Human Cognition and Behavior

Support: ERC-STG multsens

Title: Cortical tracking reveals how the brain forms hierarchical representations based on linguistics and memory

Authors: *G. DEGANO, U. NOPPENEY
Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Speech comprehension requires the brain to construct hierarchical linguistic structures such as phrases and sentences from smaller linguistic units such as words. Using Concurrent Hierarchical Tracking approach (CHT) recent electroencephalography and magnetoencephalography EEG/MEG research has suggested that neural activity at different timescales tracks the formation of linguistic structures at different hierarchical levels. Yet, the extent to which these entrained rhythms are specific to linguistic processing (e.g. phrase and sentence structure building) remains unclear. Using CHT, we investigated whether prior learning of four word sequences (e.g. four nouns, four adjectives) that did not involve any syntactic binding generates EEG activity at multiple timescales reflecting the formation of hierarchical units based on memory encoding. Next, we directly compared the cortical activity that tracks the formation of hierarchical units based on memory encoding (i.e. word sequences) and syntactic processing. Prior to the EEG study participants learnt a set of four-word English sentences (i.e. adjective + noun + verb + noun) and four word sequences (recall >80% for each set). In the EEG study, participants listened to (1) the learnt four word sentences, (2) the learnt four word sequences and (3) novel four word sequences. Critically, all words were monosyllabic and presented at exactly 3.12Hz thereby generating an auditory steady-state signal. Using EEG we statistically assessed the phase coherence corresponding to three different linguistic hierarchical levels: 3.12Hz for the word level, 1.56Hz for the phrase level and 0.78Hz for the sentence level. Our results show increased phase coherence in the EEG signal at 3.12Hz (word level), 1.56Hz (phrase level) and 0.78Hz (sentence level) for learnt sentences and learnt word sequences. By contrast, the new word sequences showed only significant entrainment at the word level. We also observed significantly stronger phase coherence for sentences than learnt word sequences at 1.56 Hz and 0.78 Hz. Moving beyond previous research our results show that CHT can track the formation of representations at different hierarchical levels based on both linguistic and memory processing. Critically, linguistic processing was more powerful in driving steady state signals than the formation of units based on prior memory. Collectively, these results show that CHT is a generic approach that can track the formation of representations at different hierarchical levels in the brain.

Disclosures: G. Degano: None. **U. Noppeney:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.06

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DC014589

Title: An integrated analysis of language networks using CSM and DTI

Authors: *P. ROLLO[1], K. FORSETH[2], C. M. KADIPASAOGLU[3], C. DONOS[5], N. TANDON[4]
[1]UTHSC at Houston, Houston, TX; [2]UT Hlth. Sci. Ctr. in Houston, Houston, TX; [3]Neurosurg., [4]Neurolog. Surgery, Univ. of Texas Med. Sch. at Houston, Houston, TX; [5]Neurosurg., Univ. of Texas Hlth. Sci. Ctr. at Houst, Houston, TX

Abstract: Introduction: Cortical stimulation mapping (CSM) remains the gold standard methodology for the localization of eloquent cortex in planning resection of neoplasms and seizure foci. The resulting language map is often used in conjunction with structural imaging to inform the surgical approach. Here, we combine these functional and structural measures in a large patient population to understand the interplay between the spatially distributed substrates that support visual and auditory naming.
Methods: We prospectively collected data in 75 patients undergoing either intra-operative (awake craniotomy, n = 55) or extra-operative (intracranial electrodes: subdural grids, n = 13; stereotactic depths, n = 7) language mapping (5-10mA, 50Hz, 2s). Language function was evaluated with a battery of tasks including visual picture naming and auditory naming to definition. Stimulation-induced depolarization was transformed onto the pial surface with a current spread model to generate subject-specific representations of language disruption; these were then co-registered with diffusion tensor imaging (DTI). In several regions of interest, we generated distinct volumetric density representations of white matter tracts underlying either positive or negative stimulation sites. The resulting subject-specific CSM (surface-based) and DTI (volumetric) were projected onto a standard group atlas with a nonlinear combined surface-volume transform that maximizes surface-landmark similarity and minimizes volumetric distortion.
Results: CSM at the group-level revealed four regions which consistently disrupted both auditory and visual naming function: inferior frontal gyrus, posterior middle temporal gyrus, middle fusiform gyrus, and dorsomedial prefrontal cortex. DTI maps in each of these regions of interest revealed strong intra-network connectivity for positive stimulation sites, but diffuse and inconsistent cortical connectivity for negative stimulation sites.
Conclusion: This analysis, integrating two essential surgical planning tools, constitutes a significance advance in large-scale multimodal population-level maps of human language. Analyses at the single-subject level will improve understanding of the language network at risk during surgical interventions for tumors and epilepsy.

Disclosures: P. Rollo: None. **K. Forseth:** None. **C.M. Kadipasaoglu:** None. **C. Donos:** None. **N. Tandon:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.07

Topic: H.02. Human Cognition and Behavior

Support: MRC-UK SUAG019 RG91365

Title: Using auditory steady state response and visual gamma band response in eeg/meg to test embodied theories of semantics

Authors: *O. HAUK[1], M. KEEMINK[1], R. FARAHIBOZORG[1], G. PERRY[2], S. CHENNU[3,1]
[1]Univ. of Cambridge, Cambridge, United Kingdom; [2]Cardiff Univ., Cardiff, United Kingdom; [3]Univ. of Kent, Canterbury, United Kingdom

Abstract: It is not fully established yet to what degree semantics relies on sensorimotor brain areas ("embodiment"). Answering this question requires both the unambiguous localization in space to sensorimotor areas and in time to early semantic processing stages. Unfortunately, non-invasive neuroimaging methods provide either high spatial resolution (e.g. fMRI) or temporal resolution (EEG/MEG), but not both. Here, we utilised the high temporal resolution of EEG/MEG while "circumventing the inverse problem" to probe the involvement of primary sensory areas in semantic word processing. For this purpose, we evoked auditory steady state and visual gamma band responses (ASSRs, VGBRs), known to originate from primary auditory and visual cortices, respectively, and monitored their time courses during processing of auditory- and visual-related words. We pre-registered our study protocol (https://osf.io/e3djb/). EEG and MEG were recorded (Elekta Neuromag) for 20 participants. 60 words per category plus 120 filler items were presented in a lexical and semantic target detection task. ASSR (35Hz, 250 Hz tone) and VGBR (annular grating, 3 deg/cycle) were evoked simultaneously for 1.7s. Words were presented visually in the centre of the display after 0.7s. Participants had to respond to target stimuli in 10% of trials. ASSR and VGBR were also evoked in separate trials in a localizer session. Time-frequency analysis was performed in signal space using Morlet wavelets (MNE-Python) in order to obtain power ratio time courses (300ms baseline) for each channel. Peak channels and frequencies were determined from localizer scans for individual participants. Amplitudes were averaged across 5 peak channels for ASSR and VGBR, per word category and participant, and were entered into 2-by-2 ANOVAs (Word Category by Brain Response), for channel types separately in latency ranges around 100ms, 150ms, 230ms, and 250-400ms. We did not find significant interactions of Word Category and Brain Response in any of our comparisons. This was also the case when we focussed only on VGBRs (which were more reliable than ASSRs), and when we analysed the two tasks separately. Thus, our pre-registered

study failed to provide evidence for modulation of primary sensory brain areas during semantic word processing.

Disclosures: O. Hauk: None. **M. Keemink:** None. **R. Farahibozorg:** None. **G. Perry:** None. **S. Chennu:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.08

Topic: H.02. Human Cognition and Behavior

Support: FWO Grant G0925.15
KU Leuven C14/17/108

Title: Semantic processing in the dorsal stream

Authors: *A. G. LIUZZI[1], P. DUPONT[2], R. PEETERS[3], S. DE DEYNE[4], G. STORMS[4], R. R. VANDENBERGHE[5]
[1]KU Leuven / Lab. for Cognitive Neurol., Leuven, Belgium; [2]Lab. for Cognitive Neurol., KU LEUVEN, Leuven, Belgium; [3]Radiology, Univ. Hosp., Leuven, Belgium; [4]Lab. for Exptl. Psychology, Leuven, Belgium; [5]Univ. Hosp Gasthuisberg, Leuven 3000, Belgium

Abstract: The dual stream model suggests that the dorsal stream maps sound to articulation and the ventral stream maps sound to meaning. Here we investigate whether and how the input-modality - written words, spoken words and pictures - affects the semantic processing in the dorsal stream. An event-related fMRI study was run on a Philips Achieva 3T equipped with a 32-channel coil in 17 subjects. Twenty-four animate entities were used. From the concept-feature matrix (De Deyne et al., 2008), the pairwise cosine dissimilarity was calculated for each pair of entities (semantic matrix). The entities were selected such that the standard deviation of the pairwise semantic similarity was maximized and the correlation between the semantic and phonological similarity was minimized. During fMRI, entities were presented as written words, spoken words or pictures with auditory and visual controls for each modality. For half of the trials, subjects were asked to pronounce the entity. Spoken responses were recorded via a noise-cancelling MRI microphone (FOMRI-III Optoacoustics). fMRI data were modelled using a General Linear Model (GLM). By calculating the cosine dissimilarity between trial pairs, 6 fMRI matrices (all conditions, written words, pictures, spoken words, pronounced and not pronounced trials) were generated in each VOI: Left Broca area 44 and 45, supramarginal gyrus (PF PFop PFt PFm PFcm) and angular gyrus (PGa PGp). All regions were extracted from Julich probability maps (Eickhoff et al., 2007). A representational similarity analysis was conducted between the semantic similarity matrix and each subject-specific fMRI matrix. Inferential

statistical analyses were performed using a two-sided Wilcoxon signed-rank test across subject-specific RSA correlations. Results were corrected for number of VOIs. A one-way repeated measure ANOVA with accuracy as outcome showed a main effect of input modality (written words: μ 0.99, SD 0.011; pictures: μ 0.81, SD 0.07; spoken words: μ 0.92, SD 0.06) ($F(1,10)=32,4$; $p=.00000$). Semantic similarity and the similarity between fMRI response patterns correlated significantly in BA45 when all conditions were pooled (median Spearman correlation (ρ) = 0.07, $p= 0.0019$) and also for pictures ($\rho= 0.13$, $p= 0.0014$), but not for written ($\rho= -0.006$, $p= 0.5$) or spoken ($\rho= 0.02$, $p= 0.2$) words. A significant correlation was also present in PFm for the pooled conditions ($\rho= 0.04$, $p= 0.0008$) and for pictures ($\rho= 0.13$, $p= 0.003$), but not for written ($\rho= -0.02$, $p= 0.5$) or spoken ($\rho= 0.004$, $p= 0.3$) words. The results suggest a role of the dorsal stream in coding the semantic meaning of entities during picture naming but not during word repetition or reading words aloud

Disclosures: A.G. Liuzzi: None. **P. Dupont:** None. **R. Peeters:** None. **S. De Deyne:** None. **G. Storms:** None. **R.R. Vandenberghe:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.09

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 1R01EY02391501A1
DFG Grant GR 4850/1-1

Title: Functionally-defined white-matter shows segregated pathways for math and reading in the human brain

Authors: *M. GROTHEER[1], K. GRILL-SPECTOR[1,2]
[1]Dept. of Psychology, [2]Stanford Neurosciences Inst., Stanford Univ., Stanford, CA

Abstract: Math and reading are crucial for functioning in modern society, yet how our brain supports these skills is not fully understood. While math and reading are different cognitive processes, they have shared subcomponents, such as assigning meaning to visual stimuli and keeping items in working memory. However, it is unclear if these tasks also share neural resources. Here, we close this fundamental gap in knowledge by comparing the gray- and white-matter substrates of math and reading within 14 subjects. Participants performed reading, math, and color tasks on the same visual stimuli (number/letter morphs), while undergoing fMRI. Using these data, we identified in each participant gray-matter regions involved in processing math and reading by detecting regions that showed significantly higher responses for one task vs. the other two. We found that regions involved in math neighbored, but largely did not overlap

with, regions involved in reading. Then, we determined white-matter tracts of these networks. Using diffusion weighted imaging, ensemble tractography with spherical deconvolution, and automatic fascicle quantification, we generated an optimized whole-brain connectome and then identified the fascicles that intersected with each of the cortical regions activated during math or reading. Results indicate that the left superior longitudinal fasciculus (SLF) and the arcuate fasciculus (AF) were shared across networks, i.e. they showed significant connections to at least two regions within each network. However, within these fascicles, fibers connecting areas within the math network or within the reading network remained segregated. Interestingly, quantitative MRI measurements of relaxation time (T1) showed lower T1 in fibers of the SLF and AF associated with reading than with math, suggestive of higher myelination of the former than the latter. Together, our data explicate the functional organization and white-matter tracts of the math and reading networks. Further, our data support a new hypothesis that frequently used cognitive processes that involve networks distributed across the brain (such as reading) may lead to increased myelination of white matter tracks within these networks.

Disclosures: M. Grotheer: None. **K. Grill-Spector:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.10

Topic: H.02. Human Cognition and Behavior

Support: 1F30DC017083-01

Title: Dissecting the hidden neural states of overt language production

Authors: *K. FORSETH[1], A. GIAHI SARAVANI[2], X. S. PITKOW[2], N. TANDON[3]
[1]UT Hlth. Sci. Ctr. in Houston, Houston, TX; [2]Neurosci., Baylor Col. of Med., Houston, TX; [3]Neurolog. Surgery, Univ. of Texas Med. Sch. at Houston, Houston, TX

Abstract: The process of human speech production involves an integrated multistage process that seamlessly translates appropriate conceptual representations in the brain to acoustic output. It has been proposed that complex intermediary states reflected by transients derived from the dynamics between distributed substrates are integral to the process of word generation. The evaluation of this hypothesis requires high-resolution recordings and an analytic approach to model discrete neural states. We used Hidden Markov Models (HMMs) to resolve trial-by-trial state transition sequences in distributed sub-networks derived from a large-scale electro-corticographic dataset.Intracranial electrodes (n = 18,350; 109 patients), including both surface grid electrodes and penetrating stereotactic depth electrodes, were implanted as part of an electrocorticographic evaluation for epilepsy. Patients performed picture naming for large

number of common objects. A surface-based mixed-effects multilevel analysis of broadband gamma activity in the language-dominant hemisphere was used to identify loci with significant activity. This revealed 9 regions of interest: early visual cortex, fusiform gyrus, intraparietal sulcus, supplementary motor area, anterior insula, inferior frontal gyrus, subcentral gyrus, early auditory cortex, and superior temporal gyrus. First, we isolated activity patterns in the global naming network: early visual cortex, fusiform gyrus, inferior frontal gyrus, subcentral gyrus, and superior temporal gyrus. This overview captured 3 network states: a fixed length initial state corresponding to visual processing, a variable-length second state driven primarily by activity in the mid fusiform and inferior frontal gyri, and a third state during overt articulation dominated by activity in ventral sensorimotor cortex and superior temporal gyrus. Critically, the second state is consistent with the variable demands - semantic, lexical, and phonological - for each stimulus. To further elucidate the network dynamics of this second state, we focused on two sub-networks corresponding to the generation of motor and auditory for language production. The first comprised of Broca's area, ventral sensorimotor cortex, Heschl's gyrus, and the Sylvian-parietal-temporal junction. The second comprised of the supplementary motor area, anterior insula, and Brocas area, regions that drove network state behavior early in the variable-length second state. Our work pairs large-scale electrocorticography with sub-network state analyses to answer long-standing questions regarding network dynamics of language production.

Disclosures: K. Forseth: None. **A. Giahi Saravani:** None. **X.S. Pitkow:** None. **N. Tandon:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.11

Topic: H.02. Human Cognition and Behavior

Support: NIH, 5R01 EY015545-12
T &C Chen Brain-machine Interface Center at Caltech
Boswell Foundation
Conte Center

Title: Neural population structure for action verbs and visually observed actions in human posterior parietal cortex

Authors: *T. AFLALO[1], G. A. ORBAN[2], C. Y. ZHANG[1], E. ROSARIO[3], N. POURATIAN[4], R. A. ANDERSEN[5]
[1]Div. of Biol. and Biol. Engin., Caltech, Pasadena, CA; [2]Deptmt of Neurosci., Univ. of Parma, Parma, Italy; [3]Res. Inst., Casa Colina Hosp. and Centers for Healthcare, Pomona, CA; [4]Neurosurg, UCLA, Los Angeles, CA; [5]BBE, Calif Inst. of Technol., Pasadena, CA

Abstract: Lesion and functional imaging studies have pointed to representations of semantic knowledge that are highly distributed across the human cortex (Huth et al. 2016, Martin 2016). Using the fine grain of recording populations of single neurons, we wished to establish the organization of action concepts in terms of specific action verbs and observed actions at the single neuron level. Single neurons were recorded from the anterior intraparietal cortex (AIP) of two paralyzed patients implanted with multi-channel electrode arrays as part of a brain-machine interface clinical trial. Prior functional imaging results have indicated that AIP is activated to action verbs as well as observed actions.
Patients viewed videos of five manipulative actions presented in 3 formats (two lateral views differing in body posture and one frontal view) as well as written text of the associated action verbs. Over 1500 units were recorded during 18 recording sessions. We found that selectivity for action verbs was robust (~30% units selective, fdr cor.) but less than any single video format (~40-50%). We found no evidence for complete invariance. In contrast, we found single neurons to be selective for different combinations of formats and actions. However, the neuronal representation was not random, the population being more likely to have overlapping representations across formats for the same action identities. The consequence of this organization is a rich structure with text linking both to partially overlapping and distinct aspects of the visual formats. These links mirrored the statistics of how visual formats were encoded with respect to each other independent of text.A number of theories emphasize that semantic cognition relies on cortical regions that operate on abstracted symbolic representations in combination with the distributed system. "Concept cells" in the medial temporal lobe provide an example of highly-invariant symbolic neural coding. However, the sensory and motor systems that form the distributed component of semantic cognition do not exhibit such invariance, instead depending on presentation details like view-point. The current findings show for the first time that the action concept representations in sensory-motor cortices are consistent with partially mixed selectivity, in which there is a greater degree of overlap between variables coding the same action concept, than between action concepts. Partially mixed selectivity was found for movement intention and observed and experienced sensations in AIP (Zhang et al. 2017 a,b) and may represent a general structure for representing semantic meaning within many association cortices.

Disclosures: T. Aflalo: None. **G.A. Orban:** None. **C.Y. Zhang:** None. **E. Rosario:** None. **N. Pouratian:** None. **R.A. Andersen:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.12

Topic: H.02. Human Cognition and Behavior

Support: China National Natural Science Foundation

Title: Left versus right arcuate fasciculi make unique contributions to reading skill across languages

Authors: *Y. GAO[1], J. R. BOOTH[2], L. LIU[1], X. MENG[3]
[1]Beijing Normal Univ., Beijing, China; [2]Dept. of Psychology and Human Develop., Vanderbilt Univ., Nashville, TN; [3]Peking Univ., Beijing, China

Abstract: The arcuate fasciculi connect temporoparietal regions with frontal regions implicated in language and reading. The left arcuate fasciculus is related to phonological processing and reading skill in alphabetic scripts. Little is known about the role of the right arcuate fasciculus in reading, but some have suggested that it may play a role in the prosodic components of language or visual spatial aspects of reading. This suggests that the right arcuate fasciculus may be more important for skilled reading in Chinese because of the relatively greater visual spatial demands of reading characters or due to the role of tones in disambiguating meaning of words, but this hypothesis has yet to be tested. In order to address this question, we examined the relation of white matter integrity in bilinguals with a wide range of reading skill in their first language (Chinese) and in their second language (English). We studied 42 bilingual children ranging in age from 8.8 to 11.8 years old. Using Diffusion Tensor Imaging (DTI), left and right arcuate fasciculi were reconstructed by an automated fiber-tract quantification (AFQ) method. Fractional anisotropy (FA) was calculated at 100 nodes along the left and right direct long segment of the arcuate fasciculi. First language reading ability was assessed by a Chinese character recognition test, and second language reading ability was assessed by an English word identification test. When controlling for Chinese reading ability, English reading ability was significantly correlated with the posterior part of the left arcuate fasciculus (i.e. posterior nodes 80 - 98). When controlling for English reading ability, Chinese reading ability was significantly correlated with the right arcuate fasciculi (i.e. middle nodes 50 - 61). These results suggest that reading skill in alphabetic scripts relies more on phonological networks in the left hemisphere, whereas reading skill in logographic scripts relies more on visual spatial or prosodic networks in the right hemisphere.

Disclosures: Y. Gao: None. **J.R. Booth:** None. **L. Liu:** None. **X. Meng:** None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.13

Topic: H.02. Human Cognition and Behavior

Title: Note-taking and language interference in monolingual and bilingual brains

Authors: *M. ORKODASHVILI
Vanderbilt Univ., Tbilisi, Georgia

Abstract: The present research attempts to understand the brain operation peculiarities during *the note-taking process* first in L1 and afterwards in L2, in both monolingual and bilingual subjects. The research also looks into the possible language interference during *note-taking process.*

Note-taking is a well-known language acquisition strategy, which is used not only in real life situations but in language testing as well. It is a relatively complex activity and involves the following stages: 1) active, intense listening to a speech, dialogue, etc.; 2) swift identifying and extracting of the most important information from the listened piece; 3) writing down / typing of the extracted information; 4) keeping up with the speaker's pace of speech while writing / typing so that the core information does nor escape the listener's attention while taking down the notes. The process presents an interesting case study for neuroscientists in terms of looking at brain plasticity workings in the individuals of various with different language competencies.

The present study researched note - taking process in 20 monolinguals and 20 bilinguals. The age range of the subjects was between 12 and 56. Out of 20 bilinguals, 5 were multilinguals with multiple language competencies. The gender distribution was equal in each group, i.e. 10 males and 10 females.

The monolingual subjects were asked to listen and take notes of most important information in their L1.

The bilingual subjects were asked to listen and take notes of most important pieces of information first in their native language, and then in the second language.

The EEG findings revealed that the listening and writing efficiency in L2 language interfered with the efficiency and speed of note-taking in L1 language in most of the bilingual cases, while the vice versa was not always true, meaning that the efficiency in reading and listening of L1 did not always affect the efficiency in L2 language taking. The difference in milliseconds between bilinguals and multilinguals was insignificant and not always apparent in this case.

Compared with monolinguals, bilinguals and multilinguals outperformed monolinguals in almost all cases.

Thereafter, the differences in the speed and efficiency of note-taking between monolinguals and bilinguals were accounted for by the possible brain plasticity development in bilinguals as a result of continuous training in code switching from one language into another and by the interference of L2 acquisition strategies during all four stages of note-taking during L1 note-taking process.

Disclosures: M. Orkodashvili: None.

Nanosymposium

362. Human Cognition and Behavior: Language and Communication

Location: SDCC 23

Time: Monday, November 5, 2018, 1:00 PM - 4:30 PM

Presentation Number: 362.14

Topic: H.02. Human Cognition and Behavior

Support: PICT joven 2015-1787
IBRO return home fellowship
Subsidio interno para la investigación, Universidad Austral

Title: Sex differences in brain functional organization for semantic processing and pragmatic language

Authors: M. BENDERSKY[1,2], C. F. LOMLODJIAN, 1141[2], J. SABATTE[3], M. GARGIULO[3], S. F. KOCHEN, 1141[2], *L. M. ALBA-FERRARA[4,2]
[1]Living Anat. Lab., Univ. de Buenos Aires, Buenos Aires, Argentina; [2]ENyS-CONICET, Florencio Varela, Argentina; [3]Psychiatry, Hosp. Rivadavia, Buenos Aires, Argentina; [4]Biomed. Sci., Univ. de Austral, Florencio Varela, Argentina

Abstract: Introduction: Sex differences in cognitive abilities are a relatively popular topic that has been studied across various domains. Increasing evidence supports the existence of sex differences in the structural and functional organization of the brain. A long- held hypothesis proposes that (beyond cultural, historical, social and environmental factors) there are biological sex differences in the functional organization of the brain for language networks, especially those supporting higher linguistic functions. Purpose: To study patterns of activation of accessory language areas in both sex. Methods: 19 normal, right-handed subjects (9 women and 10 men), mean age 32.66, were studied by fMRI during a semantic categorization task (semantic categorization vs. letter categorization as baseline) and pragmatic language task (figurative sentence comprehension vs. literal sentencecomprehension as a baseline) on a Siemens Trio 3T scanner. Randomized effects were analyzed with SPM12, computing a BOLD contrast image for each subject and comparing both groups using *t tests.* Results: All the participants had a performance significantly higher than the chance level. The results reported were obtained with a $P_{unc}<0.05$, $T>4$. All the subjects activated, in both hemispheres, clusters surrounding the pars triangularis, supramarginal gyrus and orbitofrontal regions in the semantic task vs semantic baseline. For figurative language comprehension minus baseline, activation included T1 anterior and posterior, pars triangularis, and F3 opercular, bilaterally. Comparisons between groups showed that brain activation in males was lateralized leftwards, while women activated similar areas in both hemispheres. Conclusion: These data support the increasing evidence about sex differences in the neural correlates of higher order language processing, being males strongly lateralized compared to females.

Disclosures: M. Bendersky: None. **C.F. Lomlodjian:** None. **J. Sabatte:** None. **M. Gargiulo:** None. **S.F. Kochen:** None. **L.M. Alba-Ferrara:** None.

Nanosymposium

363. Schizophrenia: Circuits and Systems

Location: SDCC 2

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 363.01

Topic: H.03. Schizophrenia

Support: Pritzker Neuropsychiatric Research Consortium
NIH: R01MH104261
Hope for Depression Research Foundation

Title: Human thalamus gene-expression highlights functional nodes in thalamocortical circuits vulnerable in schizophrenia

Authors: *R. CALZAVARA[1], H. AKIL[1], J. D. BARCHAS[2], W. E. BUNNEY[3], F. S. LEE[2], R. M. MYERS[4], A. F. SCHATZBERG[5], S. J. WATSON[1]
[1]Mol. and Behavioral Neurosci. Inst., Univ. of Michigan Med. Sch., Ann Arbor, MI; [2]Dept. of Psychiatry, Weill Cornell Med. Col., New York, NY; [3]Psychiatry and Human Behavior, Univ. of California Irvine, Irvine, CA; [4]Hudson Alpha Inst. for Biotech., Huntsville, AL; [5]Dept. of Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA

Abstract: Perception, attention, cognition and motivation are affected in schizophrenia. Those functions are processed throughout a brain-wide network which critically involved cortical connectivity with the thalamus. Increasing evidence implicates thalamic dysfunction in schizophrenia, although the role of specific nuclei is not established. In our study, we are generating a molecular mapping of the whole human thalamus to identify gene-expression markers of thalamic neurons and their regional or nuclear distributions. We used mRNA in situ hybridization for selective markers throughout the thalamus. Our gene-expression map of the human thalamus highlights critical differences within the cytoarchitectonic nuclear boundaries. This is the case for the medio-dorsal (MD) nucleus which sub-regions feature specific markers differentially expressed. While the medial part of MD highly express PVALB (parvalbumin), the lateral part of MD has a lower expression of PVALB and little or none expression of CALB1 (calbindin). The latter region is primary connected to the dorsolateral prefrontal cortex (DLPFC), which is considered key for executive functions. Interestingly, this MD sub-region was found to be selectively impaired in post-mortem studies in schizophrenia (Popken at al., 2000). Similarly, within the pulvinar complex, the anterior and medial pulvinar nuclei are characterized by a very dense PVALB expression. The pulvinar, which is one of the largest areas in the human thalamus, is primarily connected to posterior parietal cortex but also to the DLPFC and is recognized for its role in attention and perception. The intralaminar nuclei can also been characterized on the basis

of their genetic markers. The anterior nuclei paracentral and central lateral express a combination of calcium-binding proteins, neurotransmitter and neuropeptides markers. On the contrary, the caudal intralaminar nuclei parafascicularis and centro-median do not express these markers. These molecular features of the human thalamus are relevant in understanding thalamocortical connectivity and its evolution and development in mammals, particularly in primates. Moreover, our findings aim to undercover critical thalamic nodes, circuits and cells types, potentially vulnerable in schizophrenia.

Disclosures: R. Calzavara: Other; The author is member of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. **H. Akil:** Other; The author is member of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. **J.D. Barchas:** Other; The author is member of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. **W.E. Bunney:** Other; The author is member of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. **F.S. Lee:** Other; The author is member of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. **R.M. Myers:** Other; The author is member of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. **A.F. Schatzberg:** Other; The author is member of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. **S.J. Watson:** Other; The author is member of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C..

Nanosymposium

363. Schizophrenia: Circuits and Systems

Location: SDCC 2

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 363.02

Topic: H.03. Schizophrenia

Support: FRM (Fondation pour la Recherche Biomédicale)

Title: Structural and functional characteristics of the default mode network in bipolar disorder and schizophrenia: A multimodal neuroimaging study

Authors: *M. E. PAULING[1,2,3], C. HENRY[4,2], J. HOUENOU[2,4,1]
[1]Neurospin (CEA), Saclay, France; [2]INSERM, Créteil, France; [3]UPEC, Créteil, France; [4]Hôpitaux Universitaires Mondor, Créteil, France

Abstract: The default mode network (DMN) is a well established network active during non-directed behaviours but deactivated during cognitive and sensimotor tasks (Greicius et al., Proc Natl Acad Sci USA, 2002, 100(1):253-258). The medial prefrontal cortex, cingulate cortex and inferior parietal lobule are considered as core areas (Davey et al., Neuroimage, 2016, 132:390-397). Abnormalities in the DMN have been implicated in both schizophrenia (SZ) and bipolar disorder (Mohan et al., Yale J Biol Med, 2016, 89(1):49-57, Ongur et al., Psychiatry Res, 2010, 183(1):59-68). Based on this, the goal of this study is to investigate differences in the default mode network (DMN) between healthy controls (HC), patients with bipolar disorder and patients with schizophrenia, using a multimodal approach. In total, the resting state fMRI, diffusion and structural (T1) scans of 119 adults, 52 HC, 32 patients with BD and 32 patients with SZ were used in the analysis. First, structural imaging (T1) was pre-processed and segmented using CAT12 and SPM to identify regions of interest and compare gray matter volume in the areas associated with DMN. Building on this, fractional anisotropy, an indirect measure of white-matter integrity, was obtained from the diffusion images, using tract-based-spatial-statistics within FSL. Then, resting state data was processed and the default mode network identified using independent components analysis. Preliminary data point to differences across groups in the diffusion analysis. Gray matter volume was significantly decreased in the medial prefrontal cortex and left inferior parietal lobule between HC and patients with SZ, but not between HC or patients with BD. The next step in the analysis will be to fully take advantage of the multimodal nature of the design by combining the three modalities into one analysis. Together, they will provide a better insight into the complex neuropathology of both BD and SZ.

Disclosures: M.E. Pauling: None. **C. Henry:** None. **J. Houenou:** None.

Nanosymposium

363. Schizophrenia: Circuits and Systems

Location: SDCC 2

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 363.03

Topic: H.03. Schizophrenia

Support: National Natural Science Foundation of China No. 81401115
Beijing Municipal Administration of Hospitals' Youth Programme QML20172001
NIH grant R01MH112180

Title: Functional fractionation of default network in first episode schizophrenia: Small graph, big brain

Authors: *F. FAN, Y. TAN[1], Z. WANG[1], F. YANG[1], H. FAN[1], H. XIANG[2], H. GUO[3], E. HONG[4], S. TAN[1], X.-N. ZUO, SR[5]
[1]Beijing Huilongguan Hosp., Beijing, China; [2]Chongqing Three Gorges Central Hosp.,

Chongqing, China; [3]Zhumadian Psychiatry Hosp., Zhumadian, China; [4]Maryland Psychiatric Res. Ctr., Baltimore, MD; [5]Inst. of Psychology, Chinese Acad. of Sci., Beijing, China

Abstract: Aim. The goal of the current study was to examine the abnormalities of different subsystems in the default mode network (DMN) in first episode schizophrenia, and to investigate associations between these abnormalities and individual psychopathology. **Methods.** We recruited 203 patients with first episode schizophrenia, and 131 healthy controls. Clinical symptoms, magnetic resonance imaging (MRI) were assessed. After preprocessing, we performed seed-based functional connectivity (FC) analysis in 2D surface. Individual matrix was then obtained by calculating spatial correlation between pairs of FC maps, characterizing the functional fractionation of DMN. The degree centrality and the strength of connection were used for subsequent group analysis. **Results.** Patients showed similar patterns but markedly reduced strength of DMN fractionation where the degree centrality of posterior inferior parietal lobule, retrosplenial cortex, parahippocampal cortex and hippocampal formation is significantly reduced in schizophrenia. Patients exhibited hypo-connectivity between lateral temporal cortex and retrosplenial cortex and parahippocampal cortex, suggesting a functionally disconnection particularly in the MTL subsystems. **Conclusion.** We observed hyper-fractionation of different DMN components, implying that communication and coordination throughout the dissociated components of the DMN are functionally over-segregated in schizophrenia.

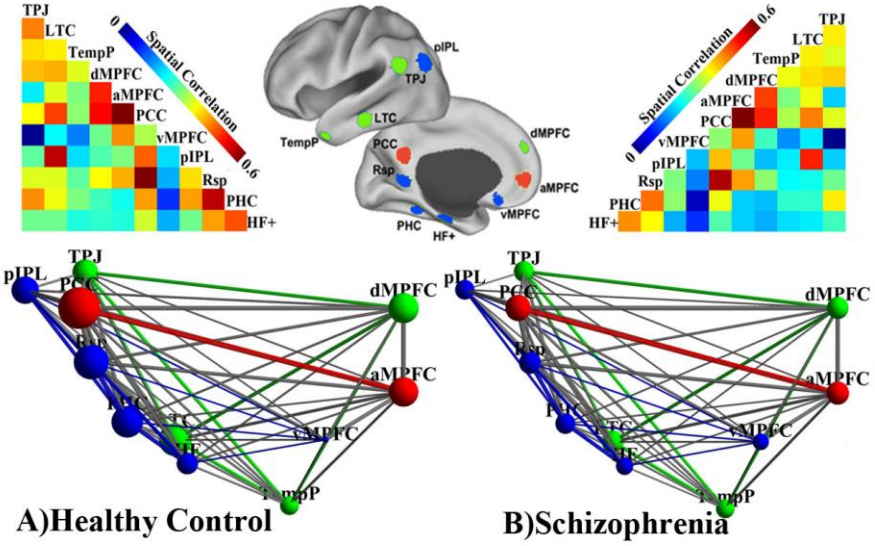


Figure 1. Correlation strengths among regions within the default network are shown using network centrality measures in the two groups. The size of the circle represents the centrality of a given node. The thickness of the lines reflects the strength of the correlation between regions.

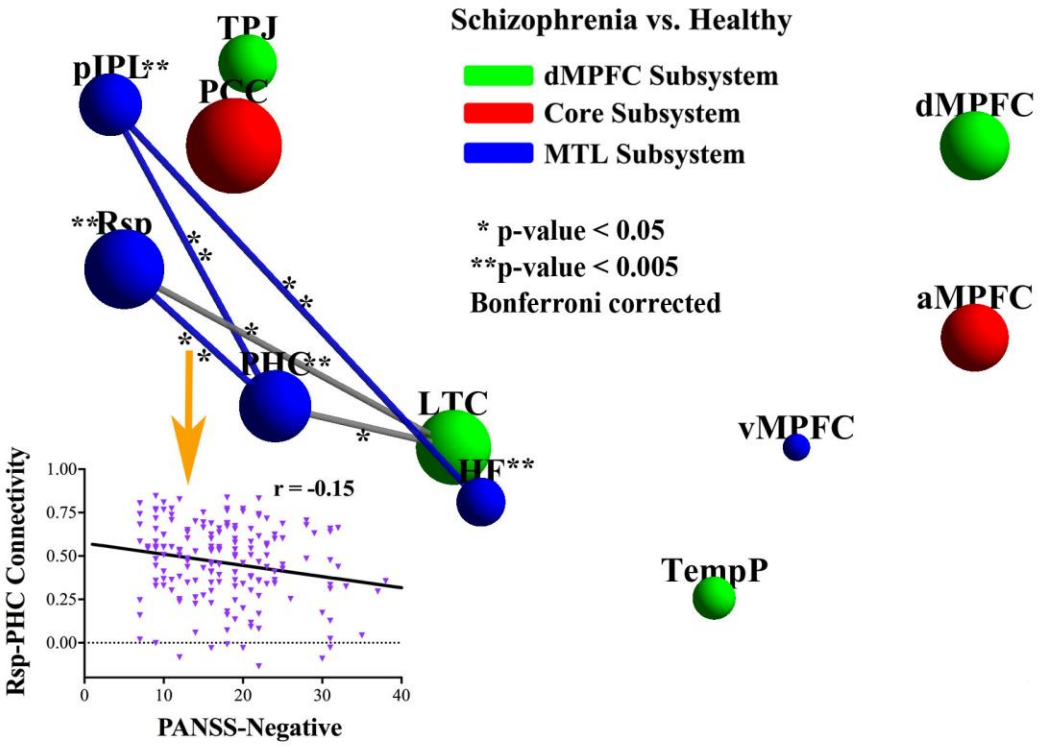


Figure 2. Group differences in nodal centrality and edge strength, and its relationship with PANSS.

Disclosures: F. Fan: None. **Y. Tan:** None. **Z. Wang:** None. **F. Yang:** None. **H. Fan:** None. **H. Xiang:** None. **H. Guo:** None. **E. Hong:** None. **S. Tan:** None. **X. Zuo:** None.

Nanosymposium

363. Schizophrenia: Circuits and Systems

Location: SDCC 2

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 363.04

Topic: H.03. Schizophrenia

Title: Using machine learning to identify novel neuroimaging phenotypes associated with cognitive dysfunction in schizophrenia

Authors: *V. SADASHIVAIAH[1], A. GOLDMAN[1], B. ULRICH[1], E. RADULESCU[1], K. F. BERMAN[2], V. S. MATTAY[1], D. R. WEINBERGER[1], Q. CHEN[1]

[1]Lieber Inst. for Brain Develop., Baltimore, MD; [2]Clin. and Translational Neurosci. Br., NIH/National Inst. of Mental Hlth., Bethesda, MD

Abstract: Introduction:
Neuroimaging-based intermediate phenotypes (NIPs) have been used as a promising approach to identify genetic mechanisms associated with cognitive dysfunction in schizophrenia (SZ). However, most of the current NIPs are based on univariate approaches, either for activation or connectivity, which are limited in uncovering the complexity of neural circuits involved in information processing. In this study, we used a machine learning based approach to identify novel imaging phenotypes embedded in functional magnetic resonance imaging (fMRI) data collected from subjects during a declarative memory task.
Methods:
fMRI data from 54 SZ patients and 54 healthy controls (HC) were included in this study. Sex and age were well matched across groups. Subjects performed a declarative memory task (Rasetti *et. al.*, 2014) during BOLD fMRI (3T), that entailed simple incidental encoding and retrieval of complex visual scenes. We used support vector machine (SVM) to classify contrast images of two condition blocks (neutral and aversive) from two groups of subjects (controls and patients). In SVM, a linear kernel classifier was used and eight-fold cross-validation was conducted to evaluate the classification accuracy.
Results:
The classification accuracy of training was 95%, and the classification accuracy of cross validation was 70%. Among the top brain regions contributing to classification, hippocampus and amygdala had strong effects. Both left and right hippocampi played an important role in classifying valence versus diagnosis groups. Interestingly, left amygdala had a greater contribution than right amygdala in classification except for the neutral encoding condition. Activation patterns in prefrontal and parietal regions also contributed significantly.
Conclusions:
Our results show that a multivariate based machine learning method could identify relationships of brain regions in a more comprehensive way. The features extracted from classification represent not only the activation patterns of these brain regions but also relationship among these regions. We will explore the heritability of the classifying features using our fMRI data collected from healthy siblings of patients with schizophrenia.

Disclosures: V. Sadashivaiah: None. **A. Goldman:** None. **B. Ulrich:** None. **E. Radulescu:** None. **K.F. Berman:** None. **V.S. Mattay:** None. **D.R. Weinberger:** None. **Q. Chen:** None.

Nanosymposium

363. Schizophrenia: Circuits and Systems

Location: SDCC 2

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 363.05

Topic: H.03. Schizophrenia

Support: Beijing Municipal Natural Science Foundation (7162087)
National Natural Science Foundation of China (31671145)

Title: Abnormal functional connectivity of amygdala subregions and the dysconnectivity correlation with positive symptom in first episode schizophrenia

Authors: M. ZHANG[1], F. FAN[1], Z. WANG[1], X. HONG[2], F. YANG[1], Y. TAN[1], *S. TAN[1]
[1]Beijing Huilongguan Hosp., Beijing, China; [2]Chongqing San Xia Central Hosp., Chongqing, China

Abstract: Background: Altered resting-state functional connectivity (rsFC) of the amygdala has been implicated in participating in schizophrenia neuropathology. However, it is rarely investigated whether rsFC of amygdala subregions are differentially affected in schizophrenia. To evaluate this issue, we compared the functional networks of each amygdala subdivision in healthy controls (HC) and patients with first-episode schizophrenia (FES).
Methods: 43 FES patients and 47 health controls (HC) were recruited. The amygdala was divided into three subregions, including basolateral amygdala (BLA), centromedial amygdala (CMA), and superficial amygdala (SFA) using probabilistic anatomic maps. The rsFC of three amygdala subdivisions were computed and compared between the two groups. All participants underwent resting-state functional magnetic resonance imaging (rsfMRI).
Results: Compared with healthy controls, only left CMA and bilateral SFA subregions exhibited abnormal FC in schizophrenia. Increased positive FC values (FCs) were observed in the right superior occipital gyrus (SOG). decreased negative FCs were observed in left median cingulate and paracingulate gyri (MPCG), bilateral superior parietal gyrus (SPG), right precuneus (PCUN), right angular gyrus (AG) (TFCE, P<0.05). Besides, the FC of right SFA with right SOG were positively associated with positive symptom scores (r=0.375, p=0.019).
Conclusion: The selective rsFC abnormalities in the left CMA and bilateral SFA in FES patients were observed, and the abnormally increased positive right SFA-right SOG network may be involved in the emergence of positive symptoms.

Table1. Demographics of participants

Variable	HC (n = 47)		FES (n = 43)		X^2/T	P
	Mean	SD	Mean	SD		
Sex(male/female)	26/21		21/22		0.378	0.539
Age (years)	24.96	5.34	24.79	5.97	0.140	0.899
Education (years)	10.02	2.98	10.05	2.75	-0.042	0.967
IQ	96.91	13.31	83.95	10.66	5.068	<0.000
PANSS total score			73.84	14.72		
P subscore			19.72	5.42		
N subscore			16.58	6.68		
G subscore			37.53	7.95		

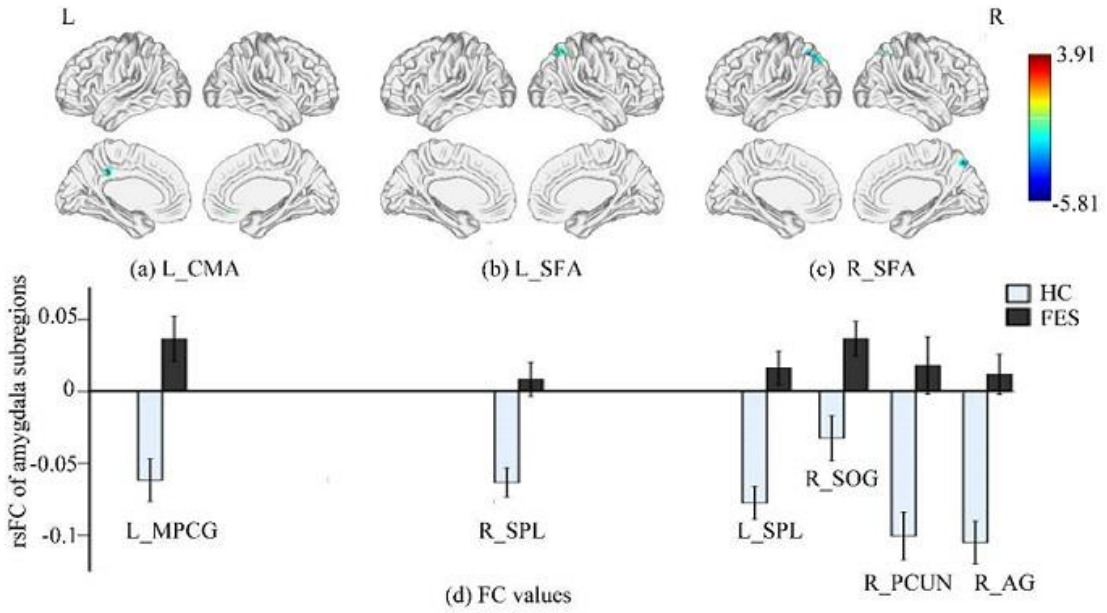


Figure 1. Comparison of rsFC of the left CMA and bilateral SFA between HC and FES. Note: A two-sample t-test assessed the differences in rsFC of the left CMA and bilateral SFA between the two groups (Fig.1a & Fig.1b& Fig.1c). Mean intensity functional connectivity of the amygdala subregions with the different brain regions was shown in Fig.1d. The Bar diagrams and error bars represent the mean Z values and standard errors of the functional connectivity

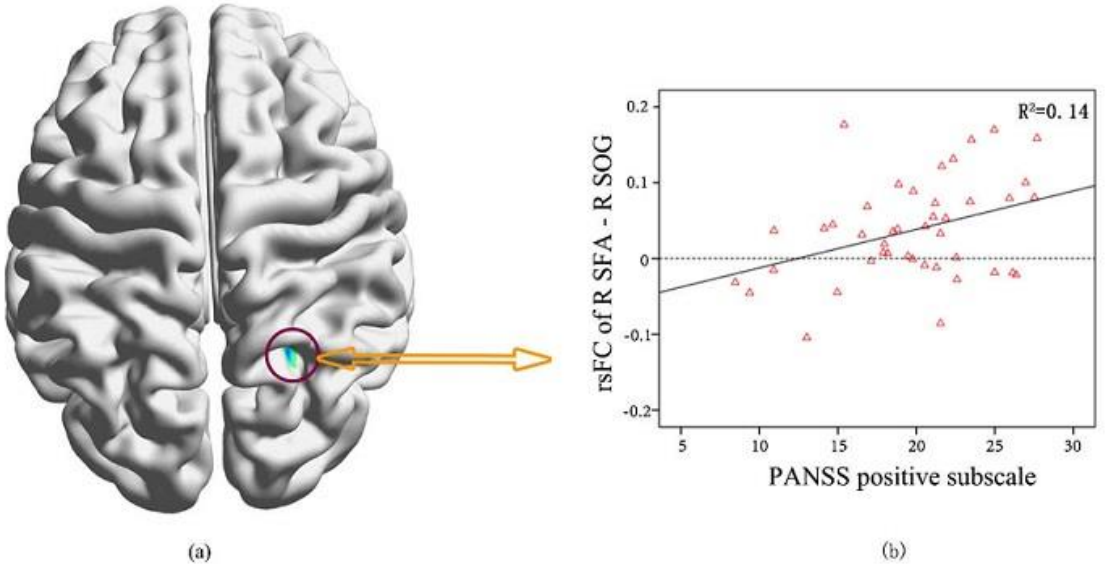


Figure 2. Correlation between right SFA connectivity and positive symptom in patients(Fig2b). The right superior occipital gyrus was showed in Fig2a.

Disclosures: M. Zhang: None. **F. Fan:** None. **Z. Wang:** None. **X. Hong:** None. **F. Yang:** None. **Y. Tan:** None. **S. Tan:** None.

Nanosymposium

363. Schizophrenia: Circuits and Systems

Location: SDCC 2

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 363.06

Topic: H.03. Schizophrenia

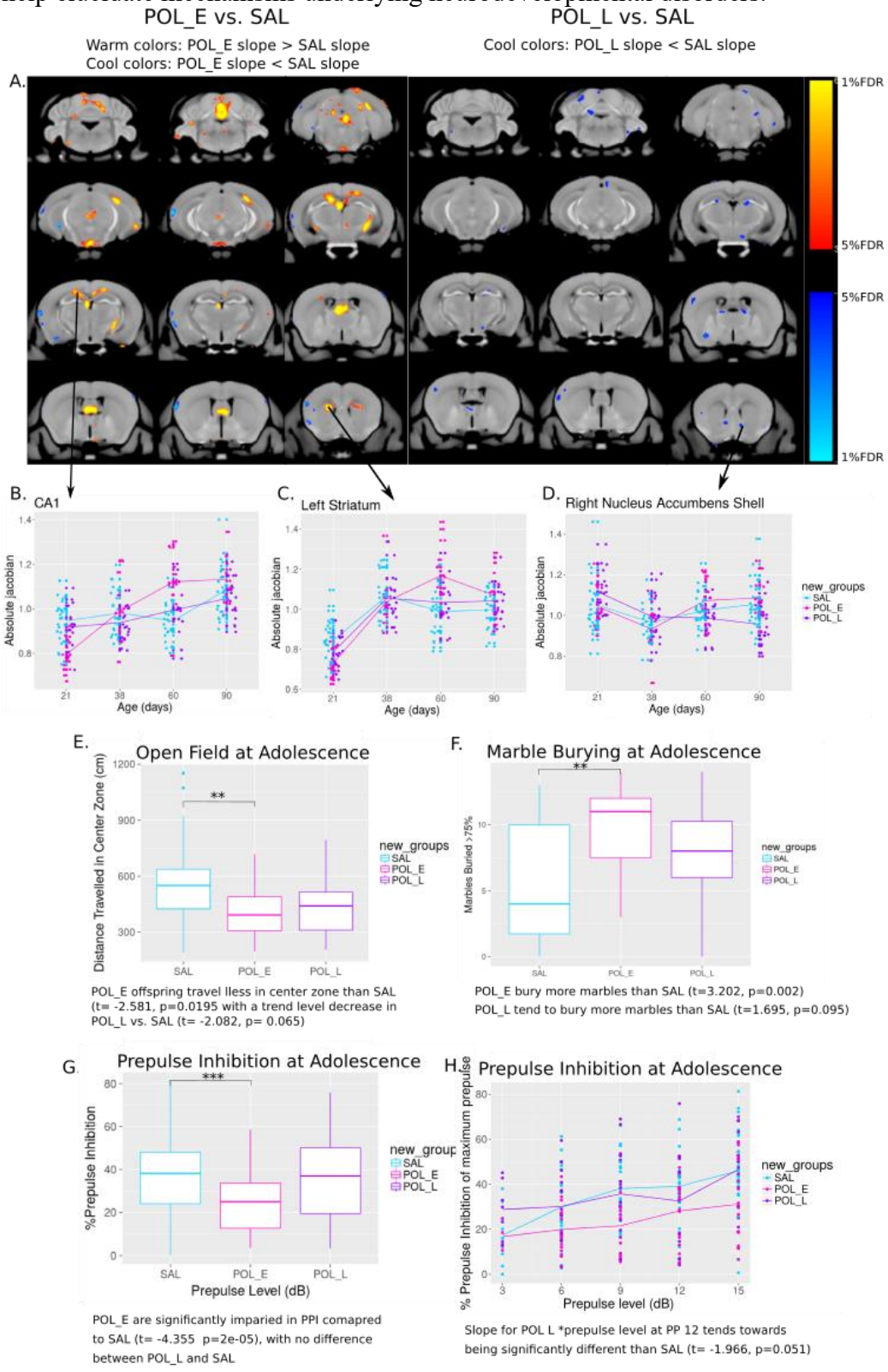
Support: Brain Canada 68680
FRQS 35520

Title: Mapping of postnatal neurodevelopment in response to early and late prenatal maternal immune activation in mice

Authors: *E. GUMA[1], C. ANASTASSIADIS[1], J. GERMANN[3], D. R. GALLINO[3], G. AYRANCI[2], G. A. DEVENYI[3], M. CHAKRAVARTY[1]
[2]Neurosci., [1]McGill Univ. Douglas Res. Ctr., Montreal, QC, Canada; [3]Cerebral Imaging Ctr., Douglas Res. Ctr., Montreal, QC, Canada

Abstract: Epidemiological studies have demonstrated that prenatal exposure to infection in mid-to-late gestation is a risk factor for neurodevelopmental disorders. Rodent studies have linked prenatal maternal immune activation (MIA) with anatomical and behavioural changes in offspring mirroring those of schizophrenia and autism. This study aims to link precise timing of MIA with neuroanatomical and behavioural phenotypes in offspring.
Pregnant dams (C57BL6) were injected (IP) with Poly I:C (POL; 5mg/kg) or vehicle (SAL) at gestational day 9(E) or 17(L) - end of first and second trimesters in humans, respectively. Structural MRIs (100um^3) were collected on offspring (n= SAL=36, POL_E=21, POL_L=25) *in vivo* on postnatal day (P) 21, 38, 60 and 90. Deformation based morphometry was used to investigate voxel-level brain volume differences. Voxel-wise linear mixed effects modeling was performed to investigate deviations in brain maturation for POL_E and L compared to SAL offspring (False Discovery Rate [FDR] corrected). Open field, social preference, marble burying, and prepulse inhibition (PPI) were performed at adolescence (P40) and adulthood (P92).
Differences in brain development trajectories were observed in regions showing variation in neurodevelopmental disorders such as the prelimbic cortex, caudate, thalamus, dentate gyrus, and lateral septum. This variation was largest in POL_E offspring (>5% FDR; Fig1A-D). At adolescence, POL_E exhibited more anxiety and stereotypic behaviours and had impaired sensorimotor gating ($p<0.01$, Fig1E-G). POL_L offspring had subthreshold anxiety ($p=0.07$) and stereotypic behaviours ($p=0.09$). POL_E behavioural deficits normalized in adulthood, apart from stereotypic behaviours ($p=0.08$).
Early MIA induces greater alterations to neurodevelopmental trajectories than late MIA does. Furthermore, early MIA induces greater behavioural deficits at adolescence, many of which

normalized by adulthood. A better understanding of how MIA timing impacts offspring could help elucidate mechanisms underlying neurodevelopmental disorders.



POL_E offspring travel lless in center zone than SAL (t= -2.581, p=0.0195 with a trend level decrease in POL_L vs. SAL (t= -2.082, p= 0.065)

POL_E bury more marbles than SAL (t=3.202, p=0.002)
POL_L tend to bury more marbles than SAL (t=1.695, p=0.095)

POL_E are significantly imparied in PPI comapred to SAL (t= -4.355 p=2e-05), with no difference between POL_L and SAL

Slope for POL L *prepulse level at PP 12 tends towards being significantly different than SAL (t= -1.966, p=0.051)

Disclosures: E. Guma: None. **C. Anastassiadis:** None. **J. Germann:** None. **D.R. Gallino:** None. **G. Ayranci:** None. **G.A. Devenyi:** None. **M. Chakravarty:** None.

Nanosymposium

363. Schizophrenia: Circuits and Systems

Location: SDCC 2

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 363.07

Topic: H.03. Schizophrenia

Support: SFB 1080

Title: Synaptic phospholipids as a new target for cortical hyperexcitability and E/I-balance in psychiatric disorders

Authors: *G. HORTA[1], C. THALMAN[1], I. TEGEDER[2], K. RADYUSHKIN[3], T. SIGURDSSON[4], R. NITSCH[1], J. VOGT[1]
[1]Inst. of Microscopic Anat. and Neurobio., Mainz, Germany; [2]Goethe-Universität Frankfurt a. Main, Frankfurt a. Main, Germany; [3]Mouse Behavior Unit, Mainz, Germany; [4]Goethe Univ. Frankfurt, Frankfurt, Germany

Abstract: Lysophosphatidic acid (LPA) is a synaptic modulator which regulates cortical excitation-inhibition balance and controls sensory information processing in mice and man while altered synaptic LPA-signaling is associated with psychiatric disorders like schizophrenia. Here, we show that the LPA-synthesizing enzyme autotaxin (ATX) is specifically expressed in the astrocytic compartment of excitatory synapses. ATX-sorting towards fine astrocytic processes and its enzymatic activity are dynamically regulated by neuronal activity via astrocytic glutamate receptors. Pharmacological and genetic ATX-inhibition both rescued schizophrenia-related hyperexcitability syndromes due to altered bioactive lipid signaling in two genetic mouse models for psychiatric disorders while not affecting naive animals. Moreover, pharmacological ATX-inhibition rescued electrophysiological and behavioral schizophrenia-like phenotype in a ketamine model of schizophrenia. Targeting ATX might thus be a versatile strategy for a novel drug therapy of schizophrenia.

Disclosures: G. Horta: None. **C. Thalman:** None. **I. tEGEDER:** None. **K. Radyushkin:** None. **T. Sigurdsson:** None. **R. Nitsch:** None. **J. Vogt:** None.

Nanosymposium

363. Schizophrenia: Circuits and Systems

Location: SDCC 2

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 363.08

Topic: H.03. Schizophrenia

Support: Howard Hughes Medical Institute
Office for Naval Research
UCSD (RO1-MG065571; MH042228; MH079777; MH087889; Brain Behavioral Research Foundation; sidney R. Baer Jr. Foundation)
MSSM (R01-MH065554)
UCLA (R01-MH65707)
PENN (R01-MH65578)
UW (R01-MH65558)

Title: Nonlinear dynamics underlying auditory mismatch detection reveals previously unidentified subgroups in large cohorts of schizophrenia patients and healthy participants

Authors: *R. KIM[1,2], C. LAINSCSEK[1,5], A. L. SAMPSON[1,2], M. L. THOMAS[3], T. COGS INVESTIGATORS[3], T. J. SEJNOWSKI[1,5,4], G. A. LIGHT[3]
[1]Computat. Neurobio. Lab., Salk Inst. For Biol. Studies, La Jolla, CA; [2]Neurosci., [3]Psychiatry, [4]Div. of Biol. Sci., UCSD, La Jolla, CA; [5]Inst. for Neural Computation, La Jolla, CA

Abstract: Background
Auditory sensory information processing and integration are critical for the development of normal cognitive processes. Schizophrenia (SZ), a complex mental disorder, has been associated with diminished responses to unexpected sensory events and perceptual mismatch indicating sensory information dysfunction as a possible etiology of SZ. The proposed study investigates large-scale nonlinear dynamics of brain signals (electroencephalography; EEG) recorded from SZ subjects and non-psychiatric comparison (NC) subjects in order to characterize neural substrates underlying auditory information processing.
Methods
The Consortium on the Genetics of Schizophrenia (COGS-2) is a large, multi-center dataset that contains mismatch negativity (MMN) EEG recordings from SZ subjects (n = 877) and NC subjects (n = 753). Delay differential analysis (DDA), a novel method based on dynamical systems theory, was first employed to extract nonlinear features from these EEG signals. A clustering algorithm was then developed to group signals with similar DDA features.
Results
The subgroups identified by our clustering algorithm were correlated with (1) leading candidate neurophysiological biomarkers including MMN amplitude and (2) cognitive functioning as

measured by a battery of neuropsychological tests. In both SZ and NC groups, we found subgroups with attenuated MMN amplitude. These subgroups were also associated with poor cognitive functioning (as measured by California Verbal Learning Test-Second Edition, Wechsler Memory Scale, and Penn's Computerized Neurocognitive Battery) compared to other subgroups within each cohort. In summary, our clustering algorithm along with DDA revealed unique nonlinear features that are closely related to neurophysiological and functional characteristics of auditory information processing.

Conclusions

Nonlinear analysis of EEG signals revealed possible neural substrates of auditory deviance detection and could provide an avenue for identifying clinically useful biomarkers for SZ.

Disclosures: R. Kim: None. **C. Lainscsek:** None. **A.L. Sampson:** None. **M.L. Thomas:** None. **T. COGS Investigators:** None. **T.J. Sejnowski:** None. **G.A. Light:** None.

Nanosymposium

363. Schizophrenia: Circuits and Systems

Location: SDCC 2

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 363.09

Topic: H.03. Schizophrenia

Support: NIH 5K23MH100623
NIH R01MH112706
NIH RO1MH92440
NIH K24MH104449
NIH UL1 RR025758
Sidney R. Baer Jr. Foundation
MINDlink Foundation

Title: Breakdown of functional connectivity in cerebellar-prefrontal network underlies negative symptoms in schizophrenia

Authors: *R. O. BRADY, JR[1], I. GONSALVEZ[2], D. ÖNGÜR[3], J. D. SCHMAHMANN[4], S. EACK[5], M. KESHAVAN[1], A. PASCUAL-LEONE[6], M. A. HALKO[7]
[1]Beth-Israel Deaconess Med. Ctr., Boston, MA; [2]St. Elizabeth's Med. Center,, Boston, MA; [3]McLean Hosp., Belmont, MA; [4]Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [5]irenegonsalvez@gmail.com, Pittsburgh, PA; [6]Ctr. Noninvasive Brain Stimulation, Beth Israel Deaconess Med. Cente, Boston, MA; [7]Neurol., Harvard Med. Sch. / Beth Israel Deaconess Med., Boston, MA

Abstract: The interpretability of results in psychiatric neuroimaging is significantly limited by an overreliance on correlational relationships. Purely correlational studies cannot alone

determine if behavior-imaging relationships are causal to illness, functionally compensatory processes, or purely epiphenomena. Here we take a two-step approach to identifying and then empirically testing a brain network model of schizophrenia symptoms. Negative symptoms (e.g. anhedonia, amotivation, and expressive deficits) are refractory to current medications and are one of the foremost causes of disability in this illness. Using a data-driven resting-state functional connectivity fMRI analysis, we show that in schizophrenia patients (n=44), dysconnectivity in a dorsolateral prefrontal cortex (DLPFC) to cerebellum network directly corresponds to negative symptom severity. We then empirically tested this network-symptomatology relationship by directly modulating network connectivity in a separate cohort (n=11) with 5 days of twice-daily transcranial magnetic stimulation. Our results demonstrate that network disconnectivity between the cerebellum and DLPFC is associated with negative symptom severity and that correction of this disconnectivity ameliorates negative symptom severity (r= -.809, p=.003). Our results support a novel network hypothesis for medication refractory negative symptoms, and indicates network manipulation may establish causal relationships between biomarkers and clinical phenomena.

Disclosures: R.O. Brady: None. **I. Gonsalvez:** None. **D. Öngür:** F. Consulting Fees (e.g., advisory boards); Neurocrine Inc. **J.D. Schmahmann:** F. Consulting Fees (e.g., advisory boards); Cadent, Biogen, Biohaven, Pfizer. **S. Eack:** None. **M. Keshavan:** None. **A. Pascual-Leone:** F. Consulting Fees (e.g., advisory boards); Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Neosync. **M.A. Halko:** None.

Nanosymposium

363. Schizophrenia: Circuits and Systems

Location: SDCC 2

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 363.10

Topic: F.01. Neuroethology

Support: NARSAD Young Investigator Grant 25163
NIH Grant MH103374
NIH Grant NS059957
NIH Grant MH112883

Title: Mechanism of a gene to neural circuit pathology driving social dysfunction

Authors: *I. KIM[1], N. KIM[3], K. TODA[3], C. CATAVERO[2], H. YIN[3], S. SODERLING[2]
[1]Psychiatry and Behavioral Sci., [2]Cell Biol., Duke Med. Ctr., Durham, NC; [3]Psychology and Neurosci., Duke Univ., Durham, NC

Abstract: The behavioral endophenotypes of psychiatric disorders represent the pathogenic results of gene mutational effects on neuronal circuit function, however, interactions between

mutations and neural circuits relevant to behavioral abnormalities remains largely uncharted. Here we report the manipulation of gene function within an isolated neural circuit, allowing us to image and functionally define a pathological mechanism of sociability dysfunction. We demonstrate how gene loss within a long-range circuit from prefrontal cortex leads to abnormal neuronal excitation of the circuit, resulting in reduced preference for social interactions. Moreover, using this approach we both selectively image and manipulate this circuit in vivo during social interactions, demonstrating its role in sociability under normal and pathological conditions. Together these results highlight a pathogenic gene-circuit interaction that drives impaired sociability as well as a new generalizable approach to uncovering the gene-to-circuit basis of behavioral abnormalities.

Disclosures: I. Kim: None. **N. Kim:** None. **K. Toda:** None. **C. Catavero:** None. **H. Yin:** None. **S. Soderling:** None.

Nanosymposium

363. Schizophrenia: Circuits and Systems

Location: SDCC 2

Time: Monday, November 5, 2018, 1:00 PM - 3:45 PM

Presentation Number: 363.11

Topic: H.03. Schizophrenia

Support: NIH Grant T32MH017168
CHOP/UPENN IDDRC 1U54HD086984-01
Foerderer Grant from CHOP Research Institute
NIH Grant 5T32MH019112-27

Title: Circuit-based therapies rescue social memory performance in a 22q11.2 deletion mouse model

Authors: *J. B. KAHN[1], R. G. PORT[2], S. A. ANDERSON[3], D. A. COULTER[4]
[1]Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [2]Neurosci. Grad. Group, Univ. Of Pennsylvania, Philadelphia, PA; [3]Psychiatry, Children's Hosp. of Philadelphia/Upenn Sch. Med., Philadelphia, PA; [4]Pediatrics Div. of Neurol., Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: One in four patients born with the 22q11.2 deletion develops schizophrenia, making this heterozygous deletion the most significant genetic risk factor for the disorder. Several groups have reported hippocampal deficits in 22q11.2DS mouse models. The ventral hippocampus becomes an interesting circuit to investigate as it has the potential to affect positive, negative, and cognitive symptoms in schizophrenia, and abnormal ventral hippocampal activity is one of the most commonly reported neurological findings in schizophrenia patients. The ventral hippocampus is critical for social memory in mice, so we used a social discrimination paradigm to assess ventral hippocampal function in a mouse model of 22q11.2DS (Df(h22q11)/+). In the

discrimination task, a novel mouse and a familiar mouse are placed in small chambers at opposite ends of an arena. The subject mouse can freely explore the arena, and the amount of time the subject mouse investigates each chamber is quantified. While control animals preferentially explored the novel mouse, the 22q11.2DS mice failed to discriminate between the novel mouse and the familiar mouse, exploring both mice equally. In vitro voltage sensitive dye recordings revealed that the ventral CA1 in 22q11.2DS mice is hyperactive. We used excitatory DREADDs (designer receptors exclusively activated by designer drugs) to recreate the ventral hippocampal hyperactivity in healthy mice and found that this circuit phenotype was sufficient to compromise social memory performance. We then sought to reduce the hyperactivity in our disease model to see if we could affect the behavioral output. Two types of inhibitory DREADDs (hM4Di and KORD) were co-injected into the ventral hippocampi of 22q11.2DS mice. When treated with saline, the mice failed to discriminate on the social discrimination task, repeating the previously observed deficit. However, activating either inhibitory DREADD with the appropriate ligand (CNO or Salvinorin B respectively) rescued the subjects' ability to discriminate between the familiar and novel mice. Finally, when the animals were tested on a reversal trial sans ligand, they lost their ability to distinguish between the cue mice, suggesting that the circuit-based interventions were responsible for the subjects' improved behavioral performance. These data provide evidence for a causal link between ventral hippocampal circuit phenotypes and behavioral deficits in this mouse model of schizophrenia.

Disclosures: J.B. Kahn: None. **R.G. Port:** None. **S.A. Anderson:** None. **D.A. Coulter:** None.

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.01

Topic: I.03. Anatomical Methods

Support: Brain Mapping of Integrated Neurotechnologies for Disease Studies (Brain/MINDS) from the Japan Agency for Medical Research and Development, AMED
NIH Grant 5R01EB022899
Crick-Clay Professorship in CSHL
H.N. Mahabala Chair, IIT Madras

Title: Towards a mesoscale connectivity map of the common marmoset: A partial connectivity matrix and an online data portal

Authors: *M. LIN[1], M. HANADA[1], B. C. LEE[2], J. NAGASHIMA[1], Y. S. TAKAHASHI[1], B.-X. HUO[1], X. LI[3], K. RAM[4], B. SHI[5], M. I. MILLER[2], M. G. ROSA[5], H. OKANO[6], P. P. MITRA[3]
[1]Ctr. for Brain Sci., Riken, Wakoshi, Japan; [2]Johns Hopkins Univ., Baltimore, MD; [3]Cold Spring

Harbor Lab., Cold Spring Harbor, NY; [4]Indian Inst. of Technologies Madras, Tamil Nadu, India; [5]Biomedicine Discovery Inst. and Dept. of Physiol., Monash Univ., Melbourne, Australia; [6]Keio Univ. Sch. of Med., Tokyo, Japan

Abstract: There has been significant progress in recent years in mapping brain-wide connectivity in the mouse based on the grid-based approach of injecting tracers on an array of locations covering the brain, and assembling the resulting data sets. Here we present progress on brain-wide connectivity mapping in a second vertebrate species, the common marmoset (*Callithrix Jacchus*), mirroring the approach that was first proposed and used in the Mouse. The data were generated as part of the Japanese Brain/MINDS initiative, which has focused on the common marmoset as a model organism, and was generated using a high-throughput neuro-histological pipeline adapted from the Mouse Brain Architecture Project (http://mouse.brainarchitecture.org/) to map mesoscale connectivity in the mouse brain. We present our results through an online resource (http://riken.marmoset.brainarchitecture.org/). We present whole-brain image series from >30 marmoset brains displaying the results of >100 tracer injections, both retrograde (FastBlue, CTB) and anterograde (AAV GFP, AAV TdTom). Brains are serially sectioned ($20\mu m$ section spacing, with Nissl and Myelin stained sections interleaved with tracer-labelled sections). Each brain is accompanied by pre and postmortem MRI scans to assist the registration of the serial sections into 3D stacks that are atlas registered. The injection sites, axonal fragments from anterograde projections and retrogradely labelled somata are computationally detected, and compiled into a regional connectivity matrix, also available from the online resource. We link our connectivity resource to a large (>100 injections) set of retrograde injections from Monash University which is already available online, together with a regional connectivity matrix based on that data (http://monash.marmoset.brainarchitecture.org/). We believe that the resulting online resource is the most comprehensive one to date, for mesoscale connectivity mapping in any primate brain, that is accompanied by full resolution images of the underlying high resolution histological data.

Disclosures: M. Hanada: None. **B.C. Lee:** None. **J. Nagashima:** None. **Y.S. Takahashi:** None. **B. Huo:** None. **X. Li:** None. **K. Ram:** None. **B. Shi:** None. **M.I. Miller:** None. **M.G. Rosa:** None. **H. Okano:** None. **P.P. Mitra:** None.

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.02

Topic: I.03. Anatomical Methods

Support: AMED

Title: Prefrontal projection mapping of the common marmoset

Authors: *A. WATAKABE[1], J. WANG[1], M. TAKAJI[1], H. MIZUKAMI[2], A. WOODWARD[1], H. SKIBBE[3], K. NAKAE[3], Y. YAMAGUCHI[1], S. ISHII[3], T. YAMAMORI[1]
[1]CBS, RIKEN, Wako, Japan; [2]Jichi Med. Univ., Shimotsuke, Japan; [3]Kyoto Univ., Kyoto, Japan

Abstract: The prefrontal cortex (PFC) plays a critical role in a variety of cognitive functions including executive control and is associated with neuropsychological disorders such as autism and schizophrenia. It is also a brain region that evolved greatly in primate lineage. The key to understand the diverse functions of PFC is to clarify its connectivity within and outside PFC. In particular, it is important to examine the PFC connectivity in a model primate animal to the level that enables detailed comparison across species. For this purpose, we chose the common marmoset, a New World monkey, with a relatively small and smooth brain but with characteristic "granular" PFC areas. In this presentation, we introduce our strategy to map PFC projections at the whole brain scale using serial two-photon tomography (STPT) imaging. Each sample brain was MR-imaged ex vivo before sectioning to registrate to the averaged 3D template with anatomical annotation (Woodward et al. 2018). A TET-enhanced AAV tracer was injected at a single site per animal. This tracer labels both the projection pathway and the connection targets, which will be useful for comparison with DWI (diffusion weighted imaging). For long-range cortical connection, the pathway and target can be effectively distinguished by extracting the gray matter signal. We show here that the dorsolateral PFC (A9, A8aV, A8aD, A46) makes dense connections within the frontal region including the premotor areas, as well as long-range connections to the parietal, temporal and cingular areas, while bypassing the motor and auditory areas. We are now trying to decipher the rule of projection by systematic comparison of nearby injections within this connection network. At a finer level of analysis, we found that PFC projections often converge in a column of approximately 300μm, as has been reported for macaques. To clarify the input-output relationship at this scale, we established a non-fluorescent antero/retrograde labeling method that is compatible with STPT imaging. Despite long-standing view for the importance of columnar architecture in cortical circuit, its true significance still remains enigmatic. We believe that clarifying the connectivity structure of PFC at area- and columnar-level will provide insight into the functions of PFC circuits.

Disclosures: A. Watakabe: None. **J. Wang:** None. **M. Takaji:** None. **H. Mizukami:** None. **A. Woodward:** None. **H. Skibbe:** None. **K. Nakae:** None. **Y. Yamaguchi:** None. **S. Ishii:** None. **T. Yamamori:** None.

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.03

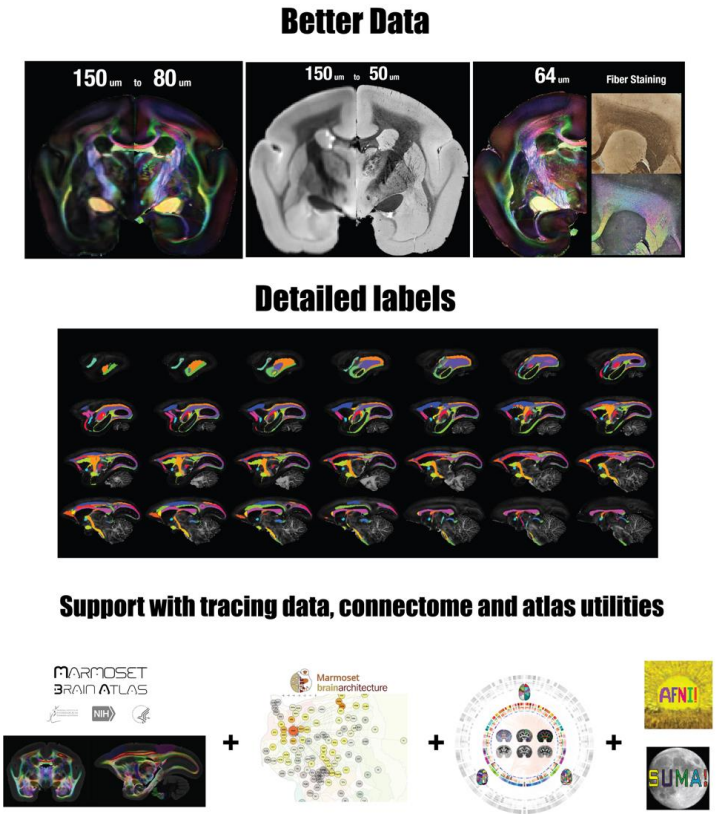
Topic: I.03. Anatomical Methods

Support: the Intramural Research Program of the NIH, NINDS
Australian Research Council CE140100007
International Neuroinformatics Coordinating Facility

Title: NIH marmoset brain atlas v2.0: Using ultra-high-resolution diffusion MRI and a cortical tracing database to map white matter pathways

Authors: *C. LIU, F. YE[1], C. YEN[2], J. D. NEWMAN[3], D. GLEN[1], P. MAJKA[4], D. SZCZUPAK[2], J. GUY[2], S. HA[2], D. A. LEOPOLD[1], M. G. ROSA[5], A. C. SILVA[2]
[1]NIMH/NIH, Bethesda, MD; [2]NINDS/NIH, Bethesda, MD; [3]NICHD/NIH, Bethesda, MD; [4]Nencki Inst. of Exptl. Biol., Warsaw, Poland; [5]Biomedicine Discovery Inst., Monash Univ., Melbourne, Australia

Abstract: Last SfN (2017), we released the first version of the NIH Marmoset Brain Atlas that focused on cortical parcellation. This year (SfN2018), we are releasing a new version that maps white matter pathways. Because marmosets are lissencephalic, the organization of major white matter tracts appears to be "rather simple", but in fact different fiber tracts are "bundled" in complex multi-layer structures. These complexities bring challenges for dissecting white matter pathways and were thus very poorly depicted in any previously existing atlases. To dissect and label white matter tracts, we pushed the resolution of structural MRI from 150 μm^3 (our previous version) to 50 μm^3 (the new version), and we collected multi-shell diffusion MRI at both 7T (80 μm^3) and 14T (64 μm^3). Bielschowsky fiber staining was also performed on brain slices to guide building of the atlas. With the ultra-high-resolution data, we have, hitherto, labeled more than 80 white matter structures based on probabilistic tractography and manual segmentation, some of which have been largely ignored in current literatures. Our detailed inspection and analysis demonstrates that the marmoset brain features a complex white matter structure, with many areas aggregating multiple different fiber pathways. For example, the corona radiata shows multi-layered bundles where fibers of each bundle pass through in different directions. In addition to the tracts that connect distant cortices, multi-layered bundles could also be observed locally, such as in the occipital lobe. These complex structures are hard to be dissected or identified without the current high-resolution images. In addition, the white matter atlas will be combined with real tracing data from the Marmoset Brain Architecture Project to provide detailed information about how any two cortical regions are connected (via which white matter tracts). All the above data will be integrated into the AFNI software to provide fully-featured atlas functions and will be the most comprehensive white matter atlas published to date.



Disclosures: F. Ye: None. **C. Yen:** None. **J.D. Newman:** None. **D. Glen:** None. **P. Majka:** None. **D. Szczupak:** None. **J. Guy:** None. **S. Ha:** None. **D.A. Leopold:** None. **M.G. Rosa:** None. **A.C. Silva:** None.

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.04

Topic: I.03. Anatomical Methods

Support: Wellcome Trust Investigator award 108089/Z/15/Z
MRC Programme Grant MR/M023990/1
Behavioural and Clinical Neuroscience Institute funded by Wellcome Trust and Medical Research Council of Great Britain

Title: Trajectories and milestones of cortical and subcortical development of the marmoset brain from infancy to adulthood

Authors: *A. C. ROBERTS[1], S. SAWIAK[1], Y. SHIBA[1], L. OIKONOMIDIS[1], C. WINDLE[1], A. SANTANGELO[1], H. GRYDELAND[3], G. COCKCROFT[1], E. BULLMORE[2]
[1]Physiology, Develop. and Neurosci., [2]Psychiatry, Univ. of Cambridge, Cambridge, United Kingdom; [3]Psychology, Univ. of Oslo, Oslo, Norway

Abstract: As half of adult patients will already be diagnosed with a mental illness by age 14, rising to 75% by age 24, this is strongly suggestive of developmental factors in the pathogenesis of mental health disorders. However, we currently have limited knowledge of the developmental trajectories of cortical and subcortical brain circuits that, if disrupted, could plausibly contribute to early life incidence of psychiatric symptoms. Animal models are essential not only to elucidate how insults from the environment lead to such varied neuropsychiatric symptoms but to evaluate potential therapeutic interventions. Marmosets are primates with complex social and emotional behaviour and their compact lifespan (c. 14 years) makes them ideally suitable for studying all stages of development. We scanned 41 marmosets in 141 sessions in a mixed cross-sectional and longitudinal design, with the youngest animals scanned at 3 months of age. A 4.7T scanner was used to produce images optimised for grey-white matter contrast at a resolution of 250 μm. These were compared using tensor-based morphometry (TBM), using local deformation volume to find where changes occurred through development. Growth curves of structural volume were then extracted from each region and fitted with cubic b-splines for analysis. For TBM, t-tests (FDR-corrected $p < 0.05$) were used. For trajectory milestones, bootstrap resampling was used ($p < 0.05$). We reveal striking differences in the growth and maturation of different brain regions characterised by three milestones: the time taken to reach peak grey matter volume, the time before significant volume loss occurs, and the time at which that volume loss is greatest. We show that primary cortical areas peak earliest and have a short delay before volume loss (occurring before puberty); whereas secondary and association cortex peaks later, with most subsequent change occurring post-puberty. Using cluster analysis we show that the prefrontal association areas display the greatest heterogeneity of growth trajectories. Comparison of covariance between brain regions showed striking differences in structural connectivity in younger compared to older animals. In conclusion, our findings provide an atlas of structural growth with milestones of development. This will guide future developmental stress models of psychiatric disorders, providing critical insight into the different windows of sensitivity of different prefrontal circuits for targeting such impact. These models have the potential to reveal distinct behavioural phenotypes arising from these different developmental epochs that may cause a specific spectrum of neuropsychiatric symptoms.

Disclosures: A.C. Roberts: None. **S. Sawiak:** None. **Y. Shiba:** None. **L. Oikonomidis:** None. **C. Windle:** None. **A. Santangelo:** None. **H. Grydeland:** None. **G. Cockcroft:** None. **E. Bullmore:** A. Employment/Salary (full or part-time):; GlaxoSmithKline. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GlaxoSmithKline.

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.05

Topic: I.03. Anatomical Methods

Support: JSPS Grant 16J02485
Brain/MINDS from AMED
ImPACT from JST

Title: Dynamic muscle representations in marmoset motor cortex: Static lower limb position modulates upper limb motor somatotopy

Authors: *A. IRIKI[1,2], M. TAKEMI[3,2,4], B. TIA[5,2], A. KOSUGI[4,1,2], E. CASTAGNOLA[6,5], D. RICCI[5], L. FADIGA[5], J. USHIBA[4,7]
[1]RIKEN Ctr. For Biosystems Dynamics Res., Wako-Shi, Saitama, Japan; [2]RIKEN Brain Sci. Inst., Saitama, Japan; [3]Grad. Sch. of Educ., Univ. of Tokyo, Tokyo, Japan; [4]Grad. Sch. of Sci. and Technology, Keio Univ., Kanagawa, Japan; [5]Ctr. for Translational Neurophysiology, Inst. Italiano di Tecnologia, Ferrara, Italy; [6]Ctr. for Sensorimotor Neural Engineering, San Diego State Univ., San Diego, CA; [7]Keio Inst. of Pure and Applied Sciences, Keio Univ., Kanagawa, Japan

Abstract: Neurons in primary motor cortex (M1) alter their preferred movement directions depending on arm postures (Kakei et al. 1999). While this represents the sensorimotor-driven flexibility of motor representations at single neuron level, little is known about flexibility of global M1 somatotopic organization, particularly through inter-limb interactions. This study tested spatial changes in the upper limb motor representations in adult common marmosets (n=3) under three different whole body postures: horizontal (trunk fixed to a horizontal pole and four limbs touched to the pole), vertical (trunk fixed to a vertical pole and four limbs touched to the pole), and vertical sit (same to the vertical except lower limbs touched to the ground). With these postures, two sensorimotor-driven factors affecting the motor representations could be dissociated – 1) whether the modulation relies on tonic muscle contraction against gravity and 2) to what extent the motor representations rely on sensorimotor inputs from lower limbs.
The marmoset brain is lissencephalic with dura mater much thinner than macaques, which allowed us to perform cortical stimulation mapping by chronically installed 64-ch epidural micro-electrocorticographic electrodes over the left M1. EMG activity was recorded from four right upper limb muscles by chronically implanted thin wire electrodes. M1 mapping was performed under awake conditions, by the procedures developed for accurate short-time M1 mapping (~ within 10 min). That is, motor maps were represented by motor threshold (MT: the stimulus intensity at which EMG activity is elicited with 50% probability at rest), which was

estimated for each electrode by using a modified maximum-likelihood algorithm (Kosugi et al., 2018) and an automatic high-speed cortical stimulator (Takemi et al., 2017). M1 mappings were repeated 14−16 times per posture for each marmoset to confirm stability and reproducibility of detected changes.
The results demonstrated that the upper limb muscle representations were dynamically regulated by whether the glabrous surface of the lower extremity had contact to the ground, but not by the orientation of body axis relative to the ground. The modulations occurred mostly in the M1 regions adjacent to the hotspot (where lowest MT was observed) of the target muscle representation. These indicate that the sensorimotor inputs from lower limbs may regulate the upper limb muscle representations in the intermediate corticomotor regions, which receive much axon collaterals from the area innervating other body parts (Weiss & Keller, 1994), resulting in dynamic somatotopic motor representations in the marmoset M1.

Disclosures: **A. Iriki:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); President and CEO of Rikaenalysis Corporation (RIKEN Venture). **M. Takemi:** None. **B. Tia:** None. **A. Kosugi:** None. **E. Castagnola:** None. **D. Ricci:** None. **L. Fadiga:** None. **J. Ushiba:** None.

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.06

Topic: I.03. Anatomical Methods

Support: Brain Mapping of Integrated Neurotechnologies for Disease Studies (Brain/MINDS) from the Japan Agency for Medical Research and Development, AMED, Grant JP17dm0207001
National Institutes of Health (NIH) Grant 5R01EB022899
National Health & Medical Research Council (NHMRC) Project Grant 1081441
The Australian Research Council Centre of Excellence for Integrative Brain Function CE140100007

Title: Cortical connections of marmoset dorsal lateral geniculate nucleus and inferior pulvinar nuclei

Authors: ***B.-X. HUO**[1], N. ZEATER[2,3], M. LIN[1], Y. S. TAKAHASHI[1], M. HANADA[1], J. NAGASHIMA[1], B. C. LEE[4], U. GRUNERT[2,3], M. I. MILLER[4], M. G. ROSA[5], H. OKANO[1,6], P. R. MARTIN[2,3], P. P. MITRA[1,7]
[1]Ctr. for Brain Sci., RIKEN, Wako, Japan; [2]Save Sight Inst. and Dept. of Clin. Ophthalmology, [3]Australian Res. Council Ctr. of Excellence for Integrative Brain Function, The Univ. of Sydney, Sydney, Australia; [4]Dept. of Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [5]Physiol.,

Monash Univ., Melbourne, Australia; [6]Keio Univ. Sch. of Med., Tokyo, Japan; [7]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: In primates, the dorsal lateral geniculate nucleus (LGN) and pulvinar contribute to multiple pathways for visual processing. The parvocellular (P) layers, magnocellular (M) layers, and koniocellular (K) layers of LGN send parallel outputs to different areas of visual cortex. Likewise, outputs of the lateral pulvinar and subdivisions of inferior pulvinar (IPul) are segregated to dorsal and ventral cortical pathways. These regions receive feedback from cortical areas in a selective manner. Here we developed a high-throughput neuro-histology pipeline to study these thalamocortical connections in marmosets. Anterograde and retrograde tracers were placed in visual cortices V1, V2 and dorsomedial area (DM, a "third-tier" visual area). By treating interleaving sections with different staining methods, we could simultaneously identify brain regions using Nissl stained sections and localize fluorescent tracer-labeled neurons. Interactive brain region segmentation was enabled by a web-based annotation tool. An automated computational routine was established to register fluorescent neurons to the Nissl stained sections and map to the corresponding brain regions. We found that both K layers of LGN and IPul project to V1 and V2, but not DM; whereas dominant outputs of M and P layers were to V1 only. Feedback from V1 and DM reach both K layers and IPul, yet neither LGN nor IPulL received afferents from V2. Retrograde labeled cells in lateral division of IPul (IPulL) merged seamlessly into the retrograde labeled cells in K layers. Similarly, anterograde neurons projecting from V1 and DM formed continuous terminal bands through IPulL and K layers. The continuity and common connectivity pattern between K layers of LGN and IPulL suggest functional contiguity of these parts of the dorsal thalamic matrix.

Disclosures: B. Huo: None. **N. Zeater:** None. **M. Lin:** None. **Y.S. Takahashi:** None. **M. Hanada:** None. **J. Nagashima:** None. **B.C. Lee:** None. **U. Grunert:** None. **M.I. Miller:** None. **M.G. Rosa:** None. **H. Okano:** None. **P.R. Martin:** None. **P.P. Mitra:** None.

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.07

Topic: I.03. Anatomical Methods

Support: AMED Brain/MINDS 17dm0207001h0004
NPO Rett Syndrome Supporting Organization

Title: Generation and analysis of Rett syndrome model marmosets

Authors: *N. KISHI[1], K. SATO[2], M. OKUNO[1], T. ITOU[1], H. J. OKANO[3], E. SASAKI[2], H. OKANO[1]
[1]RIKEN CBS, Saitama, Japan; [2]CIEA, Kawasaki, Japan; [3]Jikei Univ. Sch. of Med., Tokyo, Japan

Abstract: Our human brains are composed of structures conserved through evolution and those unique to primates. Recently-evolved brain structures involve the enlargement of the cerebral neocortex and provide essential substrates for acquisition of novel brain functions unique to primates, and eventually humans. Because of the unique structure and function of the primate brain, it is impossible to gain a full, accurate understanding of either normal human brain function or mental illness (neurological and psychiatric disorders) through rodent-based studies. Traditionally-used rats and mice only possess fundamental neuronal circuits conserved across mammalian species. Particularly, the primate prefrontal cortex is responsible for higher cognitive processes, and it contains vulnerable domains involved in some psychiatric disorders. The prefrontal cortex has no clear structural or functional homolog in rodents, which suggests advantages of using non-human primates to model human neurological and psychiatric diseases. The pathophysiology of human neurological and psychiatric diseases is not always recapitulated in genetically modified (GM) rodent models, possibly due to the differences in genome information, life span, and brain structure and functions between humans and rodents. To overcome these issues, we are developing a technique for creating knockout marmosets using zinc finger nuclease (ZFN) and CRISPR/Cas9 technology. 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. Very recently, we also obtained MECP2-null marmoset, which has a smaller brain even at early developmental stages.

Disclosures: N. Kishi: None. **K. Sato:** None. **M. Okuno:** None. **T. Itou:** None. **H.J. Okano:** None. **E. Sasaki:** None. **H. Okano:** None.

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.08

Topic: I.03. Anatomical Methods

Support: Australian Research Council (grants DP140101968 and CE140100007)
National Health and Medical Research Council (grant 1122220)
International Neuroinformatics Coordinating Facility (INCF) seed grant scheme

Title: Neuronal density across the cerebral cortex of the marmoset monkey (callithrix jacchus)

Authors: *N. ATAPOUR[1,2], P. MAJKA[1,2,3], I. H. WOLKOWICZ[1], D. MALAMANOVA[1], K. WORTHY[1], M. ROSA[1,2]
[1]Physiol., Monash Univ., Clayton, Australia; [2]Australian Res. Council, Ctr. of Excellence for Integrative Brain Function, Monash Univ. Node, Melbourne, Victoria, Australia; [3]Lab. of Neuroinformatics, Dept. of Neurophysiology, Nencki Inst. of Exptl. Biol. of Polish Acad. of Sci., 3 Pasteur Street, 02-093 Warsaw, Poland

Abstract: We report on neuronal density in the entire cortex of the marmoset monkey (*Callithrix jacchus*). The neuronal density was assessed across the thickness of each of the 116 cytoarchitectural areas currently recognized in the cortex of this species (Paxinos et al. 2012), through stereological analysis of sections stained for a neuron-specific marker (NeuN) and expert determination of cytoarchitectural areas. Tissue was obtained from the right hemisphere of a female marmoset (*Callithrix jacchus*) at 27 months of age.
Our results revealed that estimates of average neuronal density encompassed a greater than threefold range, from a maximum (>150,000 neurons/ mm3) in the primary visual cortex to a minimum (~50,000 neurons/ mm3) in the piriform complex. In agreement with previous studies, there was a trend for density values to decrease from posterior to anterior cortical areas, but we also observed significant local gradients, which added complexity to this pattern. For example, in the frontal lobe, neuronal density was lowest among motor and premotor areas, and increased towards the frontal pole. Likewise, in both auditory cortex and somatosensory areas, it increased from caudal to rostral subdivisions. In general, anterior cingulate, insular and ventral temporal proisocortical and periallocortical areas were characterized by low neuronal densities. Analysis across the thickness of the cortex revealed greater laminar variation in occipital, parietal and inferior temporal areas, in comparison with other regions, and that changes are more pronounced in the supragranular layers than infragranular layers. These results suggest that neuronal density values in the adult cortex result from a complex interaction of developmental/evolutionary determinants and functional requirements. The entire set of digital images used in this study is shared through a freely accessible web site (http://www.marmosetbrain.org/cell_density).

Disclosures: N. Atapour: None. **P. Majka:** None. **I. H. Wolkowicz:** None. **D. Malamanova:** None. **K. Worthy:** None. **M. Rosa:** None.

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.09

Topic: I.03. Anatomical Methods

Support: Brain Mapping of Integrated Neurotechnologies for Disease Studies (Brain/MINDS), Japan Agency for Medical Research and Development, AMED

Crick-Clay Professorship, Cold Spring Harbor Laboratory
H.N. Mahabala Chair, IIT Madras
NIH R01 EB022899

Title: An MRI-guided atlas-mapping of marmoset brain histology by and automatic registration method

Authors: *B. C. LEE[1], M. LIN[2], M. HANADA[2], J. NAGASHIMA[2], Y. FU[3], J. HATA[2], B.-X. HUO[2], Y. TAKAHASHI[2], K. K. RAM[4], H. OKANO[5], P. P. MITRA[6], M. I. MILLER[1]
[1]Johns Hopkins Univ., Baltimore, MD; [2]Lab. for Marmoset Neural Architecture, RIKEN Ctr. for Brain Sci., Wako, Japan; [3]Shanghai Jiaotong Univ., Shanghai, China; [4]Indian Inst. of Technol. Madras, Chennai, India; [5]Keio Univ. Sch. of Med., Tokyo, Japan; [6]Cold Spring Harbor Lab., Cold Spg Hbr, NY

Abstract: The common marmoset (*Callithrix jacchus*) is increasingly being used as a model organism for primate neuroscience research. Establishing the mesoscopic structural mapping of the marmoset brain is essential for future mapping of the neural circuitry, structure, and function. To accomplish this goal, it is necessary to develop a new automatic computational technique to register mesoscale datasets. Here we adapted a fully automatic registration method on histologically processed whole marmoset brains using a same-subject MRI (T2-weighted ex-vivo in 100μm isotropic) guided atlas-mapping algorithm. Our method consists of four major tasks: stack alignment, MRI-guided reconstruction, atlas-mapping, and cross-modality registration. We preserved the geometry of individual brain sections by adapting a customized tape-transfer cryo-sectioning technique. We developed an algorithm to reconstruct the histological stack based on available shape priors in the same-subject MRI or a population-typical reference atlas. Our algorithm also imposes a smoothness prior on the image volume. By using external references, we avoided the classical curvature recoverability problem of sectioned objects, thus obtaining the morphologically correct shape of the brain. Moreover, this registration framework allowed us to perform quantitative analysis of the deformative effects of histology on the marmoset brain. We examined the effects of reference guided registration and showed that the newly adapted method produces accurate reconstructions and segmentations of target brains in several modalities and is able to quantify the distortions between ex-vivo MRI and the histology stacks.
To compute the nonlinear warping between a labeled atlas and a reconstructed brain image, the registration method uses a variant of the large deformation diffeomorphic metric mapping (LDDMM) algorithm that accounts for missing structures/sections or damaged sections in the subject image. As a result, we can accurately cross-register several modalities such as fluorescence, myelin and immunohistochemical volumes to the structural stack using a mutual information image similarity metric. This adaptation improved the reconstruction accuracy and eliminated artifact warping from the unguided method, as well as reduced the metric cost of the deformable mapping. The reconstructions were then fed into a pipeline for detection of cell bodies and processes, proofreading, and annotation for connectivity mapping. Our registration method not only increases precision but also improves reliability of connectivity mapping on a brain-wide, inter-areal, weighted matrix.

Disclosures: B.C. Lee: None. **M. Lin:** None. **M. Hanada:** None. **J. Nagashima:** None. **Y. Fu:** None. **J. Hata:** None. **B. Huo:** None. **Y. Takahashi:** None. **K.K. Ram:** None. **H. Okano:** None. **P.P. Mitra:** None. **M.I. Miller:** None.

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.10

Topic: I.03. Anatomical Methods

Support: Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS)
Strategic Research Program for Brain Science from the Ministry of Education, Culture, Sports, Science, and technology of Japan (MEXT) and Japan Agency for Medical Research and Development (A-MED)
JSPS KAKENHI Grant Number JP17K14957
Grant-in-Aid for Scientific Research on Innovative Areas (Brain Protein Aging and Dementia Control) from MEXT

Title: Transgenic marmoset as a novel non-human primate model of Parkinson's disease

Authors: *R. KOBAYASHI[1,2], S. SHIOZAWA[1], J. OKAHARA[3], C. YOKOYAMA[4], T. KONDO[1], A. KOSUGI[5], J. USHIBA[6], D. KUMAR[7], M. SAKAGUCHI[7], J. TAKAHASHI-FUJIGASAKI[8], T. INOUE[3], C. HARA-MIYAUCHI[9], H. J. OKANO[9], E. SASAKI[3], H. OKANO[1]
[1]Keio Univ. Sch. of Med., Tokyo, Japan; [2]Lab. for Marmoset Neural Arch., RIKEN Ctr. for Brain Sci., Wako-shi, Japan; [3]Central Inst. for Exptl. Animals, Kanagawa, Japan; [4]RIKEN Ctr. for Life Sci. Technologies (CLST), Kobe-Shi, Japan; [5]Grad. Sch. of Sci. and Technol., [6]Keio Univ., Kanagawa, Japan; [7]Univ. Tsukuba, WPI-IIIS, Tsukuba-Shi, Japan; [8]Brain Bank for Aging Res., Tokyo Metropolitan Inst. of Gerontology, Tokyo, Japan; [9]Jikei Univ. Sch. of Med., Minato-Ku, Japan

Abstract: Parkinson’s disease (PD) is a progressive neurodegenerative disease characterized by movement disorder such as tremor, rigidity and akinesia. Although PD is one of the major neurodegenerative diseases, the pathogenic mechanisms of PD remain still unclear and therefore, fundamental treatment has not been established yet.
To elucidate the mechanisms of PD pathogenesis, rodent models have been established and used so far. In addition to characteristic motor dysfunction, recent studies have revealed the importance of non-motor symptoms in PD such as sleep disorder and olfactory disorder because these pathologies appear in the very early stages of PD. However, rodent models are not sufficient to reproduce several early symptoms, most likely due to their differences from human in the structure and function of brains, and thus, the development of non-human primate models

have been desired.
The common marmoset (*Callithrix jacchus*), a small New World monkey, has several advantages for use as an experimental non-human primate. These advantages include their small size, ease of breeding, and high reproductive efficiency. In addition, the marmoset is strongly expected to be useful as a non-human primate model for neurodegenerative disease due to their genetic and physiological similarities to human, such as brain structure, high cognitive function, metabolic pathway, and sleep pattern (Izpisua Belmonte et al., 2015; Kishi et al., 2014; Okano et al., 2012; Crofts et al., 2001). In addition, our group developed transgenic technique in the marmoset (Sasaki et al., 2009). By using this technology, we generated transgenic marmoset lines harboring aggregation-prone α-Synuclein mutation, which is found in human familial PD. To evaluate the transgenic marmoset as a disease model, we analyzed phenotypes found at multiple stages in human PD progression in the transgenic marmoset. As a result, the mutated α-Synuclein transgenic marmoset exhibited early to middle stage of PD phenotypes. Furthermore, we found that the fiber number of nigra-striatal pathway was reduced in the transgenic marmoset brain. It is notable that basal ganglia circuits change in transgenic marmoset like in PD patients. Therefore, this animal model would be a powerful tool for investigating the pathogenesis of PD.

Disclosures: R. Kobayashi: None. **S. Shiozawa:** None. **J. Okahara:** None. **C. Yokoyama:** None. **T. Kondo:** None. **A. Kosugi:** None. **J. Ushiba:** None. **D. Kumar:** None. **M. Sakaguchi:** None. **J. Takahashi-Fujigasaki:** None. **T. Inoue:** None. **C. Hara-Miyauchi:** None. **H.J. Okano:** None. **E. Sasaki:** None. **H. Okano:** None.

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.11

Topic: I.03. Anatomical Methods

Support: JP18dm0207001
17K13274

Title: Axonal projections from area MT in the common marmoset

Authors: *H. ABE[1], T. TANI[1], H. MASHIKO[1], N. KITAMURA[1], K. SAKAI[3], T. HAYAMI[3], S. WATANABE[3], W. SUZUKI[3], H. MIZUKAMI[4], A. WATAKABE[2], T. YAMAMORI[2], N. ICHINOHE[3]
[1]Ichinohe Group, Lab. for Mol. Analysis of Higher Brain Function, [2]Lab. for Mol. Analysis of Higher Brain Function, RIKEN Ctr. for Brain Sci., Wako, Saitama, Japan; [3]Dept. of Ultrastructural Res., Natl. Inst. of Neuroscience, Natl. Ctr. of Neurol. and Psychiatry, Tokyo, Japan; [4]Div. of Genet. Therapeutics, Ctr. for Mol. Med., Jichi Med. Univ., Tochigi, Japan

Abstract: Neural activity in middle temporal (MT) area is modulated by direction and speed of motion of watching visual stimuli. Previous studies on this area have been giving insights about neural coding and neural mechanisms of motion perception and decision-making. Although this area is buried in a sulcus in macaque monkeys, it's exposed to the cortical surface in marmosets, which is ideal for array electrode implantation and imaging experiments. Thus, marmosets can be a good animal model for studying MT. To understand more details of the roles of this area in cognition, underlying anatomical connections need to be clarified. Because most of the anatomical tracing studies with marmosets used retrograde tracers, anterograde connections remain unclear. In order to examine axonal projections from area MT, we injected an AAV, which works as an anterograde tracer by expressing either green or red fluorescent protein in infected neurons, to three sites in area MT representing a central (green, monkey 1), lower (red, monkey 1) and upper (red, monkey 2) visual fields in the left hemisphere. The injection sites were chosen based on retinotopy maps obtained from the animals using optical intrinsic signal imaging while presenting wedge or annulus stimuli under anesthesia. After a 3 week waiting period, the animals were perfused, and the post-mortem brain was sectioned. The sections were divided to three series, one for fluorescent image scan and two for myelin and Nissl substance staining to identify brain areas of the animals. We followed the nomenclature of a published brain atlas. All injection sites were histologically confirmed in area MT. Overall projection patterns were similar across three injections. Area MT projected to occipital visual areas, V1, V2, V3 (VLP), V4(VLA), and surrounding areas in the temporal cortex, MTC (V4T), MST, FST and FSTv(PGa/IPa). There were also projections to the parietal cortex, V3A(DA), V6(DM), V6A, AIP, LIP, MIP and the prefrontal cortex, A8aV. Each injection site projected to the corresponding visual field location in the occipital visual areas. Also, in the animal two tracer injections were made, the projection targets of the tracers were slightly different in A8aV, suggesting topological projections from MT to A8aV. According to a retrograde labeling study, most of these projected areas are known to send projections back to MT, suggesting that those areas are reciprocally connected with MT.

Disclosures: H. Abe: None. **T. Tani:** None. **H. Mashiko:** None. **N. Kitamura:** None. **K. Sakai:** None. **T. Hayami:** None. **S. Watanabe:** None. **W. Suzuki:** None. **H. Mizukami:** None. **A. Watakabe:** None. **T. Yamamori:** None. **N. Ichinohe:** None.

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.12

Topic: I.03. Anatomical Methods

Support: JSPS KAKENHI 16H01493
JSPS KAKENHI 18H05090

JSPS KAKENHI 23700317
JSPS KAKENHI 25330180
AMED Brain/MINDS

Title: Brain mapping of the neural circuitry underlying conspecific call perception in marmosets

Authors: *C. YOKOYAMA[1,2], M. KATO[3,4], A. KAWASAKI[1,2], C. TAKEDA[1,2], T. KOIKE[3], H. ONOE[2,5], A. IRIKI[1,3,6]
[1]RIKEN Ctr. for Biosystems Dynamics Res., Kobe-Shi, Japan; [2]RIKEN Ctr. for Life Sci. Technologies, Kobe, Japan; [3]Brain Sci. Inst., Wako, Japan; [4]Hokkaido Univ., Sapporo, Japan; [5]Human Brain Res. Center, Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; [6]Lee Kong Chian Sch. of Med. and RIKEN-NTU Res. Ctr. for Human Biol., Singapore, Singapore

Abstract: Common marmosets (*Callithrix jacchus*) often produce whistle-like calls, namely "phee" calls, being exchanged to each other when they are visually separated from conspecifics. The neural processes underlying the marmoset's perception of conspecific phee call are largely unknown, though these processes are expected to be involve social information. Here we examined whole-brain mapping of the detection of individual conspecific phee calls using positron emission tomography (PET) with [^{18}F] fluorodeoxyglucose (FDG). We first found that phee calls evoked sound exploratory responses when the caller changed, indicating that marmosets can discriminate between caller identities. FDG-PET revealed that perception of phee calls from a single subject was associated with activity in the dorsolateral prefrontal, medial prefrontal, orbitofrontal cortices, and the amygdala, which are implicated in cognitive and affective processing of social information. However, phee calls from multiple subjects induced brain activations in only a part of these regions, such as the dorsolateral prefrontal cortex. We also found distinctive functional connectivity in the cerebello-prefrontal circuit which depend on the caller change. According to changes in pupillary size, phee calls from a single subject induced a higher arousal level compared with those from multiple subjects. These results suggest that marmosets may have a special neural response to a signal from phee calls from a single subject and phee calls may convey information about individual identity and affective valence depending on the consistency or variability of the caller. The flexible perception of others may suggest shared neural mechanism between humans and marmosets in conspecific vocal perception.

Disclosures: C. Yokoyama: None. **M. Kato:** None. **A. Kawasaki:** None. **C. Takeda:** None. **T. Koike:** None. **H. Onoe:** None. **A. Iriki:** A. Employment/Salary (full or part-time):; The president and CEO of RIKAENALYSIS Corporation (RIKEN Venture, Tokyo).

Nanosymposium

364. The Marmoset Brain: Brain Mapping and Circuit Tracing

Location: SDCC 1

Time: Monday, November 5, 2018, 1:00 PM - 4:15 PM

Presentation Number: 364.13

Topic: I.03. Anatomical Methods

Support: Brain/MINDS grant from MEXT, Japan

Title: Mapping of afferent projections to superior colliculus in common marmoset

Authors: *D. MATROV, C.-Y. CHEN, K. ISA, T. ISA
Dept. of Neurosci., Grad. Sch. of Medicine, Kyoto Univ., Kyoto-shi, Japan

Abstract: Superior colliculus (SC) is an important brain center for programming saccadic eye movements, especially corresponding to visually salient locations. Herein we present results of retrograde tract-tracing by AAV2retro-CAGGS-EGFP vector (titer 6 * 10^9 vg/µl) injection into the superficial and intermediate layers of the superior colliculus (SC) in a common marmoset (*Callithrix jacchus*). The viral construct is picked up at presynaptic terminals of neurons that project into SC and is transported retrogradely into the soma. Thus, neurons projecting into SC can be counted by the presence of EGFP expression in the soma.
In marmoset I4240 (female, BW 398 g) 0.2 µl of viral vector was injected into the center of rostral tip of SC. In marmoset I4952 (female, BW 314g) about 0.5 µl of viral vector was injected into medial part of SC at about center in rostro-caudal orientation. As volume of the injection was larger, the tracer filled most of the SC except for the lateral edge. In both cases no leakage of the tracer below the SC proper nor in the contralateral SC nucleus was observed. The cortical reflux was also insignificant. The main contamination of the results may come from the tracer pickup up by injured axons of the corpus callosum, especially for a more rostrally located injection site in animal I4240. The tracer was definitely picked up by oligodendrocytes there but that signal died out rather quickly away from the location of the injury.
Coronal serial sections through the whole brain except for the most occipital visual areas were plotted in Neurolucida software. In addition to the retrogradely labeled soma, identifiable brain regions were outlined from the adjacent Nissl/NeuN sections.
In both animals the prefrontal cortical areas showed a strong projection into SC while the number of projection neurons was significantly reduced in premotor and motor areas. In the rostrally placed SC injection case of the animal I4240 the labeled cells were mostly located at the dorsolateral-ventrolateral junction of prefrontal cortex. Larger injection volume combined with a more central SC placement in the animal I4952 labeled cells almost in the entire prefrontal cortex except for ventromedial areas. The projections from parietal areas were somewhat less intense than from prefrontal areas and quite broad. However, in contrast to other parietal areas where only cells in layer 5 were labeled, in the vicinity of the putative area LIP cells in the layers

2-3 were also labeled.
Labeled cell counts for each brain region, as well as projection density values will be presented.

Disclosures: D. Matrov: None. **C. Chen:** None. **K. Isa:** None. **T. Isa:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.01

Topic: A.03. Stem Cells and Reprogramming

Support: MH83862
MH64168
MH40210
NS090415
MH94888
MH090964
MH098786

Title: Hippocampal neurogenesis is not preserved with aging in major depressive disorder

Authors: *M. BOLDRINI[1], C. FULMORE[2], A. TARTT[2], Y. LIU[5], G. ROSOKLIJA[2], M. J. BAKALIAN[6], S. KASSIR[5], A. J. DWORK[7], V. ARANGO[3], R. HEN[4], A. SAHAY[8], J. MANN[2]
[1]Psychiatry - Mol. Imaging and Neuropathology, Columbia Univ. - NYSPI, New York, NY; [3]Psychiatry, [4]Neurosci. and Psychiatry, [2]Columbia Univ., New York, NY; [5]New York State Psychiatric Intitute, New York, NY; [6]Mol. Imaging and Neuropathology, [7]Neuropathology, New York State Psychiatric Inst., New York, NY; [8]MGH Psychiatry, HMS, HSCI, Ctr. For Regenerative Med., Boston, MA

Abstract: Neurogenesis decreases with age in mice, yet it may persist in the human brain. We examined the effect of age on nestin+= neural progenitor cells (NPCs) and new capillaries, Ki-67+ mitotic cells, cell expressing doublecortin, polysialylated neural cell adhesion molecule (PSA-NCAM), and neuronal nuclear antigen (NeuN), as well as Krüppel-like Factor 9 (Klf9) and vascular endothelial growth factor receptor2 (VEGFR2), in the dentate gyrus (DG) postmortem from subjects without neuropsychiatric disease or treatment (controls) and individuals with untreated major depressive disorder (MDD).
Frozen hippocampi from control and MDD subjects, age 14-83 yrs. (n=28/group), were fixed and processed for immunohistochemistry, radioactive in situ hybridization, stereology and film densitometry. Clinical and neuropathological data were obtained by psychological autopsy and brain examination. Medication status was confirmed by toxicology screenings.
In controls, but not MDD, we found smaller total capillary area and shorter and less branched

capillaries correlating with fewer PSA-NCAM+ cells in anterior-mid DG ($p<.05$). Nestin+ NPCs and DCX+ immature neurons declined with older age in anterior and posterior DG in MDD subjects ($p<.050$), not controls. Mitotic cells and mature granule neurons did not correlate with age in MDD or controls. MDD had fewer NPCs selectively in anterior-DG and fewer immature neurons and mature granule neurons than controls in anterior and mid DG ($p<.05$).
Klf9 mRNA was lower with older age in women ($p=0.012$) and men ($p=0.017$). We found higher Klf9 mRNA in the DG of female MDD compared with female controls ($p=0.013$) and no change between male MDD and controls. VEGFR2 expression was found in fewer endothelial cells and DG cells with older age in MDD and control subjects ($p<.05$).
Fewer PSA-NCAM+ and less angiogenesis in the aging human DG may contribute to less neuroplasticity and normal age-related memory or emotional regulation decline. In MDD, long-lasting exposure to stress/corticosteroids may explain fewer NPCs and immature neurons with aging, not observed in healthy aging individuals. The age-related downregulation of Klf9 could result in decreased neurogenesis-dependent synaptic plasticity, while less VEGFR2 could explain less angiogenesis.

Disclosures: M. Boldrini: None. **C. Fulmore:** None. **A. Tartt:** None. **Y. Liu:** None. **G. Rosoklija:** None. **M.J. Bakalian:** None. **S. Kassir:** None. **A.J. Dwork:** None. **V. Arango:** None. **R. Hen:** None. **A. Sahay:** None. **J. Mann:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.02

Topic: A.03. Stem Cells and Reprogramming

Support: Merit Award from the Department of Veterans Affairs/VA BLR&D Merit Award
Grant number: BX003431

Title: Modeling neuronal circadian rhythms in bipolar disorder using human induced pluripotent stem cells

Authors: H. K. MISHRA[1,2], N. YING[1,2], A. LUIS[1,2], *M. MCCARTHY[1,2]
[1]VA San Diego Healthcare Syst., San Diego, CA; [2]Dept. of Psychiatry and Ctr. for Circadian Biol., UCSD, San Diego, CA

Abstract: Bipolar disorder (BD) is a chronic neuropsychiatric condition with a developmental course, characterized by recurrent manic and depressive episodes and an increased lifetime risk for suicide. The age of BD onset is typically in late adolescence as brain development is undergoing completion. In addition to mood symptoms, BD is also associated with altered daily rhythms in activity, energy, cognition, and appetite. These symptoms suggest that circadian

rhythms may be disrupted in BD. The risk for BD is inherited and polygenic, but the underlying molecular mechanisms are not well understood. However, in light of the phenotypic presentation, altered circadian rhythms in neurons and developmental pathways have been implicated. Recent advancements in reprogramming technologies have enabled the use of induced pluripotent stem cells (iPSCs) as powerful tools for investigating the relationships between genotype and phenotype in human neuropsychiatric disease-relevant cells. We employed a set of 10 induced pluripotent stem cells (iPSCs) lines from six BD patients and four age-matched controls (CTRLs). We differentiated these iPSCs into the lineages leading to forebrain VGlut2+ neurons and Prox1+ hippocampal neurons. Early neuronal progenitors (NPCs) and differentiated neurons modelling distinct neurodevelopmental stages of brain development were used to investigate the stage-specific circadian rhythms profile and temporal differences in clock genes related transcriptional activities in BD and CTRL cells. BD patient-derived NPCs exhibit weak rhythms in bioluminescent reporter Per2::Luc activity compared to CTRLs. Time course analysis using qPCR revealed a distinct pattern of clock gene expression in BD cells compared to CTRLs. Single cell rhythm analyses using bioluminescent imaging corroborate this finding and indicate a reduced number of rhythmically active NPCs and decreased amplitude in NPCs from BD patients compared to CTRLs. Taken together, these data indicate that NPCs show aberrant rhythms in BD. Our neuronal model of circadian rhythms is an ideal platform for future studies to define new targets for pharmacological modulation of cellular rhythms in NPCs and neurons from BD patients.

Disclosures: H.K. Mishra: None. **N. Ying:** None. **A. Luis:** None. **M. McCarthy:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.03

Topic: A.03. Stem Cells and Reprogramming

Support: Grant NAP-B KTIA_NAP_13-2014-0011
Grant NAP-A KTIA_13_NAP-A-I/6

Title: Investigating the biological significance of de novo mutations in schizophrenia case-parent trios using induced pluripotent stem cell based disease modelling

Authors: *J. RÉTHELYI[1], E. HATHY[1], Á. APÁTI[2], L. HOMOLYA[2], Z. NEMODA[1]
[1]Semmelweis Univ., Budapest, Hungary; [2]Inst. of Enzymology, Hungarian Acad. of Sci., Budapest, Hungary

Abstract: De novo mutations (DNMs) have been implicated in the etiology of schizophrenia, a chronic debilitating psychiatric disorder characterized by hallucinations, delusions, cognitive

dysfunction and poor community functioning. The large scale identification of DNMs has become feasible with the advent of next generation sequencing, primarily whole exome sequencing. While several DNMs have been demonstrated by examining schizophrenia cases and their unaffected parents, moreover the DNMs can be evaluated by bioinformatics prediction tools with regard to their disease-causing effects, in most cases the biological significance of these mutations remains inconclusive. To overcome this limitation we have developed an approach of using somatic cell reprogramming to generate induced pluripotent stem cell (IPSC) lines from each member of a schizophrenia case-control trio, in order to investigate the effects of DNMs in cellular progenies of interest, particularly in dentate gyrus granule cells. Here we describe two patients with schizophrenia characterized clinically by early disease onset and negative symptoms. The first one is a carrier of 3 non-synonymous DNMs in genes LRRC7, KHSRP, and Killer Cell Immunoglobulin-Like Receptor, Two Domains, Long Cytoplasmic Tail, 1 (KIR2DL1). LRRC7 encodes densin-180, a postsynaptic density protein in glutamatergic synapses, KHSRP is an RNA-binding protein implicated in axonal growth and dendritic spine development, while KIR2DL1 encodes killer cell immunoglobulin-like receptors (KIRs) that are transmembrane glycoproteins. The second patient carries a nonsense mutation in Zinc Finger MYND-Type Containing 11 (ZMYND11), a gene that has been implicated by de novo mutations in mental retardation. IPSC lines were generated from the patients and their parents using Sendai virus based reprogramming of peripheral blood mononuclear cells. IPSCs were characterized using alkaline phosphatase staining, quantitative PCR and immunostainig of pluripotency markers. The DNMs were validated in the IPSC lines by Sanger sequencing. After characterization the IPSCs were differentiated into neuronal progenitor cells (NPCs) and hippocampal dentate gyrus granule cells for the investigation of various cellular phenotypes. We use RNASeq to investigate transcriptomic differences associated with the identified de novo mutations. The approach of reprograming trios represents a possibility of investigating disease causing mutations and comparing cell lines with reduced variation of genetic background.

Disclosures: J. Réthelyi: None. **E. Hathy:** None. **Á. Apáti:** None. **L. Homolya:** None. **Z. Nemoda:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.04

Topic: A.03. Stem Cells and Reprogramming

Support: NIH HG008105
NIH NS101996
NIH AG056151
NIH AG058447

NIH AG058476

Title: Harnessing human cns disease models with robotics and deep learning to find causes and treatments

Authors: *S. FINKBEINER[1,3], J. KAYE[2], A. JAVEHERIAN[2]
[2]Ctr. for Systems and Therapeut., [1]Gladstone Inst., San Francisco, CA; [3]Neurol. and Physiol., Univ. of California San Francisco, San Francisco, CA

Abstract: Patient-derived cells can now be used to generate a variety of cell types in the human brain including different types of neurons and glia. But the maturity and the composition of cultures cells can vary depending on the differentiation protocol and as more complex models are built that incorporate multiple cell types, heterogeneity can pose a challenge to population-based analysis approaches. To overcome these hurdles, we combined robotics with imaging to perform longitudinal single cell analysis in high throughput, allowing us to apply statistical tools normally used in clinical trials to uncover robust disease-associated phenotypes with high sensitivity. In addition, we developed an array of over 270 biosensors to visualize a variety of cell structures and functions to enable the characterization of neuronal dysfunction as well as degeneration. Lastly, we are incorporating advanced computational techniques, including deep learning, to extract new insights from the images we collect, even features that are otherwise invisible to the human eye. We have used these approaches to develop and characterize human models of Huntington's disease, amyotrophic lateral sclerosis, Parkinson's disease, frontotemporal dementia, Alzheimer's disease, autism and schizophrenia and used these models to conduct genetic screens to better understand mechanisms of disease and to find treatments. In this presentation, we will provide an update on our progress.

Disclosures: S. Finkbeiner: None. **J. Kaye:** None. **A. Javeherian:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.05

Topic: A.03. Stem Cells and Reprogramming

Support: Maryland Stem Cell Research Fund Exploratory Grant-MSCRFD-3815
Hussman Foundation Pilot Grant-HIAS15004

Title: Isolation and enrichment of subtypes of cortical interneurons from human induced pluripotent stem cell organoids

Authors: J. W. LUNDEN[1], R. DERANIEH[2], *M. W. NESTOR[2]
[1]Neurosci., Hussman Inst. for Autism, Baltimore, MD; [2]The Hussman Inst. For Autism, Sykesville, MD

Abstract: Interneuron dysfunction is implicated in modulating excitatory/inhibitory and circuit function in Autism. The effect of interneurons on circuits is dependent on the subtype specificity of these cells. The calcium-binding protein expressing neurons, including calbindin (CB), calretinin (CR), and parvalbumin (PV)-positive make up major classes of interneurons in the brain. The underlying mechanism behind γ-Aminobutyric acid (GABA)ergic regulation of human cortical circuitry is not clearly understood, partly due to the difficulty of generating interneurons. Although much progress has been made in the past few years, current protocols generate mixed neuronal cultures, with only a small percentage of interneurons generated. Here, we demonstrate an approach to differentiate and enrich for specific subtypes of human interneurons. Using human induced pluripotent stem cells (hiPSCs), serum free embryoid bodies (SFEBs) were generated and induced using standard dual-SMAD inhibition combined with placement of the SFEBs on Millipore Organotypic inserts (Nestor et al., 2013). Following four weeks of differentiation, interneurons were isolated using magnetic activated cell sorting, after which the neurons were allowed to recover for 2 weeks on poly-L-ornithine and laminin. Using this method we found a significant increase in the numbers of CB, CR, and PV interneurons when compared to conventional 2D cultures. Thus magnetic activated cell sorting of SFEBs allows the generation of human interneurons that can be used to study the mechanisms behind developmental disorders, as well as the potential to identify novel drug targets for therapeutic treatments.

Disclosures: J.W. Lunden: None. **R. Deranieh:** None. **M.W. Nestor:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.06

Topic: A.03. Stem Cells and Reprogramming

Support: BMBF, 01GQ113, 01GM1520A, 01EK1609B
University Hospital Erlangen E25 and MD fellowship
DFG grant 410/45-1 FUGG
DFG funded research training group GRK2162
The Tom Wahlig Foundation

Title: Tideglusib rescues the neurodegenerative phenotype of hereditary spastic paraplegia type 11

Authors: *T. PISMENYUK[1], A. SCHRAY[1], T. BÖRSTLER[1], I. BUCHSBAUM[2], M. REGENSBURGER[1], H. WEND[1], Z. KOHL[3], S. CAPPELLO[1], J. WINKLER[3], B. WINNER[1]
[1]Dept. of stem cell biology, Friedrich-alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [2]Max Planck Inst. für Psychiatrie, Munich, Germany; [3]Univ. Hosp. Erlangen, Erlangen, Germany

Abstract: Hereditary spastic paraplegia (HSP) is a heterogeneous group of rare motor neuron disorders characterized by progressive weakness (paraplegia) and spasticity of the lower limbs. HSP type 11 (SPG11), the most common form of complex autosomal recessive HSP, is accompanied by a thin corpus callosum (TCC), intellectual disability, dysarthria, sensory and motor neuropathy, and amyotrophy. The wide range of symptoms can be further categorized into neurodevelopmental and neurodegenerative phenotypes. Our previous studies (Mishra et al. 2016) identified decreased proliferation of SPG11-NPCs due to overactivity of GSK3ß. By using a GSK3ß inhibitor, tideglusib, it was possible to rescue some of the observed neurodevelopmental defects. Moreover, tideglusib treatment also led to an increase in the size of SPG11 organoids, thus indicating the potential significance of the treatment. However, for becoming clinically applicable, the effect has to be tested on SPG11 patient mature neurons. For this aim, we used SPG11 iPSC cells, as well as SPG11 knock down human embryonic stem cell line that was generated by CRISPR/Cas9 system. The cells were differentiated to forebrain neurons, treated with Tideglusib and transfected with dTomato for neurite visualization of a single neuron. In order to examine the effect of tideglusib on cell death, the neurons were stained for cleaved caspase-3 marker. The analysis revealed that the treatment rescued the neurodegenerative phenotype by increasing neurite length and complexity, as well as reducing apoptosis. Our results strengthen the therapeutic potential of the compound for HSP type 11. FDA approval of tideglusib in combination with the current lack of treatment for the disorder renders the compound suitable for future clinical application.

Disclosures: T. Pismenyuk: None. **A. Schray:** None. **T. Börstler:** None. **I. Buchsbaum:** None. **M. Regensburger:** None. **H. Wend:** None. **Z. Kohl:** None. **S. Cappello:** None. **J. Winkler:** None. **B. Winner:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.07

Topic: A.03. Stem Cells and Reprogramming

Support: AMED Grant: Investigation of Pathogenic Mechanisms and Development of New Therapies for Neurological Diseases-Specific iPSCs

Title: Modeling and clustering sporadic ALS pathologies using iPSCs-based phenotyping

Authors: *H. OKANO[1], G. SOBUE[2], K. FUJIMORI[1]
[1]Keio Univ. Sch. of Med., Tokyo, Japan; [2]Nagoya Univ., Naogoya, Japan

Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating and heterogeneous motor neuron disease with no effective treatment. The majority (90-95%) of ALS cases are non-familial form (sporadic ALS (SALS)) with unknown etiology and unidentified causative genes. Thus, it is extremely difficult to construct disease models by simple genome editing of control induced pluripotent stem cells (iPSCs). Nevertheless, it is considered that genetic backgrounds substantially contribute to their pathogenic mechanisms in certain population of SALS cases. Thus, it will be important to model SALS and examine their phenotypic clustering of motor neurons-derived from patients-derived iPSCs for the development of new therapeutics for ALS. Here, we generated multi-patient iPSC models in bulk from lymphoblastoid B-cell lines of 32 SALS patients, induced them into motor neurons using rapid and efficient methods we recently developed (Fujimori et al., 2017) and investigated ALS-related motor neuron phenotypes. These iPSC-derived SALS motor neuron models showed significant phenotypic differences in pattern of neuronal degeneration, axonal retraction, types of abnormal protein aggregates, cell death mechanisms, and onset and progression of these phenotypes in vitro, which lead to develop a novel system for case clustering to subdivide these heterogeneous SALS models. Notably, type of phenotypic progression pattern detectable in vitro was consistent with the clinical findings of same SALS patients. We found that such a phenotypic clustering of SALS is crucially important to predict responders and non-responders against a new anti-ALS therapeutic drug we have identified using the FDA-approved drug library. These results support the sufficient utility of iPSCs-based SALS models for elucidating the pathological characteristics of specific cases and identifying novel candidate drugs. Our iPSC-based analysis/clustering/drug screening system could be applicable not only to SALS but also to other sporadic neurodegenerative diseases for developing their disease modifying therapies in the future.

Disclosures: H. Okano: 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.; Supported by a Grant from AMED: Investigation of Pathogenic Mechanisms and Development of New Therapies for Neurological Diseases-Specific iPSC. F. Consulting Fees (e.g., advisory boards); Advisory Boards of SanBio Co Ltd and K Pharma Inc. **G. Sobue:** None. **K. Fujimori:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.08

Topic: A.03. Stem Cells and Reprogramming

Support: Takeda-SCRM Alliance Innovation Grant
SNSF
Striem

Title: Studying mechanisms of treatment resistance using major depressive disorder patient derived neurons

Authors: *K. C. VADODARIA[1], Y. JI[2], M. SKIME[3], A. C. PAQUOLA[4], T. NELSON[3], K. HEARD[4], C. MARCHETTO[4], R. WEINSHILBOUM[3], F. H. GAGE[4]
[1]LOG-G, Salk Inst. For Biol. Sci., La Jolla, CA; [2]Univ. of Utah, Salt Lake City, UT; [3]Mayo Clin., Rochester, MN; [4]Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: Major depressive disorder (MDD) is the most prevalent neuropsychiatric disorder, yet the cellular and molecular mechanisms underlying the disorder remain poorly understood. Selective serotonin reuptake inhibitors are the most prescribed class of antidepressants, but an estimated 30-40% of MDD patients fail to respond to SSRIs, and the neurological mechanisms of SSRI resistance remain largely unknown. Stratifying patients based on biological phenotypes - for example, pharmacological responsiveness - offers an approach for potentially identifying disease-associated phenotypes, especially at the cellular level. iPSC technology offers a unique opportunity for generating neural cells from subsets of psychiatric patients, enabling the study of cellular and molecular aspects of neurotransmission. From a larger cohort of well-characterized MDD patients, we have generated induced pluripotent stem cells (iPSCs) from SSRI-responders (R) and SSRI-nonresponders (NR). We study the pre-synaptic and post-synaptic components of serotonergic neurotransmission using patient-derived neurons in vitro and our data suggests that aberrant serotonergic neurotransmission may play a role in SSRI-resistance in MDD.

Disclosures: K.C. Vadodaria: None. **Y. Ji:** None. **M. Skime:** None. **A.C. Paquola:** None. **T. Nelson:** None. **K. Heard:** None. **C. Marchetto:** None. **R. Weinshilboum:** None. **F.H. Gage:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Takeda-Sanford Consortium for Regenerative Medicine Alliance Innovative Grant.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.09

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant 1R01HG004659-01

Title: Single injection of AAV-shPTB in mouse midbrain reverses the Parkinson's disease phenotype

Authors: *H. QIAN, X.-D. FU
UCSD, San Diego, CA

Abstract: Parkinson's Disease results from lost dopamine neurons in the brain. This and other types of neurodegenerative diseases are currently incurable and the foreseeable approach to this major medical burden is to regenerate the lost neurons and reconstruct disrupted neural circuits. We report efficient conversion of isolated mouse and human astrocytes to functional neurons in a single step by depleting a single RNA binding protein PTB. Applying this approach directly in mouse midbrain, we provide evidence for astrocyte-converted neurons to reconstitute the nigrostriatal dopamine pathway and demonstrate potent reversal of chemical-induced Parkinson's Disease phenotype. These findings potentiate a general strategy for treating neurodegenerative diseases in humans.

Disclosures: H. Qian: None. **X. Fu:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.10

Topic: A.03. Stem Cells and Reprogramming

Support: Helis Biological Research Fund for PD research
Maryland Stem Cell Research Fund fellowship
NINDS R01 to H.S.
NINDS R35 to G-l.M
research resources to Song's lab and Dawson's lab from the Johns Hopkins University

Title: Single-nucleus RNA-Seq analysis of dopaminergic neuron degeneration

Authors: *Y. ZHU[1], S. S. KARUPPAGOUNDER[1], T.-I. KAM[1], V. L. DAWSON[1], G.-L. MING[1,2], T. M. DAWSON[1], H. SONG[1,2]
[1]Inst. for Cell Engin., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Dept. of Neurosci., Univ. of Pennsylvania Sch. of Med., Philadelphia, PA

Abstract: Understanding the progressive degenerative process is fundamental for neurodegenerative diseases research. However, defining the precise molecular changes in disease-related neuron subtypes in the mammalian brain is challenging. Here we adapted single nucleus-RNA Sequencing (snRNA-Seq) to examined dopaminergic neurons in mouse Parkinson's models as well as in human iPSC derived dopaminergic organoids. We observed an

in-silico continuum of transcriptomes that reflected a spatial transition from the Ventral Tegmental Area (VTA) to Substantia Nigra Compacta (SNC). The differential gene expression analysis identified novel markers and biology for SNC vs VTA neurons. During the aging process, many of SNC-enriched genes and processes were upregulated. We further performed snRNA-seq at different time points in a model of dopaminergic neuron (DA) degeneration with MPTP treatment. We found a specific sub-population of DA neurons that are extremely vulnerable to MPTP treatment. Using a new computational algorithm, we identified genes whose expression levels correlate with vulnerability in the spatial continuum. These vulnerability-related genes include known key players in the pathology of Parkinson's Diseases and novel pathways underlying neurodegeneration. Those include novel genes of diverse processes including innate immunity, DNA damage signaling, and dopamine metabolism. We also profiled degenerating DA neurons in the model of pre-formed fibril alpha-synuclein (PFF) treatment. Interestingly, PFF induced toxicity correlated with the expression of multiple vulnerability-related genes found in the MPTP model. We are also looking at human iPSC derived Dopaminergic organoids to study the relevance of these findings in human. Together, our data provide a holistic transcriptomic landscape and suggests novel mechanisms underlying dopaminergic neuron degeneration.

Disclosures: Y. Zhu: None. **S.S. Karuppagounder:** None. **T. Kam:** None. **V.L. Dawson:** None. **G. Ming:** None. **T.M. Dawson:** None. **H. Song:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.11

Topic: A.03. Stem Cells and Reprogramming

Support: DFG GRK2162/1

Title: Using human iPSC derived neurons to shed light on pathogenic mechanisms linked to SPG4

Authors: *T. RIZO GARZA[1], N. DENGUIR[1], R. ALLISON[2], G. PEARSON[2], J. R. EDGAR[3], Z. KOHL[4], E. REID[2], J. WINKLER[4], B. WINNER[1]
[1]Dept. of Stem Cell Biol., Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [2]Dept. of Med. Genet., [3]Dept. of Clin. Biochem., Univ. of Cambridge, Cambridge, United Kingdom; [4]Dept. of Mol. Neurol., Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany

Abstract: Mutations in the SPG4 gene coding for spastin account for roughly 40% of all Hereditary Spastic Paraplegia cases. Patients harboring SPG4 mutations develop progressive

lower limb spasticity and paraplegia caused by length dependent degeneration of the corticospinal tracts.
Extensive research has focused on the microtubule severing activity of spastin using primarily cancer cell lines as model, but conversely, the specific function of spastin in neurons remains poorly characterized. Moreover, although altered neuronal excitability has been identified as an important common pathogenic mechanism in motor neuron diseases very little is known about the role of spastin neuronal electrophysiology.
To study the relevance of spastin in the CNS we generated neurons from human induced pluripotent stem cells (hiPSCs), previously reprogrammed from SPG4 patients' fibroblasts. Using CRISPR/Cas9 technology we genome edit SPG4 mutations to generate isogenic controls. To analyze the impact of SPG4 mutations on neuronal electrophysiology we examined excitability, action potential shape as well as sodium and potassium current densities in single neurons using patch-clamp. To determine excitability and the formation of networks in neuronal populations we used a multielectrode array system.
The SPG4 patient derived neurons were electrically active and mirrored phenotypes previously described in different SPG4 disease models including reduction in spastin as well as neurite swellings. SPG4 neurons accumulate membranous structures and disrupted microtubules within the swellings and in cell bodies.
hiPSCs derived neurons are a powerful tool to study neuronal function or dysfunction as well as the beginning and course of a disease.

Disclosures: T. Rizo Garza: None. **N. Denguir:** None. **R. Allison:** None. **G. Pearson:** None. **J.R. Edgar:** None. **Z. Kohl:** None. **E. Reid:** None. **J. Winkler:** None. **B. Winner:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.12

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant U19MH106434

Title: Using cellular models to study neuroinflammation in bipolar disorder

Authors: *C. MARCHETTO[1], K. C. VADODARIA[1], R. SANTOS[2], A. MEI[1], A. P. D. MENDES[1], R. KEITHLEY[1], K. HEARD[1], G. ERIKSON[1], J. R. KELSOE[3], F. H. GAGE[1]
[1]Salk Inst., La Jolla, CA; [2]Inst. of Psychiatry and Neurosci. of Paris, Paris, France; [3]Univ. of California San Diego, La Jolla, CA

Abstract: Astrocytes are glial cells of the central nervous system that are critical for the development and maintenance of synaptic transmission and homeostasis of synaptically

connected neuronal ensembles. Astrocyte dysfunction and neuroinflammation are detrimental features in multiple pathologies of the central nervous system. Bipolar disorder (BD) is a complex multifactorial disorder estimated to affect 2.8% of U.S. adults and is characterized by mood swings and episodes of mania and depression. BD has been associated with alterations of cytokines in the immune system, and serum levels of inflammatory cytokines (ex. IL6 and TNFa) have been shown to be significantly higher in manic, depressive and mixed state of BD patients. Astrocytes have been proposed to play a role in the progression of BD, as these cells can amplify the inflammatory response and maintain glutamate homeostasis, preventing excitotoxicity. Current data provide preliminary evidence of a link between the cognitive decline observed in BD and mechanisms of neuroinflammation and neuroprotection. To investigate the role of astrocyte function and neuroinflammation on BD pathology, we generated induced pluripotent stem cell (iPSC)-derived astrocytes from 6 BD patients and 4 age/gender-matched controls. We used our previously described protocol to generate functional inflammation-responsive astrocytes (Santos et al 2017). Analysis of transcriptome from iPSC-derived astrocytes indicates that the BD-derived astrocytes have a distinct expression signature compared to controls. Additionally, stimulation with cytokine treatment also demonstrated differential pro-inflammatory response on BD compared to control astrocytes. Follow-up transcriptional analysis will identify the impaired pathways in BD glial cells that can potentially be targeted for future therapies focusing on inflammation pathways. These results represent an important step for modeling in-a-dish neurological diseases with an inflammatory component, allowing for the investigation of the role of diseased astrocytes in neuronal function.

Disclosures: C. Marchetto: None. **K.C. Vadodaria:** None. **R. Santos:** None. **A. Mei:** None. **A.P.D. Mendes:** None. **R. Keithley:** None. **K. Heard:** None. **G. Erikson:** None. **J.R. Kelsoe:** None. **F.H. Gage:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.13

Topic: A.03. Stem Cells and Reprogramming

Support: Grant-in-Aid for Scientific Research on Innovative Areas (Brain Protein Aging and Dementia Control) (26117007) from MEXT

Title: *In vitro* disease modeling of the FTDP-17 TAU R406W mutation using patient-derived iPSCs

Authors: *M. NAKAMURA[1,2], H. WATANABE[1], S. SHIOZAWA[1], S. MAEDA[1], S.-I. HISANAGA[3], N. SAHARA[4], T. KIMURA[4], T. MIYASAKA[5], A. TAKASHIMA[6], T. IKEUCHI[7], H. OKANO[1]

[1]Dept. of Physiol., Keio Univ., Tokyo, Japan; [2]Univ. of Tokyo, Tokyo, Japan; [3]Tokyo Metropolitan Univ., Tokyo, Japan; [4]Natl. Inst. of Radiological Sci., Chiba, Japan; [5]Doshisha Univ., Kyoto, Japan; [6]Gakushuin Univ., Toshima,Tokyo, Japan; [7]Niigata University, Brain Res. Inst., Niigata, Japan

Abstract: Background Frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17) is a neurodegenerative disease caused by mutations in the microtubule-associated protein tau (*MAPT*) gene, which encodes the tau protein. Among the *MAPT* mutations, the R406W mutation located on exon 13 is a unique missense mutation whose patients have been reported to exhibit Alzheimer disease (AD)-like phenotypes, rather than the more typical FTDP symptoms, without Aβ accumulation in most cases. To date, there is no treatment known to be effective for FTDP-17, including the R406W mutation. The objective of this study is to establish a suitable model for studying the abnormalities induced by R406W mutant tau and elucidating the pathological role of tau in neurodegenerative diseases, as a basis for drug screening.
Materials and Methods Induced pluripotent stem cells (iPSCs) were generated from patients harboring the *MAPT* R406W mutation and manipulated with a genome-editing technique to create isogenic lines. The iPSCs were differentiated into cerebral organoids, which were either cultured three-dimensionally or dissociated into cortical neurons onto typical two-dimensional plates. Using these neuronal cultures, phosphorylation and proteolysis of tau was investigated by western blotting. Furthermore, localization of tau and neurite morphology were examined using a high-content imaging microscope.
Results iPSC lines from patients heterozygous for the *MAPT* R406W mutation were established. These lines were gene-edited using CRISPR/Cas-9 to establish isogenic lines with the mutation corrected, or homozygous for the mutation. iPSCs were then induced into cerebral organoids, which were dissociated into cultures with more than 85% neuronal purity. In these neurons, R406W tau exhibited hypophosphorylation, as well as increases in fragmentation by calpain. Furthermore, axonal degeneration was found in R406W mutant neurons which could be rescued by microtubule stabilization, and an increased percentage of R406W tau was mislocalized to the dendrites.
Conclusion In this study, we elucidated certain aspects of R406W mutant tau-mediated pathology using iPSC-derived neurons. The next step is to explore how these abnormalities lead to further neurodegeneration.

Disclosures: M. Nakamura: None. **H. Watanabe:** None. **S. Shiozawa:** None. **S. Maeda:** None. **S. Hisanaga:** None. **N. Sahara:** None. **T. Kimura:** None. **T. Miyasaka:** None. **A. Takashima:** None. **T. Ikeuchi:** None. **H. Okano:** None.

Nanosymposium

443. Stem Cells and Disease Modeling: Neuropsychiatric and Neurodegenerative Disease

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 8:00 AM - 11:30 AM

Presentation Number: 443.14

Topic: A.03. Stem Cells and Reprogramming

Support: Krembil Foundation

Title: Genome-editing of the rere super-enhancer in human neural precursor cells alters expression of genes in independent schizophrenia associated regions

Authors: *C. L. BARR[1], Y. FENG[1], K. G. WIGG[1], C. MARCHETTO[2], F. H. GAGE[3]
[1]Krembil Res. Inst., Toronto, ON, Canada; [3]LOG-G, [2]Salk Inst., La Jolla, CA

Abstract: Background: The majority of associated markers for complex genetic traits reside in gene regulatory regions, particularly enhancers and super-enhancers. Enhancers can reside megabases from the gene they regulate (target gene) and their targets are often not the nearest gene. Thus, the assumption that the gene nearest a GWAS-significant marker will be the risk gene will in many cases be incorrect.
Methods: To identify the target genes of enhancers with GWAS significant markers, we analyzed Capture-HiC data selecting enhancers for functional studies using CRISPR/Cas9 in human neural precursor cells (hNPCs) derived from embryonic stem cells. The impact on expression was measured by digital droplet PCR and RNA-seq in the edited versus the mock-transfected cells.
Results: We selected the super-enhancer spanning the 3' end of the *RERE* gene for study, the site of GWAS significant SNPs for schizophrenia and major depression. Capture-HiC data indicate interactions of the super-enhancer with *RERE* (co-repressor/co-activator involved in retinoic acid signaling and the key gene in 1p36 deletion syndrome, a developmental disorder with autism spectrum symptoms), *PARK7* (Parkinsons 7, protects neurons from oxidative stress and regulates dopamine neurotransmission) and *PER3* (Period 3). These 3 genes are transcription co-regulators or transcription factors. Using CRISPR/Cas9, we deleted a 2kb region of the super-enhancer in hNPCs and analyzed the transcriptome by RNA-seq. We identified 107 genes that were differentially expressed, including 14 regulated by retinoic acid. Importantly, 3 of these are located in independent GWAS regions for schizophrenia.
Conclusions: Capture-HiC provides important new leads in pinpointing the target genes of enhancer-mediated regulation emanating from the GWAS findings and functional studies confirm altered expression of interacting genes. The finding of altered expression of genes in independent GWAS regions is an important new lead in understanding the regulation of psychiatric disorder risk genes. We are currently differentiating the CRISPR/Cas9 edited NPCs to neurons to examine the impact of the edits on differentiation and neuronal phenotypes. Further, we have created clonal edited ES cell lines for the creation of cerebral organoids.

Disclosures: C.L. Barr: None. **Y. Feng:** None. **K.G. Wigg:** None. **C. Marchetto:** None. **F.H. Gage:** None.

Nanosymposium

444. LTP: Intracellular Signaling, Pre- and Postsynaptic Mechanisms

Location: SDCC 25

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 444.01

Topic: B.07. Synaptic Plasticity

Support: NIH Grant MH094792

Title: Dual phosphorylation of ERK provides a mechanism for coincidence detection in a cellular model of repeated-trial learning

Authors: *N. KUKUSHKIN, T. J. CAREW
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Any neural representation of memory reflects a response to temporally structured information, such as repetition of a stimulus or coincidence of multiple stimuli. During repeated-trial learning, the effect of a previous stimulus must coincide with the effect of ongoing stimulus repetition, yielding more persistent changes in the system. We have previously described in the mollusk *Aplysia* a powerful training paradigm that induces long-term memory (LTM) for sensitization, consisting of only two stimuli that must be separated by a surprisingly specific time interval, 45 min. This type of repeated-trial learning, and its correlates at cellular and molecular levels, are ideally suited to distinguish the delayed effects of initial stimulus presentation (a "molecular context") from the ongoing effects of stimulus repetition (coincidence detection). We have previously shown that the permissive time window for LTM induction 45 minutes after the initial training trial is defined in part by a transient surge of ERK phosphorylation, which becomes persistent if it coincides with the second trial. However, the nature of this delayed time window of ERK phosphorylation, and the mechanism by which it becomes persistent, remain unexplained. Enzymatic activation of all MAP kinases, including ERK, involves unusual dual threonine/tyrosine phosphorylation, with neither of the singly phosphorylated forms possessing activity. We now show in isolated *Aplysia* sensory neurons that the build-up of phospho-ERK 45 minutes after a training-mimicking pulse of serotonin (5HT) is not accounted for by a corresponding build-up of dually phosphorylated ERK, suggesting that the "molecular context" induced by the first training trial involves the production of a large pool of inactive, singly phosphorylated ERK. Upon coincidence with the second 5HT pulse, this pool rapidly yields dually phosphorylated ERK in larger quantities than observed after the first pulse alone, presumably by undergoing a second round of phosphorylation. Thus, dual phosphorylation of ERK, coupled with distributed dynamics of phosphorylation and/or dephosphorylation, provides a system *for delayed coincidence detection*. We hypothesize that this pattern recognition mechanism is a conserved feature of all eukaryotic MAP kinases.

Disclosures: N. Kukushkin: None. **T.J. Carew:** None.

Nanosymposium

444. LTP: Intracellular Signaling, Pre- and Postsynaptic Mechanisms

Location: SDCC 25

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 444.02

Topic: B.07. Synaptic Plasticity

Support: NIMH RO1 MH 041083
NIMH 5T32 MH019524
NIMH T32 MH 963314

Title: The role of *Aplysia* cysteine-rich neurotrophic factor in the induction of activity-dependent long-term synaptic plasticity

Authors: *A. ALEXANDRESCU, T. J. CAREW
New York Univ., New York, NY

Abstract: The molecular mechanisms governing long-term memory (LTM) formation are highly conserved across species. One such conserved mechanism is neurotrophic factor signaling which, in addition to being critical for developmental plasticity, also contributes to adult synaptic plasticity underlying LTM. While it is known that neurotrophic factors are released locally at synapses in response to neuronal activity during LTM formation, their precise pre- and postsynaptic effects remain to be elucidated. The marine mollusk *Aplysia californica* is a powerful model system for studying cellular and molecular mechanisms of LTM formation. In *Aplysia*, long-term facilitation (LTF) of monosynaptic connections between identified sensory and motor neurons (SNs and MNs) contributes significantly to LTM for sensitization. Moreover, the SN-MN microcircuit can be reconstituted in culture, offering single cell spatial resolution for the examination of endogenous neurotrophic factor signaling *in vitro*. Our laboratory has identified a novel neurotrophic factor, *Aplysia* cysteine-rich neurotrophic factor (ApCRNF), which shares structural and functional characteristics with mammalian neurotrophic factors (Pu et al. 2014). We previously showed that: (i) ApCRNF is released in the the CNS in an activity-dependent manner, and ii) when paired with subthreshold analog training for sensitization, exogenous application of recombinant ApCRNF induces ERK/MAPK activation in SNs, and LTF of SN-MN synapses, which are well-characterized molecular and cellular correlates of LTM formation in *Aplysia*. Here we show that blocking endogenously released ApCRNF with an anti-ApCRNF antibody during and immediately after training, blocks the induction of activity-dependent LTF. Next, we sought to investigate the pre- and postsynaptic molecular mechanisms by which ApCRNF participates in the induction of activity-dependent LTF, focusing on transcription. To that end, we performed a time course of gene expression following activity-dependent training in both SN clusters and single MNs using qPCR. We focused our analysis on two genes: ApCRNF itself and C/EBP, an immediate-early gene downstream of CREB

transcription required for LTF. Thus far, our results suggest that the mRNA levels of both ApCRNF and C/EBP are regulated differentially by activity-dependent training in presynaptic SNs and postsynaptic MNs. Our current studies are testing the hypothesis that ApCRNF release during activity-dependent training regulates its own mRNA levels as well as those of C/EBP in the SN-MN circuit to induce LTF.

Disclosures: A. Alexandrescu: None. **T.J. Carew:** None.

Nanosymposium

444. LTP: Intracellular Signaling, Pre- and Postsynaptic Mechanisms

Location: SDCC 25

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 444.03

Topic: B.07. Synaptic Plasticity

Support: NIMH RO1 MH 041083 Grant to TJC
Hellenic Medical Society of New York, Leonidas Lantzounis Research Grant to AAM

Title: Growth factor mediated post-transcriptional regulation of the immediate early gene c/ebp by the RNA-binding protein ELAV is critical for long-term memory formation in *Aplysia*

Authors: *A. A. MIRISIS, T. J. CAREW
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Signaling through distinct growth factor (GF) pathways is required for long-term memory (LTM) formation in unique temporal and spatial domains in *Aplysia*. Specifically, in a two-trial training paradigm, TrkB signaling is required for gene expression of *apc/ebp*, an immediate-early gene, at 45 minutes following Trial 1, but prolonged *apc/ebp* gene expression necessary for LTM, in addition, requires TGFβ signaling during Trial 2 (Kopec et al., 2015). The *apc/ebp* transcript contains multiple AU-rich elements (AREs) in its 3' UTR, conferring increased susceptibility to degradation and/or stabilization due to the AREs' ability to bind various RNA-binding proteins (Yim et al., 2006). In this study, we show that (i) Trial 1-dependent *apc/ebp* gene expression is transcription-dependent, whereas Trial 2-dependent *apc/ebp* gene expression is transcription-independent, but is dependent on p38 MAPK activation downstream of TGFβ signaling; (ii) Treatment with recombinant human (rh)TGFβ-1 at 45 min, even in the presence of transcriptional inhibitors, is sufficient for increased *apc/ebp* gene expression at 1 hour; (iii) ApELAV-*apc/ebp* mRNA interaction increases after Trial 2, and TGFβ signaling is critical for this increase, (iv) A potent inhibitor of ELAV-mRNA interactions, CMLD-2, significantly reduces the expression of Trial 2-dependent *apc/ebp* mRNA at 1 hour, and (v) CMLD-2 blocks LTM formation. Collectively, these results elucidate a novel role for a unique form of post-transcriptional regulation: stabilization of a specific transcript, *apc/ebp* by ELAV-like proteins, as a necessary molecular step in LTM formation. Further experiments have

revealed translocation of ELAV from the sensory neuron nucleus at 30 min following Trial 2, an effect that is dependent on p38 MAPK activation downstream of TGFβ signaling. Taken together with previous findings of ARE-containing mRNAs in dendrites and at synapses (Alberini, 2009; Arguello et al., 2013), this observation suggests a critical role for ELAV-mediated transcript shuttling in LTM formation.

Disclosures: T.J. Carew: None.

Nanosymposium

444. LTP: Intracellular Signaling, Pre- and Postsynaptic Mechanisms

Location: SDCC 25

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 444.04

Topic: B.07. Synaptic Plasticity

Support: HBP SGA1

Title: Purification and proteomic profiling of PSD-95 interactors at *in vivo* potentiated synapses

Authors: *M. MAINARDI[1], F. GOBBO[1], A. JACOB[1], L. ZENTILIN[2], C. CATERINO[1,3], A. CELLERINO[1,3], A. ORI[3], A. CATTANEO[1]
[1]Lab. of Biol., Scuola Normale Superiore, Pisa, Italy; [2]ICGEB, Trieste, Italy; [3]Franz Lipmann Inst., Jena, Germany

Abstract: The acquisition of new memories is accompanied by long-lasting modifications in the strength of information transmission between neurons i.e., synaptic plasticity. The structural substrate for synaptic plasticity is a reorganization of the protein content of the synapses. This includes changes in the subunit composition of pre-existing complexes, synthesis or accumulation/relocalization of new proteins, and the formation of new interactions, which can be induced or stabilized by posttranslational modifications (Herring & Nicoll, Ann Review Physiol 2016;78, 351-65). The postsynaptic density (PSD) is a hub of these processes; indeed, PSD-95 interacts with many structural proteins (Shank3, PSD-93) and effectors (AMPARs, NMDARs, CaMKII) (Okabe, Mol Cell Neurosci 2007;34, 503-18). While the set of PSD-95 interactors in the forebrain has been defined by means of proteomic analysis (Fernández et al., Mol Syst Biol 2009;5, 269), to date it has not been possible to describe how the interactome of PSD-95 changes in response to synapse potentiation. To fill this gap, we exploited the SynActive toolbox, which we recently developed to achieve specific expression of proteins of interests at potentiated synapses (Gobbo et al., Nat Comm 2017;8, 1629), to selectively purify the interactors of PSD-95 from in vivo potentiated synapses. A SynActive-controlled, FLAG-tagged version of PSD-95 was delivered via AAV to the hippocampus of mice, which were subsequently challenged with contextual fear conditioning. PSDs were then isolated by affinity purification and their protein content analysed by mass spectrometry. As a reference set, we analysed the interactomics of

FLAG-tagged PSD-95 constitutively expressed in home caged animals. Our proteomics data, validated by Western Blot, are the first report of an unbiased comparison of the protein content of the PSD between unstimulated and potentiated synapses. Our data provide a deeper understanding of the mechanisms acting in concert at the synapse during learning. This approach can be applied also to mouse models for neurodegenerative pathologies, like Alzheimer's disease, to look for activity-dependent structural alterations at early stages of the disease, thus helping in the search for early therapeutic interventions.

Disclosures: M. Mainardi: None. **F. Gobbo:** None. **A. Jacob:** None. **L. Zentilin:** None. **C. Caterino:** None. **A. Cellerino:** None. **A. Ori:** None. **A. Cattaneo:** None.

Nanosymposium

444. LTP: Intracellular Signaling, Pre- and Postsynaptic Mechanisms

Location: SDCC 25

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 444.05

Topic: B.07. Synaptic Plasticity

Title: Mapping potentiated synapses in the hippocampus during acquisition and consolidation of a contextual fear memory

Authors: *F. GOBBO[1], B. PINTO[2], A. JACOB[1], M. MAINARDI[1], L. CANCEDDA[2], A. CATTANEO[1]
[1]Bio@SNS, Scuola Normale Superiore, Pisa, Italy; [2]Neurosci. and Brain Technologies, Inst. Italiano Di Tecnologia, Genova, Italy

Abstract: The acquisition of new information correlates with synaptic plasticity; in particular, potentiation of synaptic transmission plays a key role in the encoding of new memories (Rogerson et al., Nat Rev Neurosci 2014;15, 157-69). This leads to postulate that synaptic engrams, as opposed to cellular engrams, can represent the physical information storage unit of the brain. So far, research has focused on cellular engrams, mainly by detecting the activity-dependent expression of immediate early genes, such as c-fos (Kubik et al., Learn Mem 2007;14, 758-70; Ramirez et al., Front Behav Neurosci 2013;7, 226). Until recently, extending activity mapping to the synaptic level was hindered by the lack of a suitable tool. To this end, we designed the SynActive toolbox, and achieved tagging and labelling of potentiated synapses (Gobbo et al., Nat Comm 2017;8, 1629). Here, we applied SynActive to the cartography of synapse potentiation during the encoding of a contextual fear memory. A SynActive-controlled fluorescent reporter was delivered to the hippocampus CA1 via triple-electrode in utero electroporation and the timing of expression was controlled with doxycycline using the TetON system. This allowed us to compare the distribution of potentiated synapses during the encoding (<90 min from the task) and the subsequent consolidation phases. Using a c-fos reporter, we also simultaneously identified engram cells and engram synapses. Neurons activated during the

encoding of a memory have a higher probability to be reactivated during the recall; however, the two sets do not overlap completely (Roy et al., Cell 2017;170, 1000-12; Ramirez et al., Science 2013;341, 387-91). Therefore, we also mapped c-fos activation the day after presenting the animal the conditioned context (recall) or an unrelated context, to understand if the number of potentiated synapses is predictive of the reactivation chance. Taking into account that consolidation occurs on a longer time scale than acquisition (van de Ven et al., Neuron 2016;92, 968-74) and based on our maps of potentiated synapses, we propose a two-stage model characterized by two epochs of synapse potentiation. Our findings provide new information on the establishment and maturation of a memory trace, and can be applied to understand memory transfer across brain areas.

Disclosures: F. Gobbo: None. **B. Pinto:** None. **A. Jacob:** None. **M. Mainardi:** None. **L. Cancedda:** None. **A. Cattaneo:** None.

Nanosymposium

444. LTP: Intracellular Signaling, Pre- and Postsynaptic Mechanisms

Location: SDCC 25

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 444.06

Topic: B.07. Synaptic Plasticity

Support: NSF NeuroNex 1707356
NIH R01MH104319
NIH R01MH095980
NIH NS21184
NIH MH0959080
NIH NS074544
NIH MH095980

Title: Impact of LTP on information storage capacity at hippocampal synapses

Authors: T. M. BARTOL[1], *C. BROMER[2], T. J. SEJNOWSKI[1,3], K. M. HARRIS[3], J. MENDENHALL[3], J. BOWDEN[3], P. PARKER[3], M. KUWAJIMA[3], D. HANKA[3], D. HUBBARD[3], W. ABRAHAM[4]
[1]Computat. Neurosci. Lab., Salk Inst., LA Jolla, CA; [2]LA Jolla, CA; [3]Ctr. for Learning and Memory, Univ. of Texas, Austin, Austin, TX; [4]Dept. of Psychology, Univ. of Otago, Otago, New Zealand

Abstract: We previously demonstrated variability in information storage capacity at synapses in the hippocampus based on an analysis of serial section electron microscopy (3DEM) from young adult Long Evans rats. 3DEMs were generated from hippocampal tissue that was perfusion-fixed in vivo in control animals, for area CA1, as well as from middle molecular layer of the dentate

gyrus at 30 min and 120 min following induction of LTP. The contralateral hippocampus of the same animals served as dentate gyrus controls. Newly developed tools in Blender were used to measure spine head volume as a predictor of individual synaptic weights. In control conditions, we found that more bits of information were available per dendritic spine in stratum radiatum of hippocampal area CA1 (~4.7 bits) compared to the middle molecular layer of the dentate gyrus (~2.7 bits) (Bromer et al., 2017). By 30 minutes following the induction of LTP there was an increase in information storage capacity in dentate gyrus (~3.7 bits) compared to the dentate control condition (~3.2 bits), if the whole range in spine sizes under the LTP condition was also applied to the dentate control condition. Current observations suggest that the increase in information content observed at 30 minutes was sustained for 120 minutes following LTP (~3.6 bits) compared to control hemispheres from the same animals (~3.2 bits). Thus, the shift in the information storage capacity at synapses was sustained for 2 hours after LTP in the dentate gyrus. Whether sustained shifts in information content are a general mechanism of learning and memory will require comparisons of LTP, learning, and memory in this and other brain regions.

Disclosures: T.M. Bartol: None. **C. Bromer:** None. **T.J. Sejnowski:** None. **K.M. Harris:** None. **J. Mendenhall:** None. **J. Bowden:** None. **P. Parker:** None. **M. Kuwajima:** None. **D. Hanka:** None. **D. Hubbard:** None. **W. Abraham:** None.

Nanosymposium

444. LTP: Intracellular Signaling, Pre- and Postsynaptic Mechanisms

Location: SDCC 25

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 444.07

Topic: B.07. Synaptic Plasticity

Support: Mentoring Environment Grant (MEG)
NIH Grant R15NS078645

Title: Hippocampal stratum oriens interneurons express endocannabinoid biosynthetic enzymes and undergo CB1 and anandamide-dependent potentiation

Authors: *I. OSTLUND[1], L. N. FRIEND[3], J. G. EDWARDS[2], C. B. MERRILL[4], M. B. CHRISTENSEN[5], S. NEWTON[6], R. WILLIAMSON[7]
[1]Physiol. and Developmental Biol., [2]Brigham Young Univ., Provo, UT; [3]NIH, North Bethesda, MD; [4]Mol. Med., Salt Lake City, UT; [5]Bioengineering, Univ. of Utah, Salt Lake City, UT; [6]BYU, Centerville, UT; [7]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The hippocampus is thought to mediate learning and memory by altering the strength of synapses within its circuitry. In many cases, this synaptic plasticity can be induced by signaling molecules. Lipid-based signaling molecules called endocannabinoids can modulate synaptic plasticity among hippocampal pyramidal cells and stratum radiatum interneurons;

however, the role of endocannabinoids in mediating synaptic plasticity among hippocampal stratum oriens interneurons is still unclear. Using patch-clamp electrodes to extract single cells we analyzed the expression of endocannabinoid biosynthetic enzyme mRNA using RT-PCR. In this analysis, we determined interneuron subtype by examining cellular expression of several calcium-binding proteins and neuropeptides. We also analyzed cellular expression of endocannabinoid biosynthetic enzymes, N-acyl phosphatidylethanolamine phospholipase D, diacylglycerol lipase alpha (DAGLa), and 12-lipoxygenase, as well as type 1 mGluRs. Immunohistochemistry confirmed DAGLa protein expression in GAD67-positive oriens interneurons. Data also indicate that stratum oriens interneurons express mRNA necessary for endocannabinoid biosynthetic enzymes. To test the role of endocannabinoids in synaptic plasticity, stratum oriens interneurons were patched and glutamate currents were recorded in the presence of a fatty acid amide hydrolase inhibitor (URB597) to increase endogenous anandamide. We observed a 30% enhancement above baseline ($n=7$, $p<.001$) that was blocked by the CB1 inhibitor AM-251 ($n=6$, $p<.001$). In addition, we attempted to induce long-term potentiation (LTP) with high frequency stimulation and noted cells exhibiting LTP were in general somatostatin-positive O-LM cells ($n=8$), while LTP-negative cells were not ($n=4$). AM-251 blocked LTP in O-LM positive cells ($n=6$; $p<0.05$). We are currently confirming these results in CB1 knock-out mice. These results demonstrate a novel endocannabinoid-mediated mechanism for synaptic plasticity in stratum oriens interneurons.

Disclosures: I. Ostlund: None. **L.N. Friend:** None. **J.G. Edwards:** None. **C.B. Merrill:** None. **M.B. Christensen:** None. **S. Newton:** None. **R. Williamson:** None.

Nanosymposium

444. LTP: Intracellular Signaling, Pre- and Postsynaptic Mechanisms

Location: SDCC 25

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 444.08

Topic: B.07. Synaptic Plasticity

Title: Arc interacts with polyadenylate binding protein 2 during *in vivo* LTP and regulates the formation of PAB2 nuclear speckles

Authors: *T. KANHEMA[1], K. PAROBCZAK[2], D. HOLM[2], S. PATIL[1], A. SZUM[1], G. WILCZYNSKI[2], C. BRAMHAM[1]
[1]Univ. of Bergen, Bergen, Norway; [2]Nencki Inst. of Exptl. Biol., Warsaw, Poland

Abstract: Arc is a highly specialized immediate early protein of critical importance for long-term synaptic plasticity in the mammalian brain. While Arc is known to act within dendritic spines, a large fraction of activity-induced Arc protein enters the nucleus. Previous work implicates Arc in transcriptional regulation, but the role of Arc in the nucleus is still little understood. Here, we first analyzed the subnuclear localization of Arc protein by confocal

microscopy. Follow seizure activity (KA or PTZ-treated) in awake rats or LTP induction in the dentate gyrus of anesthetized rats, Arc protein preferentially occupied the nuclear interchromatin space of dentate granule cells. Subcellular fractionation of LTP-treated dentate gyrus similarly showed enhancement of Arc expression in the nucleoplasm relative to the chromatin-bound nuclear fraction. Arc immunoprecipitation and mass spectrometry analysis of tissue lysates identified two candidate interaction partners: polyadenylate-binding protein 2 (PABP2) and polypyrimidine tract-binding protein-associated splicing factor (PSF). Coimmunoprecipitation and GST-Arc pulldown assays confirmed interraction of Arc with PAB2 and PSF in nuclear fractions following induction of the LTP in the dentate gyrus in vivo. In cultured hippocampal neurons, chemical LTP treatment increased the abundance of PAB2 nuclear puncta. Knockdown of Arc blocked activity-dependent increases in PAB2 nuclear foci. Thus, Arc forms a complex with nuclear PAB2 and regulates PAB2 abundance and nuclear distribution. These results couple Arc function to nuclear PAB2, a major regulator of post-transcriptional RNA processing.

Disclosures: T. Kanhema: None. **K. Parobczak:** None. **D. Holm:** None. **S. Patil:** None. **A. Szum:** None. **G. Wilczynski:** None. **C. Bramham:** None.

Nanosymposium

444. LTP: Intracellular Signaling, Pre- and Postsynaptic Mechanisms

Location: SDCC 25

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 444.09

Topic: B.07. Synaptic Plasticity

Support: R01 MH070957

Title: Role of the amino-terminal domain in AMPA receptor synaptic trafficking

Authors: *J. DÍAZ-ALONSO[1,2], Y. J. SUN[2], A. J. GRANGER[4], R. A. NICOLL[3]
[1]San Francisco, CA; [3]Dept Cell & Mol Pharmacol, [2]UCSF, San Francisco, CA; [4]Harvard Med. Sch., Boston, MA

Abstract: The amino-terminal domain (ATD) of AMPA receptors (AMPARs) accounts for approximately 50% of the protein, yet its functional role is not fully understood. In order to study its function in AMPARs synaptic trafficking we employed an inducible molecular replacement strategy, where endogenous AMPARs are replaced by recombinant truncated receptors, expressed in a doxycycline-dependent manner, in mouse hippocampal slices of either sex. Using electrophysiology, we have discovered that the translocation of surface GluA1, but not GluA2, AMPAR subunits to the synapse requires the ATD. Furthermore, GluA1A2 heteromers in which the ATD of GluA1 is absent fail to translocate, establishing a critical role of the ATD of GluA1. A GFP tag inserted into the GluA1 ATD interferes with the constitutive synaptic trafficking of GluA1, mimicking the deletion of the ATD. GluA2, however, can traffic to the synapse even

with the addition of GFP, further supporting a subunit-specific role of the AMPAR ATD in synaptic trafficking. Remarkably, long-term potentiation (LTP) can override the masking effect of the GFP tag. In contrast, GluA1, but not GluA2, lacking the ATD fails to show LTP. These findings uncover a prominent role for the ATD in subunit-specific synaptic trafficking of AMPARs, both constitutively and during plasticity.

Disclosures: J. Díaz-Alonso: None. **Y.J. Sun:** None. **A.J. Granger:** None. **R.A. Nicoll:** None.

Nanosymposium

445. Network Interactions, Oscillations, and Synchrony

Location: SDCC 24

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 445.01

Topic: B.09. Network Interactions

Support: NIH Grant R21HD087128
NIH Grant R21HD090453

Title: The effect of startling acoustic stimulation on intracortical facilitation and inhibition - A SAS-TMS study

Authors: *Y.-T. CHEN, S. LI, P. ZHOU, S. LI
Physical Med. and Rehabil., UTHealth, Houston, TX

Abstract: It has been well established that a startling acoustic stimulation (SAS) causes a transient effect on the primary motor cortex (M1) non-reflexively. Specifically, SAS reduced transcranial magnetic stimulation (TMS) induced motor evoked potential (MEP) amplitude at rest, but not during voluntary contraction. However, the effect of SAS on intracortical facilitation and inhibition is still not clear. Therefore, the purpose of this study was to investigate the SAS effect on short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) using TMS.
Four healthy subjects participated in this study. TMS was delivered to the hot spot of right M1 at rest and during isometric right elbow flexion (10% of maximum voluntary contraction, MVC). There were two SAS conditions: 1) No SAS; 2) SAS was delivered 90ms prior to TMS. There were three TMS delivery conditions: 1) single-pulse: a single pulse of test TMS; 2) SICI: a conditioning TMS delivered 2 ms prior to a test TMS; 3) ICF: a conditioning TMS delivered 10 ms prior to a test TMS. The conditioning TMS was set to 80% of resting motor threshold (rMT) at rest, and 80% of active motor threshold (aMT) during contraction task. The test TMS was set to 120% of rMT at rest, and 120% of aMT during contraction task. TMS-induced MEP was calculated as the peak to peak amplitude of the MEP with the time window from the MEP onset to 50ms after the test TMS delivery.
We confirmed that SAS reduced MEP amplitude induced by single-pulse TMS stimulation at

rest, but not during voluntary contraction. SAS caused opposite effect on ICF at rest and during voluntary contraction. Specifically, SAS decreased the MEP amplitude induced by ICF stimulation at rest. However, SAS increased the MEP amplitude induced by ICF stimulation during the voluntary contraction task. Moreover, SAS had no significant effect on SICI at rest or during voluntary contraction. Our results suggest that the transient effects of startling acoustic stimulation on the motor cortex excitability are mainly mediated by modulation of intracortical excitatory mechanisms.

Disclosures: Y. Chen: None. **S. Li:** None. **P. Zhou:** None. **S. Li:** None.

Nanosymposium

445. Network Interactions, Oscillations, and Synchrony

Location: SDCC 24

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 445.02

Topic: B.09. Network Interactions

Support: Hungarian Brain Research Program 20017-1.2.1-NKP-00002
EFOP-3.6.2-16-2017-00008

Title: Network effects of dendritic inhibition in the medial entorhinal cortex

Authors: *C. VARGA, M. KECSKES, N. HENN-MIKE, Z. KRABOTH, A. AGOCS-LABODA, S. SZOCS, Z. PETYKO
Physiol., Univ. of Pecs, Med. Sch., Pecs, Hungary

Abstract: Superficial and deep layer principal neurons in the medial entorhinal cortex (MEC) convey distinct signals into and from the hippocampus, respectively. Their incoming inputs from cortical and subcortical areas, however, largely overlap, which further emphasizes the potential role of specific inhibitory microcircuits in tuning the network activity in different layers. Grid and other spatially modulated cells are abundantly found in layerII but rarely occur in deeper areas, thus we asked whether we see a correlation between layer/principal cell type differences and the nature of their inhibitory inputs. For this, we compared the network effects of the two most abundant interneuronal population: parvalbumin (PV) and somatostatin (SOM) expressing GABAergic cells. ChR2 expression was induced by vector delivery into the MEC of PV-cre and SOM-cre animals. With the combination of optogenetics and whole cell patch clamp techniques we found that PV+ inhibitory interneurons show not target selectivity: they innervate principal cells in all layers. However, the dendritic targeting SOM+ interneurons showed much larger effect on layerIII-V pyramidal cells than on layerII stellate and pyramidal cells. Moreover, the SOM+ innervation was strong enough to cease the persistent firing recorded in deep layer pyramidal cells. Juxtacellular and silicon probe experiments on awake mice proved that the optogenetic activation of SOM+ cells in the MEC is able to inhibit the firing of deep layer

principal cells for several hundred milliseconds. Our data indicate that dendritic inhibition by SOM+ interneurons might be more influential on non-spatial information processing in the medial entorhinal cortex.

Disclosures: M. Kecskes: None. **N. Henn-Mike:** None. **Z. Kraboth:** None. **A. Agocs-Laboda:** None. **S. Szocs:** None. **Z. Petyko:** None. **C. Varga:** None.

Nanosymposium

445. Network Interactions, Oscillations, and Synchrony

Location: SDCC 24

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 445.03

Topic: B.09. Network Interactions

Support: NIH Grant R01 EY026156

Title: Dynamics of state transitions in laminar cortical circuits

Authors: *N. KHARAS[1], S. R. DEBES[2], A. R. ANDREI[3], V. DRAGOI[4]
[1]Neurobio. and Anat., Univ. of Texas at Houston/McGovern Med. Sc, Houston, TX; [2]Neurobio. and Anat., Univ. of Texas at Houston, Houston, TX; [3]Neurobio. & Anat., McGovern Med. Sch., Houston, TX; [4]Dept Neurobiol/Anat, Univ. of Texas at Houston Dept. of Neurobio. and Anat., Houston, TX

Abstract: Spontaneous fluctuations in neuronal firing are observed at the timescale of milliseconds. Traditionally, synchronized neural activity was characterized as ON and OFF state transitions during sleep, whereas desynchronized activity was viewed as a hallmark of wakefulness. However, recent studies have indicated that ON and OFF states are present during wakefulness, but the prevalence of synchronized activity and its dependence of behavioral state remain unclear. To determine whether synchronized fluctuations in ON and OFF states occur in different behavioral states, we recorded single- and multi-unit activity along a cortical column in monkey visual cortex (areas V1 and V4) while animals performed a behavioral task or were sleeping. We subsequently employed a hidden Markov model to identify ON and OFF response states in neuronal populations, and measured the frequency of transitions between the two states within a column. The number of transitions per second between states was significantly greater in sleep than in wakefulness. The trial-by-trial frequency of the transitions was negatively correlated with the global brain state measured by arousal. We further examined the presence of synchronized state transitions in the supragranular, granular, and infragranular layers of V1 and V4 during wakefulness, and discovered that synchronized fluctuations in population activity were rare events across layers. Furthermore, we induced ON and OFF state transitions using optogenetics stimulation in one cortical layer to determine whether synchronized fluctuations spread towards adjacent layers. However, the rapid fluctuations in cortical activity caused by

light did not propagate to other layers despite strong inter-layer connectivity. Our findings indicate that cortical laminar networks operate in a desynchronized mode during wakefulness and switch to synchronized activity during sleep.

Disclosures: N. Kharas: None. **S.R. Debes:** None. **A.R. Andrei:** None. **V. Dragoi:** None.

Nanosymposium

445. Network Interactions, Oscillations, and Synchrony

Location: SDCC 24

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 445.04

Topic: B.09. Network Interactions

Support: RO1 MH110311
Whitehall Foundation 2015-12-71
BBRF NARSAD 23017
WNPRC Pilot Project

Title: Central lateral thalamus causally influences states of consciousness by regulating fronto-parietal cortical dynamics

Authors: *M. J. REDINBAUGH[1], J. M. PHILLIPS[1], N. A. KAMBI[1], S. MOHANTA[1], A. RAZ[2,3], Y. B. SAALMANN[1]
[1]Psychology, Univ. of Wisconsin-Madison, Madison, WI; [2]Dept. of Anesthesiol., Univ. of Wisconsin, Madison, WI; [3]Anesthesiol., Rambam health Care Campus, Haifa, Israel

Abstract: Although frontal-parietal and thalamo-cortical circuits have been implicated in the neural correlates of consciousness, how activity in these circuits influences consciousness remains unclear. Frontal and parietal cortices connect via direct feedforward (FF) and feedback (FB) pathways, as well as indirectly via the intralaminar thalamic central lateral nucleus (CL). Damage to intralaminar thalamus has been linked to disorders of consciousness such as coma. We hypothesized that CL influences consciousness by regulating information transmission across fronto-parietal cortex.
We simultaneously recorded from the frontal eye field (FEF), lateral intraparietal cortex (LIP), and CL in 2 macaques during general anesthesia (propofol or isoflurane), wakefulness (resting state or fixation task), and non-rapid eye movement sleep (NREM). In each state, we used a passive auditory oddball paradigm to assess thalamo-cortical processing. We recorded spikes and local field potentials (LFPs) using laminar probes that were imaged in situ to confirm desired positioning. To manipulate thalamo-cortical dynamics, we electrically stimulated thalamic sites across 16 probe contacts with 100-300 μA at 10, 50 or 200Hz. We analyzed data during stable eye epochs at baseline, in the oddball paradigm, and with thalamic stimulation. To monitor consciousness level, we recorded EEG, EMG, eye position, and vital signs. Awake and

anesthetized recordings took place in a dark room with the animal's head stabilized.
Preliminary results suggest CL stimulation at 50Hz, mimicking the wakeful spike rate of CL neurons, counteracted propofol and isoflurane anesthesia: stimulation reduced EEG power at delta frequencies, increased fronto-parietal coherence at higher frequencies, and permitted eye openings and purposeful movements. These effects were time-locked and specific to stimulation within CL; stimulating other nearby thalamic nuclei did not have the same effects. 50Hz CL stimulation also augmented cortical responses to auditory oddballs under anesthesia and NREM. Stimulating at 10Hz, mimicking the unconscious spike rate of CL neurons, or 200Hz, akin to clinical deep brain stimulation (DBS), did not produce the same effects. Current source density analyses also suggest that conscious and unconscious states differentially affect FF and FB processing across fronto-parietal cortex.
Our data suggest that CL influences states of consciousness by modulating information processing in fronto-parietal cortex. Accounting for the frequency specificity of CL stimulation effects may improve clinical DBS outcomes in disorders of consciousness.

Disclosures: M.J. Redinbaugh: None. **J.M. Phillips:** None. **N.A. Kambi:** None. **S. Mohanta:** None. **A. Raz:** None. **Y.B. Saalmann:** None.

Nanosymposium

445. Network Interactions, Oscillations, and Synchrony

Location: SDCC 24

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 445.05

Topic: B.09. Network Interactions

Support: NSF Grant CNS1446578

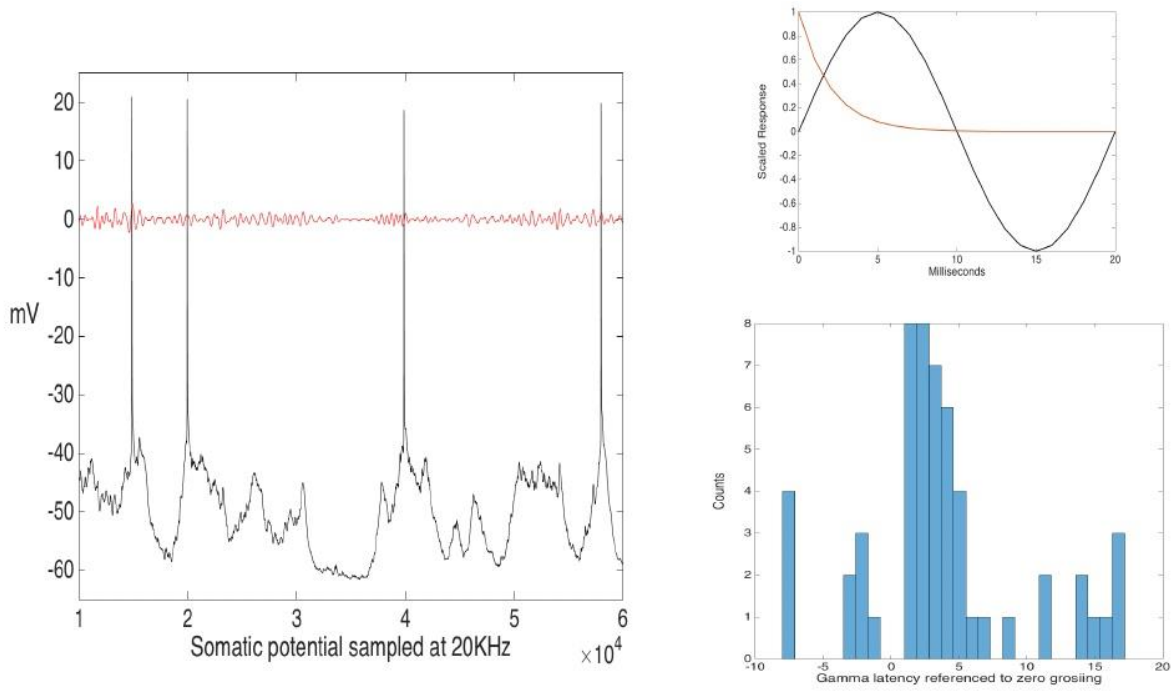
Title: Cortical spike multiplexing using gamma frequencies

Authors: R. ZHANG[1], S. KOBAYASHI[2], L. GENTET[3], *D. H. BALLARD[1]
[1]Computer Sci., [2]Neurosci., Univ. of Texas at Austin, Austin, TX; [3]Lyon Neurosci. Res. Ctr., Lyon, France

Abstract: Traditional ways of measuring cortical cell action potentials may be a correlate of a more complex code that allows multiple simultaneous processes [1]. We have developed and tested a model [2], that shows how the cortex can manage separate simultaneous computations, each requiring a functionally separate network, a capability impossible with Poisson models. Poisson action potential (AP) distributions can be understood as a correlate of a more basic gamma phase coding model that can mix several independent computations non-destructively. The model shows how to choose circuits probabilistically so that separate computations do not interfere. A primary prediction of the model is that action potentials signal an analog quantity as a delay from a gamma frequency zero crossing. The test of this hypothesis, using six exemplars

of 7second long recordings of mouse V1 cortical cell patch clamp data [3], shows the somas' gamma modulation varies in the way required by the model. A central hypothesis is that the action potentials are timed with respect to modulations in the somatic gamma potential. To make this relationship apparent, we filter the somatic potential with a Butterworth zero phase filter with a gamma frequency passband of [35~55] Hz, after removing the AP transits above -37 mV so they do not bias the filtering operation. The filtered signal (in red) is easy to compare to the action potentials in the left of the Figure. A Close examination of the APs shows that they are correlated with the upswing of the gamma cycle. Using high resolution (20kHz) sampling of the somatic potential, the relationship between the action potential and local gamma phase can be established accurately. The right columns of the Figure compare the model's prediction (top) with delay amplitude coding with a histogram of six somatic potential records like the one shown on the left. The experimentally observed spike delays with respect to the gamma phase show close agreement to the theoretical prediction.

1. Elife 5, e10989 (2016)
2. BIORXIV/2018/313320
3. PLoS biology 14, e1002383 (2016)



Disclosures: R. Zhang: None. **S. Kobayashi:** None. **L. Gentet:** None. **D.H. Ballard:** None.

Nanosymposium

445. Network Interactions, Oscillations, and Synchrony

Location: SDCC 24

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 445.06

Topic: B.09. Network Interactions

Support: NS067249
MH115592
MIT Picower Institute Innovation Fund

Title: Central thalamic deep brain stimulation enhances dominant spiking activity profiles of cortical neurons in healthy and behaving non-human primates

Authors: *J. L. BAKER[1,2], J.-W. RYOU[1], J. A. DONOGHUE[2], S. J. KORNBLITH[2], E. K. MILLER[2], N. D. SCHIFF[1], K. P. PURPURA[1]
[1]Brain and Mind Res. Institute, Div. of Systems Neurol. and Neuroscienc, Weill Cornell Med. Col., New York, NY; [2]2The Picower Inst. for Learning and Memory and Dept. of Brain & Cognitive Sciences, Massachusetts Inst. of Technol., Cambridge, MA

Abstract: Central thalamic deep brain stimulation (CT-DBS) is an investigational therapy for chronically impaired cognitive function in severely brain injured (SBI) patients (Schiff et al., 2017, UH3NS095554). We hypothesize that DBS within a specific region of the central thalamus, the medial dorsal tegmental tract (DTTm), can artificially activate excitatory thalamocortical and corticothalamic fibers in SBI patients to reestablish arousal regulation within the anterior forebrain structures that support executive function and cognition. However the mechanisms of DBS have been almost exclusively studied in the context of experimentally induced Parkinsonism. Here we report that a novel method of multi-lead CT-DBS called 'field-shaping' (fsCT-DBS) reliably and robustly modulated arousal regulation in healthy non-human primates (NHP), while simultaneously enhancing relevant behavioral performance and anterior forebrain local field potential physiology, when directly compared to conventional CT-DBS (Baker et al., 2016). We also demonstrate that fsCT-DBS has immediate and carry-over effects on cellular spiking activity recorded in the prefrontal and premotor cortices (Baker et al., 2018). Of note, the enhancement in the dominant task-related average firing rate profiles during CT-DBS was reflected in the CT-DBS OFF trials that followed. These findings, only visible at the cellular level, strongly support our hypothesis that CT-DBS can be used to robustly modulate anterior forebrain regions in SBI patients to restore cognitive function.

Disclosures: J.L. Baker: None. **J. Ryou:** None. **J.A. Donoghue:** None. **S.J. Kornblith:** None. **E.K. Miller:** None. **N.D. Schiff:** None. **K.P. Purpura:** None.

Nanosymposium

445. Network Interactions, Oscillations, and Synchrony

Location: SDCC 24

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 445.07

Topic: B.09. Network Interactions

Support: NIMH R01MH115592

Title: Thalamic stimulation defragments cortical networks and wakes up anesthetized monkeys

Authors: *J. A. DONOGHUE[1,2,3], S. J. KORNBLITH[1], M. LUNDQVIST[2], J. E. ROY[2], M. MAHNKE[2], J. YANAR[1], E. N. BROWN[2,3], E. K. MILLER[2]
[1]Brain and Cognitive Sci., [2]The Picower Inst. for Learning and Memory and Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA; [3]Hlth. Sci. and Technol., Harvard Med. Sch., Boston, MA

Abstract: General anesthesia is often regarded the greatest discovery in medical history, yet the neural dynamics producing the unconscious brain state are remarkably not understood. Theoretical and electrophysiological studies support the hypothesis that awake, conscious experience emerges from the integration of information within fine-tuned cortical networks. The central thalamus is also known to have a special role in modulating conscious states; deep brain stimulation (DBS) of this region can drive behavioral improvements in minimally conscious patients. It is unknown, however, what role the thalamus plays in coordinating the emergence, maintenance, and recovery from general anesthesia. We developed a non-human primate model of anesthesia to study how populations of neurons across these networks mediate changes in conscious states. We simultaneously recorded spikes and local field potentials from chronically-implanted multielectrode arrays in prefrontal, posterior parietal, and auditory cortex and from central thalamic probes during the administration of the GABAergic anesthetic propofol. We discovered that the unconscious state is characterized by spatiotemporal fragmentation across cortical networks. Hyperconnectivity and functional disconnection simultaneously emerge across distinct brain regions via changes in spiking and oscillatory synchrony. These population dynamics preclude normal sensory stimuli encoding and impede information flow across hierarchical networks. We sought to establish a causal role for the thalamus in maintaining this unconscious state by activating the intralaminar nuclei with high-frequency electrical stimulation. Remarkably, thalamic DBS immediately and continuously reversed general anesthesia. Behavioral wakefulness was characterized by eye opening, air-puff responses and restored limb movement, despite continued anesthetic infusion. Thalamic activation produced an awake-like cortical state across the brain, eliminating slow oscillations and inducing a shift to higher frequency rhythms with awake spiking dynamics. Furthermore, state-space models of population spiking responses during DBS match awake dynamics. We demonstrate that sensory representations in prefrontal cortex are lost in anesthesia and restored with DBS via support

vector machine based decoding. Interestingly, behavioral and cortical “re-awakening” regularly outlasted stimulation, with loss-of-consciousness reoccurring up to minutes after DBS cessation. Together, these results uncover the network architecture and dynamical systems required to support cortical processing, cognition, and consciousness.

Disclosures: J.A. Donoghue: None. **S.J. Kornblith:** None. **M. Lundqvist:** None. **J.E. Roy:** None. **M. Mahnke:** None. **J. Yanar:** None. **E.N. Brown:** None. **E.K. Miller:** None.

Nanosymposium

445. Network Interactions, Oscillations, and Synchrony

Location: SDCC 24

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 445.08

Topic: B.09. Network Interactions

Support: B.R.A.I.N. - MH111439
EYE24776
DC015780

Title: Physiology of broadband high-frequency activity: Evidence from intracortical recordings in human and nonhuman primates

Authors: *C. E. SCHROEDER[1], A. BARCZAK[2], Y. KAJIKAWA[3], I. TAL[4], A. Y. FALCHIER[3], I. ULBERT[5], R. T. KNIGHT[6], M. LESZCZYNSKI[7]
[1]Nathan Kline Inst. - Translational Neurosci. Div., Columbia Univ. Col. of Physicians and Surgeons, Orangeburg, NY; [2]Nathan S. Kline Inst. for Psychiatric Res., Orangeburg, NY; [3]Nathan Kline Inst., Orangeburg, NY; [4]Nathan Kline Inst. for Psychiatric Res., Orangeburg, NY; [5]Hungarian Acad. of Sci., Budapest, Hungary; [6]Univ. of California Berkeley, Berkeley, CA; [7]Columbia Univ., New York, NY

Abstract: Broadband High-frequency Activity (BHA; 70-150Hz) of the intracranial field potential (FP), also known as "high gamma", is often assumed to reflect local population neural firing (i.e. multi-unit activity; MUA). Although critical for interpreting electrocorticographic (ECoG) signals in human and non-human primate studies, this assumption remains controversial and the physiology of this signal remains unknown. Using laminar recordings from macaque visual (VC; 2 monkeys) and auditory cortex (AC; 2 monkeys) during sensory stimulation we observed a bimodal distribution of the stimulus-evoked BHA across the depth of a cortical column: an early-deep (i.e. granular and infragranular) layers response, followed by later-superficial (i.e. supragranular) layers BHA increase. Across primary visual (V1) and auditory (A1) cortex, middle/deep layer BHA had a clear local MUA correlate, while superficial layer BHA had a weak or undetectable local MUA. In many cases, particularly in V1 (70%), supragranular sites showed strong BHA in lieu of any detectable MUA signal. Because of

volume conduction, BHA from both the early-deep and the later-superficial generators contribute to the field potential at the pial surface. Our results support the view that modulations of the BHA reflect a mixture of the cell body spiking and dendritic processes sub-threshold to neural firing. Laminar recordings using the same methods from the prefrontal cortex in two surgical epilepsy patients also point to the supragranular layers as the primary source of the BHA signal in ECoG recordings. Our findings in both human and nonhuman primates have 2 main implications. 1) The supragranular cortical layers are the major origin of the BHA signal in ECoG in primary visual and auditory cortices. 2) The correlation between BHA and neuronal firing, particularly in the supragranular layers, is surprisingly weak; the fact that strong BHA in this site is reliable, while concomitant MUA is sparse and often not detectable suggests that a significant component of the BHA signal may be sub-threshold to neuronal firing.

Disclosures: C.E. Schroeder: None. **A. Barczak:** None. **Y. Kajikawa:** None. **I. Tal:** None. **A.Y. Falchier:** None. **I. Ulbert:** None. **R.T. Knight:** None. **M. Leszczynski:** None.

Nanosymposium

445. Network Interactions, Oscillations, and Synchrony

Location: SDCC 24

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 445.09

Topic: B.09. Network Interactions

Support: NIH Grant MH103479

Title: Properties of narrow and broadband gamma activity in human visual cortex

Authors: *E. BARTOLI, W. H. BOSKING, M. BEAUCHAMP, D. YOSHOR, B. L. FOSTER
Dept. of Neurosurg., Baylor Col. of Med., Houston, TX

Abstract: ‘Gamma’ range activity is often proposed to support perceptual and cognitive processes by coordinating neural activity within and between brain regions. Historically, studies using non-human primate electrophysiology have repeatedly observed narrow band gamma oscillations (30-70 Hz) in response to visual stimuli. In contrast, work using human intracranial electrophysiology has often emphasized a broadband high-gamma range activity (e.g. 70-150 Hz), typically not confined to visual responses. Growing evidence suggests that these two gamma range activity patterns reflect different biophysical processes and display different functional properties regarding stimulus selectivity and anatomical substrates. To quantify these predicted differences and integrate findings across species we employed high-density intracranial recordings from human visual cortex. Following prior work, we presented participants (n = 7) with large field static grating stimuli (1cycle/degree, 500ms duration, 1.5-2s inter-stimulus interval) at three levels of contrast (20, 50, 100%). Spectral analysis revealed that grating stimuli induced both narrow and broadband gamma activity. Interestingly, the time course of narrow

band gamma oscillations was sustained throughout stimulus presentation, while broadband gamma activity was transiently increased at stimulus onset and offset. Separation of evoked and induced activity indicated these broadband transients were not exclusively due to the visual event related potential. In addition, the frequency of narrowband gamma oscillations was dependent on stimulus contrast, increasing in peak frequency with higher contrast levels (36 Hz at 20%; 40 Hz at 50%; 44 Hz at 100%). The specific frequency of narrowband gamma oscillations differed across individuals but was consistently localized to only early visual cortex (~V1/V2). This was not the case for broadband gamma activity which was not modulated in frequency by stimulus contrast, being observed within and beyond early visual cortex. On average the onset latency of narrowband gamma activity was between 150-200 ms, consistent with non-human primate recordings. Finally, narrowband gamma oscillations were not phase synchronous across trials, dissociating them further from the evoked activity at stimulus onset. Overall, our findings integrate prior observations made in human and non-human primate visual cortex, suggesting highly dissociable and stimulus dependent properties of narrow and broadband gamma activity. These findings have important implications for the functional significance of gamma range activity and how signals in this range should be dissociated.

Disclosures: E. Bartoli: None. **W.H. Bosking:** None. **M. Beauchamp:** None. **D. Yoshor:** None. **B.L. Foster:** None.

Nanosymposium

446. Seizure, Trauma, and Post-Traumatic Stress Disorder

Location: SDCC 1

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 446.01

Topic: B.10. Epilepsy

Support: NIH2R25NS070682-07
U54HD090255
Translational Research Program at Boston Children's Hospital

Title: Neuronal loss of Depdc5 causes dysplastic neurons, seizure susceptibility, early mortality and increased mTORC1 signaling that is rescued by rapamcyin in a mouse model of DEPDC5-related epilepsy

Authors: *C. J. YUSKAITIS[1], E. BAINBRIDGE[1], S. GURNANI[1], B. M. JONES[1], M. SAHIN[1], A. PODURI[2]
[1]Neurol., [2]Epilepsy & Clin. Neurophysiol., Boston Children's Hosp., Boston, MA

Abstract: *DEPDC5* is a newly identified epilepsy-related gene implicated in focal epilepsy, brain malformations, and Sudden Unexplained Death in Epilepsy (SUDEP). *In vitro*, DEPDC5 negatively regulates amino acid sensing by the mTOR complex 1 (mTORC1) pathway. The role

of DEPDC5 in neurodevelopment and epilepsy is yet to be elucidated. Germline *Depdc5* knockout rodent models are embryonic lethal and *Depdc5* heterozygous loss does not recapitulate the neurological phenotypes seen in patients. We created a neuron-specific *Depdc5* conditional knockout mouse by cre-recombination under the *Synapsin1* promotor. *Depdc5*$^{flox/flox}$-*Syn1*^{Cre} (*Depdc5*cc+) mice survive to adulthood but with early mortality (median survival = 115 days) compared to littermate heterozygous *Depdc5*cw+ and control mice that all survived until sacrifice at 250 days. After controlling for body weight, *Depdc5*cc+ brains weights were 75% larger ($p < 0.001$) than littermate controls after 60 days of age. Analysis of sectioned brains, revealed a 22% increase in cortical thickness ($p < 0.01$) and neuronal soma size ($p < 0.001$) but not neuronal number in *Depdc5*cc+ mice compared to littermate controls. Dysplastic neurons were present throughout the cortex of *Depdc5*cc+ mice, comparable to the abnormal neurons seen in human focal cortical dysplasia specimens. The *Depdc5* loss in *Depdc5*cc+ results in constitutive mTORC1 hyperactivation exclusively in neurons as measured by the increased phosphorylation of the downstream ribosomal protein S6. We demonstrate that *Depdc5*cc+ mice have lowered seizure thresholds, as evidenced by decreased latency to seizures ($p<0.05$) and increased mortality ($p < 0.05$) after injection of the chemoconvulsant pentylenetetrazole. Chronic treatment of the mTOR inhibitor rapamycin rescues the early mortality ($p<0.001$) demonstrated in *Depdc5*cc+ mice. In summary, the neuron-specific *Depdc5* knockout mouse model recapitulates clinical, pathological, and biochemical features of human *DEPDC5*-related epilepsy and brain malformations. We provide evidence that mTOR inhibitors represent a viable treatment option for *DEPDC5*-related epilepsy.

Disclosures: C.J. Yuskaitis: None. **E. Bainbridge:** None. **S. Gurnani:** None. **B.M. Jones:** None. **M. Sahin:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; research support from Roche, Novartis, Pfizer, LAM Therapeutics, Neuren, Ibsen, and Rugen unrelated to this study. **A. Poduri:** None.

Nanosymposium

446. Seizure, Trauma, and Post-Traumatic Stress Disorder

Location: SDCC 1

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 446.02

Topic: B.10. Epilepsy

Support: ERC Grant 682345
FRM grant DEQ2015033
FRM grant ECO20160736027

Title: Focal mosaic inactivation of Depdc5 in the developing mouse brain causes focal cortical dysplasia-associated epilepsy

Authors: *T. RIBIERRE[1,2], C. DELEUZE[1], A. BACQ[1], S. BALDASSARI[1], E. MARSAN[1], D. ROUSSEL[1], S. BAULAC[1,2]
[1]Inst. du Cerveau et de la Moelle Epiniere (ICM), Paris, France; [2]INSERM U1127, Paris, France

Abstract: DEP domain-containing 5 protein (DEPDC5) is a repressor of the recently recognized amino acid-sensing branch of the mTORC1 pathway. So far, its function in the brain remains largely unknown. Germline loss-of-function mutations in *DEPDC5* have emerged as a major cause of familial refractory focal epilepsies, with case reports of sudden unexpected death in epilepsy (SUDEP). Remarkably, a fraction of patients also develops focal cortical dysplasia (FCD), a neurodevelopmental cortical malformation. We therefore hypothesized that a somatic second-hit mutation arising during brain development may support the focal nature of the dysplasia. Here, subsequently to the definite evidence of a two-hit mutational mechanism in *DEPDC5* from postoperative brain tissue, we demonstrate the causality of a *Depdc5* mosaic biallelic inactivation using CRISPR-Cas9 editing and *in utero* electroporation in a mouse model recapitulating focal epilepsy with FCD and SUDEP-like events. We further unveil a key role of Depdc5 in shaping dendrite and spine morphology of excitatory neurons. This study reveals promising therapeutic avenues for treating drug-resistant focal epilepsies with mTORC1-targeting molecules.

Disclosures: T. Ribierre: None. **C. Deleuze:** None. **A. Bacq:** None. **S. Baldassari:** None. **E. Marsan:** None. **D. Roussel:** None. **S. Baulac:** None.

Nanosymposium

446. Seizure, Trauma, and Post-Traumatic Stress Disorder

Location: SDCC 1

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 446.03

Topic: B.10. Epilepsy

Support: European Research Council (N° 682345)

Title: Brain somatic mutations in the GATOR1-mTORC1 pathway in epilepsies associated to malformations of cortical development

Authors: *S. BAULAC[1,2], S. BALDASSARI[2], E. MARSAN[2], M. CHIPAUX[3]
[1]INSERM U1127, Paris, France; [2]ICM, Paris, France; [3]Dept. of Pediatric Neurosurg., Fondation Rothschild, Paris, France

Abstract: Germline mutations in genes encoding components of the amino acid-sensitive branch of the mTORC1 signaling pathway are a major cause of familial focal epilepsies. DEPDC5,

together with NPRL2 and NPRL3 form the GAP Activity Towards Rags complex 1 (GATOR1), a negative regulator of mTORC1. The pathogenic mechanism linked to GATOR1 variants is haploinsufficiency, leading to hyperactivation of the mTORC1 pathway. Remarkably, a fraction of patients also develops focal cortical dysplasia (FCD), a neurodevelopmental cortical malformation. We therefore hypothesized that somatic mutations in genes of the mTORC1-pathway arising during brain development may support the focal nature of the dysplasia. Here, we provide the proof of concept, from postoperative human FCD tissue, that a biallelic two-hit - brain somatic and germline - mutational mechanism in *DEPDC5* causes focal epilepsy with FCD. We further discover a mutation gradient with a higher mosaicism rate in the seizure-onset zone than in the surrounding epileptogenic zone. In other sporadic FCD patients, we report activating brain somatic mutations in the *MTOR* gene itself, as well as other genes of the mTORC1 pathway.

Disclosures: S. Baulac: None. **S. Baldassari:** None. **E. Marsan:** None. **M. Chipaux:** None.

Nanosymposium

446. Seizure, Trauma, and Post-Traumatic Stress Disorder

Location: SDCC 1

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 446.04

Topic: B.10. Epilepsy

Support: NIH Grant F31-NS098597
VA Merit Award I01-BX002949
NIH Grant RO1-NS080979
NIH Grant P30-NS061800
Ellison Medical Foundation

Title: Altered vesicle release properties of sprouted mossy fiber synapses in epilepsy

Authors: *W. HENDRICKS[1], G. L. WESTBROOK[1], E. SCHNELL[2]
[1]Vollum Inst., Portland, OR; [2]Portland VA Med. Ctr., Portland, OR

Abstract: Seizures alter brain metabolism, gene expression, neural circuits, and can drive the development of epilepsy. How physical or functional circuit changes increase susceptibility to seizures is unknown, but circuit alterations are widely hypothesized as a primary factor in epileptogenesis. In temporal lobe epilepsy, dentate granule cells sprout aberrantly targeted mossy fiber axons into the inner molecular layer and form synapses on granule cell dendrites, a phenomenon known as mossy fiber sprouting. Despite their proximal location, large presynaptic terminals, and excitation of target neurons, the ultimate impact sprouted mossy fiber activity is unclear. To specifically target sprouted mossy fiber axons, we labeled dentate granule cells using DcxCreER^{T2}::Channelrhodpsin2 transgenic mice, and used optogenetic stimulation to drive

activity in sprouted mossy fibers. Sprouted mossy fiber synapses have altered short-term plasticity compared to healthy mossy fiber synapses, most notably rapid depression of transmitter release during repetitive activation. Alongside the prominent short-term depression of sprouted mossy fiber terminals, we find that these cells have an increased probability of release during single stimulation episodes. Additionally, optogenetic activation of sprouted mossy fibers reliably triggered action potential firing in postsynaptic dentate granule cells. Taken together, these data suggest sprouted mossy fibers can quickly propagate recurrent excitation through the dentate gyrus and might be able to initiate a burst of recurrent excitation. We are examining the mechanisms driving the altered properties of these synapses.

Disclosures: W. Hendricks: None. **G.L. Westbrook:** None. **E. Schnell:** None.

Nanosymposium

446. Seizure, Trauma, and Post-Traumatic Stress Disorder

Location: SDCC 1

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 446.05

Topic: B.10. Epilepsy

Support: Donors to TGen's C4RCD

Title: De novo mutation in mammalian Dynamin1 (DNM1) causing epileptic encephalopathy is associated with mitochondrial dysfunction

Authors: *L. LLACI, E. FRANKEL, R. GUPTA, G. MILLS, B. GERALD, W. JEPSEN, K. RAMSEY, C. BALAK, N. BELNAP, M. NAYMIK, I. S. PIRAS, A. SINIARD, S. SZELINGER, R. RICHHOLT, M. DE BOTH, I. SCHRAUWEN, D. W. CRAIG, M. HUENTELMAN, V. NARAYANAN, S. RANGASAMY
Ctr. for Rare Childhood Disorders (C4RCD), Neurogenomics, Translational Genomics Res. Inst. (TGen), Phoenix, AZ

Abstract: Whole exome sequencing has led to the identification of several causal genes in individuals with epileptic encephalopathies (EE), and the list of genes has expanded dramatically. We and others have identified *de novo* missense mutations in *DNM1* (DNM1, OMIM: 602377) in patients with early infantile EE (infantile spasms or Lennox-Gastaut syndrome (OMIM: 616346). Mutations in *DNM1* cause defects in synaptic vesicle recycling and clathrin-mediated endocytosis (CME), resulting in altered neuronal firing and epilepsy. At the Center for Rare Childhood Disorders (C4RCD), we have assembled a cohort of EE patients with *de novo* heterozygous mutations in dynamin 1 (DNM1) and established patient-derived (skin biopsy) fibroblast cultures to understand the cell biology of DNM1 epileptic encephalopathy. Patient-derived *DNM1*- mutant fibroblast cells demonstrate impaired CME, showing that *DNM1* mutations cause a functional deficit. Besides, altered phosphorylation levels of the Dynamin 1

protein found in these patients imply dysregulation of endocytosis. Surprisingly, mitochondrial dysfunction (complex I or IV deficiency) was the primary finding in two of the patients in our cohort. Muscle biopsy from these patients confirmed mitochondrial dysfunction, and this remained the neurological diagnosis for over ten years, until the discovery of the primary *DNM1* mutation. We characterized oxygen consumption rate (OCR) on patient-derived fibroblast cell lines to assess the mitochondrial function using the Seahorse XF Analyzer (Agilent, CA). We observed a significant decrease in the ATP generation and mitochondrial spare capacity in *DNM1* mutant patient cells compared to control cells. Collectively, our results demonstrate mitochondrial involvement in the *DNM1* epileptic encephalopathy. It is interesting to note that the dynamin superfamily members share a conserved GTPase domain, which plays a critical role in mitochondrial fission and fusion. However, mammalian Dynamin 1 has never been linked to mitochondrial function, and our results suggest a mechanistic link between mitochondrial function and Dynamin 1.

Disclosures: E. Frankel: None. **R. Gupta:** None. **G. Mills:** None. **B. Gerald:** None. **W. Jepsen:** None. **K. Ramsey:** None. **C. Balak:** None. **N. Belnap:** None. **M. Naymik:** None. **I.S. Piras:** None. **A. Siniard:** None. **S. Szelinger:** None. **R. Richholt:** None. **M. De Both:** None. **I. Schrauwen:** None. **D.W. Craig:** None. **M. Huentelman:** None. **V. Narayanan:** None. **S. Rangasamy:** None.

Nanosymposium

446. Seizure, Trauma, and Post-Traumatic Stress Disorder

Location: SDCC 1

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 446.06

Topic: B.10. Epilepsy

Title: Pre-stimulus epileptogenic activity predicts task related neural and behavioural response

Authors: *S. M. WONG[1], J. SATO[1], G. M. IBRAHIM[2]
[1]Neurosciences & Mental Hlth., [2]Neurosurg., Hosp. for Sick Children, Toronto, ON, Canada

Abstract: Introduction. Epilepsy is a brain disorder characterized by frequent and recurrent seizures and affects approximately 1-2% of children, and is known to result in significant behavioural and psychological comorbidities including difficulties with attention, memory, social communication, and executive function even if seizures are adequately controlled through medication. Little is known about the specific mechanisms by which these deficits arise and the interaction between the entrainment of a seizure network interfering with eloquent networks and epileptic activity including interictal discharges actively interfering with cognitive processes. Here we show data from intracranial recordings in a series of cases that demonstrate epileptogenic activity interferes with eloquent activity.
Methods. We recruited patients with epilepsy admitted to the Hospital for Sick Children in

Canada for clinically-indicated invasive monitoring with stereotactically-placed bilateral anterior cingulate cortex (ACC) depth electrodes and with or without cortical grids. Patients performed a 1-back visual working memory paradigm (174 new, 100 repeated trials, 1500±200 ms ISI) presented on a laptop placed on their tray table. Patients responded to the task using a wireless handheld controller and were asked to press a button when presented with a repeated image. The data were recorded at 2500 Hz and filtered from 1-300 Hz. Data were analyzed using the Fieldtrip toolbox. Time-and-frequency resolved power were estimated with the wavelet transform using the 7-cycle Morlet wavelet.
Results. Induced analyses showed high frequency (HF) power (80-300 Hz, 200-350 ms) in the lesion was associated with missed (incorrect) repeat trials. Furthermore, pre-stimulus HF power (80-300 Hz, -200 to 0 ms) in the epileptogenic lesion was correlated with post-stimulus HF power (150-300 ms, 200-300 Hz) in the right ACC (R=0.51) in false alarm (incorrect hits) new trials.
Conclusions. We present data from an extremely rare and unique dataset demonstrating epileptogenic activity interference with eloquent cortical network activity. These findings further elucidate the mechanisms of cognitive deficits in children with epilepsy and may guide future clinical treatment to treat both epilepsy and the resultant comorbidities.

Disclosures: S.M. Wong: None. **J. Sato:** None. **G.M. Ibrahim:** None.

Nanosymposium

446. Seizure, Trauma, and Post-Traumatic Stress Disorder

Location: SDCC 1

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 446.07

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Directors' New Innovator Award (1DP2OD007363) to ABN
VA Merit Award (2I01CX000139) to ABN

Title: Precision medicine for stress disorders: Diagnostic biomarkers and repurposed drugs

Authors: *A. NICULESCU[1], H. LE-NICULESCU[1], K. ROSEBERRY[1], D. LEVEY[1], P. PHALEN[1], F. MAMDANI[2], A. SEQUEIRA[2], S. KURIAN[3]
[1]Psychiatry, Indiana Univ. Sch. of Med., Indianapolis, IN; [2]Psychiatry, UC Irvine, Irvine, CA; [3]The Scripps Res. Inst., La Jolla, CA

Abstract: The biological fingerprint of environmental adversity may be key to understanding health and disease, as it encompasses the damage induced as well as the compensatory reactions of the organism. Metabolic and hormonal changes may be an informative but incomplete window into the underlying biology. We endeavored to identify objective blood gene expression biomarkers for psychological stress, a subjective sensation with biological roots. To quantify the

stress perception at a particular moment in time, we used a simple visual analogue scale for life stress in psychiatric patients, a high risk group. Then, using a stepwise discovery, prioritization, validation, and testing in independent cohorts design, we were successful in identifying gene expression biomarkers that were predictive of high stress states, and of future psychiatric hospitalizations related to stress, more so when personalized by gender and diagnosis. Some of these biomarkers are increased in expression in high stress states (being putative risk genes), and others are decreased in expression (being putative protective/resilience genes). One of the top biomarkers that survived discovery, prioritization, validation and testing was FKBP5, a well-known gene involved in stress response, which serves as a de facto reassuring positive control. We also compared our biomarker findings with telomere length (TL), another well-established biological marker of psychological stress, and show that newly identified predictive biomarkers are comparable or better state or trait predictors of stress than TL or FKBP5. Over half of the top predictive biomarkers for stress also had prior evidence of involvement in suicide, and the majority of them had evidence in other psychiatric disorders, providing a molecular underpinning for the effects of stress in those disorders. Some of the biomarkers are targets of existing drugs, of potential utility in patient stratification and pharmacogenomics approaches. Moreover, the biomarkers gene expression signatures yielded new drug candidates and natural compounds upon bioinformatics drug repurposing analyses. Our work may lead to improved diagnosis and treatment for stress disorders such as PTSD, that result in decreased quality of life and adverse outcomes including addictions, violence and suicide.

Disclosures: A. Niculescu: None. **H. Le-Niculescu:** None. **K. Roseberry:** None. **D. Levey:** None. **P. Phalen:** None. **F. Mamdani:** None. **A. Sequeira:** None. **S. Kurian:** None.

Nanosymposium

446. Seizure, Trauma, and Post-Traumatic Stress Disorder

Location: SDCC 1

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 446.08

Topic: G.06. Post-traumatic Stress Disorder

Support: Collaborative Health Initiative Research Program grant (308431-9.00-64532)

Title: Gene expression analyses in amygdala and anterior cingulate cortex of PTSD-like mouse model

Authors: *M. TANAKA[1], H. LI[1], X. ZHANG[2], J. SINGH[2], C. L. DALGARD[1], M. WILKERSON[2], Y. ZHANG[1]
[1]APG, [2]CHIRP, USUHS, Bethesda, MD

Abstract: Posttraumatic stress disorder (PTSD) is developed by exposure to a threatening and/or horrifying event and characterized by the presence of four major symptom clusters: anxiety,

hyperarousal, avoidance, and sleep-wake cycle abnormality for a prolonged period of time. In order to investigate cellular and molecular alterations along with the development of PTSD symptoms, we constructed a PTSD-like rodent model by electric foot shock (FS) to male C57BL/6 mice. Mice received FS acquired anxiety-like abnormality based on open field test. Their startle response to acoustic stimulus was higher than that of the control mice. Avoidance latency and freezing time were longer in stressed mice than control mice. Thus, those behavioral tests including abnormal static behavior in sleeping period showed that our animal model acquired PTSD-like behavioral propensities. We then analyzed the gene expression in anterior cingulate cortex (ACC) and amygdala (AMY) in 2 and 5 weeks post FS. Using deep RNA sequencing, we identified more than 1000 genes that were differentially expressed in both regions. The most affected pathways included circadian entrainment, neurotransmitters, small G-protein and MAPK signaling, endocannabinoid, and neuroendocrine pathway, which were regulated in region- and time-specific manners. Immunoblotting and qRT-PCR confirmed that corticotropin-releasing hormone signaling genes (*Crh*, *Crhbp, Crhr1*, and *Crhr2*) as well as somatostatin signaling genes (*Sstr2* and *Sstr5*) were significantly regulated in ACC, suggesting shifting toward anxiogenic status. Expression of circadian entrainment genes including *Per1* were affected by FS in ACC and AMY. Endocannabinoid (eCB) related genes were also altered (*Faah, Daglb*). In this study we report several signaling pathways and genes were regulated in our PTSD-like mouse model in long-term.

Disclosures: M. Tanaka: None. **H. Li:** None. **X. Zhang:** None. **J. Singh:** None. **C.L. Dalgard:** None. **M. Wilkerson:** None. **Y. Zhang:** None.

Nanosymposium

446. Seizure, Trauma, and Post-Traumatic Stress Disorder

Location: SDCC 1

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 446.09

Topic: G.06. Post-traumatic Stress Disorder

Support: Spanish National Plan on Drugs. Spanish Ministry of Health, Social Services and Equality. Grant 2015/016.
National Thematic Networks in Health-related Cooperative Research. Spanish Network on Addictive Disorders. Grant RD12/0028/0019

Title: Effects of a new post-traumatic stress disorder animal model on anxiety-like behaviors and ethanol voluntary consumption in C57BL/6J mice

Authors: *F. NAVARRETE RUEDA, A. GASPARYAN, E. CAPARRÓS, J. MANZANARES
Inst. de Neurociencias, Univ. Miguel Hernández - CIF: Q5350015C, San Juan de Alicante, Spain

Abstract: Post-traumatic stress disorder (PTSD) is a severe and chronic mental illness associated with other neuropsychiatric disorders such as substance abuse, being alcohol use disorder (AUD) the most prevalent. The difficult therapeutic management of PTSD-AUD comorbidity makes necessary the development of animal models for the discovery of new pharmacological strategies. The purpose of this study was to validate and characterize a new PTSD-like animal model with long-lasting emotional disturbances to facilitate increased vulnerability to ethanol consumption. C57BL/6J mice were exposed to several unpredictable stressful stimuli (fox urine, movement restriction, electric shock, tilted cage, wet bedding, food restriction) at different time points during 5 weeks, alternating 3 weeks of exposure with 2 weeks of resting. Emotional alterations were evaluated by the fear conditioning and the light-dark box paradigms, and motor activity was also analyzed using the open-field test. Furthermore, voluntary ethanol consumption was evaluated by the two-bottle choice paradigm. In this experiment, mice were individually housed in cages equipped with two feeding bottles, one containing water and the other filled with gradually increasing ethanol solution concentrations (2, 4, 6 and 8%, v/v). Daily ethanol and water intake was carefully measured to calculate the amount of ethanol consumption (g/kg) and the percentage of preference for the bottle containing ethanol. Mice exposed to the new PTSD-like animal model presented significantly higher freezing time (fear conditioning) at weeks 6 and 12 (t-test; $p<0.001$), increased anxiety-like behavior (light-dark box) at week 11 (t-test; $p<0.001$), and no differences in motor activity (open field) at week 12 (t-test; $p>0.05$), in comparison with control mice. In addition, PTSD-exposed mice showed a significantly higher ethanol intake (Two-way RM ANOVA; $p<0.05$) and preference for ethanol (Two-way RM ANOVA; $p<0.05$) in the two-bottle choice paradigm (weeks 7 to 12). In conclusion, the results obtained suggest that mice exposed to the new PTSD-like animal model develop pronounced long-lasting behavioral alterations with significantly increased vulnerability to ethanol consumption. Additional studies are needed to improve the characterization of the behavioral and neurochemical mechanisms involved in PTSD-AUD comorbidity.

Disclosures: F. Navarrete Rueda: None. **A. Gasparyan:** None. **E. Caparrós:** None. **J. Manzanares:** None.

Nanosymposium

446. Seizure, Trauma, and Post-Traumatic Stress Disorder

Location: SDCC 1

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 446.10

Topic: G.06. Post-traumatic Stress Disorder

Support: Veterans Administration National Center for PTSD

Title: Transcriptome alterations in posttraumatic stress disorder across multiple regions of frontal cortex

Authors: *M. J. GIRGENTI[1], J. WANG[1], D. JI[1], D. A. CRUZ[2], D. WILLIAMSON[2], M. FRIEDMAN[3], H. ZHAO[1], J. H. KRYSTAL[1], R. S. DUMAN[4]
[1]Yale Univ. Sch. of Med., New Haven, CT; [2]Psychiatry & Behavioral Sci., Duke Univ., Durham, NC; [3]Dartmouth Sch. of Med., Hanover, NH; [4]Yale Univ. Sch. Med., New Haven, CT

Abstract: Post-traumatic stress disorder (PTSD) is a psychiatric disorder that occurs after life threatening, traumatic events. It is estimated that 7.8% of the general population will experience PTSD in their life-time and there has been increased interest due to the high incidence of PTSD in military personnel returning from duty. Despite extensive study of the neurobiological correlates of PTSD little is known about the molecular alterations in the brain that underlie PTSD neuropathology. Here, combining differential expression and gene coexpression network analyses of postmortem brains, we provide a comprehensive characterization of transcriptional profiles associated with PTSD across two cortical regions: Area 25 (subgenual prefrontal cortex) and Area 11 (medial orbital frontal cortex). We performed next generation RNA-sequencing on A25 and A11 regions on cases within three cohorts: PTSD, a psychiatric control (major depressive disorder, MDD), and control group. We find significant differential gene expression across diseases and identify shared and distinct gene expression perturbations across cortical regions. The results demonstrate a dramatic rearrangement of the subgenual transcriptome, particularly in immune and inflammatory transcripts in A25. Area 11 of the PTSD transcriptome is markedly altered from control with changes occurring in pathways associated with cell-to-cell signaling and neural tissue assembly. Together, our findings demonstrate PFC as a key site of transcriptional regulation in PTSD, and highlight region-specific gene expression changes across these two cortical regions.

Disclosures: M.J. Girgenti: None. **J. Wang:** None. **D. Ji:** None. **D.A. Cruz:** None. **D. Williamson:** None. **M. Friedman:** None. **H. Zhao:** None. **J.H. Krystal:** None. **R.S. Duman:** None.

Nanosymposium

447. Parkinson's Disease: Alpha-Synuclein: Models and Mechanisms

Location: SDCC 32

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 447.01

Topic: C.03. Parkinson’s Disease

Support: HFSP Long Term Fellowship
EMBO Long Term Fellowship
JBP foundation
ERC Advanced Grant
Swiss National Research Foundation grant

Title: Development of a high-content genome-wide RNAi screen to identify genetic modifiers of a-synuclein propagation

Authors: *E. KARA[1,1], A. CRIMI[1], D. P. PEASE[1], M. EMMENEGGER[1], D. HEINZER[1], M. AVAR[1], C. AEMISEGGER[1], Z. FAN[2], J. MARKS[2], J. HARDY[3], B. T. HYMAN[2], A. AGUZZI[1]
[1]Univ. of Zurich, Zurich, Switzerland; [2]Harvard Med. Sch., Boston, MA; [3]Univ. Col. London, London, United Kingdom

Abstract: Introduction: Aggregation of a-synuclein is the hallmark neuropathological feature of Parkinson's disease (PD). It is widely accepted that a-synuclein pathology starts from the olfactory bulb and the dorsal motor nucleus of the vagus and spreads rostrally to the neocortex through neuron-to-neuron propagation of the misfolded protein. However, the rate of a-synuclein propagation varies greatly between individuals with PD. It is unknown what causes this remarkable variability. Identification of genetic modifiers of a-synuclein propagation would greatly advance the understanding of the pathogenesis of PD and aid the development of effective treatments.
Methods: We have cloned a construct encoding GFP-2a-synuclein-RFP. In a transient transfection tissue culture system, the cells that have been transfected are positive for GFP and RFP fluorescence, whereas cells that have uptaken a-synuclein through propagation are positive only for RFP fluorescence, owing to the prior cleavage of the transcribed protein at the 2a peptide within the donor cells. For the initial characterization of this system, three cell lines were used: HEK cells stably overexpressing a-synuclein, wt HEK cells and SHSY5Y (both of which do not express endogenously a-synuclein). The amount of propagation was quantified through single cell analysis by flow cytometry. For the high content screenings, the HEK-synuclein cell line will be used. A commercially available library (ThermoFisher) containing 64,752 siRNAs, 3 for each transcript, targeting a total of 21,584 genes is being used in a 384 well format. High content imaging is undertaken on a GE InCell analyzer 2500HS.
Results: Flow cytometry analysis over the course of seven days showed that a-synuclein could propagate both in the presence and absence of endogenous a-synuclein and that up to 10% of the cells receive the propagating protein. The mosaicism percentage affected the propagation efficiency, with higher propagation observed when 20-40% of the cells expressed the GFP-2a-synuclein-RFP construct. The high content screening system is currently under development. Quality control assessments show a good separation between the positive control (siRNA targeting a-synuclein) and the negative control (scrambled siRNA). An automatic analysis pipeline using MATLAB and Python has been developed.
Conclusions: We have developed a reporter-based assay that robustly quantifies a-synuclein propagation and is suitable for miniaturization and high content genetic perturbation screenings. It is anticipated that novel genetic modifiers of a-synuclein propagation will be identified through our siRNA screening system.

Disclosures: E. Kara: None. **A. Crimi:** None. **D.P. Pease:** None. **M. Emmenegger:** None. **D. Heinzer:** None. **M. Avar:** None. **C. Aemisegger:** None. **Z. Fan:** None. **J. Marks:** None. **J. Hardy:** None. **B.T. Hyman:** None. **A. Aguzzi:** None.

Nanosymposium

447. Parkinson's Disease: Alpha-Synuclein: Models and Mechanisms

Location: SDCC 32

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 447.02

Topic: C.03. Parkinson’s Disease

Support: Joseph Drown Foundation

Title: A human iPSC-based model of early onset sporadic Parkinson's disease

Authors: *A. LAPERLE[1], S. SANCES[1], N. YUCER[1], V. DARDOV[1], R. HO[1], A. FULTON[1], Z. SHU[2], D. HERNANDEZ[3], A. B. SINGLETON[3], N. T. MAIDMENT[2], J. VAN EYK[1], M. TAGLIATI[4], C. N. SVENDSEN[1]
[1]Cedars-Sinai Regenerative Med. Inst., Los Angeles, CA; [2]Dept. of Psychiatry and Biobehavioral Sci., UCLA, Los Angeles, CA; [3]Lab. of Neurogenetics, NIH Natl. Inst. on Aging, Baltimore, MD; [4]Dept. of Neurol., Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: Parkinson’s Disease (PD), one of the most prevalent and debilitating neurodegenerative conditions present in our population, is classically characterized by the progressive loss of dopamine (DA) neurons in the substantia nigra as well as the presence of cytoplasmic inclusions known as Lewy bodies and Lewy neurites within specific brain regions. These inclusions contain large amounts of the protein α-synuclein, which is also associated with a rare form of genetic PD caused by triplication of the *SNCA* gene. Previous iPSC-based models derived from patients with monogenic mutations in PD genes have shown accumulation of α-synuclein in differentiated DA neurons however, these monogenic mutations account for only a small minority of PD cases. Here, we have utilized multiple iPSC lines derived from sporadic PD patients with very early onset of disease symptoms (early onset sporadic PD: EOSPD). These iPSC lines provide an opportunity to better understand sporadic PD and to investigate the hypothesis that early onset sporadic patients carry unidentified genetic risk factors that cause a more aggressive form of the disease. DA neurons differentiated from these EOSPD iPSCs produce and release dopamine and, critically, exhibit multiple pathologies classically associated with PD including the accumulation of α-synuclein protein. Further proteomic and transcriptomic analysis of these EOSPD DA neurons reveals a full signature PD-in-a-dish model, including dysregulation of pathways associated with mitophagy, synaptic transmission, and lysosomal protein degradation. This is the first iPSC-based model to have demonstrated classical PD phenotypes in a sporadic PD background. The fact that patient iPSC lines acquire these phenotypes demonstrates a clear genetic contribution to EOSPD. Finally, screening with these sporadic PD lines has identified a novel drug that rescues α-synuclein accumulation, increases TH expression, and implicates a new signaling pathway in sporadic Parkinson’s disease.

Disclosures: **A. Laperle:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder. **S. Sances:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder. **N. Yucer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder. **V. Dardov:** None. **R. Ho:** None. **A. Fulton:** None. **Z. Shu:** None. **D. Hernandez:** None. **A.B. Singleton:** None. **N.T. Maidment:** None. **J. Van Eyk:** None. **M. Tagliati:** None. **C.N. Svendsen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder.

Nanosymposium

447. Parkinson's Disease: Alpha-Synuclein: Models and Mechanisms

Location: SDCC 32

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 447.03

Topic: C.03. Parkinson’s Disease

Support: NIH NS088533
American Parkinson Disease Association
Parkinson Association of Alabama

Title: 14-3-3s reduce cell-to-cell transfer of alpha-synuclein

Authors: *T. A. YACOUBIAN[1], B. WANG[2], R. N. UNDERWOOD[3]
[1]Dept Neurol, Univ. Alabama Birmingham, Birmingham, AL; [2]Univ. of Alabama at Birmingham, Birmingham, AL; [3]Neurol., Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Alpha-synuclein (αsyn) plays a critical role in Parkinson’s disease (PD). Research points to a prion-like mode for αsyn toxicity: αsyn is released as aggregated species that cause further aggregation and toxicity in neighboring cells. We have studied the role of 14-3-3 proteins in regulating αsyn propagation. 14-3-3s are chaperone-like proteins that reduce protein aggregation, regulate protein secretion, and promote cell survival. We tested the effect of 14-3-3s on αsyn propagation in an αsyn fibril model. Treatment of wildtype cultures with preformed fibrils (PFFs) induced the formation of Triton X-100 insoluble inclusions that were positive for S129-phosphorylated (pS129) αsyn. The level of pS129-αsyn staining was dramatically reduced in 14-3-3θ transgenic neurons at 10 and 14 days after PFF treatment. We also observed a dramatic reduction in neuron loss at 14 days after PFF treatment. In contrast, we observed that 14-3-3 inhibition by the pan 14-3-3 peptide inhibitor difopein potentiated αsyn toxicity. pS129-αsyn-positive aggregation was increased in difopein neurons at 10 and 14 days after PFF treatment compared to control. Neuronal loss induced by PFFs was observed earlier in difopein cultures at ten days after PFF treatment, at a time point when neuronal loss is normally not

observed in wildtype cultures. At 14 days after treatment, difopein cultures showed a 31% increase in neuronal death compared to wildtype cultures. To test whether 14-3-3θ blocks cell-to-cell spread of pathogenic αsyn in the PFF model, we used microfluidic culture devices with three separate compartments connected by microgrooves. We plated wildtype or 14-3-3θ neurons in the first compartment and wildtype neurons into the second and third compartments. PFFs were added to the first compartment at DIV5. At 14 days after treatment, pS129-αsyn was detectable in all three chambers when wildtype neurons were plated in all three compartments, with a gradient of highest pS129-αsyn in chamber one to lowest pS129-αsyn in the most distal chamber. When 14-3-3θ neurons were plated in the first compartment and treated with PFFs, pS129-αsyn staining was dramatically reduced in all three compartments, with almost no detectable pS129-αsyn in chambers 2 and 3. Conversely, when difopein neurons were plated in the first compartment, we saw a significant increase in pS129-αsyn positive aggregates in chambers 2 and 3 compared to microfluidic devices plated with only wildtype neurons in all chambers at 14 days after treatment. We conclude that 14-3-3θ regulates αsyn propagation and may serve as a target for therapeutic intervention in Parkinson's disease.

Disclosures: T.A. Yacoubian: Other; I have a US patent on the use of 14-3-3 proteins for neurodegeneration. **B. Wang:** None. **R.N. Underwood:** None.

Nanosymposium

447. Parkinson's Disease: Alpha-Synuclein: Models and Mechanisms

Location: SDCC 32

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 447.04

Topic: C.03. Parkinson's Disease

Support: UCB

Title: Behavioural and metabolic characterization of alpha-synuclein pathology spreading in the mouse brain

Authors: *J. BURTSCHER[1], J.-C. COPIN[1], C. SANDI[2], H. LASHUEL[1]
[1]LMNN/ EPFL, Lausanne, Switzerland; [2]LGC/ EPFL, Lausanne, Switzerland

Abstract: Alpha-synuclein (aSyn) containing Lewy body pathology is a hallmark of synucleinopathies, such as Parkinson's disease (PD). Interest in non-motor symptoms, including affective disorders, of this group of diseases has increased recently due to their impact on patients' quality of life and their implications for disease progression and the development of early intervention strategies. Furthermore, accumulating evidence points to affective disorders as predisposing risk factors for neurodegeneration.
It is still unclear to which extend aSyn pathology contributes to non-motor symptoms. But models building on the capacity of aSyn seeds, such as aSyn preformed fibrils (PFFs), to spread

through the central nervous system and template the formation of new aSyn aggregations, offers an excellent tool to investigate behavioural effects caused by aSyn pathology.
Herein, we provide extensive behavioural and metabolic characterization of a mouse model of intrastriatal injection of aSyn PFFs triggering prominent aSyn pathology spreading to behaviour-relevant brain regions, such as amygdala, substantia nigra (SN) and cortex. We applied a model of depression in combination with aSyn pathology to study potentially predisposing effects. We report subtle behavioural changes due to aSyn pathology spreading 2 months after injection of aSyn PFFs, while motor symptoms were observed only 6 months after injection. aSyn pathology spreading was aggravated and resulted in early SN neurodegeneration in depressed-like mice. Mitochondrial metabolism of the amygdala, which had the highest aggregated aSyn load of all investigated brain regions 2 months after injection of PFFs appeared unaltered.
In conclusion we present extensive behavioural characterization and correlations with pathology spreading in this model. Although, we observed subtler behavioural effects than expected considering the observed neuropathology in the PFF injected animals, we sawaggravated neuropathology in combination with a model for depression. In addition to shedding new light on the yet unclear association of aSyn pathology and behavioural manifestations, our work suggests that aSyn pathology spreading requires additional insults/predisposing factors to induce strong pathological and behavioural manifestations.

Disclosures: J. Burtscher: None. **J. Copin:** None. **C. Sandi:** None. **H. Lashuel:** None.

Nanosymposium

447. Parkinson's Disease: Alpha-Synuclein: Models and Mechanisms

Location: SDCC 32

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 447.05

Topic: C.03. Parkinson’s Disease

Title: Reduction of alpha-synuclein in human iPSC-derived dopaminergic neurons harboring the A53T mutation as a therapeutic strategy for Parkinson’s disease

Authors: *J. D. GRAEF, V. VILLEGAS, A. M. CACACE
Fulcrum Therapeut., Cambridge, MA

Abstract: Parkinson’s Disease (PD) is progressive neurodegenerative disease that predominantly affects midbrain dopaminergic (DA) neurons. Genome wide association studies have linked single nucleotide polymorphisms in the alpha-synuclein gene, *SNCA,* with increased risk of PD. One well-studied missense mutation that causes an alanine to threonine substitution at amino acid 53 (A53T) has been associated with an early-onset, familial form of Parkinson’s Disease. We therefore first sought to assess whether there were functional sequelae of reducing both A53T and wild type endogenous alpha-synuclein in human dopaminergic neurons. Spontaneous electrical activity of commercially available iPSC-derived dopaminergic neurons with or without

expression of A53T alpha-synuclein protein was assessed using a multielectrode array (MEA). This allowed for a true physiological comparison between the A53T alpha-synuclein dopaminergic neurons (A53T-dopa neurons) and isogenic control neurons. We further assessed the effects of reducing the levels of alpha-synuclein protein using specific antisense oligonucleotides (ASOs). One of the three alpha-synuclein ASOs tested was able to both significantly reduce the amount of alpha-synuclein expression (~80%) and correct the functional phenotype by preventing reduced spontaneous activity and increased spike variability in later-stage cultures. A high-content chemical target-annotated probe screen was conducted to identify potential biochemical mechanisms to reduce alpha-synuclein protein levels. Several small molecules within a specific biologic pathway were identified that selectively reduced alpha-synuclein. These data suggest that small molecules have the potential to regulate alpha-synuclein expression and that reducing A53T alpha-synuclein protein levels may be a potential disease-modifying approach in Parkinson's Disease.

Disclosures: J.D. Graef: A. Employment/Salary (full or part-time):; Fulcrum Therapeutics. **V. Villegas:** A. Employment/Salary (full or part-time):; Fulcrum Therapeutics. **A.M. Cacace:** A. Employment/Salary (full or part-time):; Fulcrum Therapeutics.

Nanosymposium

447. Parkinson's Disease: Alpha-Synuclein: Models and Mechanisms

Location: SDCC 32

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 447.06

Topic: C.03. Parkinson's Disease

Title: Amyloid beta plaques promote seeding and spreading of alpha-synuclein in lewy body disorders

Authors: *F. BASSIL[1,2], H. BROWN[2], S. PATTABHIRAMAN[2], B. ZHANG[2], J. TROJANOWSKI[2], V. L. LEE, 19104[2]
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Univ. of Pennsylvania, Ctr. for Neurodegenerative Dis. Res., Philadelphia, PA

Abstract: Amyloid beta (Aβ) plaques and α-synuclein (α-syn) rich lewy bodies (LBs) are the major hallmarks of Alzheimer's disease (AD) and Parkinson's Disease (PD). Several studies have shown an overlap of both pathologies in about 35% of PD and more than 50% of AD patients. Interestingly, these patients show increased severity of motor and cognitive phenotype that is reflected neuropathologically by increased Aβ and α-syn burden. Although the occurrence of Aβ and α-syn pathology has been previously described, the consequence of the primary amyloidogenic protein on the secondary pathology remain poorly understood. To determine if enhanced α-syn burden in LB cases with concomitant AD can be recapitulated in model systems, we injected mouse- α-syn preformed fibrils (α-syn pffs) into AD transgenic mice with abundant

Aβ plaques (5xFAD mice). We report that Aβ deposits accelerated the formation and spread of α-syn in 5xFAD mice compared to wild-type (WT) littermates. Aβ deposition increased in 5xFAD mice injected with α-syn compared to PBS injected mice. These results were also associated with significant neuronal loss that was mirrored by cognitive and motor performance decline. Our findings suggest a "feed-forward" mechanism where Aβ plaques provide a pathologoical environment for α-syn to pool and be seeded by exogenous pffs. Interestingly, when similar concentration of pathological α-syn from brain lysates of α-syn pff- injected 5xFAD mice or α-syn pff-injected WT mice were added to primary cultured neurons, lysates from α-syn pff-injected 5xFAD mice were more potent than lysates from PFF-injected WT mice in inducing Lewy pathology. We here provide in-vivo evidence of amyloidogenic protein synergism. We show that the presence of Aβ plaques induces a more potent α-syn strain and further highlights the effect of the environment on α-syn strain.

Disclosures: F. Bassil: None. **H. Brown:** None. **S. Pattabhiraman:** None. **B. Zhang:** None. **J. Trojanowski:** None. **V.L. Lee:** None.

Nanosymposium

447. Parkinson's Disease: Alpha-Synuclein: Models and Mechanisms

Location: SDCC 32

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 447.07

Topic: C.03. Parkinson's Disease

Support: NIH Grant AG002132
NIH Grant AG031220
Dana Foundation
the Glenn Foundation
the Sherman Fairchild Foundation
the Henry M. Jackson Foundation
Daiichi Sankyo

Title: A cultured astrocyte model of human multiple system atrophy prion propagation

Authors: *Z. KREJCIOVA[1], G. CARLSON[1,2], K. GILES[1,2], S. B. PRUSINER[1,2]
[1]Inst. for Neurodegenerative Dis., UCSF, Weill Inst. For Neurosciences, San Francisco, CA; [2]Dept. of Neurol., UCSF, Weill Inst. for Neurosciences, San Francisco, CA

Abstract: Glial cytoplasmic inclusions containing aggregated and hyperphosphorylated α-synuclein are the signature neuropathological hallmark of multiple system atrophy (MSA). A growing body of evidence suggests that astrocytes contain α-synuclein inclusions in MSA and other α-synucleinopathies at advanced stages of disease. Native α-synuclein misfolds into a conformation that initiates self-propagation, resulting in prions that spread throughout the brain

leading to neurodegeneration. To study the role of astrocytes in the α-synucleinopathies, we developed an *in vitro* model of MSA prion propagation.
Primary cultures of astrocytes were isolated from the brains of transgenic mice expressing either the wild-type (wt) form of human α-synuclein or the A53T or A30P mutation associated with familial Parkinson's disease. Astrocytes were exposed to α-synuclein prions derived from (1) brain tissue from MSA patients, (2) transgenic mice in which MSA had been passaged, (3) cell lysate from MSA-infected astrocyte cultures, or (4) recombinant wt α-synuclein fibrils. After exposure, the cells were thoroughly washed and cultured in fresh medium. Confocal microscopy and high content analysis were used to examine α-synuclein intracellular morphology and inclusion formation at multiple time points.
When recombinant α-synuclein fibrils were used to infect the cells, the fibrils persisted; however, while the fibrils did not become phosphorylated, they efficiently induced aggregation and phosphorylation of endogenously expressed α-synuclein in exposed astrocytes. Following exposure of the astrocytes to MSA brain homogenate, aggregation of α-synuclein and inclusion formation was rapid, progressive, and dose-dependent in cells expressing either wt, A53T, or A30P human α-synuclein. Furthermore, by confocal microscopy, α-synuclein aggregates appeared in two morphologically distinct assemblies: filamentous and granular. Both types progressively formed juxtanuclear glial cytoplasmic inclusions and had multiple hallmarks of lesions seen in MSA patients: they were hyperphosphorylated, ubiquitinated, co-localized with the p62 marker, and thioflavin S positive.
These studies demonstrate that α-synuclein inclusions form in astrocytes exposed to MSA prions, providing a cell culture model in which to examine various pathological forms of α-synuclein prions. This model may allow studies on neurotoxicity mechanisms and may provide a novel tool for drug discovery against MSA and other α-synucleinopathies.

Disclosures: Z. Krejciova: None. **G. Carlson:** None. **K. Giles:** None. **S.B. Prusiner:** None.

Nanosymposium

447. Parkinson's Disease: Alpha-Synuclein: Models and Mechanisms

Location: SDCC 32

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 447.08

Topic: C.03. Parkinson's Disease

Support: The Michael J. Fox Foundation 12829

Title: Alpha-synuclein suppresses mitochondrial protease ClpP to trigger mitochondrial oxidative damage and neurotoxicity

Authors: *D. HU, X. SUN[1], X. LIAO[1], S. ZARABI[2], A. SCHIMMER[2], Y. HONG[3], C. FORD[4], Y. LUO[5], X. QI[1]
[1]Physiol. and Biophysics, Case Western Reserve Univ., Cleveland, OH; [2]Princess Margaret

Cancer Ctr., Toronto, ON, Canada; [3]La Trobe Univ., Melbourne, Australia; [4]Univ. of Colorado, Denver, CO; [5]Univ. of Cincinnati, Cincinnati, OH

Abstract: Both α-Synuclein (αSyn) accumulation and mitochondrial dysfunction have been implicated in the pathology of Parkinson's disease (PD). Although studies suggest that αSyn and its missense mutant, A53T, preferentially accumulate in the mitochondria, the mechanisms by which αSyn and mitochondrial proteins regulate each other to trigger mitochondrial and neuronal toxicity are poorly understood. ATP-dependent Clp protease (ClpP), a mitochondrial matrix protease, plays an important role in maintaining mitochondrial protein turnover and bioenergetics activity. Here we show that the protein level of ClpP selectively decreases in αSyn-expressing cell culture and PD patient fibroblasts and in DA neurons of αSyn-A53T mice and PD patient postmortem brains. Deficiency in ClpP induces an overload of mitochondrial misfolded/unfolded proteins, suppresses mitochondrial respiratory activity, increases mitochondrial oxidative damage and causes cell death. Moreover, αSyn-A53T mutant interacts with ClpP to impair its peptidase activity. Whereas loss of ClpP decreases the αSyn non-toxic tetramer, overexpression of ClpP *in vitro* and *in vivo* enhances αSyn tetramer stabilization. Significantly, compensating for the loss of ClpP in the substantia nigra of αSyn-A53T mice by viral expression of ClpP suppresses mitochondrial oxidative damage, and reduces pathological αSyn accumulation and behavioral deficits of mice. Our findings provide novel insights into the mechanism underlying αSyn-induced neuronal pathology, and they suggest that ClpP might be a useful therapeutic target for PD and other synucleiopathies.

Disclosures: X. Sun: None. **X. Liao:** None. **S. Zarabi:** None. **A. Schimmer:** None. **Y. Hong:** None. **C. Ford:** None. **Y. Luo:** None. **X. Qi:** None.

Nanosymposium

448. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms

Location: SDCC 7

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 448.01

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: RO1 NS44025
RO1 NS76726
R21 NS098514

Title: CD36-mediated effects on acute neuroinflammation and long-term injury after neonatal stroke

Authors: *Z. S. VEXLER[1], J. FAUSTINO[1], J. AMARAL[1], M. LALANCETTE HÉBERT[2], S. LIU[1], S. MAHUVAKAR[1], J. KRIZ[2]
[1]Dept Of Neurol., UCSF, San Francisco, CA; [2]Laval Univ., Quebec, QC, Canada

Abstract: The scavenger receptor CD36 plays a key role in the macrophage phenotypes after various brain injuries. CD36 was shown to exacerbate injury in a model of transient middle cerebral artery occlusion (tMCAO) in the adult (*Cho et al* 2005). In neonatal mice (postnatal day 9-10 mice) subjected to tMCAO, we previously reported attenuation of acute injury by CD36, rather than injury exacerbation; more severe injury was observed in mice with *genetic deletion of CD36 (*CD36ko mice) than in wild-type (WT) mice (*Woo et al Ann Neurol, 2012*). **Aim:** Determine if CD36-dependent effects in neonatal stroke are mediated via interaction with one of its receptor co-partners, Toll-Like receptor 2 (TLR2), and whether CD36 modulates long-term injury after neonatal stroke. **Methods:** tMCAO in P9-P10 WT and CD36ko mice of both sexes, LPS administration, *in vivo* monitoring of luc-TLR2 signal induction in neonatal TLR2-luc/GFP mice, identification of cell origin of GFP signal by immunofluorescence, endothelial cell proliferation, neurogenesis, myelination, histological and behavior outcomes. **Results:** Considering that TLR2 activation depends on TLR2/CD36 binding within plasma membrane, we examined TLR2 activation in WT and CD36ko mice bred to mice that co-express luciferase and GFP reporter under TLR2 transcriptional control. Monitoring of TLR2 signal induction in living neonatal TLR2-luc/GFP mice and defining cell origin of GFP signal by immunofluorescence demonstrated that essentially all GFP+ cells are Iba1+ microglia/macrophages following tMCAO or LPS. Lack of CD36 essentially abolished TLR2 induction in activated microglia but greatly increased the number $TLR2^{GFP+}$ cells within the vessels 72h after tMCAO. Injury was significantly smaller in CD36ko than in WT 1 and 2 weeks after tMCAO. At 14 days after injury tissue volume was significantly preserved in CD36ko Vs. WT mice, 72.0±4.4% (n=17) as compared to 54.0±4.0% (n=11) in WT mice, respectively. There were no significant male/female differences in volumes of residual tissue. Based on known anti-angiogenic effects of CD36 we expected that enhanced angiogenesis is the underlying effect. However, our preliminary data (n=4-5/group) show that while enhanced neurogenesis is apparent, angiogenesis does not fully account for brain recovery, suggesting the presence of additional mechanisms that we currently study. LPS induction of TLR2 was blunted in mice treated with an anti-CD36 antibody. **Summary/Conclusions:** CD36 modulates several aspects of brain injury and repair following neonatal stroke.

Disclosures: Z.S. Vexler: None. **J. Faustino:** None. **J. Amaral:** None. **M. Lalancette Hébert:** None. **S. Liu:** None. **S. Mahuvakar:** None. **J. Kriz:** None.

Nanosymposium

448. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms

Location: SDCC 7

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 448.02

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH NINDS KO8 NS096115 (RCV)
NIH grant R01HD070996 (FJN)
Clinician Scientist Award JHU SOM (RCV)
Sutland-Pakula Endowment for Neonatal Research (RCV)

Title: Impaired expression of voltage-gated K+ channels and formation of PNNs in hippocampal PV+ interneurons following neonatal hypoxia ischemia and therapeutic hypothermia

Authors: *R. CHAVEZ-VALDEZ, P. EMERSON, D. SEVERIN, J. GOFFIGAN-HOLMES, F. NORTHINGTON, L. MARTIN, A. KIRKWOOD
Johns Hopkins Univ., Baltimore, MD

Abstract: Background: Hippocampal GABAergic interneurons (INs) are known to mature biochemically and functionally during the postnatal period. Our group has shown that in the hippocampus, neonatal hypoxia-ischemia (HI) prevents the rise in the number of parvalbumin (PV) + INs, decreases the expression of GAD65/67 and induces somatodendritic attrition 8 days after the exposure. These effects are not fully prevented by therapeutic hypothermia (TH). We aimed to study if neonatal HI persistently impaired in CA1 PV+INs: i) the expression of K^+channels and formation of the myelin sheath in axonal domains, and ii) the formation of PNNs in somatodendritic domains; suggesting impaired electrophysiology (EP) properties. **Methods:** We induced cerebral HI in C57BL6 at p10 with right carotid ligation and 45m of hypoxia (FiO_2=0.08), followed by normothermia (36°C, NT) or TH (30°C) for 4h with anesthesia-shams as controls. At 24 hours (p11), 8 days (p18) and 30 days (p40) after injury, we assessed in C57BL6 mice, the expression of voltage-gated K^+ channels (RT-PCR and IF-IHC), the formation of the myelin sheath (Myelin Basic Protein [MBP], IF-IHC) and the formation of PNNs (WFA IF-IHC). Non-parametric statistics were used for analysis. **Results:** The expression of K^+ channels known to be involved in mature fast-spiking electrical activity of PV+INs (Kv3.2, Kv3.1, Kir2.2, K2p1.1 and K2p9.1) increased between p11 and p18. Neonatal HI decreased: i) the expressions of Kv3.2, Kv3.1 and Kir2.2 by 40 to 50% (vs. sham, $p<0.05$) 8 days after HI but not earlier; and ii) the axonal localization of Kv3.1b and Kv3.2 channels in CA1 PV+INs. MBP was increasingly expressed between p18 and p40 in the oriens, radiatum and lacunosum moleculare layers of the CA1 subfield of the hippocampus and was decreased in proximity to axonal domains of PV+INs in response to HI. Formation of PNNs was only evident at p40, and

impaired by neonatal HI. TH provided no protection against these late changes. **Conclusions:** Delayed and late impairments in the expression of K^+ channels, and the formation of myelin sheath and PNNs may account for compromised electrical maturation of PV+INs after neonatal HI.

Disclosures: R. Chavez-Valdez: None. **P. Emerson:** None. **D. Severin:** None. **J. Goffigan-Holmes:** None. **F. Northington:** None. **L. Martin:** None. **A. Kirkwood:** None.

Nanosymposium

448. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms

Location: SDCC 7

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 448.03

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Wellcome Trust (WT094823)
Medical Research Council

Title: Optic atrophy (OPA)1 degradation may facilitate mitochondrial dysfunction after neonatal hypoxic-ischaemic brain injury

Authors: *C. THORNTON[1], A. JONES[1], P. GRESSENS[2], H. HAGBERG[3]
[1]King's Col. London, London, United Kingdom; [2]Inserm U1141, Paris, France; [3]Clin. Sci., Univ. of Gothenburg, Goeteborg, Sweden

Abstract: Background: Hypoxic-ischaemic encephalopathy affects 2-3 in every 1000 term infants and, depending on severity, brings about life-changing neurological consequences or death. Hypoxic-ischaemic (HI) injury results in initial neuronal energy depletion followed, with a delay, by a secondary energy failure during which the majority of brain injury occurs. Perturbation of mitochondrial function and subsequent induction of cell death pathways are key hallmarks in neonatal HI injury, both in animal models and in term infants. **Study:** In our current study, we investigate mitochondrial dynamics (fission, fusion) after HI *in vivo* in C57Bl6 wild-type mice and oxygen/glucose deprivation (OGD) *in vitro* in mouse primary neurons. We find that as well as the characteristic impaired ATP production, mitochondrial fission is rapidly induced, which correlates with degradation of the pro-fusion protein OPA1 into short, potentially fusion-incompetent forms. OPA1 is a dynamin-related guanosine triphosphatase protein, regulating both mitochondrial cristae junction formation and mitochondrial dynamics. Physiological function of OPA1 is mediated by interaction of its short (S-OPA1) and long (L-OPA1) forms generated by balanced action of Yme1L and Oma1 proteases. Following HI *in vivo* and subsequent mitochondrial permeabilisation, we find preferentially relocation of S-OPA1 rather than L-OPA1 forms in the cytosol. OPA1 cleavage is normally regulated by a balanced

action of the proteases Yme1L and Oma1. However, in primary neurons subjected to OGD, we find that YmelL is degraded whereas we observe very little change in Oma1 expression, and this is accompanied by an increase in S-OPA1 forms (21.8% ± 3.5% to 37.9% ± 3.1% 0h post injury). Recapitulating this Yme1L reduction using siRNA *in vitro* results in similar degradation of OPA1 and substantial mitochondrial fission. Using CRISPR, we have generated a cell line in which endogenous OPA1 expression is reduced by >50% (C17-OPA1$^{+/-}$) and we find that the C17-OPA1$^{+/-}$ cell line has altered susceptibility to OGD (by lactate dehydrogenase assay). We are currently using C17-OPA1$^{+/-}$ to investigate pharmacological interventions (e.g. BGP-15, recently reported to induce mitochondrial fusion) which may ameliorate the consequences of OPA1-mediated mitochondrial dysfunction. **Significance:** Safeguarding the integrity and function of OPA1 following HI may represent a new mechanism to prevent the development of neonatal brain injury. Interventions based on maintaining OPA1 activity may provide additional neuroprotection for infants following birth asphyxia, where therapeutic hypothermia alone is inadequate.

Disclosures: A. Jones: None. **P. Gressens:** None. **H. Hagberg:** None.

Nanosymposium

448. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms

Location: SDCC 7

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 448.04

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Action Medical Research UK Grant GN2485
Medical Research Council UK strategic award P19381
Swedish Brain Foundation Grant FO2015-0094
Swedish Brain Foundation Grant FO2017-0032
Lilla Barnets Foundation Grant SLL 2017-0863

Title: Exendin-4 provides neuroprotection and enhances therapeutic hypothermia in a model of hypoxic-ischemic encephalopathy

Authors: *E. ROCHA FERREIRA[1], L. POUPON[2], A. ZELCO[2], A.-L. LEVERIN[3], S. NAIR[3], A. JONSDOTTER[3], Y. CARLSSON[3], C. THORNTON[4], H. HAGBERG[3], A. RAHIM[2]
[1]Dept. of Obstetrics and Gynecology, Univ. of Gothenburg, Goeteborg, Sweden; [2]Pharmacol., Univ. Col. London, London, United Kingdom; [3]Dept. of Obstetrics and Gynecology, Univ. of Gothenburg, Goeteborg, Sweden; [4]King's Col. London, London, United Kingdom

Abstract: Neonatal hypoxia-ischemia (HI) is a global health burden, and despite the introduction of therapeutic hypothermia (TH) as routine treatment, over 50% of treated infants are not

protected. Moreover, TH is not administered in preterm cases or low resource settings. Therefore, establishing alternative or adjunct therapies are urgently needed. Exendin-4 is a drug currently used for treating Type 2 diabetes mellitus and has shown neuroprotective aspects with current ongoing clinical trials for Alzheimer's and Parkinson's diseases. We hypothesised that exendin-4 may also exert a neuroprotective effect in neonatal brain injury, particularly in the treatment of HI.
Immunofluorescence and qPCR studies were used to examine presence of GLP-1 receptor for exendin-4 in the neonatal murine and human brain. CD1 mice underwent HI at P7 (human equivalent late preterm) and P10 (term). Different exendin-4 treatments were tested to identify optimal dosing in P7 mice: 1 high-dose directly after HI (0.5µg/g), 4 high-doses starting at 0h, then at 12h intervals; 4 low-doses (0.05µg/g) of exendin-4 12h apart started directly after HI; and delayed 2h start of the 4 high-dose regimen. Brains were assessed 48h after HI for tissue infarction (Nissl), cell death (TUNEL), astrogliosis (GFAP), microglial (alphaM) and endothelial (ICAM-1) cell activation. P10 mice underwent combined 1 high-dose of exendin-4 and 5h TH (33°C), as well as either treatment alone, and their brains assessed for volume loss (MAP-2). Statistical analyses were performed using Kruskal-Wallis followed by post-hoc Dunn's.
GLP-1R was expressed in the neurons of human and mouse neonatal brain. 48h post-HI, exendin-4 treatment was significantly protective in all high-dose regimens. Tissue infarction and TUNEL+ cell death analyses showed that optimal therapeutic efficacy was obtained following 4 high-doses started directly post-HI or even with a 2h delay. Exendin-4 significantly reduced glial activation. Blood glucose levels were not altered by exendin-4. Exendin-4 did not result in adverse visceral organ histopathology (H&E) or macrophage-mediated inflammation (CD68). Observed initial reduced weight gain was recovered following treatment termination.
Overall, high-dose exendin-4 administration was well tolerated. In P10 mice, both exendin-4 and TH resulted in significant neuroprotection alone. 1 high-dose exendin-4 enhanced TH protection. The demonstrated safety and tolerability of high-dose exendin-4 administrations, combined with its significant neuroprotective effects alone or in conjunction with TH make the repurposing of exendin-4 for the treatment of neonatal HI very promising.

Disclosures: E. Rocha Ferreira: None. **L. Poupon:** None. **A. Zelco:** None. **A. Leverin:** None. **S. Nair:** None. **A. Jonsdotter:** None. **Y. Carlsson:** None. **C. Thornton:** None. **H. Hagberg:** None. **A. Rahim:** None.

Nanosymposium

448. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms

Location: SDCC 7

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 448.05

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Genetically encoded death indicators (GEDI) for live fluorescence imaging of neurodegeneration *in vitro* and *in vivo*

Authors: *J. LINSLEY[1], K. SHAH[1,2], S. FINKBEINER[1,2]
[1]Ctr. for Systems and Therapeut., Gladstone Inst., San Francisco, CA; [2]Univ. of California, San Francisco, San Francisco, CA

Abstract: Time-lapse fluorescence imaging of neurons undergoing neurodegeneration is a powerful method for quantitatively relating intermediate changes within a neuron to its fate. However, acutely and accurately distinguishing live neurons from dead neurons and cellular debris in time-lapse imaging has not previously been possible without the use of dyes or indicators that have associated toxicity, limited longevity, or characterize only a specific type of cell death. Here we introduce a newly engineered family of ratiometric, genetically encoded death indicators (GEDI) that rapidly demarcate a broad spectrum of cell death types. Using high-throughput time-lapse robotic microscopy, we show that automated quantification of GEDI signal provides higher fidelity live/dead classification than human image curation of neuronal death without significant additional toxicity. Once GEDI signal is activated, it stably marks dead neurons and debris as long as they remain in culture, facilitating automated longitudinal studies of neurodegeneration. We demonstrate the use of GEDI across a variety of rodent and human iPSC-derived neurodegenerative disease models as well as *in vivo* in live imaged zebrafish larvae. We believe the use of GEDI will further enhance our understanding of the pathology and physiology that contribute to neurodegenerative diseases and provide a new tool for analysis of neurodegenerative disease models.

Disclosures: K. Shah: None. **S. Finkbeiner:** None.

Nanosymposium

448. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms

Location: SDCC 7

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 448.06

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: FRM/DEQ20180339181

Title: The role of protein persulfidation in polyglutamine diseases

Authors: *M. FILIPOVIC, J. ZIVANOVIC, E. KOUROUSSIS
IBGC CNRS UMR595, Univ. of Bordeaux, Bordeaux, France

Abstract: Signaling by hydrogen sulfide (H_2S) emerges as an important way to regulate cellular functions and most of these effects could be attributed to the oxidative posttranslational

modification of cysteine residues called protein persulfidation (alternatively *S*-sulfhydration). Due to their reactivity persulfides are difficult to study and tools for selective labeling are lacking. We report here a new dimedone-based tag switch method for selective labeling of protein persulfides and use this tool to understand the role of protein persulfidation in health and disease. Our results show that persulfidation is evolutionary conserved modification that serves as a protective mechanism from cysteine hyperoxidation (sulfinylation and sulfonylation). Waves of persulfidation seem to be an integral part of cellular response to reactive oxygen species (ROS) even when ROS are used as a signal. For example, cysteine oxidation by H_2O_2 produced as a response to insulin biding to its receptor on neurobalstoma cells is immediately resolved by intracellular H_2S and persulfides are formed. However, in polyglutamine disease states, such as Huntington's disease and spinocerebellar ataxia 3 (SCA3) the levels of H_2S producing enzyme cystathionine gamma lyase (CSE) become negligible, in both animal models and postmortem human brain samples. Our results confirm that the overall persulfidation levels are also barely detectable in STHdh(*Q111*) striatal cells and in heads of SCA3 *Drosophila melanogaster*. The STHdh(*Q111*) are therefore very sensitive to oxidative stress and show much enhanced cell death when exposed even to physiological concentrations of H_2O_2. Pharmacological restoration of persulfidation levels in these cells by D-cysteine restores their survival rate. On the other hand, overexpression of CSE in SCA3 *Drosophila melanogaster* restores back the persulfidation levels and rescues the disease phenotype, i.e. the eye degeneration is dramatically reduced. Our preliminary proteomic data hint that not only that persulfidation has general protective role but that some specific signaling pathways could be tuned in order to achieve beneficial effects on polyQ disease.

Disclosures: M. Filipovic: None. **J. Zivanovic:** None. **E. Kouroussis:** None.

Nanosymposium

448. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms

Location: SDCC 7

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 448.07

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CHDI Foundation

Title: Harnessing the Golgi stress response confers cytoprotection in Huntington's disease

Authors: *B. D. PAUL, J. I. SBODIO, S. H. SNYDER
The Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Similar to ER stress response, Golgi stress response is emerging as a distinct signaling process. The Golgi apparatus is a dynamic organelle that plays a vital role in protein trafficking,

serving as the shipping and sorting center in cells. Disruption of the Golgi structure has frequently been associated with neurodegenerative processes. We show that mild Golgi stress can actually prove beneficial and counteract cytotoxicity occurring during neurodegeneration. We have identified one of the signal transduction cascades that can afford neuroprotection. We show herein that Golgi stressors such as monensin act via the Protein Kinase RNA-like ER Kinase/Activating Transcription Factor 4 (PERK/ATF4) signaling pathway. ATF4 is the master regulator of amino acid metabolism that is induced during amino acid depletion and cell stress. One of the genes regulated by ATF4 is Cystathionine gamma lyase (CSE), a key enzyme in the reverse transsulfuration pathway, which plays central roles in the maintenance of redox homeostasis. CSE, the biosynthetic enzyme for cysteine and hydrogen sulfide, is depleted in Huntington's disease, leading to impaired stress response and amino acid metabolism. Stimulating CSE expression or activity decreases levels of reactive oxygen species and restores cytoprotective response to stress stimuli. We show that the golgi protein, Acyl-CoA Binding Domain Containing 3 (ACBD3) stimulates CSE activity to generate hydrogen sulfide. Hydrogen sulfide signals via a post-translational modification termed persulfidation, which occurs on reactive cysteine residues of target proteins. Thus, the golgi stress response elicited by monensin results in persulfidation of several signaling networks involved in redox homeostasis and amino acid metabolism. We have identified for the first time, a molecular link between redox imbalance and Golgi stress during neurodegeneration in HD. This may be beneficial for not only HD, but other diseases involving redox imbalance and is amenable for therapeutic intervention.

References

1. Paul BD, Sbodio JI, Xu R, Vandiver MS, Cha JY, Snowman AM, Snyder SH. ***Nature*** 2014, 509:96-100.
2. Sbodio JI[#], Snyder SH* and Paul BD[#]*. ***Proc Natl Acad Sci USA*** 2016, 113:8843-8848.
3. Sbodio JI[#], Snyder SH* and Paul BD[#]*. ***Proc Natl Acad Sci USA*** 2018, 115(4):780-785.
4. Paul BD*, Sbodio JI and Snyder SH* ***Trends Pharmacol*** 2018, 39(5):513-524.
[#]Co-first, *Co-corresponding

Disclosures: B.D. Paul: None. **J.I. Sbodio:** None. **S.H. Snyder:** None.

Nanosymposium

448. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms

Location: SDCC 7

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 448.08

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R01 NS046673
NIH R01 AG044420
NIH R01 AG038710

NIH R01 AG021173

Title: Membralin-deficient astrocytes can trigger motor neuron death

Authors: *L.-L. JIANG, B. ZHU, Y. ZHAO, T. HUANG, D. ZHANG, H. XU
Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA

Abstract: Membralin is a newly identified component of the endoplasmic-reticulum-associated degradation (ERAD) system, which is required for maintaining protein homeostasis. Previously, we found that membralin mediates the turnover of a key γ-secretase component, nicastrin. Membralin downregulation in an Alzheimer's Disease (AD) mouse model elevated γ-secretase activity and exaggerated β-amyloid associated neurotoxicity and memory impairment. Interestingly, homozygous membralin deletion results in early lethality at ~P5 and is obligately associated marked motor defects. This suggests that in addition to a role in limiting AD pathogenesis, membralin has other fundamental roles in the CNS. Thus, using cell-type specific Cre mouse lines, we generated membralin deletion mouse lines in motor neurons, microglia and astrocytes and surprisingly, no obvious phenotypes were observed with membralin deletion in motor neurons or microglia. However, astrocyte-specific membralin deletion resulted in early lethality, and was associated with extensive gliosis in the CNS. In addition, conditioned media from membralin KO (mem-KO) astrocytes was toxic to cultured wildtype motor neurons; we identified dramatic elevations in excess glutamate secreted in conditioned mem-KO astrocyte media by gas chromatography-mass spectrometry. In search for components that can modulate extracellular glutamate levels in mem-KO astrocytes, we observed decreased expression of the glutamate transporter Glt1 with mem-KO deletion. This implicates a model where membralin limits extracellular glutamate levels by facilitating Glt1 expression and consequent glutamate uptake in astrocytes. Together, this indicates that membralin has cell-specific neuroprotective functions in limiting proteotoxic Aβ generation in neurons, and glutamate uptake in astrocytes.

Disclosures: L. Jiang: None. **B. Zhu:** None. **Y. Zhao:** None. **T. Huang:** None. **D. Zhang:** None. **H. Xu:** None.

Nanosymposium

448. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms

Location: SDCC 7

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 448.09

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NINDS grant R37NS033123
NINDS grant U01NS103883

Title: STAU1-dependent activation of the unfolded protein response leads to apoptosis in cellular and animal models of SCA2

Authors: *M. M. GANDELMAN, S. PAUL, W. DANSITHONG, K. P. FIGUEROA, D. R. SCOLES, S. M. PULST
Univ. of Utah, Salt Lake City, UT

Abstract: Pathological expansions of the ataxin 2 (*ATXN2)* CAG repeat cause spinocerebellar ataxia type 2 (SCA2) and increase the risk for amyotrophic lateral sclerosis (ALS). However, the downstream targets of ATXN2 and the mechanisms that trigger neuronal death are not well understood. We have previously shown that ATXN2 interacts with Staufen 1 (STAU1), a protein involved in RNA metabolism. In SCA2, Huntington's disease and ALS models STAU1 becomes highly elevated and accumulates in stress granules. Genetic reduction of STAU1 in SCA2 animal models improves their motor symptoms and reverts molecular markers of disease, indicating that the interaction between ATXN2 and STAU1 is relevant to the disease and could modulate neuronal survival. We hypothesized that STAU1 mediates ATXN2 pathological effects and set out to characterize the mechanisms. We found that skin fibroblasts derived from patients with SCA2 and HEK293 cells modified with CRISPR/Cas9 to express ATXN2 with an expanded CAG repeat (ATXN2-Q58) present an activated unfolded protein response (UPR) in basal conditions. The UPR was activated in a pro-apoptotic manner, as CHOP, the death executioner of the UPR was significantly elevated along with an increase in caspase 3 cleavage. Silencing STAU1 attenuated the UPR and prevented caspase cleavage, indicating it plays a central role in the activation of stress and apoptosis pathways downstream of mutated ATXN2. The pathological elevation of STAU1 was a consequence of alterations in cytoplasmic calcium signaling, as STAU1 levels were normalized by modulating cytoplasmic calcium with a chelator or by inhibiting calcium release from the ER. An increase in STAU1 levels in both WT and ATXN2-Q58 cells was elicited by triggering a raise in cytoplasmic calcium, indicating cellular calcium derangement can activate the STAU1-stress pathway in absence of mutated ATXN2. In support of this, overexpression of STAU1 in WT cells was sufficient to activate the UPR in WT cells. In a mouse model of SCA2 expressing ATXN2-Q127 we found UPR activation that was decreased by reducing STAU1 levels by genetic interaction with STAU1 knockout mice, evidencing the STAU1-stress pathway was be activated in vivo and could contribute to neuronal death. Our results highlight the importance of STAU1 in mediating the pathogenic effects of ATXN2 expansions and calcium derangement, establishing STAU1 as a novel target for preventing neuronal death in SCA2 and ALS and in neurodegenerative diseases where alterations in cytoplasmic calcium are present.

Disclosures: M.M. Gandelman: None. **S. Paul:** None. **W. Dansithong:** None. **K.P. Figueroa:** None. **D.R. Scoles:** None. **S.M. Pulst:** None.

Nanosymposium

448. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms

Location: SDCC 7

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 448.10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Field Neurosciences Institute of Ascension Health
John G. Kulhavi Professorship at Central Michigan University

Title: Solid lipid curcumin particles inhibit more autophagy markers than by natural curcumin in an invitro model of glioblastoma

Authors: *P. MAITI[1,2,3], A. AL-GHARAIBEH[4], D. SENGUPTA[3], G. L. DUNBAR[5]
[1]Psychology and Neurosci. Program, Central Michigan University/St. Mary's of Michigan, Saginaw, MI; [2]Neurosci. and Biol., Saginaw Valley State Univ., Saginaw, MI; [3]St. Mary's of Michigan, Field Neurosciences Inst., Saginaw, MI; [4]Central Michigan Univ., Mount Pleasant, MI; [5]Neurosci., Central Michigan Univ., Central Michigan University, MI

Abstract: Autophagy, or self-destruction, plays a pivotal role in cell death and survival in glioblastoma (GBM). Induction of autophagy increases cell survivability, whereas its inhibition can induce cell death. Therefore, inhibition of autophagy could be detrimental for GBM growth and proliferation. Previously, we have shown the greater anti-cancer role of solid lipid curcumin particles (SLCP) over natural curcumin (Cur) on glioblastoma (GBM) *in vitro*. In the present study, we have compared the autophagy mechanisms in three different GBM cell lines (U87Mg, GL261, and F98), along with their respective control cells (C6-glioma and N2a) after treatment with Cur and or SLCP. The U87Mg, GL261, F98, C6-glioma and N2a cells were grown in their respective media and treated with 25 μM Cur and or SLCP for 24 h. Macroautophagy markers, such as Atg5, Atg7, beclin-1, LC3A/B, mTOR, p-mTOR, as well as mitochondrial autophagy (mitophagy) markers, such as BNIP3/NIX, FUNDC1 and HIF-1α were studied by Western blot and immunocytochemistry. We observed that Cur and SLCP inhibited the levels of autophagy markers, in GBM cells compared to vehicle-treated GBM cells. Furthermore, we found greater inhibition of these markers in the case of SLCP-treated cells in comparison to Cur-treated cells. We also found the molecular chaperones HSP70 and HSP90 were downregulated by GBM and restored by Cur or SLCP treatment. Importantly, neither Cur nor SLCP inhibited autophagy markers in control glial (C6-glioma) and neuronal cell (N2a). Overall, our results suggest that SLCP can inhibit GBM growth and proliferation more than natural Cur and does so by inhibiting autophagy mechanisms.

Disclosures: P. Maiti: None. **A. Al-Gharaibeh:** None. **D. Sengupta:** None. **G.L. Dunbar:** None.

Nanosymposium

448. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms

Location: SDCC 7

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 448.11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Fellowship AG059358-01
NIH Grant NS027036

Title: TDP-43 phase transitions and co-demixing with stress granules and processing bodies

Authors: *H. YU[1], S. LU[1], B. ALADESUYI[2], C. CHEN[1], S. DA CRUZ[1], J. M. RAVITS[2], D. W. CLEVELAND[1,3]
[1]Ludwig Institute/UCSD, La Jolla, CA; [2]Neurosciences, Univ. of California San Diego Dept. of Neurosciences, La Jolla, CA; [3]Cell. and Mol. Med., UCSD, La Jolla, CA

Abstract: Nuclear clearance and cytoplasmic aggregation of wild-type TDP-43 is a pathological hallmark of over 90% of amyotrophic lateral sclerosis (ALS) patients. We have now identified de-mixing of wild-type TDP-43 into membraneless, liquid-like granules in both the nucleus and the cytoplasm of cycling non-neuronal and neuron-like (SH-SY5Y) cells. The N-terminal ubiquitin-like and C-terminal low-complexity domains are necessary for stress-induced de-mixing of TDP-43 in the cytoplasm, while RNA-binding is not required. RNA-binding deficient TDP-43 mutant de-mixes in both the nucleus and the cytoplasm. Cytosolic TDP-43 co-de-mixes with stress granules, but an RNA-binding deficient mutant de-mixes into apparently membraneless granules that are independent of stress granules or stress granule marker proteins. Aging of these cytosolic TDP-43 granules leads to TDP-43 aggregation, cleavage, phosphorylation, and ubiquitination, a chain of events that produces aggregated TDP-43 that resembles the cytosolic TDP-43 aggregates observed in postmortem ALS. Co-demixing of TDP-43 with stress granules or components of stress granules enhances arsenite-induced cell death. By tagging TDP-43 with a 50-amino acid weakly self-associating domain (by folding into a beta-solenoid structure), TDP-43 readily de-mixes without added cellular stress. Using inducible TDP-43 de-mixing as a model, and APEX2-mediated proximity labeling technology, we have identified unique RNA binding proteins that favor de-mixed TDP-43, including stress granule and P-body components. Cytosolic TDP-43 de-mixing causes dysregulation of P-body components.

Disclosures: H. Yu: None. **S. Lu:** None. **B. Aladesuyi:** None. **C. Chen:** None. **S. Da Cruz:** None. **J.M. Ravits:** None. **D.W. Cleveland:** None.

Nanosymposium

449. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 449.01

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant NS041234
NIH Grant NS101778
NIH Grant NS076054

Title: Tethered mitochondrial fate is coupled to inter-organelle contacts in Charcot-Marie-Tooth disease type 2B

Authors: *Y. C. WONG, W. PENG, D. KRAINC
Northwestern Univ., Chicago, IL

Abstract: Properly regulated mitochondrial dynamics are essential for cellular homeostasis and implicated in multiple neurodegenerative diseases including Parkinson's and Charcot-Marie-Tooth. Although mitochondria undergo fission and fusion, the majority of previous studies have assumed that mitochondrial tethering only functions as a step prior to mitochondrial fusion, but this has never been systematically analyzed in living cells. Using super-resolution and confocal live cell imaging of mitochondrial dynamics, we identify a novel untethering event in mitochondrial dynamics and demonstrate that tethered mitochondria predominantly untether rather than undergo mitochondrial fusion. Dynamic mitochondrial untethering from inter-mitochondrial contacts are surprisingly marked by both ER tubules and Drp1 oligomers and can be further spatially and temporally regulated by mitochondria-lysosome contact sites. Mitochondrial untethering is tightly coupled to a lysosome contacting either of the two mitochondria, and modulated by lysosomal Rab7 GTP hydrolysis driven by its mitochondrial GAP (TBC1D15). Importantly, we find that Charcot-Marie-Tooth disease type 2B (CMT2B) mutations in Rab7 which have defective GTP hydrolysis lead to prolonged mitochondrial tethering and consequently disrupt mitochondrial dynamics, pointing to converging disease mechanisms with CMT2A mutations in mitofusin2 (Mfn2) which regulates mitochondrial tethering and fusion. This work thus highlights an important previously uncharacterized step in mitochondrial dynamics and demonstrates that transient mitochondrial tethering which is tightly regulated by inter-organelle contact sites may be the predominant method for crosstalk between two individual mitochondria rather than fusion.

Disclosures: Y.C. Wong: None. **W. Peng:** None. **D. Krainc:** None.

Nanosymposium

449. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 449.02

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH-NINDS 4R00NS091486-03
Robert Packard ALS Center Grant

Title: Neuronal excitation and stress increase C9orf72 NRE-linked non-AUG-dependent translation

Authors: *A. R. HAEUSLER, T. WESTERGARD, K. MCAVOY, K. RUSSELL, X. WEN, Y. PANG, B. MORRIS, P. PASINELLI, D. TROTTI
Neurosci., Thomas Jefferson Univ., Philadelphia, PA

Abstract: Nucleotide repeat expansions (NREs) are prevalent mutations in a multitude of neurodegenerative diseases. Repeat-associated non-AUG (RAN) translation of these repeat regions produce mono or dipeptides that attribute to the pathogenesis of these diseases. However, the mechanisms and drivers of RAN translation are not well understood. Here we analyzed whether different cellular stressors promote RAN translation of dipeptide repeats (DPRs) associated with the G_4C_2hexanucleotide expansions in *C9orf72*, the most common cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). We found that glutamate receptors activation or optogenetically increasing neuronal activity by repetitive depolarizations, induced DPR formation in primary cortical neurons and patient derived spinal motor neurons. Activation of the integrated stress response (ISR) also increased RAN translation of DPRs, both in neurons and different cell lines. Targeting phosphorylated-PERK and the phosphorylated-eif2α complex greatly reduces DPR levels revealing a potential therapeutic strategy to attenuate DPR-dependent disease pathogenesis in NRE-linked diseases.

Disclosures: A.R. Haeusler: None. **T. Westergard:** None. **K. McAvoy:** None. **K. Russell:** None. **X. Wen:** None. **Y. Pang:** None. **B. Morris:** None. **P. Pasinelli:** None. **D. Trotti:** None.

Nanosymposium

449. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 449.03

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01NS091519

Title: Genetic rescue of deficits in the Csf1r$^{+/-}$ mouse model of ALSP

Authors: *E. R. STANLEY, F. BIUNDO, G. S. SHLAGER, M. E. GULINELLO, H. KETCHUM, K. SAHA, E. S. PARK, S. GOKHAN, M. F. MEHLER, P. WANG, D. ZHENG, V. CHITU
Dept. of Developmental and Mol. Biol., Albert Einstein Col. of Med., Bronx, NY

Abstract: Adult onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is an adult onset dementia caused by dominantly inherited inactivating mutations in the CSF-1 receptor tyrosine kinase (CSF-1R). *Csf1r*$^{+/-}$ (ALSP) mice exhibit radiologic, histopathologic and behavioral deficits reminiscent of ALSP. The brains of *Csf1r*$^{+/-}$ mice exhibit negligible monocytic infiltration. Moreover, microglia-specific allelic deletion of *Csf1r* is sufficient to produce the short-term memory deficits and olfactory dysfunction seen in the *Csf1r*$^{+/-}$ mice. Therefore, microglial dysfunction has a major role in the pathologenesis of ALSP. Elevated expression of GM-CSF (CSF-2) in ALSP mouse brain suggested that GM-CSF might play a central role in neurodegeneration by promoting microgliosis and priming associated inflammatory responses. To test this hypothesis, we characterized the behavioral and histopathological phenotypes of *Csf1r* and *Csf2* single and double heterozygous mice (blinded studies of males and females, ≥14/gender, followed from 7 to 18 months of age). *Csf2* heterozygosity on the ALSP background rescued microglial-mediated olfactory and cognitive deficits, but not the loss of motor coordination. Consistent with these findings, *Csf2* heterozygosity also prevented the elevation of Iba1+ cells in the olfactory bulb, motor cortex and hippocampus, but not in the cerebellum. RNA-Seq analysis identified 496 differentially expressed genes (DEGs) in microglia isolated from the cerebra of *Csf1r*+/- compared with *Csf1r*+/+ mice. Upregulated genes included genes that promote neurotoxic responses following the uptake of apoptotic neurons and those causing mitochondrial dysfunction. In contrast, downregulated genes encoded several anti-inflammatory proteins. *Csf2* heterozygosity reduced the numbers of DEGs to 254. Pathway analysis predicted activation of neurodegenerative pathways in *Csf1r*+/-, but not in *Csf1r*+/-;*Csf2*+/- microglia, further indicating that the reduction of GM-CSF availability has a normalizing effect. Microglia are known to regulate adult neurogenesis and myelination. We show that neurogenesis was suppressed in aged ALSP mice in

the subventricular zone and the dentate gyrus and normalized in both by *Csf2* heterozygosity. However, targeting *Csf2* only partially prevented the callosal myelin and axonal pathology. These data suggest that *Csf2* heterozygosity in the ALSP mouse model prevents olfactory and cognitive dysfunction by partially normalizing microglial function.

Disclosures: E.R. Stanley: None. **F. Biundo:** None. **G.S. Shlager:** None. **M.E. Gulinello:** None. **H. Ketchum:** None. **K. Saha:** None. **E.S. Park:** None. **S. Gokhan:** None. **M.F. Mehler:** None. **P. Wang:** None. **D. Zheng:** None. **V. Chitu:** None.

Nanosymposium

449. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 449.04

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant DK097153
HFHS Grant A10263

Title: Transomic modeling of cerebral inflammation in X linked adrenoleukodystrophy

Authors: *J. SINGH, B. OLLE, L. POISSON, H. SUHAIL, S. GIRI
Dept. of Neurol., HENRY FORD HEALTH SYSTEM, Detroit, MI

Abstract: Introduction: X-linked adrenoleukodystrophy (X-ALD) is a progressive neurodegenerative disease caused by mutations in peroxisomal ABCD1 gene. X-ALD males develop fatal cerebral demyelinating disease (ALD) the mechanism for which remains unknown. We took a novel multi-omics approach of untargeted metabolomics and next generation sequencing (HiSeq) to find regulatory (microRNA) and active (metabolite) pathways underlying the fatal demyelination in ALD.
Methods: Postmortem brain tissue (n=6) from healthy controls and ALD patients were processed for microRNA (miRNA) and metabolite extraction and analysis (HiSeq [Illumina] and Gas Chromatography Mass Spectrometry (GC-MS) [Agilent Technologies], respectively). Data analysis was performed by "MetaboAnalyst 2.5" (www.metaboanalyst.ca/) for GC-MS and Bioconductor (www.bioconductor.org) for miRNA.
Results: Each measured miRNA and metabolite was screened using appropriate ANOVA models to account for the study design. Thresholds for significance were set to control the estimated false discovery rate, per platform, at 5%. We compared postmortem brain white matter of healthy controls (CTL) with normal looking area (NLA) and periphery of plaque/lesion (PLS) regions within the ALD brain white matter. Analysis of variance ($P<0.05$) and Post-hoc t-tests identified nineteen miRNA and eleven metabolites that significantly differed ($P<0.05$) across the

three groups (control, NLA and PLS). Of the nineteen miRNA seventeen were increased with disease severity (PLS>NLA>CTL) and two were decreased (CTL>NLA>PLS). Seven metabolites were upregulated with disease severity (PLS>NLA>CTL) and four were downregulated (CTL>NLA>PLS). We calculated the Pearson's correlation coefficient between the expression of these 19 miRNA and the metabolite intensities of significantly differential metabolites for putative links between the global gene expression modulators (miRNAs), and metabolites, Interestingly, three oligodendrocyte (myelin forming cells in the white matter) enriched miRNAs (miR-338-5p, miR-92b-5p and miR-3065) negatively correlated with brain myelin lipids (glycerol-3-phosphocholines) within the ALD brain.
Conclusion: Our novel "transomic" modeling identifies, for the first time, integrated miRNA and metabolite pathways underlying demyelination in X-ALD.

Disclosures: J. Singh: None. **B. Olle:** None. **L. Poisson:** None. **H. Suhail:** None. **S. Giri:** None.

Nanosymposium

449. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 449.05

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: BMBF GO-Bio

Title: Neurogenic niche activity: Modulation by targeting tgfß-rii

Authors: *S. PETERS[1], E. ZITZELSPERGER[1], S. KUESPERT[1], R. HEYDN[1], S. JOHANNESEN[1], L. J. AIGNER[2], T.-H. BRUUN[1], U. BOGDAHN[1]
[1]Dept. for Neurol., Univ. Hosp., Regensburg, Germany; [2]Paracelsus Med. Univ., Salzburg, Austria

Abstract: The ability of the adult central nervous system to self-repair/regenerate was shown throughout the last decades, but remains in debate. In neurodegenerative disorders, reduced neurogenic niche activity, in combination with profound neuronal loss, represents fundamental hallmarks of disease course. We and others demonstrated that the TGFß system is a potential pathogenic player in disease modulation, of Amyotrophic Lateral Sclerosis (ALS) in particular, by inducing an imbalance of neurodegenerative and neuroregenerative processes. The novel primate specific LNA Antisense Oligonucleotide "BiAgil", targeting the TGFß-RII, effectively reduced its expression and lowered TGFß signal transduction *in vitro,* paralleled by boosting neurogenesis in human neuronal progenitor cells. Here, we investigated BiAgil *in vivo* safety and efficacy following repeated intrathecal injections in the non-human primate Cynomolgus.We

tested BiAgil tolerability by using a dose-escalation paradigm with increasing dose levels every single week (0.4 mg/animal to 20 mg/animal). One male and female Cynomolgus monkey each received an intrathecal BiAgil injection, physical/neurological parameters were investigated directly and following 4h after administration. In a second experiment BiAgil pharmacokinetics was evaluated for BiAgil tissue concentrations following 2 or 4 weeks after *i.t.*drug administration for two different BiAgil doses (low: 0.8 mg/animal; high: 4 mg/animal). CSF was taken to evaluate BiAgil half-life. Finally, in a third paradigm, BiAgil was injected repeatedly over a 13-week approach at 2 doses. Again, CNS tissue samples (spinal cord, brain) were collected to evaluate tissue distribution. Target modulation, expression levels of the ligands and most important downstream targets were determined within spinal cord, dentate gyrus, and subventricular zone. Consequently, effects of an altered TGFß system activity on the adult neurogenic niche were followed by measuring neuronal stem cell markers. Progenitor cell and lineage markers indicate a strong and broad modulatory effect of niche activity.The results of the current study indicate that BiAgil is well tolerated, stable and a potentially highly effective agent to modulate an overactive TGFß system. It down-regulates the target within the CNS and spinal cord, *in vivo* results point to high functional activity. BiAgil as a potential pharmacological modulator of the neurogenic niche may constitute an attractive drug candidate for a number of neurodegenerative disorders, including ALS or trauma of the CNS. Clinical application in ALS is being planed.

Disclosures: E. Zitzelsperger: None. **S. Kuespert:** None. **R. Heydn:** None. **S. Johannesen:** None. **L.J. Aigner:** None. **T. Bruun:** None. **U. Bogdahn:** None.

Nanosymposium

449. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 449.06

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Swiss National Science Foundation
Provisu Foundation

Title: EZH2 is associated with photoreceptor degeneration and potentially targets miRNAs controlling cell cycle and apoptosis

Authors: *Y. ARSENIJEVIC[1], A. PRUNOTTO[2], C. RIVOLTA[2], M. MBEFO[1]
[1]Jules-Gonin Eye Hosp., Lausanne, Switzerland; [2]Univ. of Lausanne, Lausanne, Switzerland

Abstract: Purpose: Retinitis Pigmentosa (RP) is a class of hereditary retinal dystrophy associated with photoreceptor loss and blindness. Among several actors mediating cell death, we

observed an abnormal cell cycle re-entry in photoreceptors undergoing degeneration in *Rd1* mice and identified the Polycomb repressive complex 1 (PrC1) core component BMI1 as a critical molecular factor orchestrating the cell death mechanism. The *Bmi1* deletion leads to a marked photoreceptor protection in the *Rd1* retina, but independently of the conventional *Ink4a/Arf* pathways (Zencak et al., 2013), suggesting that BMI1 acts on other targets. We thus studied during the degenerative process the potential role of components of the PCR2 interacting with BMI1, such as EZH2, which methylates Histone-3 to repress gene expression. Method: We used cross sections from male and female FVB *Rd1* and FVB WT mouse retinas at different postnatal ages to screen by immunohistochemistry for the changes of histones marks H3K27me3, which is methylated by EZH2. Photoreceptors were isolated by FACS for WB analyses. We next performed miRNA array analysis from WT and *Rd1* retina samples to potentially identify miRNA targeted by EZH2 during photoreceptor degeneration. A new method of Ontology analysis was developed to identify the most promising gene targets of the identified miRNAs. Results: We observed by WB an upregulation of EZH2 in isolated *Rd1* photoreceptors and by immunohistochemistry, a hypertrimethylation of histone 3 (H3K27me3) in photoreceptors before cell death attesting the EZH2 activity. miRNA arrays revealed a very limited number of miRNA candidates which are differently expressed in the *Rd1* retina. Interestingly, two miRNAs showing the major expression changes control cell cycle activation as well as apoptosis are known targets of EZH2. These candidates are currently tested in retinal cell cultures. Conclusions: These results are consistent with our previous findings on photoreceptor death mechanism characterization. Altogether, these data suggest that miRNAs may play a major role during retinal degeneration by controlling cell cycle reentry and cell death.

Disclosures: Y. Arsenijevic: None. **A. Prunotto:** None. **C. Rivolta:** None. **M. Mbefo:** None.

Nanosymposium

449. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 449.07

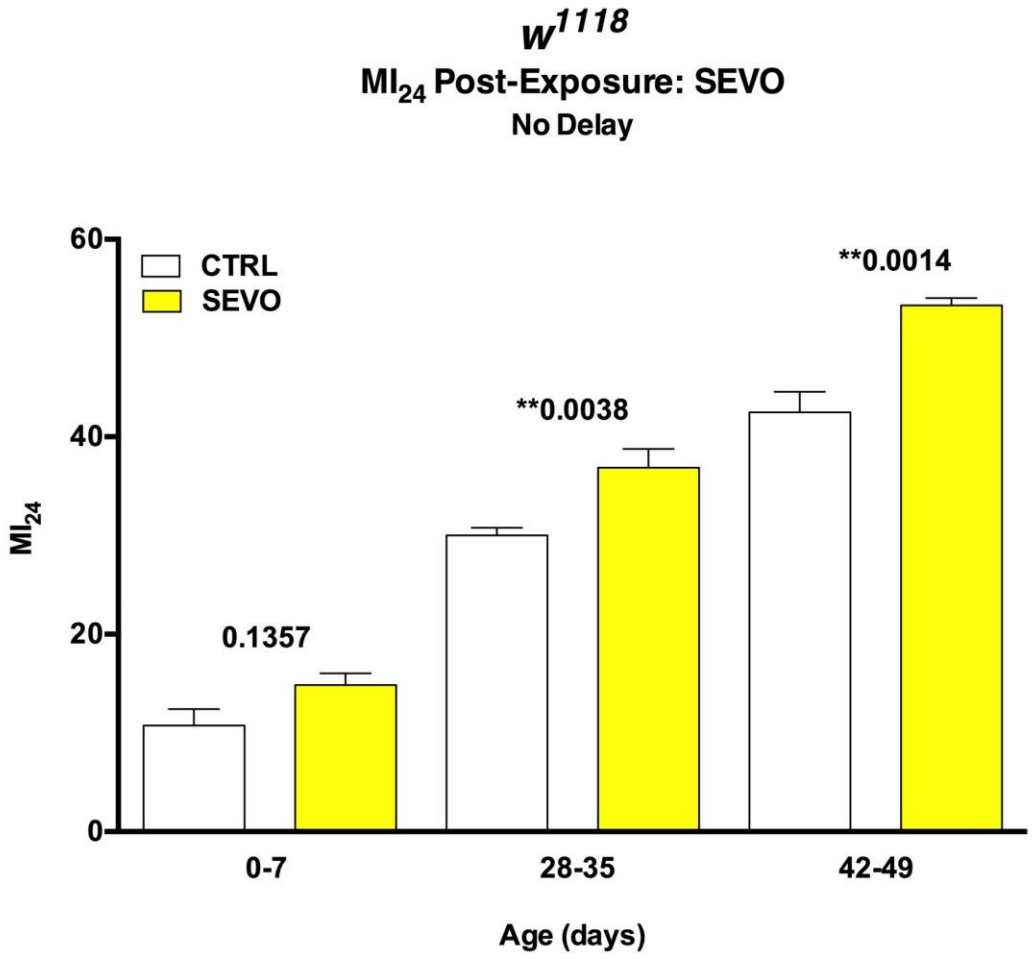
Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Departmental R&D Anesthesiology UW
NIH RO1 NS083596

Title: Anesthetics influence mortality in a *Drosophila* model of blunt trauma with TBI

Authors: *M. PEROUANSKY[1], H. J. SCHIFFMAN[2], D. A. WASSARMAN[3]
[1]Dept. of Anesthesiol., Univ. of Wisconsin Madison Dept. of Anesthesiol., Madison, WI; [2]Anesthesiol., [3]Med. Genet., Univ. of Wisconsin, Madison, WI

Abstract: Experimental investigations of the influence of general anesthetics (GAs) on outcomes from traumatic brain injury (TBI) in aged animals are sparse. We used a *Drosophila melanogaster* blunt trauma with TBI (bTBI) model (Katzenberger 2013) to investigate the effect of volatile general anesthetics (VGAs) on outcome from bTBI. Previously, we found that VGAs differentially affect outcome from bTBI in young (1-8 day-old) flies (Fischer 2018). Here we tested the influence of VGAs on bTBI outcomes in aged (42-49 day-old) flies. We administered equipotent doses of either isoflurane (ISO 2% for 2h) or sevoflurane (SEVO 3.5% for 2h) either prior to (preexposure) or after (postexposure) the infliction of bTBI. While exposure to VGAs alone did not lead to mortality in young or old flies, it influenced the risk of mortality in the context of bTBI which was further influenced by age.
Mortality 24 h after bTBI was expressed as the mortality index (MI_{24}). MI_{24} = the percentage of dead flies in the experimental group minus the percentage of dead flies in the control group. Upon preexposure, the MI_{24} of young flies decreased from 13.4±1.3 to 6.5±1.0 and 14.9±2.1 to 10.6±1.2 ($p<0.05$) for ISO and SEVO, respectively. In aged flies, mortality from bTBI was higher and preexposure to ISO did not reduce the MI_{24} (48.6±6.3 and 46.02±4.6). Postexposure to ISO increased the MI_{24} in young animals (10.4±1.1 and 14.0±1.0, $p=0.03$) while SEVO had no effect (12.1±1.7 and 14.6±1.2, $p=0.1$). Postexposure to ISO in aged animals had no effect on the MI_{24} (44±1.7 and 48±5.0, $p=0.16$). In contrast to young animals, however, SEVO increased the MI_{24} (42.5±2.1 and 53.3±0.7, $p=0.001$). We conclude that VGAs are not neutral in the context of severe experimental trauma. Processes set in motion by injury involving TBI are modulated by VGAs, ISO and SEVO have distinct effects on early mortality, and the effects change with aging. These findings highlight the need for in-depth analyses of environmental and genetic factors that modulate outcomes from exposure to VGAs



Disclosures: M. Perouansky: None. **H.J. Schiffman:** None. **D.A. Wassarman:** None.

Nanosymposium

449. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 8:00 AM - 10:00 AM

Presentation Number: 449.08

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NINDS NRSA F32 NS081964
NIH/NINDS Grant R01 NS65874
Hereditary Disease Foundation

Title: Mechanisms of exercise mimetic neuroprotection in preclinical trials

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

Abstract: From years of research in the neurodegenerative field, both shared and disease-specific mechanisms have been uncovered. Previous work from us and others indicated that an exercise mimetic can ameliorate neuropathology and motor symptoms in models of Huntington disease: patient iPSC-derived neurons and HD N171-82Q mice (Dickey, et al., 2016. NMED), models of Parkinson Disease: human iPSC-derived A9 dopaminergic neurons, and a-synuclein mice (Dickey, et al., unpublished), and models of Alzheimer disease: APP/PS1 mice (Casali, et al, 2018. J.Neuroinflam). Neuroprotective mechanisms so far elucidated include inducing oxidative phosphorylation, reducing mitochondria fragmentation, and promoting autophagy to address aggregates (Dickey, et al., 2017. STM). Our RNA-SEQ & ChIP-SEQ results indicate that this exercise mimetic/transcriptional regulator activates more neuroprotective mechanisms than previously thought, potentially applying to multiple diseases. In addition to the mechanisms above, this exercise mimetic reduces ROS, represses ER-mediated stress, calms inflammation, and regulates expression of receptor subunits. These findings were derived from studies utilizing mice, primary neuron cultures, and cell lines. We have also been investigating the mechanism(s) through which this mimetic is able to coordinate these multiple downstream effects. Sequencing data from this exercise mimic indicates that activation of a transcriptional "coordinator" differentially regulates other transcriptional pathways. Not only is the activation of gene transcription affected, but ChIP-PCR confirms that interaction with a complex of transcriptional repressors including NCoR1 and HDAC3 is also involved.

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

Nanosymposium

450. Vision: Contrast, Form, and Color

Location: SDCC 33

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 450.01

Topic: D.07. Vision

Support: NIH Grant EY021462
NIH Grant EY22428

Title: Naturalistic texture selectivity and functional architecture in macaque visual cortex

Authors: *C. M. ZIEMBA[1], A. L. BRUNING[1], J. A. MOVSHON[2], R. L. GORIS[1], I. M. NAUHAUS[1]
[1]Ctr. for Perceptual Systems, UT Austin, Austin, TX; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Along the visual hierarchy, selectivity progressively emerges at each stage. In the cortex, this selectivity is organized across the surface to form functional maps. In both V1 and V2, there is a general correspondence between functional maps, cytoarchitectonic maps, and parallel pathways initiated in the retina. For example, V2 compartments selective for color, motion, and orientation have been linked to direct input from V1 compartments that are targeted by specific subcortical pathways. It stands to reason that pathways routed through V2 may perform different computations, as they clearly do once diverging along the dorsal and ventral extremes. However, it is still unknown if V2 compartments perform novel computations, or if V2 maps are simply the inheritance of tuning from different V1 populations. This question has been difficult to address because few response properties reliably distinguish the selectivity of V2 neurons from their inputs in V1. Recent single unit electrophysiology has demonstrated that V2 neurons, but not V1 neurons, respond more vigorously to “naturalistic” images synthesized using a model capturing the higher order statistical structure of natural textures, compared to “spectral noise” images only matched for second order statistics. Here, we used optical imaging of intrinsic signals in anesthetized macaque monkeys to investigate the functional organization of naturalistic texture selectivity. We first presented a suite of basic characterization stimuli consisting of drifting achromatic and isoluminant red/green gratings of different orientations and scales presented to each eye. We identified the V1/V2 border based on ocular dominance, and were able to discriminate different V2 compartments based on color preference and orientation selectivity. We then presented naturalistic and spectral noise images drawn from 5 families derived from different original natural images. Each 3 second trial consisted of 15 physically different but statistically matched texture images in a rapid sequence. After imaging, we lowered laminar multielectrode arrays into identified locations in both V1 and V2 to compare our imaging results directly with electrophysiological recordings. We examined selectivity for higher order statistics by computing difference maps for naturalistic and spectral noise textures and were able to identify the V1/V2 border by an increase in preference for naturalistic textures. Preliminary data reveal little dependence of texture selectivity on functional architecture within V2. If this result holds, it would suggest that the emergence of texture selectivity is a general property of V1-to-V2 circuits.

Disclosures: C.M. Ziemba: None. **A.L. Bruning:** None. **J.A. Movshon:** None. **R.L. Goris:** None. **I.M. Nauhaus:** None.

Nanosymposium

450. Vision: Contrast, Form, and Color

Location: SDCC 33

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 450.02

Topic: D.07. Vision

Support: HHMI

Title: Learning a model for visual texture selectivity from natural images

Authors: *T. D. OLESKIW, E. P. SIMONCELLI
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: As visual information propagates along the ventral pathway, individual neurons respond selectively to stimulus features of increasing complexity. Most neurons in primary visual cortex (V1) respond to oriented gratings, while many neurons of the second visual area (V2) respond to visual textures, with single neurons preferring pseudo-periodic features common among natural scenes. Specifically, recent results indicate that single unit V2 activity is strongly modulated by the presence of higher-order statistics in visual textures, while V1 neurons, driven primarily by local spectral content, are largely insensitive to these higher-order statistics. However, it has proven difficult to interpret these findings in the context of physiological mechanisms, or to refine such computations into precise statements of selectivity for individual V2 neurons.
Toward these goals we construct a physiologically-plausible model of local texture representation for discriminating naturalistic textures and their spectrally-matched counterparts, optimized over a database of natural textures. We begin by decomposing texture patches with a multi-scale oriented filter bank (a “steerable pyramid”), whose linear basis functions mimic V1 selectivity for orientation and spatial frequency. We then perform principal component analysis (PCA) over the rectified filter responses, recovering a low-dimensional basis is shown to capture essential texture statistics. A classification experiment then demonstrates that a small number (approx. 3-5) of these PCA components are sufficient to distinguish naturalistic textures from noise, with remarkably high accuracy given the low number of free parameters. Furthermore, we find that our basis components resemble localized differences (derivatives) spanning four dimensions of V1 selectivity: horizontal and vertical position, orientation, and spatial frequency. Our results suggest that a simple canonical mechanism, operating on V1 afferents and constructed from local derivative filters with rectifying or squaring nonlinearities (analogous to V1 simple and complex cells, respectively) mimics the enhanced responses of single V2 neurons to higher-order texture statistics. We discuss implications for fitting this model to physiological responses of individual V2 cells, as well as generalizations of our findings to other domains of ventral visual computation (e.g. curvature or border ownership).

Disclosures: T.D. Oleskiw: None. **E.P. Simoncelli:** None.

Nanosymposium

450. Vision: Contrast, Form, and Color

Location: SDCC 33

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 450.03

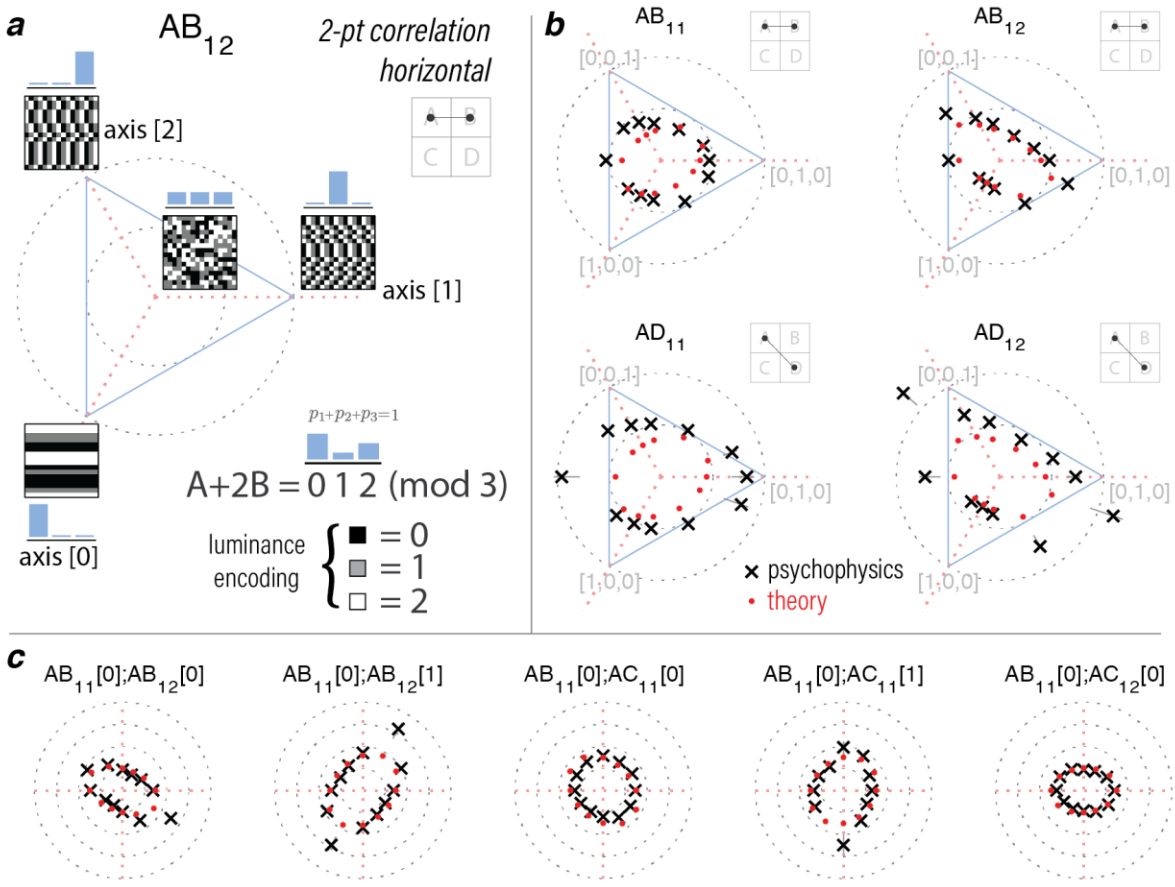
Topic: D.07. Vision

Support: NIH EY07977
Howard Hughes Medical Institute
Swartz Foundation

Title: Salience of grayscale textures from natural image statistics

Authors: *T. TESILEANU[1], M. M. CONTE[2], J. J. BRIGUGLIO[3], A. M. HERMUNDSTAD[3], J. D. VICTOR[2], V. BALASUBRAMANIAN[4]
[1]Ctr. for Computat. Biol., Flatiron Inst., New York, NY; [2]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY; [3]Janelia Res. Campus, Ashburn, VA; [4]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Texture provides an important cue for parsing visual scenes. In previous work, we found that the natural statistics of textures are related to their salience in psychophysical tasks. Specifically, we focused on binarized images, and calculated correlations between adjacent groups of pixels, resulting in a 10-dimensional parametrization of texture space. The amount of variance found along a given texture direction in natural images strongly correlated with the sensitivity that human subjects showed in that direction. This relation between variance and salience is expected if the brain evolved to efficiently encode visual textures in a regime where sampling noise was dominant. Here we extend the analysis and the psychophysics to include grayscale images with 3 luminance levels. In this case, the texture statistics can be organized in 33 texture planes. Generalizing the parametrization used in the binary case, the coordinates for ternary textures are derived from modular arithmetic applied on the luminance levels (Figure panel a). Similar to the binary case, psychophysical performance shows that perceptual thresholds to ternary textures are highly consistent across subjects. Following the variance = salience paradigm from the earlier work, a natural image analysis leads to threshold predictions that closely match the psychophysics results along several axes within single texture planes (Figure panel b), and many axes overlapping two distinct planes (Figure panel c). Importantly, this comparison involves only one fitting parameter, which sets the overall scale of the predicted thresholds. Moreover, most mismatches occur in cases where the uncertainty in the psychophysics is large. Intriguingly, a few planes show mismatches in which the psychophysics seems to follow symmetries that are not present in natural images. This suggests the possibility that the brain is operating under constraints that preclude it from fully adapting to the natural statistics. Overall, our work strengthens and refines the idea that the brain is adapted to efficiently encode visual texture information.



Disclosures: T. Tesileanu: None. **M.M. Conte:** None. **J.J. Briguglio:** None. **A.M. Hermundstad:** None. **J.D. Victor:** None. **V. Balasubramanian:** None.

Nanosymposium

450. Vision: Contrast, Form, and Color

Location: SDCC 33

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 450.04

Topic: D.07. Vision

Title: Human cortical encoding of a discrete temporal landmark for extracting syllables in continuous speech

Authors: *Y. OGANIAN[1], E. F. CHANG[2]
[1]Univ. of California, San Francisco, San Francisco, CA; [2]Neurosurg., UCSF, San Francisco, CA

Abstract: A crucial component of the speech signal is its slow amplitude envelope (4-16Hz). Speech comprehension is severely impaired if the temporal envelope is distorted. Numerous studies have found that brain activity is correlated with the amplitude envelope of speech. Commonly assumed is that the speech cortex in superior temporal gyrus (STG) encodes an analog, continuous representation of the envelope. However, not all periods in the speech signal are equally informative: Discrete landmarks such as amplitude peaks and peaks in rate of amplitude change mark high intensity periods in speech. STG might rely on temporal landmarks to segment the continuous speech into syllabic units. We directly recorded neuronal responses from the surface of STG using electrocorticography, while participants (n = 27) listened to continuous speech. As expected, neural populations in bilateral mid-STG followed modulations of the speech envelope. However, we found that neural responses reflected consecutive evoked responses to local peaks in the rate of envelope change (peakRate), but not local peaks in the envelope or its continuous shape. Notably, encoding of peakRate events was anatomically and functionally dissociated from speech onset and phonetic features encoding. We next analyzed the spectral and phonetic content of speech around peakRate events to better understand what is being cued by peakRate. We found that peakRate events were aligned to consonant-vowel transitions. Moreover, peakRate magnitude predicted whether its enclosing syllable was stressed, and this was reflected in STG responses to maxRise events. Encoding of peakRate events thus provides an internal reference point to the temporal structure of a syllable and indicates its prominence within a sentence. A non-speech control stimulus of isolated amplitude-modulated tones was used to determine how cortical activity relates to parametrically varied rates of amplitude change in absence of spectral changes. We found a monotonic encoding of peakRate magnitude, providing a basis to differentiating between stressed and unstressed syllables. Strikingly, two distinct neural populations represented peakRate at sound onsets and in ongoing sounds, allowing for a fine-grained representation of peakRate magnitude within each. Overall, our results demonstrate that the STG represents the speech envelope through detecting peaks in rate of amplitude change in the acoustic signal. These events mark the temporal structure of syllables and focus speech recognition on prominent syllables in the speech signal.

Disclosures: Y. Oganian: None. **E.F. Chang:** None.

Nanosymposium

450. Vision: Contrast, Form, and Color

Location: SDCC 33

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 450.05

Topic: D.07. Vision

Support: NIH Grant EY07977

Title: Sensitivity to local image statistics in segmentation and identification

Authors: *M. M. CONTE[1], L. EVANS[2], J. D. VICTOR[1]
[1]Weill Cornell Med. Col., New York, NY; [2]Howard Univ., Washington, DC

Abstract: Many basic visual processes begin with extraction of local features. Synthetic visual textures are useful probes of the underlying neural computations, because they provide a means to isolate and quantify the contributions of individual image statistics. However, it is unclear to what extent sensitivity to local image statistics depends on other levels of visual processing. To address this question, we examined two contrasting visual processes that utilize local image statistics: locating a target region and identifying its surface texture. The starting point for this analysis is a phenomenological model for sensitivity to local image statistics, developed from two kinds of psychophysical experiments: measurements of sensitivity to binary textures with local correlations (Victor & Conte, 2015), and measurements of sensitivity to textures with many gray levels but without local correlations (Silva & Chubb, 2014). We recently constructed a computational model, fully constrained by these two datasets, that predicts sensitivity to a much larger set of synthetic textures that contain not only spatial correlations but also multiple gray levels. This model provides a reasonable account of sensitivities to such textures, which were not part of the two kinds of datasets used to constrain the model. We focus on "stepped gradient" textures, in which the luminances of adjacent checks tend to increase gradually or decrease abruptly in one direction. For such textures, the model makes the distinctive prediction that thresholds are higher for gradients with 5 gray levels than for gradients with fewer (3) or more (11) gray levels. These textures were used in two tasks: "segmentation," in which the subject was required to locate texture boundaries, and "identification", in which the subject was required to identify the direction of the stepped gradient. Both were 4-alternative forced-choice tasks. For the segmentation task (N=5 subjects), thresholds conformed to the model prediction, both in terms of the dependence on the number of gray levels and absolute sensitivity. For the identification task (N=4), thresholds and dependence on the number of gray levels were similar, indicating a similar sensitivity to local image statistics. However, the psychometric functions for the two tasks had a consistently different shape. Specifically, although sensitivities were similar, performance rose above threshold more rapidly for segmentation than for identification. Thus, while these two visual processes rely on local image statistics, they differ in how the statistics are used for decision-making.

Disclosures: M.M. Conte: None. **L. Evans:** None. **J.D. Victor:** None.

Nanosymposium

450. Vision: Contrast, Form, and Color

Location: SDCC 33

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 450.06

Topic: D.07. Vision

Support: DOE Computational Science Graduate Fellowship (DE-FG02-97ER25308)
McDonnell Scholar Award
NIH grant 1R01DC014739-01A1
NIH grant R25GM067110
NSF grant BCS-1634050
NSF grant PHY17-48958

Title: Invariance to real-world background noise as a signature of non-primary auditory cortex

Authors: *A. J. KELL, J. H. MCDERMOTT
Brain + Cognitive Sci., MIT, Cambridge, MA

Abstract: Despite well-established anatomical differences between primary and non-primary auditory cortex, the associated representational transformations have remained elusive. Here we probed for one candidate transformation, measuring the invariance of sound-evoked responses throughout auditory cortex to the presence of real-world background noise.
Listening in noise is a core problem in everyday hearing. Sound sources of interest routinely occur amid irrelevant distractors, as when you talk with someone in a bustling coffee shop. This "background noise" distorts the pattern of spikes in the auditory nerve, often to a profound degree. Thus, to recognize sources of interest, the auditory system must somehow become robust to the effects of this noise. Many real-world background noise sources are texture-like, and these sounds' stationary statistics that may help enable their separation or suppression.
To assess the noise robustness of auditory cortical representations, we measured fMRI responses in twelve human listeners to thirty natural sounds (each two seconds long). Sounds were presented in quiet as well as embedded in thirty everyday sound textures selected to have stable statistics over time, e.g. a crowded theater, rain hitting pavement, crickets chirping. To quantify the noise robustness of cortical responses, we leveraged the fact that a voxel's response typically varies across natural sounds and we simply correlated each voxel's response to the natural sounds in isolation with its response to those same natural sounds superimposed on sound texture.
Primary cortical responses were substantially affected by background noise ($r2 \sim 0.40$), but non-primary responses were more robust ($r2 \sim 0.80$). This difference between primary and non-primary areas was replicated in a second experiment in which speech and music stimuli were excluded, suggesting that this difference cannot be attributed to previously reported speech and music selectivity in non-primary areas. Lastly, in a third experiment we found that this difference between regions was only seen when the background noises exhibited the non-stationarities found in real-world sound textures - both primary and non-primary responses were robust to spectrally-shaped Gaussian noise. Our results suggest that robustness to real-world background noise may be a signature of non-primary auditory cortical processing, demonstrating a potential representational consequence of auditory hierarchical organization.

Disclosures: A.J. Kell: None. **J.H. McDermott:** None.

Nanosymposium

450. Vision: Contrast, Form, and Color

Location: SDCC 33

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 450.07

Topic: D.07. Vision

Support: NIH DC015138

Title: A neural ensemble correlation code for sound category identification

Authors: *M. A. ESCABI[1], M. SADEGHI[2], X. ZHAI[3], I. H. STEVENSON[4]
[2]Electrical and Computer Engin., [3]Biomed. Engin., [4]Psychological Sci., [1]Univ. of Connecticut, Storrs, CT

Abstract: Humans and other animals effortlessly identify sounds and categorize them into behaviorally relevant categories. Yet, the acoustic features and neural transformations that enable the formation of perceptual categories are largely unknown. Here we demonstrate that the correlations between neuron ensembles in the auditory midbrain (inferior colliculus) of unanesthetized rabbits reflect correlated structure in sound envelopes and that these statistics can contribute to the discrimination of sound categories. Five natural texture sounds (running water, bird chorus, crackling fire, rattling snake and crowd noise) were delivered over calibrated headphones and multi-channel neural recordings (16 and 32 channels) were obtained from the inferior colliculus. We first demonstrate that neuron ensemble correlations are highly structured in both time and frequency and can be decoded to distinguish sounds. A neural classifier was developed that uses neural correlations statistics between frequency order sites as the principal response features. The sound identification performance of the neural classifier improved with the sound duration with an evidence accumulation time constant of ~1 second and accuracy rates approaching 90%. Next, we develop a probabilistic time-varying framework for measuring the nonstationary spectro-temporal correlation statistics between frequency organized channels in an auditory model. In a 13-category sound identification task, classification accuracy is consistently high (>80%), improving with soundduration and plateauing at ~ 1-3 seconds, mirroring human performance trends. The nonstationary short-term correlation statistics were more informative about the sound category than the time-average correlation statistics (84% vs. 73% accuracy). When tested independently, the spectral and temporal correlations between the model outputs achieved a similar level of performance and appear to contribute equally. These results outline a plausible neural code in which correlation statistics between neuron ensembles of different frequencies can be read-out to identify and distinguish acoustic categories.

Disclosures: M.A. Escabi: None. **M. Sadeghi:** None. **X. Zhai:** None. **I.H. Stevenson:** None.

Nanosymposium

450. Vision: Contrast, Form, and Color

Location: SDCC 33

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 450.08

Topic: D.07. Vision

Support: NIH DC015138

Title: Decoding sound texture identity via statistics of auditory neuron ensembles

Authors: *X. ZHAI[1], M. SADEGHI[1], F. KHATAMI[3], H. L. READ[2], I. STEVENSON[2], M. A. ESCABI[1]
[1]Electrical & Computer Engin., [2]Psychological Sci., Univ. of Connecticut, Storrs, CT;
[3]Neurolog. Surgery, Univ. of California, San Francisco, CA

Abstract: Although pure tones and noise stimuli have been used extensively in auditory neuroscience, there is growing evidence that the higher-order statistics of natural sounds play a key role in sound recognition and perception. Here we examine the responses of neuron ensembles in the principal auditory midbrain nucleus (inferior colliculus) of unanesthetized rabbits listening to natural sound textures using 16 and 32 channel neural recording arrays. Sound textures, such as running water, fire, wind, and speech babble have complex, but homogeneous, higher-order statistics, and are perceptually salient. Although it is well known that neural activity in peripheral and central auditory structures is modulated by statistics of sounds, such as the correlations between frequency channels or the sound modulation spectrum, how different statistics contribute to perception and recognition is unknown. Here we use texture synthesis (McDermott & Simoncelli 2011) to manipulate the different statistics of natural sound textures and explore their neural representation. Five texture sounds (running water, bird chorus, crackling fire, rattling snake and crowd noise) were manipulated by progressively incorporating statistical structure from the power spectrum, amplitude marginals, modulation spectrum, and the sound correlation structure. We demonstrate that correlated firing between frequency organized recording sites are modulated by each of the sound statistics tested and that these neural correlations can be used to decode and identify sound textures. Specifically, stimulus-driven spectro-temporal correlations were measured across the frequency organized recording array and a minimum distance classifier was applied to the ensemble correlation activity to identify the delivered sounds. For the original texture sounds, the classifier was able to decode and identify the original sound approaching near perfect accuracy (~90%). Spectral correlations between recording locations had slightly higher performance and were somewhat more informative than temporal correlations. The performance of the classifier improved as additional statistics were added to the synthetic variants and approached the performance for the original sounds when the full set of statistics was included (80% accuracy). Finally, the decoding accuracy improved with

sound duration with evidence accumulation times in the order of approximately 1 sec, mirroring human trends. These findings suggest that frequency-specific coordinated firing in auditory midbrain neuron ensembles provide a statistical signature that may contribute to perception and recognition of texture sounds.

Disclosures: X. Zhai: None. **M. Sadeghi:** None. **F. Khatami:** None. **H.L. Read:** None. **I. Stevenson:** None. **M.A. Escabi:** None.

Nanosymposium

450. Vision: Contrast, Form, and Color

Location: SDCC 33

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 450.09

Topic: D.07. Vision

Support: Sloan Research Fellowship
Whitehall Foundation (2017-12-73)
National Science Foundation (1736028)

Title: Sound texture evoked potentials encode acoustic complexity over time in avian auditory cortex

Authors: *S. S. CAIN[1], B. VOYTEK[2,3,4], T. Q. GENTNER[1,5,6,3]
[1]Psychology, [2]Cognitive Sci., [3]Neurosciences Grad. Program, [4]Halıcıoğlu Data Sci. Inst., [5]Neurobio. Section, Div. of Biol. Sci., [6]Kavli Inst. for Brain and Mind, Univ. of California San Diego, LA Jolla, CA

Abstract: How might the ascending auditory pathway derive complex object representations from the simple spectrotemporal decomposition provided by the cochlea? One possibility is that downstream neurons may be tuned to shared variation in their inputs, effectively forming receptive fields that are composites of simpler features (Kozlov & Gentner, 2016). In this view, more complex sounds have higher-order correlations of spectrotemporal features, and a sound is an object if this correlation structure varies over time - i.e., if it is nonstationary in its texture statistics (McDermott, Schemitsch, & Simoncelli, 2013). This leads to the hypothesis that simple spectral features are encoded in early components of neural responses, while complex acoustical features, such as modulations and cross-band correlations, are encoded later, as information accumulates. Our experiment required stimuli whose higher-order correlations do not change, so we constructed a library of over 120 synthetic textures, matched at 4 levels of correlation structure, 5 spectral profiles, and two durations. Using the European Starling (Sturnus vulgaris) as a model system due to its speech-like vocal communication, we previously demonstrated that single-unit firing rates in regions of avian auditory cortex are modulated by texture statistics. Here, we examine local field potential (LFP) in these multielectrode array recordings. If texture

computation is reflected in the LFP, then we expect: (1) early evoked potential deflections to be driven by a sound's spectrum, but not its complexity; (2) early offset-evoked potential deflections to be driven by the spectrum and complexity; and (3) late evoked potential features, such as oscillation amplitude, to be driven by a sound's complexity and duration, in addition to its spectrum. Each of these hypotheses was confirmed via linear mixed-effects model selection. Finally, we observed that the late oscillation amplitude is driven partially by lower trial-to-trial variability, meaning that higher-order stimulus correlation induces more precisely-timed LFP fluctuations. In sum, our characterization of evoked potential responses to sound textures provides evidence for how stationarity of stimulus features can be reflected at different timescales of neural integration.

Disclosures: S.S. Cain: None. **B. Voytek:** None. **T.Q. Gentner:** None.

Nanosymposium

450. Vision: Contrast, Form, and Color

Location: SDCC 33

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 450.10

Topic: D.07. Vision

Support: NIH Grant 1R01DC014739-01A1

Title: Illusory sound texture reveals statistical completion in auditory scene analysis

Authors: *R. MCWALTER, J. H. MCDERMOTT
MIT, Cambridge, MA

Abstract: Auditory scenes often contain multiple sound sources that vary in their temporal homogeneity. Sound textures, as arise from falling rain, galloping horses or swarming insects, lie on one end of this spectrum, having properties that remain relatively constant over modest time windows. Sound textures are well described by statistics measured from early auditory representations [McDermott & Simoncelli, 2011], and unlike speech and other non-stationary sounds are thought to be represented with statistics averaged over a multi-second window. However, little is known about their perception when present in auditory scenes containing other sources.

We investigated the perception of textures when they co-occur with other sounds that could intermittently mask the texture, making it inaudible for segments of time. We asked whether the auditory system infers the presence of background texture when it might be masked by such other sounds. We observed that when textures were interrupted by several seconds of noise, they were heard to continue during the noise provided it was sufficiently high in intensity. The effect is analogous to the well-known “continuity illusion” that occurs for tones interrupted by noise, but differs in lasting much longer than the effect for tones (~2 seconds vs. ~200 ms), and because

the extrapolated sound must be defined statistically due to the stochastic nature of texture. We next asked whether the representation of illusory texture is similar to that of actual texture.
In a second experiment listeners judged which of two textures was most similar to a reference texture [McWalter & McDermott, 2018]. The first texture underwent a change in statistics during its duration, while the second texture had fixed statistics. The experiment leveraged the fact that estimates of texture statistics are biased by several seconds of the stimulus history. We found that when interrupting noise was inserted prior to the statistic change, texture judgments were biased in a manner comparable to that if texture was actually present, suggesting that the illusory texture heard during the noise is represented like actual texture. When a silent gap was introduced prior to the noise, which disrupted the subjective impression of illusory texture, the bias was eliminated.
The results suggest that illusory sound textures can be heard over several seconds and appear to be represented similarly to actual texture, revealing new aspects of perceptual completion in auditory scenes.

Disclosures: R. McWalter: None. **J.H. McDermott:** None.

Nanosymposium

451. Respiration Control

Location: SDCC 23

Time: Tuesday, November 6, 2018, 8:00 AM - 9:30 AM

Presentation Number: 451.01

Topic: E.08. Respiratory Regulation

Support: NIH HL104101 (DKM)
NIH HL137094 (DKM)
Dravet Foundation AG180243

Title: Properties and function of CO2/H+-inhibited VGAT expressing neurons in the retrotrapezoid nucleus in control of breathing

Authors: *F. KUO[1], D. K. MULKEY[2]
[1]Univ. of Connecticut, Physiol. And Neurobio., Storrs, CT; [2]Dept. Physiol. and Neurobio., Univ. Connecticut, Storrs Manfld, CT

Abstract: A region of the ventral medullary surface called the retrotrapezoid nucleus (RTN) contains a population of Phox2b-expressing CO2/H+-activated neurons that function as respiratory chemoreceptors. Previous evidence also showed the RTN contains CO2/H+-inhibited neurons that may influence activity of RTN chemoreceptors. Consistent with this, preliminary recordings from RTN chemoreceptors in slices from neonatal mice suggest i) blockade of inhibitory receptors increased baseline activity and blunted the firing response to CO2/H+; and ii) exposure to high CO2 decreased the frequency of spontaneous inhibitory synaptic currents.

These results suggest CO2/H+-dependent disinhibition contributes to RTN chemoreceptor function. To identify the types of inhibitory neurons located in the RTN region, we isolated slices containing the region of interest from a VGAT reporter mouse model for subsequent immunolabeling using cell type specific antibodies. We found there are ~660 VGAT-expressing cells located ventral to the facial motor nucleus and within ~100 μm from the ventral surface per animal and 40% of them are immunoreactive for parvalbumin. Further, cell-attached recordings of firing activity show that 25% (N=21) of VGAT neurons in this region are inhibited by high 10% CO2, while 71% are CO2/H+-insensitive (N=60) and 4% were activated by CO2. To determine if VGAT neurons in the RTN influence breathing, we used a cre-dependent AAV delivery system to express inhibitory (Gi-coupled) DREADD receptors in VGAT neurons and measured respiratory activity before and after o.o1 mg/kg clozapine application. Following clozapine injection (SubQ), mice that express DREADD-Gi receptors in VGAT neurons near the RTN showed a reduced tidal volume response to CO2 but with no change in frequency or minute ventilation. Clozapine had no effect on breathing in mice injected with an empty virus (i.e., do not express DREADD receptors). These results support the possibly that CO2/H+-dependent disfacilitation contributes in part to RTN chemoreception.

Disclosures: F. Kuo: None. **D.K. Mulkey:** None.

Nanosymposium

451. Respiration Control

Location: SDCC 23

Time: Tuesday, November 6, 2018, 8:00 AM - 9:30 AM

Presentation Number: 451.02

Topic: E.08. Respiratory Regulation

Support: HL111598
HL69064

Title: Moderate acute hypoxia-induced phrenic long-term facilitation requires both cervical spinal $5HT_{2A}$ and $5HT_{2B}$ receptor activation

Authors: *A. TADJALLI, G. S. MITCHELL
McKnight Brain Inst., Univ. of Florida, Gainesville, FL

Abstract: Moderate acute intermittent hypoxia (mAIH) elicits a form of spinal respiratory motor plasticity known as phrenic long-term facilitation (pLTF); pLTF is a persistent enhancement of inspiratory phrenic nerve activity lasting > 1-hour post-hypoxia. Spinal serotonin receptor activation is necessary to initiate, but not maintain mAIH-induced pLTF; for example, mAIH-induced pLTF is blocked by intrathecal cervical spinal application of the serotonin-receptor antagonist methysergide maleate. However, methysergide is a broad-spectrum serotonin receptor antagonist that does not allow distinctions between the relative contributions of different 5-HT

receptor subtypes. mAIH-induced pLTF requires spinal ERK MAPK and NADPH oxidase activity, and both are linked to neuronal Gq protein signaling. Gq protein-coupled serotonin receptors include the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptor subtypes. Here, we determined the specific 5-HT_2 receptor subtypes contributing to mAIH-induced pLTF by using intrathecal pretreatment with subtype-selective antagonists. In anesthetized, vagotomized and mechanically ventilated adult rats, LTF was measured in both phrenic and hypoglossal nerve activity following mAIH (3, 5-min hypoxic episodes; PaO_2 = 35-50 mmHg, separated by 5-min intervals of control oxygen levels). Spinal 5-HT_{2C} receptor inhibition had no impact on pLTF expression, but mAIH-induced pLTF was abolished by antagonism of either 5-HT_{2A} or 5-HT_{2B} receptors. 5-HT_{2A} and 2_B receptor inhibition was confined to the spinal cord since hypoglossal LTF was unaffected by drug administration. Our results confirm that cervical spinal 5-HT receptor activation is required for pLTF; further, we demonstrate that concurrent activation of both 5-HT_{2A} and 2_B receptors is necessary. We suggest that 5-HT 2_A-2_B receptor synergy regulates the expression of plasticity in mammalian spinal respiratory motoneurons. The complex interplay between these receptor subtypes may suggest novel pharmacological targets to treat respiratory insufficiency with neuromuscular disease or injury.

Disclosures: A. Tadjalli: None. **G.S. Mitchell:** None.

Nanosymposium

451. Respiration Control

Location: SDCC 23

Time: Tuesday, November 6, 2018, 8:00 AM - 9:30 AM

Presentation Number: 451.03

Topic: E.08. Respiratory Regulation

Support: NIH Grant F32HL134207
NIH Grant R01HL126523

Title: A dynamic excitatory column shaped by inhibition generates inspiratory behaviors

Authors: *N. A. BAERTSCH[1], J. RAMIREZ[1,2]
[1]Ctr. for Integrative Brain Res., Seattle Children's Hosp., Seattle, WA; [2]Dept. of Neurosurg., Univ. of Washington, Seattle, WA

Abstract: Seminal experiments utilizing serial transverse sections through the medulla identified the core rhythmogenic region sufficient for breathing. This region, contained within a ~500µm thick transverse slice, was dubbed the preBötzinger Complex (preBötC). A subset of glutamatergic neurons (Dbx1 neurons) are required for rhythm generation in the preBotC; however, its borders are not easily defined anatomically or functionally. Dbx1 neurons are dispersed rostrocaudally throughout the medulla. If the preBötC is lesioned gradually, normal breathing (eupnea) can continue; whereas acute preBötC lesions eliminate eupnea, but

inspiration can persist in the form of gasps during hypoxia, suggesting areas outside the preBötC may reconfigure to generate inspiration. We hypothesized that inspiratory rhythm generating neurons are distributed along a rostrocaudal column within the medulla. To test this hypothesis, we developed a horizontal slice preparation to assess rhythmogenesis within the intact ventral medulla of neonatal mice. Compared to transverse preBötC slices, rhythmic population activity generated in horizontal slices was more robust with longer bursts and less irregularity in burst amplitude. Population activity maps in horizontal slices revealed a column of inspiratory activity, centered around the preBötC but extending ~1400µm rostrocaudally. Intracellular recordings identified rhythmically active excitatory (13) and inhibitory (11) neurons evenly distributed along the inspiratory column. Following blockade of synaptic inhibition, the extent of inspiratory activity was increased to ~2800µm, primarily in the rostral direction, and tonic or silent excitatory (4/6), but not inhibitory (0/3), neurons in the rostral column began to fire during inspiration. In transgenic horizontal slices, optogenetic stimulation of Dbx1 neurons from 1500µm rostral to 1000µm caudal of the preBötC evoked contralateral inspiratory bursts. Stimulation of Dbx1 neurons also evoked contralateral bursts in rostral transverse slices isolated from the preBötC. In vivo population recordings from the ventral medulla of adult urethane-anesthetized mice revealed that inspiratory activity in the rostral column was recruited and greatly increased in amplitude relative to the preBötC following removal of sensory feedback inhibition via vagal transection and also during hypoxia-induced gasping. Collectively, these results suggest that inspiratory behaviors originate from an excitatory column that is dynamically regulated by inhibition, a network configuration that may support robust, flexible, and adaptable breathing rhythms.

Disclosures: N.A. Baertsch: None. **J. Ramirez:** None.

Nanosymposium

451. Respiration Control

Location: SDCC 23

Time: Tuesday, November 6, 2018, 8:00 AM - 9:30 AM

Presentation Number: 451.04

Topic: E.08. Respiratory Regulation

Support: NIH grant HL074011
NIH grant HL28785

Title: Neuromedin B (NMB) neurons in the caudal nucleus of the solitary tract (NTS) are activated during hypoxia

Authors: *R. L. STORNETTA, G. M. P. R. SOUZA, S. B. G. ABBOTT, D. S. STORNETTA, P. G. GUYENET
Pharmacol., Univ. of Virginia, Charlottesville, VA

Abstract: Sighing frequency is increased by injecting NMB into the PreBötzinger complex (PBC) and reduced by lesions of NMB receptor-expressing PBC neurons (Li et al, 2016). NMB neurons located within the retrotrapezoid nucleus (RTN) innervate the PBC and could therefore be implicated in sigh generation. However, RTN neurons are not activated by hypoxia, a major trigger of sighs, and RTN ablation has no effect on hypoxia-induced sighing (Souza et al. 2018). Here we searched for an alternative source of NMB neurons that might be both activated during hypoxia and project to the PBC. A retrograde marker (fluorescent microbeads) was injected into the PBC in 3 mice. After 7-10 days mice were placed in whole body plethysmography chambers and subjected to 8% hypoxia for 60 min during which sighs were recorded. An additional 6 mice underwent the hypoxia protocol without fluorescent bead injection. Three control mice did not receive hypoxia. Adult mice of both sexes were used indiscriminately, sex differences were not examined. Mice were immediately killed and fixed. Brains were coded such that the experimenter counting brain sections was blinded. Fos and NMB transcripts were simultaneously identified in 30-micron brain sections using RNAScope in situ hybridization. Double-labeled neurons were found within caudal NTS in the area that receives carotid body chemoreceptor afferents. Such neurons were abundant in hypoxia-exposed mice (61 ± 8) but virtually absent in control mice (0.3 ± 0.3; data expressed as avg ± sem). Some NMB+/Fos+ neurons contained fluorescent microbeads. We conclude that the caudal NTS NMB neurons innervate the PBC and that these neurons could be implicated in sigh generation during hypoxia.

Disclosures: R.L. Stornetta: None. **G.M.P.R. Souza:** None. **S.B.G. Abbott:** None. **D.S. Stornetta:** None. **P.G. Guyenet:** None.

Nanosymposium

451. Respiration Control

Location: SDCC 23

Time: Tuesday, November 6, 2018, 8:00 AM - 9:30 AM

Presentation Number: 451.05

Topic: E.08. Respiratory Regulation

Support: FAPESP grant 2013/10484-5
CNPQ
BHF

Title: Role of synaptic inhibition and intrinsic properties of parafacial neurons for generation of active expiration in rats

Authors: D. J. A. MORAES[1], M. P. SILVA[2], *B. H. MACHADO[3], J. F. R. PATON[4], K. S. MAGALHÃES[1]
[1]Physiol., Sch. of Med. of Ribeirão Preto/USP, Ribeirão Preto, Brazil; [2]Sch. of Med. of Ribeirao Preto, Ribeirao Preto, Brazil; [3]Sch. Med. Ribeirao Preto, USP, Ribeirao Preto, Brazil; [4]Physiol., Fac. of Med. and Hlth. Sciences/University of Auckland, Auckland, New Zealand

Abstract: Hypercapnia produces active expiration in rats and the recruitment of phasic expiratory neurons located in the parafacial respiratory group (pFRG) of the ventral medullary brainstem. To understand the physiological role of pFRG oscillations and the specific conditions for their emergence, we evaluated the electrophysiological properties, neurochemical phenotype, respiratory modulated synaptic inputs and morphology of pFRG neurons, as well as the mechanisms of phasic burst generation during active expiration (hypercapnia) using whole cell recording in *in situ* preparations of rats. We also evaluated whether pFRG neurons are intrinsic $CO_2/[H^+]$ sensors. Post-synaptic GABAergic (34 ± 2.4 Hz; 145 ± 3.9 pA; n=10) and glycinergic inhibition (55 ± 2.9 Hz; 133 ± 4.9 pA; n=8) during both inspiration and expiration suppressed any phasic activity generation by pFRG found to be Phox2b-negative glutamatergic neurons. Hypercapnia induced phasic firing of these neurons that was associated with reduced glycinergic inhibition (12 ± 1.4 vs 55 ± 2.9 Hz; $p<0.05$) during expiration. These neuronal bursts were mediated by Ca^{2+} influx via low voltage activated Ca^{2+} channels, and by Ca^{2+} released from internal stores (endoplasmic reticulum). Following synaptic blockade, there was no evidence of either intrinsic bursting properties, mediated by persistent sodium current, or intrinsic $CO_2/[H^+]$ sensitivity in pFRG phasic neurons (n=15). Three-dimensional reconstruction of pFRG phasic neurons revealed three to five primary dendrites with dendritic trees extending laterally, but never with in a dorso-ventral orientation (n=7). These results suggest that synaptic inhibition and calcium oscillations are vital for generation of active expiration by pFRG phasic neurons in response to metabolic challenges in rats.

Disclosures: D.J.A. Moraes: None. **M.P. Silva:** None. **B.H. Machado:** None. **J.F.R. Paton:** None. **K.S. Magalhães:** None.

Nanosymposium

451. Respiration Control

Location: SDCC 23

Time: Tuesday, November 6, 2018, 8:00 AM - 9:30 AM

Presentation Number: 451.06

Topic: E.08. Respiratory Regulation

Support: ARC Discovery Project DP180101890
Rebecca Cooper RG172599

Title: Differential galanin expression by chemoreceptor neurons in mouse following long-term hypercapnia challenge: Evidence for regulation of galanin transmission

Authors: *A. S. DERELI, N. N. KUMAR
Univ. of New South Wales, Kensington, Australia

Abstract: Glutamatergic chemoreceptor neurons in the retrotrapezoid nucleus (RTN) are critical in mediating the central respiratory chemoreflex, the primary homeostatic mechanism used by

mammals to control blood carbon dioxide (CO_2) levels. RTN neurons extensively project to the ventral respiratory column (VRC), which is located in the ventrolateral medulla (VLM) and generates the rhythmic breathing pattern. Interestingly, 50% of RTN neurons also express the inducible neuropeptide transmitter galanin however the function of galanin in these neurons remains unknown. Previous studies have demonstrated that injection of galanin into the VRC induces apnoea by inhibiting breathing and ventilatory chemoreflex responses. We hypothesise that long-term exposure to elevated environmental CO_2 elicits chronic chemoreceptor stimulation, resulting in altered regulation of galanin expression in the RTN. Furthermore, galanin signalling from the RTN adjusts the central respiratory chemoreflex in the long-term (neuronal plasticity). We aimed first to determine the distribution of preprogalanin (ppGal) and galanin receptor 1 (GalR1) mRNA in the adult C57Bl6 mouse RTN and VLM respectively, using qualitative PCR and *in situ* hybridisation. The results showed that in the rostral brainstem, the distribution of galaninergic neurons was localised mainly to the RTN, inferior olive, paragiganticellular nucleus, nucleus of the solitary tract (NTS), and locus coeruleus (n=5). Also, the GalR1 positive neurons in the VLM were localised to nucleus ambiguous, VRC and A1 and C1 catecholaminergic populations (n=3). We next aimed to determine whether ppGal mRNA expression is altered in the RTN, VLM, NTS, or cerebellum, following hypercapnia challenge. Mice (n=5) were exposed either to room air (0% CO_2) or hypercapnia (5% CO_2, balance room air) for 3, 6 or 8 hours (short-term challenge) or continuously for 10 days (long-term challenge). Gene expression analysis was performed with quantitative PCR followed by one-way ANOVA. Our main findings were that ppGal mRNA levels increased by 62% in the RTN after long-term hypercapnia compared to room air ($p<0.001$). No changes in gene expression were observed in the RTN following short-term challenge. Conversely, ppGal expression in the VLM decreased by 32% following 6 hour short-term hypercapnia ($p<0.05$) however no changes were observed after long-term challenge. ppGal expression was not altered in the NTS and cerebellum for any of the challenges. Overall, long-term hypercapnia modulates galanin expression in the RTN suggesting a role for altered galaninergic transmission from RTN neurons during adaptation to long-term respiratory challenges.

Disclosures: A.S. Dereli: None. **N.N. Kumar:** None.

Nanosymposium

452. Brain Blood Flow and Blood Brain Barrier

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 452.01

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH T32 Pharmacology Training Grant

Title: Molecular plasticity of the blood-brain barrier in response to neural activity

Authors: *R. PULIDO[1], R. MUNJI[1], T. CHAN[1], C. QUIRK[2], G. WEINER[1], S. LEUTGEB[2], R. DANEMAN[1]
[1]Pharmacol., [2]Neurobio., Univ. of California San Diego, San Diego, CA

Abstract: The blood vessels that vascularize the central nervous system (CNS) exhibit a series of distinct properties from peripheral blood vessels. Most of these properties are possessed by brain endothelial cells, and compose the blood-brain barrier (BBB), stringently regulating what enters the CNS and thus tightly regulating the chemical microenvironment of the brain. Despite the dynamic nature of the CNS, the BBB has largely been studied in a static context. We know very little about how the cerebral vasculature and neural circuitry reciprocally interact on the molecular level to maintain brain homeostasis. The goal of this work is to identify (1) how neural activity can regulate cerebral vasculature gene expression (2) how functional changes in the cerebral vasculature can reciprocally regulate brain function, and (3) the mechanisms by which this interaction is mediated. We developed and optimized transgenic mice that express DREADDs in glutamatergic pyramidal neurons as a tool to manipulate neural activity *in vivo*. We then analyzed global gene expression in brain endothelial cells acutely isolated after activating or silencing activity. There were 2,500 brain endothelial genes that were regulated by activity, including 243 that were regulated in opposite directions in response to neuronal activation vs. neuronal silencing, suggesting that they are directly coupled to the amount of glutamatergic activity in the brain. Many of these neural activity-dependent vascular gene expression changes include changes in transport and metabolism suggesting that the BBB exhibits plasticity in response to neural activity thus inducing activity-dependent changes in the chemical environment of the brain. We are investigating how some of these functional changes in the BBB in response to neural activity reciprocally regulate brain function and behavior. We are also investigating the mechanisms by which neural activity regulates the cerebral vasculature. We have 3 major hypotheses that are not mutually exclusive: (1) through direct neuron-endothelial interaction, (2) through astrocytes, and (3) through endothelial mechanosensation of activity-dependent blood flow changes. We are testing these hypotheses with a variety of *in vitro* and *in vivo* techniques. This work provides a novel framework for how we should understand dynamic neurovascular interactions on the molecular level.

Disclosures: R. Pulido: None. **R. Munji:** None. **T. Chan:** None. **C. Quirk:** None. **G. Weiner:** None. **S. Leutgeb:** None. **R. Daneman:** None.

Nanosymposium

452. Brain Blood Flow and Blood Brain Barrier

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 452.02

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Title: Regional specializations of the blood-brain barrier is required for proper neuronal function and behavior

Authors: *M. BLANCHETTE[1], N. RUDERISCH[3], K. BAJC[4], R. DANEMAN[2]
[1]Pharmacology, Neurosciences, [2]UCSD, La Jolla, CA; [3]AbbVie, Boston, MA; [4]Univ. of California, San Diego (UCSD), La Jolla, CA

Abstract: The blood-brain barrier (BBB) consists of a set of properties expressed by brain endothelial cells (BEC), including a high expression of tight junction molecules and specific transporters, low rates of transcytosis and a low expression of leucocyte adhesion molecules. These properties allow a tight regulation of the ions, molecules and cells moving across the BBB. The specific transporters expressed at the BBB control the entrance of specific nutrients and signaling factors, mandatory for proper brain function. The different regions of the CNS are composed of different neuronal suggesting that different regions of the brain may need different levels nutrients, neurotransmitter precursors or signaling factors to achieve proper neuronal functions and behavior. However, it is not known if there are regional specializations of the BBB required to locally regulate brain properties. In order to determine if there is a regional specialization of the BBB, we performed RNA sequencing on BECs isolated from the forebrain, cerebellum and spinal cord. The different expression of BBB specific genes was compared between the three different isolated CNS regions. We found multiple genes and pathways enriched at the BBB in each CNS region. We are now exploring their function at the BBB and how they regulate proper brain function and behavior. These data suggest that the BBB has fundamental basic characteristics but also has certain heterogeneity to fulfill the specific needs of each brain regions. This opens up a whole new field of research as the BBB was thought to be specific properties displayed by all BECs.

Disclosures: N. Ruderisch: None. **K. Bajc:** None. **R. Daneman:** None.

Nanosymposium

452. Brain Blood Flow and Blood Brain Barrier

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 452.03

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Lundbeck Foundation Research Initiative on Brain Barriers

Title: Antibody affinity and valency impact uptake of transferrin receptor-targeted gold nanoparticles at the blood-brain barrier

Authors: *T. MOOS[1], K. B. JOHNSEN[1], M. BAK[2], P. J. KEMPEN[2], F. MELANDER[2], A. BURKHART[1], M. S. THOMSEN[1], M. S. NIELSEN[3], T. L. ANDRESEN[2]

[1]Aalborg Univ., Aalborg East, Denmark; [2]Dept. of Micro- and Nanotechnology, Technical University of Denmark, Denmark; [3]Dept. of Biomedicine, Aarhus University, Denmark

Abstract: The ability to treat invalidating neurological diseases is impeded by the presence of the blood-brain barrier (BBB), which inhibits the transport of most blood-borne substances into the brain parenchyma. Targeting the transferrin receptor (TfR) on the surface of brain capillaries has been a popular strategy to give a preferential accumulation of drugs or nanomedicines, but several aspects of this targeting strategy remain elusive. Here we report that TfR-targeted gold nanoparticles (AuNPs) can accumulate in brain capillaries and further transport across the BBB to enter the brain parenchyma. We find that the uptake capacity is significantly modulated by the affinity and valency of the AuNP-conjugated antibodies. Specifically, antibodies with high and low affinities mediate a low and intermediate uptake of AuNPs into the brain, respectively, whereas a monovalent (bi-specific) antibody improves the uptake capacity remarkably. We characterize this concept both in vitro using primary models of the BBB and in vivo using quantitative measurements of gold accumulation together with morphological assessments using light and transmission electron microscopy. Our findings indicate that monovalent ligands may be beneficial for obtaining transcytosis of TfR-targeted nanomedicines across the BBB, which is relevant for future design of nanomedicines for brain drug delivery.

Disclosures: T. Moos: None. **K.B. Johnsen:** None. **M. Bak:** None. **P.J. Kempen:** None. **F. Melander:** None. **A. Burkhart:** None. **M.S. Thomsen:** None. **M.S. Nielsen:** None. **T.L. Andresen:** None.

Nanosymposium

452. Brain Blood Flow and Blood Brain Barrier

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 452.04

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH 1R21DA038458
NIH 1R01NS102272
the Hope Center, and the Children's Discovery Institute
the McDonnell Center for Cellular and Molecular Neurobiology Postdoctoral Fellowship
NIH R01GM112007R
NIH R01NS084028
NIH R01NS043205

Title: Cell type specific profiling of alternative translation identifies novel protein isoforms in the mouse brain

Authors: *D. SAPKOTA[1], A. M. LAKE[1], W. YANG[1], C. YANG[1], J.-M. LEE[2], M. S. SANDS[3], H. WESSELING[5], A. GUISE[5], C. UNCU[5], J. A. STEEN[5], J. S. DALAL[5], J. D. DOUGHERTY[4]
[1]Genet., [2]Neurol., [3]Med., Washington Univ. in St. Louis, Saint Louis, MO; [4]Genet., Washington Univ. in St. Louis, St. Louis, MO; [5]Harvard Univ., Boston, MA

Abstract: Translation canonically begins at the annotated AUG initiation codon and terminates at the stop codon, generating one protein species per transcript. Some transcripts, however, may use alternative initiation sites that are upstream or downstream of the annotated AUG or sustain translation past their stop codon, generating multiple protein isoforms. Here we perform ribosome footprinting in vitro and in vivo to characterize these alternative translational events in the central nervous system. First, in neuron/glia mixed cultures we identify hundreds of neural transcripts that use alternative initiation sites and validate a subset of the corresponding protein isoforms by mass spectrometry. Many of these transcripts modulate their use of alternative initiation in response to KCl depolarization, indicating an activity-dependent regulation to this phenomenon. Next, we detect dozens of transcripts undergoing stop codon readthrough and generating novel C-terminal extended protein isoforms in vitro. Further, by coupling Translating Ribosome Affinity Purification to ribosome footprinting to enable cell-type specific analysis in vivo, we find that dozens of both neuronal and astrocytic transcripts undergo readthrough in the mouse brain. Functional analyses of one of these transcripts, Aqp4, reveal that readthrough confers a perivascular localization and that the canonical AQP4 and the readthrough-extended AQP4 are independently regulated in gliotic diseases. Our study demonstrates the extensive use of alternative translational events in the brain and suggests that the resulting protein isoforms may have functions in health and disease.

Disclosures: D. Sapkota: None. **A.M. Lake:** None. **W. Yang:** None. **C. Yang:** None. **J. Lee:** None. **M.S. Sands:** None. **H. Wesseling:** None. **A. Guise:** None. **C. Uncu:** None. **J.A. Steen:** None. **J.S. Dalal:** None. **J.D. Dougherty:** None.

Nanosymposium

452. Brain Blood Flow and Blood Brain Barrier

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 452.05

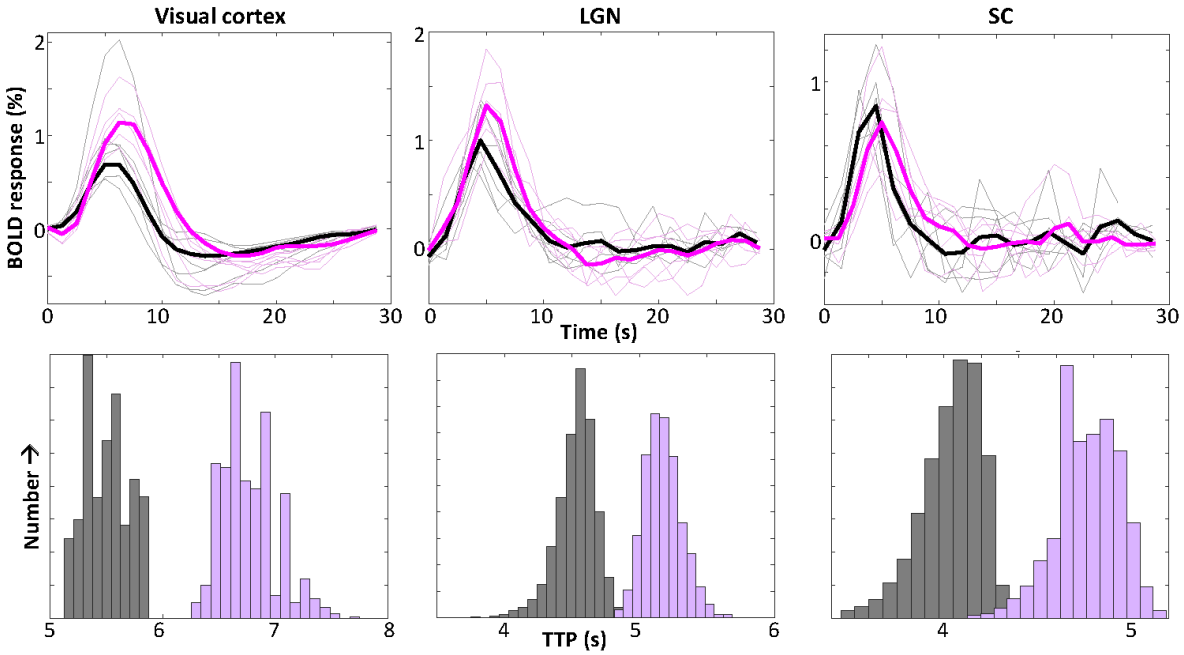
Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH R01NS095933
NIH K25HL131997

Title: Comparison of the BOLD hemodynamic response function at 3T and 9.4T

Authors: *D. RESS[1], J. KIM[1], A. J. TAYLOR[1], K. SCHEFFLER[2], G. HAGBERG[2], M. HIMMELBACH[2]
[1]Neurosci., Baylor Col. of Med., Houston, TX; [2]Univ. of Tübingen, Tübingen, Germany

Abstract: Ultra-high-field (UHF) functional magnetic resonance imaging (fMRI) has shown tremendous potential for advancing non-invasive neuroscience in the human brain. To enable analysis of fMRI data at UHF, we need to measure the hemodynamic response function (HRF) at UHF and compare it to that obtained at conventional field strengths. **Methods**: 2-s duration visual stimulation consisted of round regions of flickering colored dots that appear for 0.67 s, followed by a second differently colored region of dots at a second location, then a third. Subjects ($N = 6$) had to push a button with the color matching the dot display, a fast-paced and moderately demanding task. Each stimulus was followed by a 28-s period during which subjects performed a slow-paced color-detection task at fixation. 16 stimuli were presented per run, and 5 runs per session. fMRI data were collected using a point-spread-function-corrected EPI sequence that obtained 1.5-mm voxels at 3T, 1-mm at 9.4T, both at 1.25-s TR. We averaged the BOLD response across the 80 stimulus presentations to measure the HRF in visual cortex (V1), superior colliculus (SC), and lateral geniculate nucleus (LGN). **Results**: Good quality HRFs were measured in all regions at both field strengths (Figure, upper row). Cortical HRFs always had significant undershoots, but these were not observed in subcortical regions. No significant "initial dips" were observed. In V1, time-to-peak for 9.4T HRFs was significantly longer, 6.77±0.28 s, then was observed at 3T, 5.51±0.25 s (Figure, lower row). Subcortical HRFs were significantly faster than in cortex, but again 9.4T HRFs were slower (LGN 5.18±0.16 s, SC 4.77±0.22 s) than those measured at 3T (LGN 4.54±0.19 s, SC 4.08±0.19 s). **Conclusions**: HRFs recorded at UHF exhibit significantly slower temporal dynamics than at 3T. Also, sub-cortical HRFs are significantly faster than those observed in cortex, with minimal undershoot. Analysis of UHF and sub-cortical fMRI needs to take these differences into account to permit accurate linear analysis of experimental results.



Upper row shows HRFs obtained from areas V1, LGN, SC from 6 subjects averaging left & right. 3T data in gray/black; 9.4T data in magenta; thick lines show averages across subjects. Lower row shows time-to-peak distributions from bootstrapping across subjects; timing is significantly faster at 3T, and subcortical HRFs are significantly faster than in visual cortex.

Disclosures: D. Ress: None. **J. Kim:** None. **A.J. Taylor:** None. **K. Scheffler:** None. **G. Hagberg:** None. **M. Himmelbach:** None.

Nanosymposium

452. Brain Blood Flow and Blood Brain Barrier

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 452.06

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant AG044467
Taub Institute MRI platform seed grant

Title: The timing and shape of the task-evoked negative BOLD response in the default mode network regions

Authors: *Q. R. RAZLIGHI, A. SEDAGHAT, D. B. PARKER
Biomed. Engin., Columbia Univ., New York, NY

Abstract: Introduction
The significance of task-evoked negative BOLD response (deactivation) in the Default mode

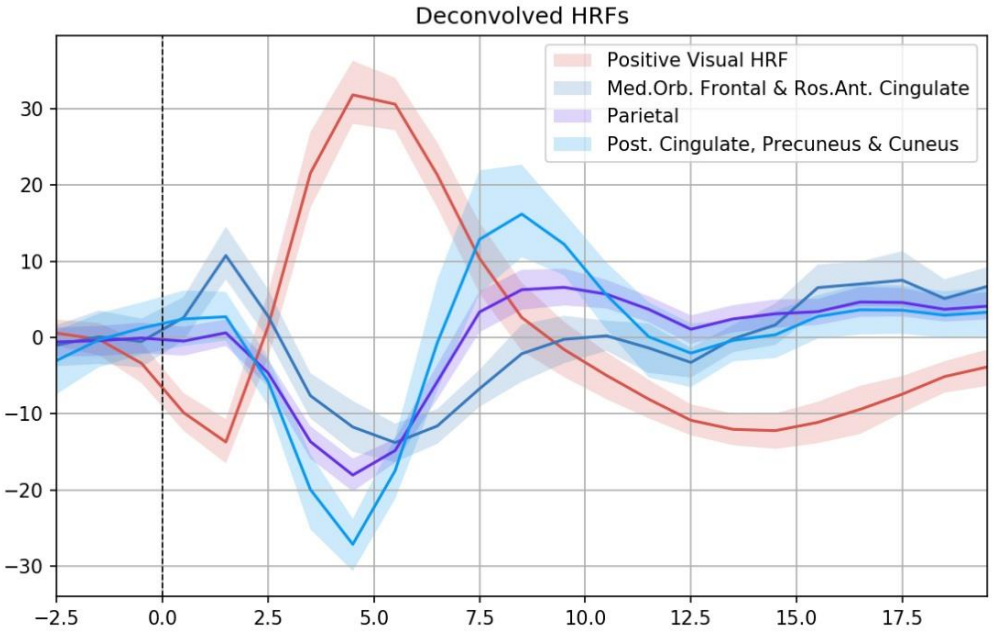
network (DMN) regions has been the focus of research in many recent studies in both healthy and clinical population. However, while there is a consensus in the field about the shape, timing, and characteristics of hemodynamic response function (HRF) for positive BOLD, little is known about the HRF for negative BOLD. All existing studies, to our knowledge, conveniently assume the same shape, timing and characteristics for negative BOLD HRF. In this work, we empirically examine the shape and timing of the negative BOLD response for a simple visual-motor task.

Results

Figure 1 shows the negative BOLD HRF extracted from different nodes of the DMN, and the positive BOLD HRF from visual cortex, in 30 young and healthy subjects performing simple visual-motor task. As seen in this figure, the shape and timing of the extracted HRFs are significantly different not only from the positive BOLD HRF but also from each other. While the HRF extracted from posterior-cingulate and cuneus regions resembles a flipped version of the positive HRF initially, it doesn't seems to have the prolong (about 15 sec) undershoot. The angular-gyrus and medial-orbito-frontal HRFs have a 2 second delay in the beginning and then start to fall below the baseline. However, both of them have a quick return to baseline (less than 5 sec) and relatively a small and fast overshoot (around 7 sec).

Discussion

The difference in the timing and shape of the HRF extracted from negative BOLD may suggest different neural/neurovascular mechanisms that underlies the negative BOLD response. The fact that HRF extracted from different nodes of the DMN may also suggest that each node of the DMN has different processes that give rise to negative BOLD response. Finally, we should emphasize that the HRF extraction methods are often based on an underlying linearity assumption. While rough linearity has been shown for positive BOLD for stimulus duration of 2~6 seconds, farther work is needed to validate the linearity assumption for negative BOLD response.



Disclosures: Q.R. Razlighi: None. **A. Sedaghat:** None. **D.B. Parker:** None.

Nanosymposium

452. Brain Blood Flow and Blood Brain Barrier

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 452.07

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: RG-1507-04951

Title: Neural-vascular uncoupling explains cognitive slowing in multiple sclerosis

Authors: *D. SIVAKOLUNDU[1], K. WEST[2], D. ABDELKARIM[2], M. D. ZUPPICHINI[2], M. P. TURNER[3], Y. ZHAO[4], J. HART[5], H. LU[6], D. OKUDA[7], B. P. RYPMA[3]
[1]Dept. of Biol. Sci., [2]Sch. of Behavioral and Brain Sci., Univ. of Texas at Dallas, Dallas, TX; [3]Sch. of Behavioral and Brain Sci., Univ. of Texas at Dallas, Richardson, TX; [4]Sch. of Behavioral and Brain Sci., Univ. of Texas At Dallas, Richardson, TX; [5]Sch. of Behavioral and Brain Sci., Univ. of Texas At Dallas, Dallas, TX; [6]Dept. of Radiology, Johns Hopkins Univ., Baltimore, MD; [7]UT Southwestern Med. Ctr., Dallas, TX

Abstract: Cognitive slowing occurs in 70% of multiple sclerosis patients (MSP). While MSP-related symptomology is idiosyncratic and intermittent, cognitive slowing is sustained and progressive. The neural mechanisms of this slowing are unknown. Neural-vascular coupling, acute localized blood flow increases following neural activity, is essential for efficient cognition. We hypothesized that neural-vascular uncoupling contributes to cognitive slowing in MSP. We isolated the neural, glial, and, vascular components of the neural-vascular coupling system to assess their contributions to MSP-related cognitive slowing. MSP and healthy controls (HC) were scanned on a Philips 3T scanner. A dual-echo calibrated functional MRI sequence permitted near-simultaneous measurement of cerebral blood flow (CBF) and blood-oxygen level dependent signal (BOLD). Participants periodically inhaled room-air and carbogen for calculation of cerebral metabolic rate of oxygen ($CMRO_2$). They then performed a block-design visual task in which radial checkerboards periodically flickered at 6Hz. Data were analyzed to obtain task- and carbogen-evoked changes in BOLD, CBF and $CMRO_2$. Cerebrovascular reactivity of arteries (CVR_a) and veins (CVR_v) were calculated as CBF and BOLD increases per unit increase in end-tidal CO_2. We compared slow- and fast- MSP and HC. Slow MSP had a simple reaction time (RT) higher than 1.5 SD from the mean HC RT. Visual task-evoked BOLD was lower in slow MSP (M=2.02, SE=0.2) compared to fast MSP (2.46, 0.2) and HC (2.76, 0.19, $p<0.05$). CBF was lower in slow MSP ($p<0.05$). No differences in $CMRO_2$ were observed between groups. Neural-vascular coupling ratio ($CBF/CMRO_2$) was lower in slow (1.61, 0.06) than fast MSP (1.76, 0.09, $p<0.05$). These results suggest that neural-vascular uncoupling contributes to cognitive slowing in MS. CVR_a was higher in fast MSP (11.85, 1.45) than HC

(8.8, 0.54, $p<0.05$). Slow MSP had similar CVR_a compared to HC. CVR_v was similar to HC in fast MSP and lower in slow MSP ($p<0.05$). These results suggest that fast MSP RTs are supported by increased arterial blood flow compared to slow MSP. In slow MSP, reduced venous compliance also contributed to cognitive slowing. Because carbogen-evoked BOLD and CBF changes occurred at an isometabolic state, in HC, CVR_a increased proportionally with increases in CVR_v. Changes in CVR_a with CVR_v (arterio-venous compliance; AVC) was positive in HC and fast MSP. AVC was lower in fast MSP compared to HC. AVC was negative in slow MSP compared to fast MSP and HC. AVC might underlie MS-related cognitive slowing. Neural-vascular uncoupling following impaired AVC forms the physiologic basis of MS-related cognitive slowing.

Disclosures: D. Sivakolundu: None. **K. West:** None. **D. Abdelkarim:** None. **M.D. Zuppichini:** None. **M.P. Turner:** None. **Y. Zhao:** None. **J. Hart:** None. **H. Lu:** None. **D. Okuda:** F. Consulting Fees (e.g., advisory boards); Biogen, Genzyme, Teva. **B.P. Rypma:** None.

Nanosymposium

452. Brain Blood Flow and Blood Brain Barrier

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 452.08

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: National Centre for Replacement, Refinement, and Reduction of Animals in Research (NC3Rs) NC/P001173/1
Wellcome Trust and the Royal Society (Grant Number 105586/Z/14/Z)
British Heart Foundation Infrastructure Award IG/15/1/31328
University of Sheffield NICAD PhD studentship

Title: A novel zebrafish model of neurovascular coupling reveals sodium nitroprusside reverses hyperglycaemia-induced neurovascular dysfunction

Authors: *K. CHHABRIA[1,2], K. PLANT[2], O. BANDMANN[3], R. N. WILKINSON[2], C. J. MARTIN[4], E. KUGLER[2], P. A. ARMITAGE[2], P. L. M. SANTOSCOY[5], V. T. CUNLIFFE[5], C. HOWARTH[4], T. J. A. CHICO[2]
[2]Dept. of Infection, Immunity and Cardiovasc. Dis., [3]Dept. of Neurosci., [4]Dept. of Psychology, [5]Dept. of Biomed. Sci., [1]Univ. of Sheffield, Sheffield, United Kingdom

Abstract: To maintain brain function, neural activity increases local blood flow by neurovascular coupling (NVC). Diabetes is increasingly recognised as a risk factor for neurological dysfunction including dementia, and impaired nitric oxide (NO) production underlies many diabetic vascular complications.

Rodent models of NVC are highly invasive but no non-mammalian species are known to exhibit NVC. We therefore developed a non-invasive zebrafish model allowing non-invasive quantification of cerebrovascular anatomy, neural activation, and cerebral vessel haemodynamics in response to sensory stimulus and examined the effect of hyperglycemia on cerebrovascular patterning and NVC.
We used (*Tg(nbt:GCaMP3;kdrl:mcherry;gata1:DsRED)*) zebrafish expressing fluorescent proteins in endothelial cells, erythrocytes and a neuronal calcium (*Ca*) sensitive reporter (GCaMP3). Non-anaesthetised larvae were mounted in a lightsheet microscope. We then quantified cerebrovascular anatomy, neuronal activation and cerebral blood flow before, during and after visual stimulus (8s light). To examine the effect of glucose ± a NO donor we incubated larvae in 20mM glucose or mannitol control between 5-9d post fertilization (dpf) ± 0.1mM sodium nitroprusside (SNP) between 8-9 dpf.
Visual stimulus significantly increased neuronal *Ca* peak frequency in the optic tectum and ΔRBC speed (RBC speed during stimulus minus baseline) specifically in tectal blood vessels, demonstrating that zebrafish do exhibit NVC.
Exposure to 20mM glucose between 5-9dpf did not affect neuronal *Ca* peak frequency in response to visual stimulus but significantly reduced ΔRBC speed (glucose: 9±4 μm/s, mannitol: 41±0.6 μm/s, p=0.0008, n=25/group). Glucose exposure also significantly reduced tectal vessel branchpoints (glucose:10.8±0.9, mannitol:19.5±1.7, p<0.0001) and total tectal vascular length (glucose:578±32μm, mannitol:833±66μm, p=0.0013). Co-incubation with SNP for 24h from 8-9dpf had no effect when co-administered with mannitol but completely reversed all the negative effects of 120h glucose exposure.
We have established the first non-mammalian model of NVC and reveal a potential strategy to offset the effects of hyperglycemia on cerebrovascular anatomy and neurovascular function.

Disclosures: K. Chhabria: None. **K. Plant:** None. **O. Bandmann:** None. **R.N. Wilkinson:** None. **C.J. Martin:** None. **E. Kugler:** None. **P.A. Armitage:** None. **P.L.M. Santoscoy:** None. **V.T. Cunliffe:** None. **C. Howarth:** None. **T.J.A. Chico:** None.

Nanosymposium

452. Brain Blood Flow and Blood Brain Barrier

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 452.09

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Grant-in Aid for Scientific Research (C) No. 16K01841

Title: Redistribution of cerebral blood flow evoked by aerobic exercise is attributable both to neuro-vascular coupling and cerebral autoregulation: A study using PET

Authors: *M. HIURA[1], T. NARIAI[2,3], M. SAKATA[3], A. MUTA[2], K. ISHIBASHI[3], K. WAGATSUMA[3], T. TAGO[3], J. TOYOHARA[3], K. ISHII[3], T. MAEHARA[2], Y. KATAYAMA[1]
[1]Ctr. for Brain and Hlth. Sci., Aomori Univ., Aomori-Shi, Japan; [2]Neurosurg., Tokyo Med. and Dent. Univ., Tokyo, Japan; [3]Tokyo Metro Inst. Gerontology, Tokyo, Japan

Abstract: [Background] Previous PET studies demonstrated that global cerebral blood flow (gCBF) increased only at the onset of aerobic exercise but regional CBF (rCBF) fluctuated throughout the course. While rCBF is regulated via neuro-vascular coupling, cerebral autoregulation (CA) may also play a role if blood pressure (BP) changes immediately. From this aspect, aerobic exercise may cause changes in rCBF due to these two regulating factors. To identify process of CA during aerobic exercise, we examined responses of rCBF and BP. Provided that acute changes in BP and cardiac output evoked by exercise would cause changes in CBF via CA, we analyzed rCBF with absolute values and normalized model, in which gCBF was assumed to stay constant. **[Methods]** Twelve healthy young males performed 20 min cycling exercise and rCBF were measured using oxygen-15-labeled water ($H_2{}^{15}O$) and PET (Discovery PET/CT, GE) at the baseline (Rest), onset (Ex1), continued phase (Ex2) and 10 and 20 min after the cessation of exercise (Post 10 and 20). Heart rate (HR) and mean blood pressure (MBP) were monitored. With the accumulated image and the measured arterial input function, rCBF was calculated using the autoradiographic method. The image data were analyzed using SPM and Dr. View software**. [Results]** During exercise HR and MBP increased to 119 ± 8 bpm and 104 ± 12 mmHg, respectively, at the endpoint of exercise. At Post 10, MBP significantly decreased compared to Rest, from 90 ± 8 to 86 ± 10 mmHg ($P < 0.05$). By analysis with absolute values, gCBF increased by 10.5 % ($P < 0.05$) only at Ex1 and did not change elsewhere compared with Rest. Compared with Ex2, rCBF increased at Ex1 in the frontal lobes, insular cortex and hippocampus (P<0.0005, uncorrected). Following exercise rCBF decreased in the frontal lobe at Ex1 (P<0.005, uncorrected). By analysis with a normalized model, where normalization of global CBF for each subject to 50 mL/100 g/min with proportional scaling, areas of increased rCBF compared with Rest were similar between Ex1 and Ex2. At Post 20, rCBF increased in the anterior and posterior cingulate gyrus and decreased in the frontal cortex compared with Rest (P<0.001, uncorrected). **[Discussion]** The present study suggests that CA may be attained at Ex2. Those areas of increased rCBF at Ex1 would be regarded as 1) regions of neuro-vascular coupling specific to exercise and 2) central autonomic regions which regulate surpassed blood flow to brain. Although we could not identify whether post exercise hypotension might cause decreased rCBF or not, redistribution of rCBF following exercise would be associated with beneficial alterations in brain function such as exercise-induced positive change in mood status.

Disclosures: M. Hiura: None. **T. Nariai:** None. **M. Sakata:** None. **A. Muta:** None. **K. Ishibashi:** None. **K. Wagatsuma:** None. **T. Tago:** None. **J. Toyohara:** None. **K. Ishii:** None. **T. Maehara:** None. **Y. Katayama:** None.

Nanosymposium

452. Brain Blood Flow and Blood Brain Barrier

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 8:00 AM - 10:30 AM

Presentation Number: 452.10

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Lundbeck Foundation
NOVO-Nordisk Foundation
Danish Medical Research Council
the NORDEA Foundation

Title: Stimulation-induced rises in cerebral blood flow and local capillary vasoconstriction depend on conducted vascular responses

Authors: *C. CAI[1], J. C. FORDSMANN[2], S. H. JENSEN[3], B. GESSLEIN[6], M. LØNSTRUP[4], S. A. ZAMBACH[4], B. O. HALD[4], B. BRODIN[3], M. J. LAURITZEN[5]
[1]Kobenhavn N, Denmark; [2]Univ. of Copenhagen/In, Kobenhavn N, Denmark; [3]Dept. of Pharm., [4]Dept. of Neurosci., [5]Univ. of Copenhagen, Copenhagen, Denmark; [6]Dept. of Neurosci. and Pharmacol., Copenhagen N, Denmark

Abstract: **Introduction** Functional neuroimaging is based on the coupling between neuronal activity and the accompanying changes in cerebral blood flow (CBF) and metabolism. However, the relationship between CBF and the events at the level of the penetrating arterioles and capillaries is not well established. Recent findings suggest an active role for capillaries in CBF control, and pericytes on capillaries may be major regulators of CBF and initiators of functional imaging signals. Our study examined: 1) whether activity-dependent rises in synaptic activity dilate, and ATP constricts, capillaries of all branching orders or only capillaries close to the penetrating arteriole; 2) whether capillaries exhibit conducted vascular responses (CVRs) similar to pial arterioles. **Methods** We used *in vivo* two-photon microscopy for imaging of the vasculature in the whisker-barrel cortex of anesthetized mice expressing DsRed in pericytes under the NG2 promotor. FITC-dextran was administered to label the blood plasma. We conducted fast and repetitive volume scanning (4D scanning, 1 s/stack, 10 planes/stack) at penetrating arteriole and near-arteriole capillaries. Multiple locations of vessel diameter changes were studied in response to 1) whisker pad stimulation; 2) local pipette puffing of 1mM ATP in proximity. The obtained 4D videos were then flattened by maximal intensity projection and analyzed by active contour algorithm for precise measurement of vessel diameters. **Results** We demonstrated that stimulation-evoked rises in synaptic activity in mouse somatosensory cortex evokes capillary dilation that mostly started at 1st or 2nd order capillary, from where it propagated up- and downstream at 5-20 μm/s. In the post-stimulation phase of vaso-responses, constriction followed a similar pattern. The gliotransmitter ATP applied by micro-pipette puffing onto 1st and

2nd order capillaries induced dilation followed by constriction that also propagated at 5-20 µm/s. Control puffing of aCSF excluded effect of mechanical stimulation. ATP-induced capillary constriction was blocked by purinergic type 2 receptors. Pipette puffing of both P2X and P2Y receptors lead to similar vessel response. We also demonstrated that perfusion of ATP increased intracellular Ca^{2+} and induced constriction of cultured cerebral pericytes. At last, ischemia led to instant and most severe constriction at 1st and 2nd order capillaries, which co-localized with pericyte soma. **Conclusion** Our data support the concept of an active role for pericytes in cerebrovascular control. CVRs in capillaries may be a novel modulator of cerebrovascular function and of functional neuroimaging signals.

Disclosures: C. Cai: None. **J.C. Fordsmann:** None. **S.H. Jensen:** None. **B. Gesslein:** None. **M. Lønstrup:** None. **S.A. Zambach:** None. **B.O. Hald:** None. **B. Brodin:** None. **M.J. Lauritzen:** None.

Nanosymposium

453. New Cortical and Subcortical Circuits for Food Reward

Location: SDCC 2

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 453.01

Topic: G.02. Motivation

Support: JPB Foundation
NIH F32 DK107077

Title: An insular cortex --> central amygdala circuit controls non-homeostatic feeding in mice in response to associative learning of contextual cues

Authors: *S. A. STERN[1,2], E. P. AZEVEDO[2], K. R. DOERIG[2], J. M. FRIEDMAN[3,2]
[1]Dept. of Mol. Genet., [2]Rockefeller Univ., New York, NY; [3]Howard Hughes Med. Inst., Chevy Chase, MD

Abstract: Feeding is a complex motivated behavior that is controlled not just by metabolic and homeostatic factors, but also by environmental factors such as emotion and the hedonic nature of the food itself. Yet, little is known about how brain regions involved in cognition and emotion might contribute to overeating, and therefore, obesity. Recently, we developed and validated a simple and rapid context-induced feeding (ctx-IF) task in which cues associated with food availability can later lead to increased food consumption in sated mice (*Stern et al 2018*). We have used this paradigm to map brain regions that are activated during Ctx-IF and found that the insular cortex and central amygdala, among others, are activated in sated mice following exposure to cues denoting the availability of food. The IC is a region critical for taste perception that has recently been shown to be involved in cue-food associations (Kusumoto-Yoshida I 2015) and taste memory. Here, we find that the insular cortex, and specifically, the IC ◊ CeA

projection, is required for overconsumption in the Ctx-IF task. To probe the molecular connectivity of these two regions, we used the recently developed method, retro-TRAP (Retrograde - Translating Ribosome Affinity Purification), to profile projections from the IC to the CeA (*Ekstrand 2014*). We injected the retrograde canine adenovirus, CAV-GFP, into the CeA of SYN-NBL10 mice which contain anti-GFP-tagged ribosomal subunit proteins. Two weeks later, we dissected out the insular cortex and immunoprecipitated GFP, therefore pulling down polysome-bound, translating mRNAs of neurons that project to CeA. High throughput RNA-sequencing has enabled us to identify markers for projections from IC to CeA and therefore to investigate the role of these projections in the non-homeostatic regulation of feeding behavior.

Disclosures: S.A. Stern: None. **E.P. Azevedo:** None. **K.R. Doerig:** None. **J.M. Friedman:** None.

Nanosymposium

453. New Cortical and Subcortical Circuits for Food Reward

Location: SDCC 2

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 453.02

Topic: G.02. Motivation

Support: German Research Foundation in the Transregional Collaborative Research Center 134
Advanced Postdoctoral Mobility fellowship from the Swiss National Science Foundation (P300P1_151174/1)

Title: Supra-additive effects of combining fat and carbohydrate on food reward

Authors: *A. G. DIFELICEANTONIO[1], G. COPPIN[2], L. RIGOUX[3], S. EDWIN THANARAJAH[4], A. DAGHER[5], M. TITTGEMEYER[3], D. M. SMALL[1]
[1]Yale Univ. Sch. of Med., New Haven, CT; [2]Swiss Ctr. for Affective Sci., Geneca, Switzerland; [3]MPI For Metabolism Res., Cologne, Germany; [4]Univerisity Hosp. of Cologne, Köln, Germany; [5]McGill Univ., Montreal, QC, Canada

Abstract: Post-ingestive signals conveying information about the nutritive properties of food are critical for regulating ingestive behavior. Here, using an auction task concomitant to fMRI scanning, we demonstrate that participants are willing to pay more for fat+carbohydrate compared to equally familiar, liked, and caloric fat or carbohydrate foods and that this potentiated reward is associated with response in areas critical for reward valuation including the dorsal striatum and mediodorsal thalamus. We also show that individuals are better able to estimate the energy density of fat compared to carbohydrate and fat+carbohydrate foods; an effect associated with functional connectivity between visual (fusiform gyrus) and valuation (vmPFC) areas. These results provide the first demonstration that foods high in fat and

carbohydrate are, calorie for calorie, valued more than foods containing only fat or carbohydrate and that this effect is associated with greater recruitment of central reward circuits.

Disclosures: A.G. DiFeliceantonio: None. **G. Coppin:** None. **L. Rigoux:** None. **S. Edwin Thanarajah:** None. **A. Dagher:** None. **M. Tittgemeyer:** None. **D.M. Small:** None.

Nanosymposium

453. New Cortical and Subcortical Circuits for Food Reward

Location: SDCC 2

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 453.03

Topic: G.02. Motivation

Support: HFSP
KAVLI NSI
JPB
HHMI

Title: Encoding of an engram for food location by satiety-promoting Drd2 hippocampal neurons

Authors: *E. AZEVEDO[1], L. POMERANZ[4], M. SCHNEEBERGER PANE[2], J. CHENG[5], S. STERN[3], P. GREENGARD[3], J. FRIEDMAN[6]
[1]Friedman Lab., [2]Mol. genetics, [3]The Rockefeller Univ., New York, NY; [4]Dept. of Mol. Genet., [5]Rockefeller Univ., New York, NY; [6]Rockefeller Univ/ HHMI, New York, NY

Abstract: Obesity is a serious illness affecting more than one-third of the adult population, and alarmingly, more than 17% of children in the USA. Obesity is associated with high mortality and increased risk of developing other medical conditions, such as diabetes. To fight obesity, the gain of knowledge on how neural circuits control feeding is vital. There are about two decades of evidence suggesting that the hippocampus, an important brain region associated with episodic memory, may control feeding. However, the mechanism by which hippocampal neurons modulate feeding and its underlying circuit remains unclear. We reasoned that the hippocampus must respond to food in a similar manner as time cells and place cells are activated by temporal or spatial changes respectively. We believe that visual, gustatory or odorant appetitive cues may be able to activate specific hippocampal cells in order to create a food engram and thus, communicate with existing feeding circuits. Thus, the molecular identification of a specific ensemble that fires in response to food or eating would enable us to perform a functional analysis of the high-order circuit that modulates energy intake by the hippocampus. Here, we report the unbiased description of a molecularly defined neuronal population within the hippocampus that expresses dopamine 2 receptor (D2R) and that is activated by appetitive cues and energy states. The selective inhibition or activation of D2R neurons using chemogenetics is sufficient to induce changes in food intake. Moreover, projection-specific manipulations of these neuronal

connections using optogenetics reveal a novel extrahippocampal circuitry that project to the septal and cholinergic basal forebrain and control feeding behavior. These findings describe a previously unidentified role for hilar mossy cells within the hippocampus and shed light on how food cues can suppress feeding through activating a specific hilar mossy cells-septal circuitry.

Disclosures: E. Azevedo: None. **L. Pomeranz:** None. **M. Schneeberger Pane:** None. **J. Cheng:** None. **S. Stern:** None. **P. Greengard:** None. **J. Friedman:** None.

Nanosymposium

453. New Cortical and Subcortical Circuits for Food Reward

Location: SDCC 2

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 453.04

Topic: G.02. Motivation

Support: NIH MH109441

Title: Deciphering hippocampus to septum to hypothalamus feeding circuits

Authors: *Y. YANG
Albert Einstein Col. of Med., Bronx, NY

Abstract: Homeostatic and emotional aspects of food intake are coordinated by hormonal interactions with multiple neuronal cell types. However, the cellular and circuit mechanisms governing stress-induced anorexia remain largely underexplored. By using the cell-type-selectivity of genetic methods, circuit mapping, and behavior assays, we find that septum, a brain region integrating information encoded in higher-order brain areas, relays suppressive appetitive information encoded in the ventral hippocampus (vHipp) to hypothalamus, an area involved in homeostatic and hedonic control of energy states. For instance, we find that ventral hippocampus, a brain region involved in emotion and anxiety, activates septum GABAergic and glutamatergic neurons via excitatory glutamatergic projections, which subsequently project to lateral hypothalamus (LH) and paraventricular nucleus of hypothalamus (PVH). Collectively, our data demonstrate novel feeding circuits, which probably mediate stress-induced anorexia, serving as therapeutic targets for the treatment of emotion-related eating disorders

Disclosures: Y. Yang: None.

Nanosymposium

453. New Cortical and Subcortical Circuits for Food Reward

Location: SDCC 2

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 453.05

Topic: G.02. Motivation

Support: NARSAD Young Investigator Award

Title: A novel micro extended amygdala neural circuits for feeding regulation

Authors: *H. CAI[1], Y. WANG[2], J. KIM[2]
[1]Neurosci., [2]Univ. of Arizona, Tucson, AZ

Abstract: The extended amygdala including the central amygdala (CEA) and the bed nucleus of the stria terminalis (BNST) is a key mediator of diverse emotional and motivational behaviors. Recent studies have identified several subpopulations of CEA neurons that play important roles in regulating food intake. However, the type of BNST neurons and the BNST neural circuits that regulate food intake are still poorly understood. Even less is known about the relationship between the BNST neural circuits and the canonical hypothalamus feeding circuits, which comprise neurons in the lateral hypothalamus (LH), paraventricular hypothalamus (PVH), and arcuate nucleus (ARC). Here we describe a novel micro BNST neural circuits that regulate food intake. We found that activation of a specific type of neurons in the oval region of BNST suppresses feeding whereas silencing these neurons increases the amount of food intake. We also dissected the BNST neural circuits that regulate food intake and established their relationship to the well-established hypothalamus feeding circuits.

Disclosures: H. Cai: None. **Y. Wang:** None. **J. Kim:** None.

Nanosymposium

453. New Cortical and Subcortical Circuits for Food Reward

Location: SDCC 2

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 453.06

Topic: G.02. Motivation

Support: NIH Grant F32DK112589
NIH DP2 DK105570
NIH R01 DK109930

McKnight Scholar Award
Pew Scholar Award
Klarman Family Foundation

Title: Hunger modulates basolateral amygdala through dopamine acting on local interneurons

Authors: *A. LUTAS, O. ALTURKISTANI, C. CARTY, V. DIAZ, A. SUGDEN, M. ANDERMANN
Endocrinol., Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: Separate neuronal ensembles in the basolateral amygdala (BLA) represent learned visual cues that are associated with salient positive and negative outcomes. Using 2-photon calcium imaging of BLA excitatory neuron activity in awake behaving mice, we show that BLA neurons that respond to a food-predicting visual cue during hunger are significantly less responsive when mice are sated. In contrast, BLA neurons activated by a punishment-predicting cue are similarly responsive in hungry and sated mice. We hypothesized that a hunger-state dependent dopamine signal from the ventral tegmental area (DA^{VTA}) to the BLA could be important for the specific modulation of food cue responses by hunger and satiety. Using fiber photometry, we recorded calcium activity of DA^{VTA} axons in BLA ($DA^{VTA->BLA}$) in response to a food cue and a punishment cue in hungry and sated mice. $DA^{VTA->BLA}$ showed increased activity in response to both food-predicting and punishment-predicting cues, unlike DA^{VTA} projections to the nucleus accumbens, which are suppressed by punishment predicting cues. The food cue response of $DA^{VTA->BLA}$ was largely abolished by satiety, whereas the punishment cue response persisted and was even enhanced in sated mice. Neuromodulatory systems can affect the excitability of local inhibitory microcircuits to shape the neuronal representations and allow for representations to change as the motivational value of outcomes change. In acute brain slices of the BLA, we found that application of dopamine boosted local inhibitory neuron excitability. *In vivo* 2-photon calcium imaging of interneurons in BLA showed that, like $DA^{VTA->BLA}$ activity, interneurons were more active in response to a food cue in hungry mice and more active to a punishment cue in sated mice. This enhanced inhibition in the presence of dopamine could improve signal-to-noise by filtering out weak signals thereby ensuring that only the strongest inputs to the circuit are learned. Our findings indicate that $DA^{VTA->BLA}$ input flexibly enhances different valence cues in a state-dependent manner to promote animal survival - food cues during hunger and aversive cues during satiety.

Disclosures: A. Lutas: None. **O. Alturkistani:** None. **C. Carty:** None. **V. Diaz:** None. **A. Sugden:** None. **M. Andermann:** None.

Nanosymposium

453. New Cortical and Subcortical Circuits for Food Reward

Location: SDCC 2

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 453.07

Topic: G.02. Motivation

Support: NIH NIMH R01-MH102441
NIH NIDDK DP2-DK-102256

Title: Basolateral amygdala microcircuits rapidly change with acute food deprivation

Authors: *A. K. SUTTON[1], G. G. CALHOON[2], C.-J. CHANG[2], A. M. LIBSTER[2], G. F. GLOBER[2], C. L. LEVEQUE[2], G. D. MURPHY[2], P. NAMBURI[2], C. A. LEPPLA[2], C. SICILIANO[2], A. BEYELER[4], K. M. TYE[3]
[2]Picower Inst. for Learning and Memory, [3]Brain and Cognitive Sci., [1]MIT, Cambridge, MA; [4]INSERM 1215, Bordeaux Cedex, France

Abstract: The ability to assign valence to external cues communicating resource availability and the perception of threats under varying homeostatic is critical to survival. We previously demonstrated the importance of two populations in the BLA that differentially encode positive and negative emotional valence. Specifically, BLA neurons projecting to the nucleus accumbens (NAc-projectors) preferentially encode positive valence, whereas centromedial amygdala-projecting neurons (CeM-projectors) preferentially encode negative valence. However, whether the dynamics of these populations are altered to differing homeostatic need states is largely unknown. Here, we use longitudinal in vivo two-photon calcium imaging to reveal increased or decreased activity of NAc-projectors (n=15 cells, 2 mice, p=0.0004) or CeM-projectors (n=22 cells, 2 mice, p=0.0029), respectively, to acute food deprivation. Moreover, we hypothesized that NAc-projectors and CeM-projectors interact locally within the BLA, and that hunger might shift these dynamics to favor the reward-promoting NAc-projector pathway. To this end, we performed ex vivo whole-cell patch clamp electrophysiology with optogenetic photostimulation to highlight surprisingly divergent interactions between BLA subpopulations in sated and hungry mice; photostimulation of CeM-projectors inhibits NAc-projectors in sated mice (n=20 cells, 8 mice, p=0.0374) but acute food deprivation shifts this interaction to facilitation (n=17 cells, 6 mice, p=0.0452). The relevance of these findings is further highlighted by decreased motivation in mice performing nose pokes in a progressive ratio task following chemogenetic-mediated NAc-projector inhibition (n (hm4Di)=5, p=0.0257; n (mCherry)=8, p=0.6609). Taken together, these data highlight projection-defined BLA microcircuits as a potential intersectional site coordinating valence assignment in response to fluctuating energy demands and availability.

Disclosures: A.K. Sutton: None. **G.G. Calhoon:** None. **C. Chang:** None. **A.M. Libster:** None. **G.F. Glober:** None. **C.L. Leveque:** None. **G.D. Murphy:** None. **P. Namburi:** None. **C.A. Leppla:** None. **C. Siciliano:** None. **A. Beyeler:** None. **K.M. Tye:** None.

Nanosymposium

453. New Cortical and Subcortical Circuits for Food Reward

Location: SDCC 2

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 453.08

Topic: G.01. Appetitive and Aversive Learning

Support: NIH grant DA038942
NIH grant DA024635
NIH grant DA035443
NIH grant MH106972
NIH grant NS087494

Title: Neural circuits of reward value encoding and retrieval

Authors: *M. MALVAEZ[1], C. SHIEH[2], M. D. MURPHY[2], V. Y. GREENFIELD[2], K. M. WASSUM[1]
[1]Psychology, [2]UCLA, Los Angeles, CA

Abstract: The value of an anticipated rewarding event is crucial information in the decision to engage in its pursuit. The networks responsible for encoding and retrieving this value are largely unknown. Using glutamate biosensors and pharmacological manipulations, we found that basolateral amygdala (BLA) glutamatergic activity tracks and mediates both the encoding and retrieval of the state-dependent incentive value of a palatable food reward. Projection-specific chemogenetic and optogenetic manipulations revealed the orbitofrontal cortex (OFC) supports the BLA in these processes. Critically, the function of lateral (lOFC) and medial (mOFC) OFC to BLA projections was found to be doubly dissociable for value encoding and retrieval, respectively. These data reveal a new circuit for adaptive reward valuation and pursuit, indicate dissociability in the encoding and retrieval of reward memories, and provide insight into the dysfunction in these processes that characterizes myriad psychiatric diseases. Ongoing experiments are evaluating the BLA efferent pathways required for value-based decision making.

Disclosures: M. Malvaez: None. **C. Shieh:** None. **M.D. Murphy:** None. **V.Y. Greenfield:** None. **K.M. Wassum:** None.

Nanosymposium

453. New Cortical and Subcortical Circuits for Food Reward

Location: SDCC 2

Time: Tuesday, November 6, 2018, 8:00 AM - 10:15 AM

Presentation Number: 453.09

Topic: G.01. Appetitive and Aversive Learning

Support: William N. & Bernice E. Bumpus foundation
National Institute of Mental Health (R01 MH060379)
Saks Kavanaugh Foundation
Bachmann-Strauss Dystonia and Parkinson Foundation
Netherlands Organization for Scientific Research - Rubicon
National Institute of Neurological Disorders and Stroke (U01 NS090473)
National Eye Institute (R01 EY007023)

Title: Two-photon imaging of striosomes and matrix in mice demonstrates overlapping and distinct functions in reinforcement learning

Authors: *B. BLOEM[1], R. HUDA[2], M. SUR[1], A. M. GRAYBIEL[1]
[1]MIT, Cambridge, MA; [2]Brain and Cognitive Sci., Picower Inst. for Learning and Memory, MIT, Cambridge, MA

Abstract: Despite being discovered several decades ago, the functional role of the striatal compartments, the striosomes and the surrounding matrix, is still largely unknown. Most data have so far been obtained by studying post-mortem tissues because direct visual identification of striosomes in vivo has been largely impossible. We use a two-photon imaging approach for visual identification of striosomes and simultaneous recording of activity of striosomal and matrix neurons. Striosomal neuropil was identified using genetic fate mapping in Mash1-CreER mice, capitalizing on the fact that striosomal neurons develop earlier than matrix neurons. With this approach, it was possible to identify striosomal cells on the basis of their anatomical location within clusters of labeled striosomal cell bodies and neuropil. Using a probabilistic auditory classical conditioning task, we found that striosomal neurons preferentially encode reward predicting cues and expected trial outcome. Cue encoding emerged as mice learn to discriminate the cues and strengthened further during overtraining. Neurons in both striatal compartments have similar activity patterns after reward delivery, with calcium transients occurring at specific times during or after consummatory licking periods. Finally, we found that striatal activity was strongly modulated by previous trial outcome, in particular in matrix neurons. These results suggest that striosomes and matrix have distinct functions in reinforcement learning.

Disclosures: B. Bloem: None. **R. Huda:** None. **M. Sur:** None. **A.M. Graybiel:** None.

Nanosymposium

454. Human Cognition and Behavior: Working Memory II

Location: SDCC 5

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 454.01

Topic: H.02. Human Cognition and Behavior

Title: Ketamine impairs behavioural performance and neural coding of spatial working memory in the primate lateral prefrontal cortex

Authors: *M. ROUSSY[1], R. LUNA[4], L. DUONG[5], L. PALANIYAPPAN[2], J. C. MARTINEZ-TRUJILLO[3]
[2]Psychiatry and Biophysics, [3]Physiol. and Pharmacol., [1]Univ. of Western Ontario, London, ON, Canada; [4]Robarts Res. Inst., London, ON, Canada; [5]Robarts Res. Inst., London Ontario, ON, Canada

Abstract: Spatial working memory (WM) relies on our ability to maintain mnemonic representations of space in the absence of external stimuli and is thought to depend on prefrontal microcircuits composed of various cell types. Pyramidal cells and interneurons act in unison to maintain a fine balance of excitation and inhibition in this circuit. A shift in this dynamic may result in faulty mnemonic representations of space, therefore reduced ability to remember spatial locations during WM. The persistent activity of excitatory cells during memory delay and normal interneuron inhibition rely on the activation of N-methyl-D-aspartic acid receptors (NMDAR). Ketamine, a non-competitive NMDAR antagonist, is consistently identified to produce deficits in WM. We propose that Ketamine induced deficits in WM are due to its impact on local prefrontal circuits resulting in a decrease in the strength and/or fidelity of mnemonic representations. To investigate this issue, we trained two male rhesus macaques to perform a spatial WM task in a virtual environment. During a trial, a visual cue appears in 1 of 9 possible locations in a virtual arena for 3 seconds. Subjects had to remember the cue location after cue offset during a 2 second delay period. They were then required to navigate to the cued location using a joystick. We recorded subject position and trajectories in the environment as well as eye position. Neural recordings were performed on both subjects using two 96 channel multi-electrode arrays located in the dorsal and ventral lateral prefrontal cortex (areas 8Ad/v). We recorded task performance before and after administration of subanesthetic doses of ketamine (0.25, 0.4 mg/kg). Performance (percent correct) significantly deteriorated after Ketamine injection (Monkey B, n=9, Kruskal Wallis (KW), p=0.005; Monkey T, n=9, p=0.0117). However, there was no change after administering a saline control. Moreover, performance on a perceptual control variant of the task did not show a significant change after Ketamine or saline injection. In addition, trajectories to target locations become less optimal during WM after Ketamine injection (Monkey B, KW, p=0.0074, Monkey T, KW, p<0.0001). We show that Ketamine produces unstable sustained activity patterns that reduce the sharpness of WM representations, which ultimately leads to this

WM impairment. Indeed, changes in spatial tuning during memory delay are evidenced in single neurons and at a population level. These findings give a first glimpse into NMDAR related impairment in primate prefrontal coding of spatial WM in a virtual environment.

Disclosures: M. Roussy: None. **R. Luna:** None. **L. Duong:** None. **L. Palaniyappan:** None. **J.C. Martinez-Trujillo:** None.

Nanosymposium

454. Human Cognition and Behavior: Working Memory II

Location: SDCC 5

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 454.02

Topic: H.02. Human Cognition and Behavior

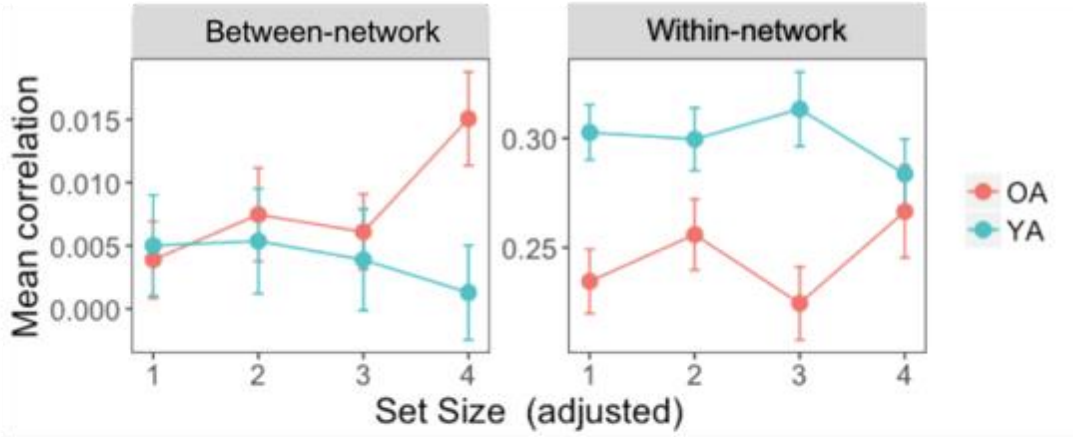
Support: NIH Grant U01AG050618

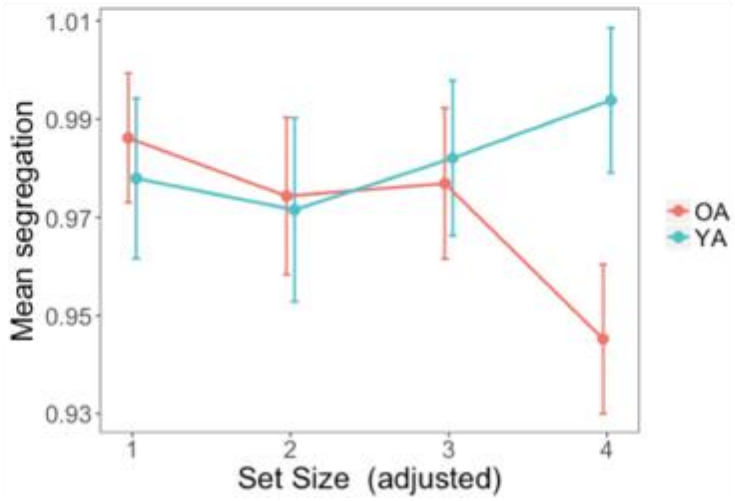
Title: Older adults benefit from more widespread network integration during working memory functioning

Authors: *C. CROWELL[1], S. W. DAVIS[2], L. BEYNEL[3], S. A. HILBIG[1], A. BRITO[1], S. H. LISANBY[5], H. PALMER[1], A. V. PETERCHEV[4], B. LUBER[6], L. G. APPELBAUM[3], R. E. CABEZA[3]
[1]Psychiatry, Duke Med., Durham, NC; [2]Neurol., [4]Psychiatry & Behavioral Sci., [3]Duke Univ., Durham, NC; [5]NIH, Bethesda, MD, MD; [6]Exptl. Therapeut. and Pathophysiology Br., Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Introduction Current models of the aging brain suggest a greater reliance on a more distributed network of regions to maintain successful levels of performance in the face of age-related neural declines. However, it is currently unclear how network interactions help to preserve this flexibility in aging brains, though competing ideas suggest a role for the recruitment of additional regions outside the typical task-related networks in young participants. Thus, an investigation into this domain may further clarify findings in univariate activity related to compensatory strategies.
Methods Older and younger adults performed a delayed-response alphabetization-based working memory task with four levels of difficulty during fMRI scanning. We modeled the delay period onset within each difficulty level to analyze univariate BOLD activity and estimate functional connectivity based on PPI. We defined a common task-related network across the groups and examined patterns of functional connectivity related to this network.
Results Both groups showed a similar pattern of general task-related activity, with both older and younger adults showing a similar inverse-U function of activity across difficulty level, suggesting that the ability to flexibly modulate brain activity in response to a task is adaptive—but limited—and stays largely preserved across the lifespan. We then examined connectivity

within the task-defined network, and between this network and the rest of the brain. Older adults showed greater connectivity between task-related and -unrelated nodes with increasing difficulty. Overall network segregation confirmed this group difference in segregation emerges in the highest level of difficulty. Additionally, older adults with higher starting set sizes have significantly less network segregation in the most difficult condition.
Discussion These results suggest that changes in network connectivity may act as a compensatory strategy, with older adults recruiting and communicating with additional regions outside the task network as the task becomes more difficult.





Disclosures: C. Crowell: None. **S.W. Davis:** None. **L. Beynel:** None. **S.A. Hilbig:** None. **A. Brito:** None. **S.H. Lisanby:** None. **H. Palmer:** None. **A.V. Peterchev:** None. **B. Luber:** None. **L.G. Appelbaum:** None. **R.E. Cabeza:** None.

Nanosymposium

454. Human Cognition and Behavior: Working Memory II

Location: SDCC 5

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 454.03

Topic: H.02. Human Cognition and Behavior

Support: NIH R01-EY025275
NHI R01-EY019882
NIH R01-MH110378
NIH P30-EY08126

Title: Context triggers the retrieval of targets stored in long-term memory

Authors: *S. ITTHIPURIPAT[1,2], G. F. WOODMAN[1]
[1]Dept. of Psychology, Vanderbilt Univ., Nashville, TN; [2]Learning Inst., King Mongkut's Univ. of Technol. Thonburi, Bangkok, Thailand

Abstract: How do we know what we are looking for in familiar scenes and surroundings? One proposal from theories of human memory is that visual working memory buffers mnemonic contents retrieved from long-term memory. The retrieved contents can then form an online mental representation (i.e., an attentional template) to control and guide attention. In the present study, we tested the hypothesis that context triggers the retrieval from long-term memory of the possible targets given that context. For example, being in the driver's seat of a car triggers the retrieval of road hazards. Here we recorded human subjects electroencephalogram (EEG) while they searched for objects on different colored backgrounds. Subjects searched for different sets of 1, 2, 4, and 6 unique real-world objects with each target set size paired with a different search context color. While learning, they also had to hold the search set of objects in mind during a blank delay to perform a visual search task at the end of each trial. After learning, subjects performed the visual search tasks in the different color contexts. During this final phase, we found that the colored backgrounds elicited EEG and event-related potentials of visual working memory maintenance that recapitulated the set size of the objects that people were to look for on that background. These results support the idea that contextual retrieval cues are sufficient for people to pull information out of long-term memory and into working memory to guide attention.

Disclosures: S. Itthipuripat: None. **G.F. Woodman:** None.

Nanosymposium

454. Human Cognition and Behavior: Working Memory II

Location: SDCC 5

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 454.04

Topic: H.02. Human Cognition and Behavior

Support: NSERC RGPIN-2017-06866
Connaught New Researcher Award

Title: The role of visual working memory in controlling access to visual long-term memory storage

Authors: *C. TOZIOS, K. FUKUDA
Psychology, Univ. of Toronto, Mississauga, ON, Canada

Abstract: We are capable of storing a virtually infinite amount of visual information in visual long-term memory (VLTM). However, not all the visual information that we encounter gets encoded into this massive offline memory storage. What, then, determines the successful memory encoding of visual information? In this study, we examined the role of visual working memory in controlling access to visual long-term memory storage. Here, we found that visual working memory, particularly its encoding mechanism but not the maintenance mechanism, gates the information flow into visual long-term memory. Additionally, we also demonstrate that our ability to voluntarily control the quality of memory encoding is up-regulatory in nature. More precisely, our behavioral and electrophysiological results demonstrate that although we can voluntarily increase the likelihood of successful VLTM encoding (=up-regulation) by preferentially representing the information in visual working memory, we cannot voluntarily decrease such likelihood (=down-regulation). To do so, one has to upregulate the memory encoding of the other visual information that accompanies the to-be-down-regulated information. Together, these results demonstrate a direct yet limited role that visual working memory plays in granting access to visual long-term memory storage.

Disclosures: C. Tozios: None. **K. Fukuda:** None.

Nanosymposium

454. Human Cognition and Behavior: Working Memory II

Location: SDCC 5

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 454.05

Topic: H.02. Human Cognition and Behavior

Support: FWO Grant 12R8817N SW
Wellcome Trust 201409/Z/16/Z
James S. McDonnell Foundation Scholar Award 220020405

Title: Tracking the competition between active and latent items during working-memory guided behaviour

Authors: *P. S. MUHLE-KARBE, N. E. MYERS, M. G. STOKES
Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom

Abstract: Increasing evidence suggests that contents of working memory (WM) are encoded in qualitatively different states depending on their task-relevance. Items that are used for current behaviour are thought to be in an "active" state that biases information processing to facilitate decision-making, whereas currently irrelevant items can be held in a "latent" state without affecting on-going cognition. It remains unknown, however, how latent working memories are transformed and consolidated into active decision circuits when behavioural priorities change. Here, we used time-resolved decoding of Electroencephalography (EEG) data to compare the neural representation of active and latent items in a task that required flexible WM-based behaviour. 30 participants judged the orientation of target stimuli (gabor patches) relative to changing decision boundaries held in WM. The task consisted of short blocks (16 trials) each starting with the presentation of two items that served as boundaries for the remainder of the block. On each trial, a high or low-pitch tone signalled which boundary should be used for decision-making. This design allowed us to obtain independent neural markers of active and latent WM items so we could examine how their representation changes when a switch of the boundary was required.
We observed that switching between boundaries created a substantial cost in performance that rapidly recovered after only a single application of the new boundary. Thus, although adjusting priorities within WM created temporary interference, participants were able to memorise both items while performing the task. Along the same lines, the EEG signal encoded both items immediately after a boundary switch, but was dominated by the active item alone after the first application. These results suggest that shifting behavioural priorities entails transient competition between active and latent WM items, likely reflecting lingering activation of the most recently used contents. Additional analyses of perceptual and decision-related signals will be presented at the meeting.

Disclosures: P.S. Muhle-Karbe: None. **N.E. Myers:** None. **M.G. Stokes:** None.

Nanosymposium

454. Human Cognition and Behavior: Working Memory II

Location: SDCC 5

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 454.06

Topic: H.02. Human Cognition and Behavior

Title: Episodic memory can substitute for active storage in visual working memory

Authors: *M. W. SCHURGIN[1], C. A. CUNNINGHAM[2], H. E. EGETH[2], T. F. BRADY[3]
[1]UCSD, La Jolla, CA; [2]Johns Hopkins Univ., Baltimore, MD; [3]Dept. of Psychology, Univ. of California San Diego, San Diego, CA

Abstract: Humans have remarkable episodic long-term memory abilities, capable of storing thousands of objects with significant detail (Shepard, 1967; Standing, 1973; Brady, Konkle, Alvarez, Oliva, 2008). However, it remains unknown how episodic long-term memory is utilized during the short-term maintenance of information. Specifically, if people have an episodic memory for an item, how does this affect subsequent working memory for that same item? To address this, participants were shown two objects they needed to hold in working memory in order to make a subsequent perceptual discrimination based on one of the two objects. We found that when a participant encounters an object that was previously encoded in episodic memory, they maintain approximately half as much perceptual information actively in working memory as when they were shown two completely new objects ($t(19)=2.57$, $p=0.02$) as indexed by the CDA - a well-known neural signature reflecting the active storage of perceptual information (Vogel & Machizawa, 2004). Despite maintaining significantly less information actively in working memory, participants did not demonstrate any differences in behavioral performance ($t(19)=0.92$, $p=0.37$). Thus, people can dynamically disengage working memory when episodic memory is available without incurring a cost. However, this does not mean that participants always utilize episodic memory when it is available. In a follow-up experiment we introduced substantial perceptual interference into the working memory task and found that participants actively stored items in working memory even when they had existing episodic memories of those items (no CDA difference across conditions, $t(19)=1.14$, $p=0.27$). These results clarify the conditions under which episodic and working memory operate. Specifically, working memory is engaged when new information is encountered or when perceptual interference is high. Episodic memory is otherwise utilized in lieu of working memory, if available. These data demonstrate the interactions between working memory and episodic memory are much more dynamic and fluid than previously thought.

Disclosures: M.W. Schurgin: None. **C.A. Cunningham:** None. **H.E. Egeth:** None. **T.F. Brady:** None.

Nanosymposium

454. Human Cognition and Behavior: Working Memory II

Location: SDCC 5

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 454.07

Topic: H.02. Human Cognition and Behavior

Support: CIHR

Title: Ensemble coding of spatial working memory and attention in primate lateral prefrontal cortex

Authors: *L. DUONG[1,2,3], M. L. LEAVITT[4], F. PIEPER[5], A. J. SACHS[6], J. C. MARTINEZ-TRUJILLO[7]
[1]Robarts Res. Inst., London Ontario, ON, Canada; [2]Western Univ., London, ON, Canada; [3]Ctr. for Neural Sci., New York Univ., New York City, NY; [4]Physiol., McGill Univ., Montreal, QC, Canada; [5]Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany; [6]The Ottawa Hosp., Ottawa, ON, Canada; [7]Physiol. and Pharmacol., Univ. of Western Ontario, London, ON, Canada

Abstract: The prefrontal cortex (PFC) has been shown to encode signals pertaining to visuospatial working memory (WM) and attention. The neural correlates of these phenomena are generally associated with sustained elevated firing rate activity while attending toward or remembering a specific location in space. However, little is known about how neurons in this cortical area flexibly encode both cognitive signals. We trained two macaque monkeys in visuospatial WM (Leavitt et al. 2017) and visuospatial attention (Tremblay et al. 2015) tasks while recording activity from ensembles of neurons with microelectrode arrays implanted in area 8a of the left lateral PFC. During the attention task, subjects were required to covertly attend and saccade toward a target surrounded by distractors following a delay period; similarly during the WM task, monkeys were to remember the location of a target during a delay period, then saccade toward its location. Simultaneous recordings allowed us to compare and contrast attentional and mnemonic coding in PFC ensembles on a single-trial basis. We found the population delay activity during WM to reflect that of when the target was presented in isolation. During the attention task however, population activity was first perturbed by the onset of distractors, and with sustained attention, gravitated toward a state resembling that of when the attended target was presented alone. By analyzing single-trial dynamics, we found the PFC population code in both tasks to span a stable subspace during the delay epochs of each task. Finally, the number of neurons needed to optimally decode the locus of spatial WM was fewer than for attention, likely driven by distractor-driven competition during the attention task. Taken together, the PFC population coding and dynamics underlying working memory and attentional filtering are similar and show that this area can adaptively switch between both cognitive processes.

Disclosures: L. Duong: None. **M.L. Leavitt:** None. **F. Pieper:** None. **A.J. Sachs:** None. **J.C. Martinez-Trujillo:** None.

Nanosymposium

454. Human Cognition and Behavior: Working Memory II

Location: SDCC 5

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 454.08

Topic: H.02. Human Cognition and Behavior

Support: University Research Priority Program "Dynamics of Healthy Aging"

Title: Refreshing and elaboration are separable processes with distinct impacts on working memory and long-term memory across the lifespan

Authors: *L. M. BARTSCH[1], V. M. LOAIZA[2], L. JÄNCKE[1], K. OBERAUER[1], J. A. LEWIS-PEACOCK[3]
[1]Univ. of Zurich, Zuerich, Switzerland; [2]Univ. of Essex, Essex, United Kingdom; [3]Dept. of Psychology, Univ. of Texas at Austin, Austin, TX

Abstract: Maintenance of information in working memory (WM) is assumed to rely on rehearsal processes such as *refreshing* in which attention is redirected to representations of the to-be-remembered information, and *elaboration* in which memory representations are explicitly linked with related knowledge in long-term memory (LTM). Clear mechanistic descriptions of these processes are lacking, however, and it is unclear whether refreshing and elaboration should be considered as two labels for the same process. Here, we developed a fMRI study to investigate the extent to which refreshing, and elaboration are distinct neural processes with dissociable behavioral outcomes. Both younger adults and older adults were recruited for this study to additionally evaluate the impact of aging on this question. We used multivariate pattern analyses (MVPA) of fMRI data to identify and differentiate brain activation patterns associated with refreshing or elaborating memory items during a WM task. These neural measures were then linked to behavioral outcomes on tests of both WM and LTM. Specifically, we compared memory performance for lists of six words under four processing conditions: re-reading half of the list during the delay period, refreshing half of the list, elaborating half of the list, or both refreshing and elaborating simultaneously. We collected fMRI data from 30 young adults and focused our analyses on predefined brain regions retrieved from an exhaustive literature search of refreshing and elaboration. In a combined mask of a priori brain regions from frontal, temporal, and parietal lobes, we found successful differentiation of brain activity associated with all three processes: *re-reading*, *refreshing* and *elaboration.* Critically, the degree of neural separation between these processes within an individual was predictive of their memory performance. Re-reading items benefited WM performance more than refreshing did, but this relative advantage was reduced when the neural processes of reading and refreshing were more

similar. That is, refreshing benefited WM when it appeared, in the brain, to be like reading. Elaboration produced no benefit to WM, but did improve LTM, and this benefit increased as the neural separation between elaboration and reading increased. Importantly, we were able to replicate the neural differentiation of these three processes in a sample of 27 older adults. In contrast to younger adults, we found that refreshing did not benefit WM, and neural measures of elaboration were inversely related to LTM performance. Taken together, this study provides deeper insight into the processes of WM rehearsal and their impacts on memory formation.

Disclosures: L.M. Bartsch: None. **V.M. Loaiza:** None. **L. Jäncke:** None. **K. Oberauer:** None. **J.A. Lewis-Peacock:** None.

Nanosymposium

454. Human Cognition and Behavior: Working Memory II

Location: SDCC 5

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 454.09

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant F32 MH111204-02

Title: Cortico-striatal control over working memory output gating

Authors: *A. KIYONAGA, J. A. MILLER, R. B. IVRY, M. D'ESPOSITO
Helen Wills Neurosci. Inst., Univ. of California Berkeley, Berkeley, CA

Abstract: As we engage in complex cognition, our thoughts can inadvertently influence our interactions with the external environment. Imagine, for instance, accidentally typing out or saying the wrong word in conversation because it was currently on your mind. These everyday cognitive slips can provide a valuable window into the generally adaptive processes by which working memory (WM) guides action. A cortico-striatal output gating mechanism has been proposed to control the selection of information from within WM to guide behavior. In this model, the most “active” internal content is gated to drive actions. However, we frequently have to maintain information relevant to a forthcoming goal, even when engaged in immediate action demands. Consequently, actively maintained WM representations may unintentionally influence ongoing, but unrelated motor behavior. Here, we examine the impact of WM maintenance on action execution and test the causal role of cortico-striatal circuitry in adaptively modulating WM output gating. In three behavioral experiments we found that verbal WM content for directional words (e.g., ‘left’, ‘up’) inadvertently influenced the trajectory and speed of hand movements toward cued locations. When the attentional state of the WM content was modulated by flagging which task representations were most behaviorally relevant, the movement bias was also modulated. Prioritized (and presumably more ‘active’) WM content strongly influenced ongoing movements during WM maintenance, while the influence of de-prioritized WM content

was diminished. We probed the causal role of cortico-striatal circuitry in this modulatory process by delivering TMS to a mid-lateral PFC site with connectivity to the striatum. We used a continuous theta-burst TMS (cTBS) protocol assumed to reduce cortical excitability and an intermittent protocol (iTBS) assumed to produce facilitation. While cTBS increased the influence of de-prioritized WM content, suggesting that the stimulation effectively opened the gate, iTBS blunted the influence of prioritized WM content (effectively closing the gate). These results show that the WM state modulates its influence over action execution and suggest that this modulation is causally dependent on PFC-striatal circuitry.

Disclosures: A. Kiyonaga: None. **J.A. Miller:** None. **R.B. Ivry:** None. **M. D'Esposito:** None.

Nanosymposium

454. Human Cognition and Behavior: Working Memory II

Location: SDCC 5

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 454.10

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01MH087214
ONR Grant N00014-12-1-0972

Title: Long-term consequences of working memory load

Authors: *M. T. DEBETTENCOURT, E. AWH, E. K. VOGEL
Univ. of Chicago, Chicago, IL

Abstract: Working memory performance declines as the number of items to be remembered increases. This phenomenon has been primarily examined within the visual working memory field, over short retention intervals. The consequences of memory load for long-term memory are less well understood. Electroencephalography (EEG) studies have revealed components (e.g., negative slow wave and/or contralateral delay activity) and oscillatory signatures (e.g., alpha power) that scale with the number of items to be remembered. In this study, we examined the long-term consequences of memory load on behavioral and neural signatures. Participants encoded trial-unique object images that were briefly and simultaneously presented in a variant of a classical visual working memory change detection task. Interleaved with these trials were long-term recognition memory tests. In the working memory phase, memory load was manipulated by presenting object images in arrays of different set sizes that ranged between one through four images. After a short (2 s) retention interval, participants were probed on one of the images from each display. Consistent with prior findings, working memory accuracy to the probed item decreased as the memory load increased. In the long-term memory phase, participants rated images from the previous encoding displays on a four-point confidence scale. Long-term recognition memory performance also declined as the initial memory load at study increased.

These performance decrements were observed even when eye fixation was maintained throughout encoding and when restricting the analyses to encoding arrays well below capacity. Furthermore, performance decrements were present even when analyses were restricted to correct trials in the working memory phase and also in a separate manipulation when the long-term memory test was a surprise. Intriguingly, performance decrements were steeper for long-term memory than working memory. EEG components reflecting apprehension and storage of information scaled with the memory load during the encoding and retention intervals. These neural indices can be used to investigate the interplay between working memory load and its long-term consequences for behavior. Our findings show that the factors that degrade storage in working memory also affect subsequent retrieval of those representations from long-term memory.

Disclosures: M.T. deBettencourt: None. **E. Awh:** None. **E.K. Vogel:** None.

Nanosymposium

454. Human Cognition and Behavior: Working Memory II

Location: SDCC 5

Time: Tuesday, November 6, 2018, 8:00 AM - 10:45 AM

Presentation Number: 454.11

Topic: H.02. Human Cognition and Behavior

Support: UT BRAIN seed grant
Provost's Graduate Excellence Award

Title: Managing cognitive control for prospective memory in dynamic environments

Authors: *S. KOSLOV, K. R. HEDGPETH, J. A. LEWIS-PEACOCK
Psychology, Univ. of Texas at Austin, Austin, TX

Abstract: Prospective memory (PM) refers to our ability to delay the execution of an intended action until the appropriate time or situation has arrived. Previous behavioral and neuroimaging evidence suggests that individuals can adjust their allocation of working memory and attentional resources to support either proactive control (characterized by maintenance of prospective information in working memory and monitoring of the environment for relevant cues) or reactive control (relying on “bottom-up” cue-response associations) for PM in situations with markedly different, but stable, external demands. However, how people use these PM strategies in more ecologically valid, less stable situations is still unclear. We designed a fMRI experiment where participants (N=30) identified the reappearance of a trial-specific PM target (a picture drawn from a set of faces and scenes, one per trial) while also performing an ongoing, orthogonal visual search task (on oriented arrows) that fluctuated in difficulty over time. Both univariate and multivariate analyses of fMRI data were used in order to investigate how individuals balanced their use of proactive and reactive control strategies as demands changed. As the ongoing task

demands increased across a trial, the behavioral marker of proactive control (dual-task interference costs on RTs, or "PM cost") dropped significantly, indicating a likely change in PM strategy from proactive to reactive control on these trials. A whole-brain GLM indicated that bilateral anterior insula and anterior cingulate regions were engaged during this transition. In the prefrontal cortex (PFC), neural patterns of activity differentiated trials that included a PM intention vs. those that did not (e.g., when participants only performed the ongoing task). This PM-specific differentiation increased when the ongoing task became easier. However, the identity of the PM target (face or scene) could not be decoded from PFC (except for a small region in right anterior PFC). In contrast, posterior sensory regions (including the ventral temporal, occipital, and medial parietal regions) were important for representing PM targets, and the strength of their representation fluctuated with the changes in the demands of the ongoing task. Interestingly, we found that incorporating behavioral measures of proactive control (RTs) with neural measures of proactive control (fMRI pattern classifier evidence) produced the best trial-by-trial prediction of accuracy on the PM task. These results provide insight into how individuals gradually adapt to changing demands on attention and memory resources in complex, dynamic environments.

Disclosures: S. Koslov: None. **K.R. Hedgpeth:** None. **J.A. Lewis-Peacock:** None.

Nanosymposium

537. Autism: From Genetic Models to Insights

Location: SDCC 4

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 537.01

Topic: A.07. Developmental Disorders

Support: Simons Foundation for Autism Research #: 514863
National Institutes of Health R01NS048453
National Institutes of Health 1F31MH116588-01
National Institutes of Health 2T32GM007790-38
Broad Institute U54HG003067
Broad Institute U54HG006504

Title: Mendelian autism caused by mutations in BAF53b that disrupt activity-dependent chromatin repression

Authors: *W. WENDERSKI[1], J. J. WALSH[2], H. LI[3], E. L. MILLER[4], S. GHOSH[5], R. D. GEORGE[5], L. ELIAS[4], M. A. GILLESPIE[6], E. Y. SON[4], A. KROKHOTIN[4], C. MONCADA[4], T. SULTAN[7], M. S. ZAKI[8], J. A. RANISH[6], L. LUO[3], R. C. MALENKA[2], J. G. GLEESON[5], G. R. CRABTREE[4]
[1]Dept. of Developmental Biol., [2]Nancy Priztker Laboratory, Dept. of Psychiatry & Behavioral Sci., Stanford Univ., Stanford, CA; [3]Dept. of Biol., [4]Departments of Pathology, Genet. and

Developmental Biol., Howard Hughes Med. Inst. - Stanford Univ., Stanford, CA; [5]Dept. of Neurosci., Howard Hughes Med. Inst. - Univ. of California, San Diego, San Diego, CA; [6]Inst. for Systems Biol., Seattle, WA; [7]Dept. of Pediatric Neurol., Inst. of Child Health, Children Hosp. Lahore, Lahore, Pakistan; [8]Clin. Genet. Department, Human Genet. and Genome Res. Div., Natl. Res. Ctr., Cairo, Egypt

Abstract: Autism spectrum disorders (ASDs) represent a group of genetically and phenotypically diverse neurodevelopmental disorders that affect over 1% of the population. While many genes have been statistically linked to autism, there are few examples of inherited, non-syndromic autism in humans. Such examples are crucial for understanding the cause of autism because they reveal mechanisms that are not confounded by syndromic features. We have identified a form of Mendelian recessive autism in humans caused by deleterious mutations in *BAF53b/ACTL6B* encoding a neuron-specific subunit of the mammalian SWI/SNF (BAF) ATP-dependent chromatin remodeling complex. Deletion of the ortholog in fly neurons resulted in stereotyped dendritic retargeting that was rescued with expression of human wild type but not autism mutant *BAF53b*. Mice carrying null mutations in *Baf53b* showed increasingly severe social deficits with decreasing gene dosage, suggesting a direct and conserved role for *Baf53b* in mammalian social behavior. Neurons cultured from these mice showed selective impairments in activity-dependent chromatin repression and early response gene regulation. Importantly, chromatin accessibility at the transcription start sites of autism risk genes failed to close during neural activity, an effect that was associated with delayed transcriptional downregulation. These results implicate activity-dependent chromatin repression mediated by BAF53b as a molecular mechanism underlying human autism. More broadly, our findings support the hypothesis that activity-dependent gene regulation is the critical function that is disrupted in autism.

Disclosures: W. Wenderski: None. **J.J. Walsh:** None. **H. Li:** None. **E.L. Miller:** None. **S. Ghosh:** None. **R.D. George:** None. **L. Elias:** None. **M.A. Gillespie:** None. **E.Y. Son:** None. **A. Krokhotin:** None. **C. Moncada:** None. **T. Sultan:** None. **M.S. Zaki:** None. **J.A. Ranish:** None. **L. Luo:** None. **R.C. Malenka:** None. **J.G. Gleeson:** None. **G.R. Crabtree:** None.

Nanosymposium

537. Autism: From Genetic Models to Insights

Location: SDCC 4

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 537.02

Topic: A.07. Developmental Disorders

Support: NIH grant P01 HD29587
NIH grant R01 AG056259
NIH grant R01 NS086890
NIH grant DP1 DA041722

NIH grant P30 NS076411

Title: hiPSC-derived disease model for autism spectrum disorder associated with MEF2C haploinsufficiency

Authors: *D. TRUDLER[1], S. GHATAK[1], J. PARKER[3], N. DOLATABADI[1], S. M. NOVERAL[3], K. LOPEZ[3], A. SULTAN[3], A. CHAN[5], Y. CHOI[5], M. V. TALANTOVA[1], N. SCHORK[6,7,8], N. NAKANISHI[4], S. CHAN[10], R. AMBASUDHAN[3,2], S. A. LIPTON[11,9,3]
[1]Mol. Med., [2]The Scripps Res. Inst., La Jolla, CA; [3]Neurodegenerative Dis. Ctr., [4]Scintillon Inst., San Diego, CA; [5]J Craig Venter Inst., Rockville, MD; [6]Human Biol., J Craig Venter Inst., La Jolla, CA; [7]Quantitative Med., TGEN, Phoenix, AZ; [8]Psychiatry and Biostatistics, [9]Dept. of Neurosciences, UC San Diego, La Jolla, CA; [10]Dept. of Med., Indiana University-Purdue Univ., Indianapolis, IN; [11]Neurodegenerative Dis. Center, Dept. of Mol. Med. & Dept. of Neurosc, The Scripps Res. Institure, La Jolla, CA

Abstract: It is estimated that 1 in 59 American children currently have Autism Spectrum Disorder (ASD). Despite extensive research identifying various genetic mutations and environmental factors that contribute to ASD, the molecular mechanisms underlying ASD remain largely unknown. This fact has hindered the development of robust diagnostics and effective therapies in this field. Myocyte enhancer factor 2 (MEF2) is a family of transcription factors that play a role in development, cell differentiation, and organogenesis. Our group previously discovered the *Mef2c* gene (Leifer *et al. PNAS*, 1993) and showed that heterozygosity or brain-specific knockout using a Nestin-Cre driver produces mice with immature electrophysiological network properties, excitatory/inhibitory (E/I) imbalance, and behavioral deficits reminiscent of ASD, and Rett syndrome (RTT) in particular (Li *et al. PNAS*, 2008; Tu *et al. Nat Commun*, 2017). Recent human genetic studies have established an association between *MEF2C* mutations and a form of ASD now known as MEF2C Haploinsufficiency Syndrome (MHS). Moreover, *MEF2C* reportedly functions as a coregulator of ASD-associated gene networks (Parikshak *et al. Cell*, 2013). To investigate the effect of *MEF2C* mutations in a human context, we developed an ASD "disease-in-a-dish" model, using human induced pluripotent stem cells (hiPSCs) generated from three ASD patients who carry heterozygous mutations in *MEF2C* (1 microdeletion and 2 point mutations). In addition, using CRISPR/Cas9, we generated an additional hiPSC line with a microdeletion in *MEF2C* to compare to the cognate isogenic WT control. We differentiated the hiPSCs to cerebrocortical neurons containing both excitatory and inhibitory cells, and found that MHS patient-derived neurons exhibited dysfunctional differentiation and maturation. MHS patient-derived hiPSCs generated fewer neurons and aberrant levels of glutamatergic and GABAergic synapses (see also Ghatak *et al*. SfN Abstr., 2018). We have also begun to use the MHS patient neurons to establish a screening paradigm to evaluate drug candidates to improve MEF2 reporter activity and thus improve the functional attributes of the neurons. Since MEF2C is a coregulator of ASD-associated gene networks gene in neurodevelopment exerting transcriptional control over many other critical ASD candidate genes, our approach may lead to personalized therapies for multiple forms of ASD.

Disclosures: D. Trudler: None. **S. Ghatak:** None. **J. Parker:** None. **N. Dolatabadi:** None. **S.M. Noveral:** None. **K. Lopez:** None. **A. Sultan:** None. **A. Chan:** None. **Y. Choi:**

None. **M.V. Talantova:** None. **N. Schork:** None. **N. Nakanishi:** None. **S. Chan:** None. **R. Ambasudhan:** None. **S.A. Lipton:** None.

Nanosymposium

537. Autism: From Genetic Models to Insights

Location: SDCC 4

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 537.03

Topic: A.07. Developmental Disorders

Support: MRC grant MR/K022377/1
SFARI grant #344763
SFARI grant #400101
Ontario Brain Institute's POND programme
NARSAD

Title: The autism-associated chromatin remodeller CHD8 regulates neurodevelopmental gene expression, brain growth and functional connectivity

Authors: *M. BASSON[1], P. SUETTERLIN[1], S. HURLEY[1], C. MOHAN[1], M. PAGANI[2], J. ELLEGOOD[4], A. GALBUSERA[5], K. L. RIEGMAN[1], A. CARUSO[6], C. MICHETTI[7], R. ELLINGFORD[1], J. P. LERCH[8], M. L. SCATTONI[9], A. GOZZI[3], C. FERNANDES[1]
[1]King's Col. London, London, United Kingdom; [2]Functional Neuroimaging Laboratory, CNCS, [3]Fondazione Inst. Italiano Di Tecnologia, Genova, Italy; [4]Mouse Imaging Ctr., Hosp. For Sick Children, Toronto, ON, Canada; [5]IIT, Rovereto, Italy; [6]Inst. Superiore Di Sanità, Roma, Italy; [7]Ctr. for Synaptic Neurosci. (NSYN)., Italian Inst. of Technol. (IIT), Genova, Italy; [8]Hosp. for Sick Children, Toronto, ON, Canada; [9]Inst. Superiore di Sanita, Roma, Italy

Abstract: Truncating *CHD8* mutations are amongst the highest confidence risk factors for autism spectrum disorders (ASD) identified to date. To investigate the role of CHD8 during brain development, we created a *Chd8* gene allelic series in the mouse. *Chd8* heterozygous mice display mild increases in brain size, pronounced hypoactivity and anomalous responses to social stimuli. Few genes show dysregulated expression at mid-gestation, whilst over 600 genes are differentially expressed in the early postnatal neocortex. Genes involved in cell adhesion and axon guidance are particularly prominent amongst the down-regulated transcripts. Resting-state functional MRI identified increased synchronised activity in cortico-hippocampal and auditory-parietal networks in *Chd8* heterozygous mutant mice, implicating altered connectivity as a potential mechanism underlying the behavioural phenotypes. Together, these data suggest that altered brain growth and diminished expression of important neurodevelopmental genes that regulate long-range brain wiring are followed by distinctive anomalies in functional brain connectivity in *Chd8*$^{+/-}$ mice. To explore the effects of step-wise, additional reductions in *Chd8* gene dosage, we created an allelic series of *Chd8*-deficient mice. *Chd8* hypomorphic mice

exhibited more pronounced changes in brain structure, neural progenitor proliferation and wide-spread dysregulation of gene expression at E12.5. Surprisingly, in contrast to the phenotypes of the hypomorphic mice, conditional deletion of *Chd8* from the developing brain resulted in severe brain hypoplasia by the end of gestation, accompanied by p53 pathway hyperactivation. Our findings suggest that a number of cellular processes show differential sensitivities to *Chd8* dosage, resulting in non-linear effects on brain growth in response to reduced levels of CHD8. These findings have important implications for interpreting the results from different model systems.

Disclosures: M. Basson: None. **P. Suetterlin:** None. **S. Hurley:** None. **C. Mohan:** None. **M. Pagani:** None. **J. Ellegood:** None. **A. Galbusera:** None. **K.L. Riegman:** None. **A. Caruso:** None. **C. Michetti:** None. **R. Ellingford:** None. **J.P. Lerch:** None. **M.L. Scattoni:** None. **A. Gozzi:** None. **C. Fernandes:** None.

Nanosymposium

537. Autism: From Genetic Models to Insights

Location: SDCC 4

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 537.04

Topic: A.07. Developmental Disorders

Support: NS034007
NS047384

Title: Ultra Rare inherited and de novo mutations in eIF2a kinases disrupt protein synthesis and contribute to autism-associated clinical phenotypes

Authors: *A. G. VOROBYEVA[1], I. IOSSIFOV[3], L. SHUFFREY[4], T. CHEN[2], S. ANIKINA[2], K. CHEN[2], M. KHOURY[2], E. KLANN[2]
[1]Ctr. for Neural Sci., [2]New York Univ., New York, NY; [3]New York Genome Ctr., New York, NY; [4]Div. of Child and Adolescent Psychiatry,, Columbia Univ., Columbia University, NY

Abstract: Autism spectrum disorder (ASD) is heritable and presents a complex genetic landscape. Although several monogenic syndromes with a high incidence of ASD have been well characterized, these only account for a small portion of all ASD cases. Therefore the majority of ASD genetic risk factors and causative genes are still elusive. Evidence indicates disrupted protein synthesis is one molecular mechanism underlying ASD molecular and clinical spectrum. Searching the Simons Simplex whole exome sequencing database for mutations in previously uncharacterized translation factors we identified >100 mutations of interest. Here we report a medium-throughput cell-based functional screen and *in vivo*animal studies of ASD-associated mutations in genes encoding eIF2 kinases and their contribution to: i) disrupted global protein synthesis *in vitro*, ii) ASD-related behaviors observed using *in vivo* animal modelswhich

revealed to be iii) consistent with clinical phenotypes observed in ASD proband carriers of the eIF2αkinase mutations of interest. Together our data strongly indicates the eIF2αmicrocircuit is a novel risk factor for autism-related behaviors such as anxiety, stereotypy, and cognitive dysfunction.

Disclosures: A.G. Vorobyeva: None. **I. Iossifov:** None. **L. Shuffrey:** None. **T. Chen:** None. **S. Anikina:** None. **K. Chen:** None. **M. Khoury:** None. **E. Klann:** None.

Nanosymposium

537. Autism: From Genetic Models to Insights

Location: SDCC 4

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 537.05

Topic: A.07. Developmental Disorders

Support: NIH MH113179

Title: Deletion of CACNG2 (Stargazin) in a personalized mouse model of autism spectrum disorder (ASD)

Authors: *M. KLEIBER[1], T. R. CHAPMAN[1], M. S. MAILE[1], A. LIPPA[2], R. PURCELL[3], J. L. SEBAT[1]
[1]Psychiatry, UCSD, San Diego, CA; [2]RespireRx Pharmaceuticals, Glen Rock, NJ; [3]RespireRx Pharmaceuticals Inc., Glen Rock, NJ

Abstract: The identification of genomic sequence variants in autism spectrum disorder (ASD) and neurodevelopmental disorder (NDD) studies have led to a significant advance in determining novel disease-causing genes. These causal genetic variants can be readily identified by clinical genomic sequencing and represent valid molecular biomarkers that may serve as a basis for individualized treatment strategies.
Effective treatment for most ASD and NDDs have been elusive due to a lack of understanding of (1) establishment that an individual genetic finding in a patient plays a causal role; (2) determination of the underlying pathogenic mechanism for a genetic disorder; and (3) establishment of an intervention that can demonstrably reverse the molecular pathology and improve cognitive function *in vivo*. The former is by far the most tractable, but it is of limited value without the latter.
To demonstrate the feasibility of personalized medicine for a rare ASD/NDD, we have identified and evaluated a test case of autosomal dominant mental retardation 10 (MRD10, OMIM:614256) using a mouse model generated by CRISPR/Cas9 genome editing of C57BL/6J to recapitulate a previously reported human mutation of an exon 2 in-frame deletion of the AMPA-receptor binding domain of *Cacng2* (*Cacng2*$^{\Delta e2}$). Homozygous *Cacng2*$^{\Delta e2/\Delta e2}$ mice present with severe motor ataxia, consistent with the classical phenotype observed in the “Stargazer” mouse

strain. *Cacng2* mRNA is expressed at normal levels in the cerebellum; however, no protein is detectable in whole-cell lysate or post-synaptic density fractions, suggesting that the mutant protein is targeted to the lysosome for degradation. Consistent with this, levels of AMPAR subunit GluA2 are reduced to 10% of normal in homozygote *Cacng2*$^{\Delta e2/\Delta e2}$ mice, while *Cacng2* and *GluA2* are expressed in heterozygotes at 40% and 60% of wildtype levels respectively. Heterozygote *Cacng2*$^{+/\Delta e2}$ males and females show significant cognitive and behavioral phenotypes such as maternal-care deficits (<40% rates of survival among pups at 5 postnatal days), hyperactivity, decreased anxiety-related behaviour (Elevated Plus Maze), decreased startle response, deficits in reversal learning, and heightened male aggression.
With the goal of reversing cognitive impairments associated with MRD10, we have initiated treatment studies using the ampakine compound CX717 at doses of 0.3 and 3 mg/kg. Given the function of CX717 as a positive allosteric modulator of AMPA receptor activity, this represents a valuable opportunity to evaluate a potential treatment for MRD10.

Disclosures: M. Kleiber: None. **T.R. Chapman:** None. **M.S. Maile:** None. **A. Lippa:** A. Employment/Salary (full or part-time):; RespireRX Pharmaceuticals Inc. **R. Purcell:** A. Employment/Salary (full or part-time):; RespireRx Pharmaceuticals Inc.. **J.L. Sebat:** None.

Nanosymposium

537. Autism: From Genetic Models to Insights

Location: SDCC 4

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 537.06

Topic: A.07. Developmental Disorders

Support: R21 MH104766
R01 MH109885
R01 MH108528

Title: Functional genomics approaches identify pathways dysregulated by the 16p11.2 autism-linked CNV

Authors: *M. AMAR[1], P. M. LOSADA[1], P. ZHANG[1], J. URRESTI[1], V. HERRERA[1], N. YU[2], J. YATES III[2], A. R. MUOTRI[3], L. M. IAKOUCHEVA[1]
[1]Univ. of California San Diego, La Jolla, CA; [2]The Scripps Res. Inst., La Jolla, CA; [3]Pediatrics/Cellular Mol. Med., UCSD, La Jolla, CA

Abstract: Background: The 16p11.2 copy number variant is one of the most frequent CNVs involved in neurodevelopmental diseases. It is implicated in multiple psychiatric phenotypes with deletions associated with macrocephaly and duplications associated with microcephaly in patients and mouse models. In our previous study, we observed KCTD13-Cul3-RhoA dysregulation as a potential mechanism contributing towards these phenotypes. To further

validate the role of KCTD13-Cul3-RhoA pathway in autism, we have recently created mouse models (KCTD13-HET, KCTD13-KO and Cul3-HET) using CRISPR/Cas9 genome editing technology. **Methods:** Advanced genomic, transcriptomic and proteomic approaches were applied to investigate the impact of KCTD13 and Cul3 mutations on cellular and molecular pathways in various brain regions and brain developmental e periods (embryonic, juvenile and adult). **Results and Conclusions:** The RhoA protein level was consistently upregulated in all mouse models during early development, and this upregulation was cortex-specific. This suggests that trans-effect of Cul3 and KCTD13 mutations may be brain region specific. In addition, genes involved in protein ubiquitination and neuronal endocytosis were detected by RNAseq as most differentially expressed genes in KCTD13-mutant early postnatal mice. We confirmed Cul3-reduction and CamK2 family proteins upregulation in Cul3 mutant mice by TMT-proteomics. The Cul3-mutant mice had lower weight at birth, and this effect was maintained into the adulthood. The behavior tests to investigate phenotypic impact of mutations are ongoing. Application of genomic approaches to investigate the impact of autism mutations on early brain development in animal experimental systems would provide further insight into molecular pathways dysregulated by these mutations.

Disclosures: M. Amar: None. **P.M. Losada:** None. **P. Zhang:** None. **J. Urresti:** None. **V. Herrera:** None. **N. Yu:** None. **J. Yates III:** None. **A.R. Muotri:** None. **L.M. Iakoucheva:** None.

Nanosymposium

537. Autism: From Genetic Models to Insights

Location: SDCC 4

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 537.07

Topic: A.07. Developmental Disorders

Title: Linking spatial gene expression patterns to sex-specific brain structural changes on a mouse model of 16p11.2 hemideletion

Authors: *T. NICKL-JOCKSCHAT[1], V. KUMAR JANGIR[2], N. M. GRISSOM[3], S. WELSH[4], H. SCHOCH[5], N. M. BOWMAN[6], R. HAVEKES[7], M. KUMAR[8], S. PICKUP[8], H. POPTANI[8], T. M. REYES[9], M. J. HAWRYLYCZ[10], T. ABEL[11]
[1]Dept. of Psychiatry, Iowa Neurosci. Instit, Iowa City, IA; [2]Max Planck Inst. for Biol. Cybernetics, Tuebingen, Germany; [3]Dept. of Psychology, Univ. of Minnesota, Minneapolis, MN; [4]Inst. for Translational Med. and Therapeutics, Univ. of Pennsylvania, Philadelphia, PA; [5]Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA; [6]Univ. of Pennsylvania Dept. of Psychiatry, Philadelphia, PA; [7]Biol., Univ. of Groningen, Groningen, Netherlands; [8]Dept. of Radiology, Univ. of Pennsylvania, Philadelphia, PA; [9]Psychiatry and Behavioral Neurosci.,

Univ. of Cincinnati, Cincinnati, OH; [10]Modeling, Analysis, and Theory, Allen Inst. Brain Sci., Seattle, WA; [11]Dept. of Mol. Physiol. and Biophysics, Univ. of Iowa, Iowa City, IA

Abstract: Neurodevelopmental disorders, such as ASD and ADHD, affect males about 3-4 times more often than females. 16p11.2 hemideletion is a copy number variation that is highly associated with neurodevelopmental disorders. Previous work from our lab has shown that a mouse model of 16p11.2 hemideletion (del/+) exhibits male-specific behavioral phenotypes. We, therefore, aimed to investigate with magnetic resonance imaging (MRI), whether del/+ animals also exhibited a sex-specific neuroanatomical endophenotype. Using the Allen Mouse Brain Atlas, we analyzed the expression patterns of the 27 genes within the 16p11.2 region to identify which gene expression patterns spatially overlapped with brain structural changes. MRI was performed ex-vivo and the resulting images were analyzed using Voxel-Based Morphometry for T1-weighed sequences and tract-based spatial statistics for diffusion-weighed images. In a subsequent step, all available in situ hybridization (ISH) maps of the genes involved in the 16p11.2 hemideletion were aligned to Waxholm space and clusters obtained by sex-specific group comparisons were analyzed to determine which gene(s) showed the highest expression in these regions. We found pronounced sex-specific changes in male animals with increased fractional anisotropy in medial fiber tracts, especially in those proximate to the striatum. Moreover, we were able to identify gene expression patterns spatially overlapping with male-specific structural changes that were associated with neurite outgrowth and the MAPK pathway. Of note, previous molecular studies have found convergent changes that point to a sex-specific dysregulation of MAPK signaling. This convergent evidence supports the idea that ISH maps can be used to meaningfully analyze imaging data sets.

Disclosures: T. Nickl-Jockschat: None. **V. Kumar Jangir:** None. **N.M. Grissom:** None. **S. Welsh:** None. **H. Schoch:** None. **N.M. Bowman:** None. **R. Havekes:** None. **M. Kumar:** None. **S. Pickup:** None. **H. Poptani:** None. **T.M. Reyes:** None. **M.J. Hawrylycz:** None. **T. Abel:** None.

Nanosymposium

538. Neurotransmitter Release

Location: SDCC 32

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 538.01

Topic: B.05. Neurotransmitter Release

Support: Deutsche Forschungsgemeinschaft (DFG), Collaborative Research Center 889, Cellular Mechanisms of Sensory Processing projects A2.

Title: Ca^{2+} dependence of inner hair cell transmitter release in near physiological conditions

Authors: *L. M. JAIME TOBON[1,2,3,4], C.-H. HUANG[1,2,3], T. MOSER[1,2,3]
[1]Synaptic Nanophysiology Group, Max Planck Inst. for Biophysical Chem., Goettingen, Germany; [2]Inst. for Auditory Neurosci., Univ. Med. Ctr. Goettingen, Goettingen, Germany; [3]Collaborative Res. Ctr. 889, Univ. of Goettingen, Goettingen, Germany; [4]IMPRS MSc/PhD Neurosci. Program, Intl. Max Planck Res. Sch., Goettingen, Germany

Abstract: Inner hair cells (IHC) are the gateway of sound stimuli to the auditory pathway. They are responsible of transforming mechanical sound-borne vibrations into electrical signals and conveying this information to the afferent spiral ganglion neurons. Upon stimulation, the receptor potential triggers the opening of voltage-gated Ca^{2+} channels, mediating the fusion of vesicles and the consequent release of neurotransmitter from the presynaptic active zone to the postsynaptic bouton (for review, see Moser & Vogl, 2016).
The coupling between Ca^{2+} influx and exocytosis critically determines how the acoustic stimulus is encoded at the synapse between the IHC and the spiral ganglion neuron. The Ca^{2+} nanodomain hypothesis of exocytosis control proposes that only few Ca^{2+} channels in nanometer proximity from the vesicular release site govern the Ca^{2+} concentration that drives the release of a synaptic vesicle (Moser, et al. 2006). However, validation of the Ca^{2+} nanodomain hypothesis by paired pre- and postsynaptic recordings that provide high resolution and specificity is required. Moreover, it remained unclear whether the Ca^{2+} nanodomain-like control operates in IHC synaptic transmission under physiological conditions. Here, we performed paired pre- and postsynaptic patch-clamp recordings in near physiological conditions on murine IHCs ribbon synapses after the onset of hearing.
To determine the apparent Ca^{2+} dependence of glutamate release, the presynaptic Ca^{2+} influx was altered by depolarizing the IHC with 2 ms voltage steps from -58 mV to -17 mV. These short stimuli were used to avoid synaptic vesicle pool depletion. The relationship of EPSC charge (Q_{EPSC}) and Ca^{2+} charge (IHC Q_{Ca}) was approximated by a power function yielding an apparent Ca^{2+} cooperativity (m) of 1.61. This suggests that few Ca^{2+} channels control vesicle fusion during physiological sound encoding.
Additionally, two independent manipulations to alter the single Ca^{2+} channel current or the number of open Ca^{2+} channels were carried out. 1 mM Zn^{2+} was perfused to cause a rapid flicker block of the Ca^{2+} channel (Winegar & Lansman, 1990) and reduce the apparent single channel current. This manipulation revealed a supralinear relationship between Q_{EPSC} and IHC Q_{Ca} (m = 3.06), most likely reflecting the high intrinsic Ca^{2+} cooperativity at the Ca^{2+} sensor. Conversely, slow wash-in of 0.5 - 2 µM Isradipine to gradually reduce the number of open Ca^{2+} channels, yielded a linear Ca^{2+} dependence with a power of 1.17. Taken together, these findings support that physiological sound encoding relies on few Ca^{2+} channels to control vesicle fusion in a Ca^{2+} nanodomain-like fashion.

Disclosures: L.M. Jaime Tobon: None. **C. Huang:** None. **T. Moser:** None.

Nanosymposium

538. Neurotransmitter Release

Location: SDCC 32

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 538.02

Topic: B.05. Neurotransmitter Release

Support: 3 Collaborative Research Center 889, University of Göttingen, Göttingen, Germany

Title: Optical detection of glutamate release at individual inner hair cell synapses

Authors: *O. OEZCETE[1,2,3,5], T. MOSER[1,2,4]
[1]Max-Planck Inst. for Exptl. Med., Goettingen, Germany; [2]InnerEarLab, Dept. of Otolaryngology, [3]Inst. For Auditory Neurosci., [4]Inst. for Auditory Neurosci., Univ. Med. Ctr. Goettingen, Goettingen, Germany; [5]Intl. Max Planck Res. Sch. for Neurosciences (IMPRS), Goettingen, Germany

Abstract: Sound is encoded at the ribbon synapses between inner hair cells (IHCs) and spiral ganglion neurons (SGNs) in the cochlea. The presynaptic mechanisms coupling the receptor potential to the release of glutamate remains to be elucidated. Membrane capacitance recordings have indicated a Ca^{2+}-nanodomain-like control of IHC exocytosis, where opening of one or few Ca^{2+} channel(s) cause(s) release of a nearby vesicles. However, since they sum over the activity of all active zones (approximately a dozen) of the IHCs, information on individual synapses is missing.
Here, we investigated the stimulus-secretion coupling in IHCs by combining perforated-patch recordings of Ca^{2+} currents and membrane capacitance changes, with imaging of glutamate release at individual synapses. Using virus injection into the ear of postnatal mice, we transduced SGNs with the glutamate sensor, iGluSnFR. We imaged the synapses by spinning disc confocal microscopy of the apical turn of the acutely excised cochlea after the onset of hearing (P15-19). Single active zones were identified by fluorescent labelling via a tagged ribbon-binding peptide, with which the IHCs were filled after perforated-patch recordings.
Fluorescence responses of single IHC synapses showed a proportional increase with stimulus duration and simultaneously recorded capacitance measurements without obvious saturation of the sensor. The sensitivity of iGluSnFR was sufficient to optically detect release with depolarizations as short as 2 ms to -23 mV from a holding potential of -87 mV.
Furthermore, we investigated the apparent Ca^{2+} cooperativity of glutamate release in the physiologically relevant voltage range. IHCs were depolarised for 10 ms to negative potentials of -62 mV to -22 mV with 5 mV increments from a holding potential of -87 mV. We found near-linear dependence of glutamate release on Ca^{2+} influx, supporting the notion of Ca^{2+}-nanodomain-like control of exocytosis.
We have thus established postnatal transduction of SGNs with glutamate sensor, which enables

the optical read-out of glutamate release from individual active zones in IHCs in a robust and reliable manner. Studying the apparent Ca^{2+} cooperativity of release, we indicate Ca^{2+}-nanodomain-like control at the single synapse level.

Disclosures: O. Oezcete: None. **T. Moser:** None.

Nanosymposium

538. Neurotransmitter Release

Location: SDCC 32

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 538.03

Topic: B.05. Neurotransmitter Release

Support: NIH Grant DA035913
ARCS Fellowship

Title: Neuromodulation of presynaptic calcium channels by dopamine and GABA receptors produces distinct forms of synaptic depression in prefrontal cortex

Authors: *K. BURKE[1], C. M. KEESHEN[1], K. J. BENDER[2]
[2]Dept. of Neurol., [1]UCSF, San Francisco, CA

Abstract: Neuromodulators are important regulators of synaptic transmission throughout the brain. At the presynaptic terminal, neuromodulation of calcium channels (CaVs) can affect transmission not only by changing neurotransmitter release probability, but also by shaping short-term plasticity (STP). Indeed, changes in STP are often considered a requirement for defining a presynaptic site of action. Nevertheless, some synapses exhibit non-canonical forms of neuromodulation, where release probability is altered without a corresponding change in STP. Here, we identify biophysical mechanisms whereby both canonical and non-canonical presynaptic neuromodulation can occur at the same synapse. Using a combination of two-photon calcium imaging, pharmacology and computational modelling, we show that at a subset of glutamatergic terminals in prefrontal cortex, $GABA_B$ and D1/D5 dopamine receptors suppress release probability with and without canonical increases in short-term facilitation by modulating different aspects of presynaptic CaV function. While D1/D5 dopamine receptors suppress the open probability of presynaptic CaVs, $GABA_B$ receptors suppress the AP-evoked current of single CaVs. Using computational modeling, we show that reduced CaV open probability minimizes both calcium accumulation and calcium-dependent facilitation. Furthermore, we show that this difference in neuromodulatory mechanism between D1/D5 and $GABA_B$ receptors is sufficient to explain the different effects of these receptors on short-term plasticity at synapses with low functional coupling between CaVs and neurotransmitter vesicles (i.e. “nanodomain synapses”). These findings establish a framework whereby signaling from multiple

neuromodulators can converge on presynaptic CaVs to differentially tune release dynamics at the same synapse.

Disclosures: K. Burke: None. **C.M. Keeshen:** None. **K.J. Bender:** None.

Nanosymposium

538. Neurotransmitter Release

Location: SDCC 32

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 538.04

Topic: B.05. Neurotransmitter Release

Support: DFG grant GK1326
DFG grant CRC 894
DFG grant CRC 1027
DFG grant Mo 2312/1-1

Title: CAPS isoforms differentially regulate synaptic transmission and peptide secretion in sensory neurons

Authors: *U. D. BECHERER[1], A. H. SHAIB[2], A. STAUDT[2], A. HARB[2], M. KLOSE[2], A. SHAABAN[2], C. SCHIRRA[2], R. MOHRMANN[2], J. RETTIG[2]
[1]Univ. des Saarlandes, Homburg-Saar, Germany; [2]Univ. des Saarlandes, Homburg, Germany

Abstract: The two isoforms of the calcium-dependent activator protein for secretion, CAPS1 and CAPS2, are priming factors for large dense-core vesicles (LDCVs) and synaptic vesicles (SVs). Yet, it is unclear whether CAPS isoforms regulate exocytosis of these two vesicles types differentially in systems where neuropeptide and neurotransmitter release are equally important. Here, we compared the ability of CAPS1 and CAPS2 to support priming of both vesicle types in knock-out mouse dorsal root ganglion (DRG) neurons using a variety of high-resolution live imaging methods. While CAPS1 localized to synapses of all DRG neurons and promoted synaptic transmission, CAPS2 was exclusively found in peptidergic neurons and mediated LDCV exocytosis. Intriguingly, ectopic expression of CAPS2 conferred the ability to drive LDCV fusion to non-peptidergic neurons, identifying CAPS2 as key molecular determinant for peptidergic signalling. Finally, our results reveal that these distinct functions of CAPS isoform are based on their differential subcellular localization in DRG neurons. Our data imply a major role for CAPS2 in neuropathic pain by controlling neuropeptide release.

Disclosures: U.D. Becherer: None. **A.H. Shaib:** None. **A. Staudt:** None. **A. Harb:** None. **M. Klose:** None. **A. Shaaban:** None. **C. Schirra:** None. **R. Mohrmann:** None. **J. Rettig:** None.

Nanosymposium

538. Neurotransmitter Release

Location: SDCC 32

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 538.05

Topic: B.05. Neurotransmitter Release

Support: National Key R&D Program of China 2016YFA0501902

Title: Interplay between VAMP2 and lipids in regulation of SNARE complex assembly

Authors: *C. LIU, C. WANG, S. ZHANG
Chinese Acad. of Sci., Shanghai City, China

Abstract: The synaptic vesicle associated membrane protein 2 (VAMP2), one of the main components of the SNARE complex, regulates the fusion of synaptic vesicles with the presynaptic membrane. The SNARE motif of VAMP2, which is essential in mediating SNARE complex formation, was found to bind certain types of membrane mimic (e.g. DPC micelles rather than nanodisc) in vitro. Whether and how VAMP2 is associated with membrane in vivo are key questions to understand the regulatory mechanism of VAMP2-mediated SNARE complex assembly. In this study, we systemically characterized the membrane binding of VAMP2 in different mammalian cells at residue-resolution by using in-cell NMR. Combining with immunofluorescence microscopy, membrane fractionation and in solution NMR, we reveal that VAMP2 recognizes different lipid molecules by distinct binding pattern, which results in different influences on VAMP2-mediated SNARE complex assembly. Thus the distinct local lipid environment on the SV membrane fine-tunes the conformation of VAMP2 for SNARE complex assembly and regulates SV trafficking.

Disclosures: C. Liu: None. **C. Wang:** None. **S. Zhang:** None.

Nanosymposium

538. Neurotransmitter Release

Location: SDCC 32

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 538.06

Topic: B.05. Neurotransmitter Release

Support: NIH grant R01NS083846
NIH grant R01NS064963

Pew Foundation fellowship

Title: α-Synuclein modulates synaptic vesicle recycling

Authors: *K. J. VARGAS[1], E. M. GIRARDI[2], P. L. COLOSI[1], S. S. CHANDRA[1]
[1]Yale Univ., New Haven, CT; [2]Brown Univ., Providence, RI

Abstract: Many neurological and psychiatric illnesses are associated with alterations in synaptic structure. Alteration of this kind also could explain the changes in synaptic activity before neurodegeneration in Parkinson disease (PD). PD is characterized by a loss of neurons in the substantia nigra and accumulation of Lewy bodies. The main component of this aggregation is the presynaptic protein α-synuclein. Point mutation, duplication, and triplication of the α-synuclein gene produces familial PD, and despite the effort to study its function, it still remains unknown. We know from the literature that α-synuclein plays a role in synaptic vesicle exocytosis and recently, using a synuclein triple knock out (TKO) mouse, we found a deficit in synaptic vesicle endocytosis. These two processes in synaptic vesicle recycling require membrane curvature, and synuclein has been shown to sense and generate membrane curvature. These properties suggest that synuclein may have an impact on presynaptic function. Finding the exact mechanism by which α-synuclein is participating in the maintenance of normal synaptic function is important and would allow us to manipulate its function as a therapeutic target in PD. In order to do this, we explored the putative molecular mechanism of α-synuclein in synaptic vesicle endocytosis. First, we found that synuclein's interaction with synaptic vesicles is dynamically controlled by KCl stimulation. Using *in vitro* membrane recruitment experiments, we found that α-synuclein is necessary to maintain appropriate recruitment of endocytic proteins such as clathrin and AP180 to synaptic membranes. In addition, synuclein promotes the formation of higher molecular species of clathrin. This could explain the changes we previously described in the kinetics of synaptic vesicle endocytosis in the TKO mice, where changes in clathrin polymerization could be responsible for this perturbation. Therefore, we can conclude that α-synuclein is maintaining the synapse through modulation of synaptic vesicle endocytosis, endocytic protein recruitment, and clathrin oligomerization. Thus, in a scenario where there are α-synuclein defects, small impairments in synaptic vesicle endocytosis first occurs, and then eventually synaptic function deteriorates, resulting in neuronal death. This could explain the progressive deficits observed in Parkinson's disease and concomitant neurodegeneration.

Disclosures: K.J. Vargas: None. **E.M. Girardi:** None. **P.L. Colosi:** None. **S.S. Chandra:** None.

Nanosymposium

538. Neurotransmitter Release

Location: SDCC 32

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 538.07

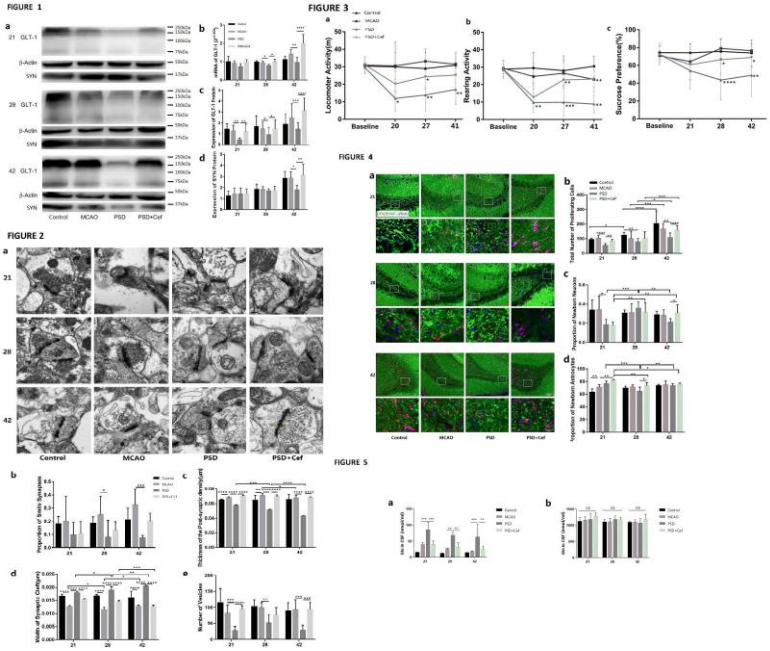
Topic: B.05. Neurotransmitter Release

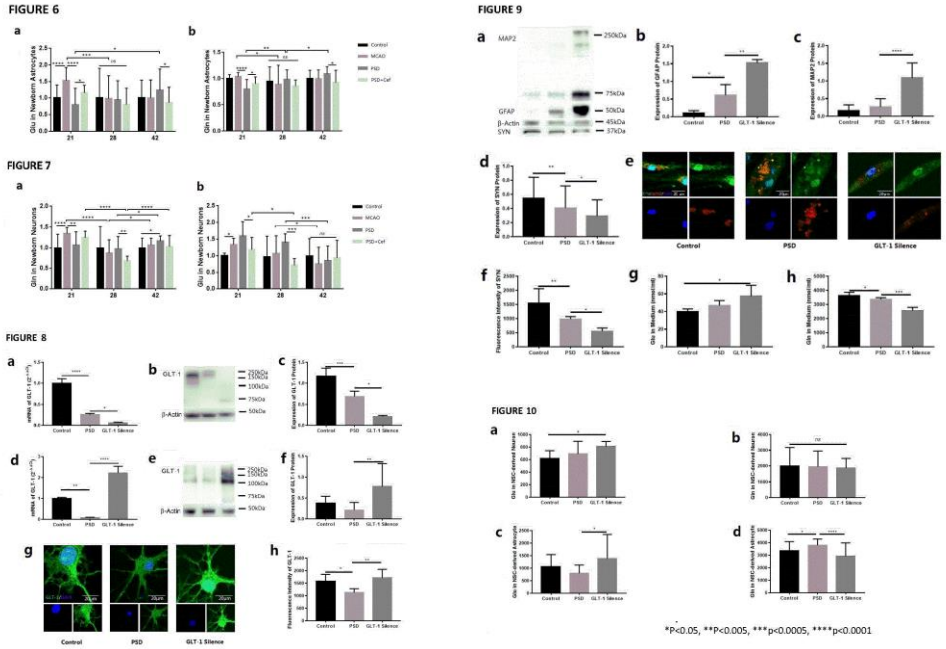
Support: National Nature Science Foundation of China （NO: 6590000127）

Title: Down-expressed GLT-1 in PSD astrocytes inhibits synaptic plasticity of NSC-derived neurons *in vivo* and *vitro*

Authors: *D. YU[1,2], Y. GUO[2], Z. CHENG[1], K. LE[2], A. I. ALI[2]
[1]Southeast Univ., Jiangsu, China; [2]Dept. of Neurol., Affiliated ZhongDa Hosp. of Southeast Univ., Nanjing, China

Abstract: ***Background/Aims:*** This study aimed to investigate whether and how glial GLT-1 of post-stroke depression(PSD) rats participates in the ouucrrence of PSD in vivo and vitro. ***Methods:*** By upregulating glial GLT-1 of PSD rats in vivo and downregulating GLT-1 in vitro, we aimed to investigate the effect of glial GLT-1 on glutamate circulation, neural and synaptic plasticity of PSD rats. ***Results:*** Downregulated glial GLT-1 was observed in the hippucampal DG(Fig. 1, 8). This was accompanied by reduction of regeneration capacity(Fig. 4), delayed reduction of synapses(Fig. 1), and changed ultrastructure of synapses(Fig. 2). Changes in hippocampal DG of PSD rats were paralleled by reduced glutamate in newborn astrocytes and higher glutamate in cerebrospinal fluid (CSF)(Fig. 5, 6, 7). Glutamine in CSF of rats remained unchanged(Fig. 5). On the contrary, upregulated glial GLT-1 in PSD rats promoted synaptic plasticity in hippocampus by improving glutamate circulation, and improved depressive behaviors(Fig. 3). This effect was reversed by GLT-1-silenced astrocytes in vitro(Fig. 8, 9, 10). With the decrease of GLT-1 expressed in co-cultured astrocytes, glutamate increased and glutamine decreased in medium. In NSC-dericed neurons and astrocytes, glutamate metabolism was also affected by the changed GLT-1. ***Conclusion:*** Collectively, our findings highlight a key role of glial GLT-1 for synaptic plasticity of PSD by influencing glutamate metablism.





Disclosures: D. Yu: None. **Y. Guo:** A. Employment/Salary (full or part-time):; National Nature Science Foundation of China (NO: 6590000127). Other; Cprresponding. **Z. Cheng:** None. **K. Le:** None. **A.I. Ali:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.01

Topic: B.06. Synaptic Transmission

Support: R01-MH100561

Title: α4βδ $GABA_A$receptors trigger synaptic pruning during adolescence in layer 5 of the prelimbic medial prefrontal cortex

Authors: *M. R. EVRARD[1], M. LI[2]
[1]Physiol. and Pharmacol., SUNY Downstate Med. Ctr., Brooklyn, NY; [2]CUNY Hunter, New York, NY

Abstract: The removal of excitatory synapses during puberty is an essential occurrence by which neural circuits are streamlined, thus permitting optimal function. The medial prefrontal cortex (mPFC) is one of the primary regions implicated in anxiety disorders which occur more frequently in women. Abnormal synaptic pruning of mPFC may influence the development of these disorders. Our lab has previously reported that in CA1 hippocampus the emergence of α4βδ $GABA_A$receptors (GABARs) initiates synaptic pruning (Afroz et al., 2016) at puberty. This study investigates if the same mechanism initiates synaptic pruning in Layer 5 of the prelimbic mPFC (PL). We used Golgi staining to assess spine density comparing pubertal (P35, assessed by vaginal opening) vs. post-pubertal (P56) female mice. Individual neurons were viewed using a 100x oil objective on a Nikon Eclipse Ci-L microscope and scanned using Z-stack projection photomicrographs (0.1 μm steps) taken using a Nikon DS-U3 camera. Spine density/typing was done in Neurolucida 360 across the entire basal dendrite or in distal and proximal regions. Spine density decreased 40%~ across adolescence (8.9 ± 0.73 spines/10 μm, pub vs. 5.5 ± 0.38 spines/10 μm, post-pub, $P<0.05$) with mushroom spines showing the greatest decrease (~62%, 1.8 ± 0.23 spines/10 μm, pub; 0.66 ± 0.12 spines/10 μm, post-pub, $P<0.05$). Spine density of the distal portion exhibited a ~35% decrease in spine density (11.1 ± 0.9 spines/10 μm, pub, 7.3 ± 0.7 spines/10 μm, post-pub, $P<0.05$) with mushroom spines, again, showing the greatest decline (~57%, 2.2 ± 0.28 spines/10 μm, pub; 0.93 ± 0.18 spines/10 μm, post-pub, $P<0.05$). While the proximal region did not have a significant decline in spine density mushroom spines significantly decreased (~77%, 1.3 ± 0.23 spines/10 μm, pub; 0.30 ± 0.11 spines/10 μm, post-pub, $P<0.05$). To test the role of α4βδ GABARs, we assessed α4 expression using immunohistochemistry; α4 expression increased at puberty, (mean ± S.E.M. $t(18)=12.6$, *P=2.2 x 10-10), localized to the spine head and dendritic shaft. Functional expression of α4βδ GABARs at puberty was confirmed by a 10-fold greater response of pyramidal cells to 100 nM gaboxadol, which is selective for α4βδ, compared to pre-puberty, (assessed using whole cell patch clamp recordings). Finally, to establish the role of pubertal α4βδ GABARs in pruning of this region, we compared spine density/spine types from pubertal and post-pubertal α4 knock-out mice. Unlike wild-type mice, there were no significant differences in spine density or type across adolescence. Taken together these data suggest that in Layer 5 of the PL adolescent synaptic pruning is initiated by the emergence of α4βδ GABARs.

Disclosures: M.R. Evrard: None. **M. Li:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.02

Topic: B.06. Synaptic Transmission

Support: DAAD fellowship to FHN

DFG GRK14592 to H.-J.K.

Title: Shank3 as a component of synaptic Ras-dependent signaling pathways which are disrupted in autism

Authors: *H.-J. KREIENKAMP[1], F. HASSANI NIA[2], V. MARTENS[2]
[2]Human Genet., [1]UKE Hamburg, Hamburg, Germany

Abstract: Shank proteins (Shank1-3; also known as ProSAPs) are major scaffolding protein of the postsynaptic density of glutamatergic synapses. Mutations found in the *SHANK3* gene are associated with autism in human patients. Both heterozygous loss of function and missense mutations have been observed in patients. For a better understanding of the pathophysiology associated with missense mutations, it will be required to understand the functional relevance of these mutations with respect to the molecular functions of Shank3 protein. We have analyzed mutations affecting the Shank/ProSAP N-terminal (SPN) and Ankyrin repeat domains of Shank3. Through 3D structural and biochemical analyses we identified the SPN domain as a Ras association (RA) domain with high affinity for active (GTP-bound) G-proteins of the Ras family (H-Ras, K-Ras, R-Ras, as well as Rap1 variants). Interaction of Shank3 with these G-proteins is in each case blocked by two mutations in the SPN domain which were found in autism patients (R12C and L68P). The structural analysis also further confirms that the SPN is involved a tight intramolecular interaction with the Ankyrin repeats. Assuming that Shank3 acts downstream as an effector in Ras mediated signaling, we analyzed the effect of active Ras variants on molecular interactions of Shank3. Here we indeed observed that binding of Shank3 to ligands of the Ankyrin repeats is altered upon Ras activation. Furthermore, we noted that access of Ras variants to the N-terminal SPN domain is regulated by parts of the central portion of the protein, involving the PDZ domain and parts of the long proline rich region. Importantly, upon expression in cultured hippocampal neurons, we observed that active Ras alters the localization of Shank3. Taken together, our data show that Shank3 is a component of a synaptic Ras-dependent signaling pathway, which is disrupted by mutations observed in autistic patients.

Disclosures: H. Kreienkamp: None. **F. Hassani Nia:** None. **V. Martens:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.03

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant NS101534

Title: Vascular endothelial growth factor (VEGF) receptor VER-1 and VER-4 regulate glutamatergic behavior by promoting cell surface levels of GLR-1 glutamate receptors

Authors: *P. JUO, E. LUTH, C. RICCIO, J. HOFER, K. MARKOJA
Tufts Univ. Sch. of Med., Boston, MA

Abstract: Regulation of glutamate receptor trafficking is important for controlling synaptic strength, learning and memory. We took advantage of a simple, mechanosensory reflex in *C. elegans* to develop an optogenetically-controlled, behavioral screen for novel genes that regulate glutamatergic signaling. Mechanical stimulation of the glutamatergic sensory neuron ASH in the head activates GLR-1/AMPA receptor-expressing command interneurons resulting in backward locomotion. Channelrhodopsin expression specifically in ASH enabled us to photostimulate the mechanosensory reflex and perform an RNAi screen for genes required for glutamatergic behavior. We identified the Vascular Endothelial Growth Factor (VEGF) Receptor-related genes *ver-1* and *ver-4* in this screen. This finding was unexpected because *C. elegans* do not possess a cardiovascular system. Mammalian VEGF signaling plays important roles in vascular development, however increasing evidence has revealed key roles for VEGF in neuronal development and plasticity. We found that *ver-1* and *ver-4* loss-of-function mutants have specific defects in glutamatergic behavior with no alterations in neuromuscular junction function. The behavioral defects can be rescued by expression of wild type *ver-1* or *ver-4* cDNA in GLR-1-expressing interneurons, but not in upstream ASH neurons of the mechanosensory reflex circuit. Consistent with these results, ASH neuron process morphology and the axonal distribution of presynaptic RAB-3 appear normal in *ver* mutants. Analysis of GLR-1 tagged with pH-sensitive-Superecliptic phluorin revealed that *ver-1* and *ver-4* mutants have reduced surface levels of GLR-1. Furthermore, blocking GLR-1 endocytosis with *unc-11*/AP180 clathrin adaptin mutations abrogates the effects of the *ver* mutants on surface GLR-1, suggesting that the VERs might act on a post-endocytic pool of receptors. Finally, loss-of-function mutations in *pvf-1*, the only known worm VEGF homolog, results in similar defects in glutamatergic behavior and in GLR-1 surface levels. Together, these data are consistent with a model where the ligand PVF-1 and the VEGFRs VER-1 and VER-4 regulate glutamatergic behavior by promoting surface levels of GLR-1 glutamate receptors. This work also suggests that VEGF signaling may have appeared first in the nervous system prior to evolution of the vasculature.

Disclosures: P. Juo: None. **E. Luth:** None. **C. Riccio:** None. **J. Hofer:** None. **K. Markoja:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.04

Topic: B.07. Synaptic Plasticity

Support: Deutsche Forschungsgemeinschaft (SFB1089: C01, B06)
CoEN (CoEN3018)
ERA-NET MicroSynDep
Fondation pour la Recherche Médicale (DEQ20160334901)
CoEN (ANR-16-COEN-0003-02)
Fondation pour la Recherche Médicale (634FDT20160435677)
Boehringer Ingelheim Fonds PhD fellowship

Title: High spine turnover in the mouse hippocampus revealed by two-photon STED microscopy *in vivo*

Authors: *S. POLL[1], T. PFEIFFER[3,4], S. BANCELIN[3,4], J. ANGIBAUD[3,4], K. V. V. G. INAVALLI[3,4], K. KEPPLER[2], M. MITTAG[1], V. U. NÄGERL[3,4], M. FUHRMANN[1]
[1]Neuroimmunology and Imaging, [2]Light Microscope Facility (LMF), German Ctr. for Neurodegenerative Dis. (DZNE), Bonn, Germany; [3]CNRS UMR 5297, Interdisciplinary Inst. for Neurosci., Bordeaux, France; [4]Univ. of Bordeaux, Bordeaux, France

Abstract: The adaption of neuronal networks upon experience is thought to underlie the formation and elimination of synaptic connections. Dendritic spines represent the postsynapse of excitatory synapses and have been extensively studied in different areas of the mouse cortex *in vivo*. By contrast, studies in the deeply embedded hippocampus, the archetypical memory center of the brain, are rare, due to limited access. Furthermore, dendritic spines are denser on hippocampal than on cortical dendrites hindering the exact measurement of density and turnover in this brain region with classical two-photon *in vivo* imaging approaches. To address this issue, we established chronic *in vivo* super-resolution microscopy in mouse hippocampus by combining a hippocampal window and two-photon stimulated emission depletion (2P-STED) microscopy. We measured two-fold higher spine density compared to previous studies using conventional two-photon microscopy. In addition, we observed a spine turnover of 40% within four days, which primarily affected small spines, underscoring the high synaptic rewiring potential of the hippocampus. Our study demonstrates chronic super-resolution microscopy in the mouse hippocampus *in vivo*, enabling longitudinal analysis of nanoscale neuroanatomical structures. This technique will be highly beneficial for the investigation of behavior-dependent structure and function relationships of synaptic connections in the living brain.

Disclosures: S. Poll: None. **T. Pfeiffer:** None. **S. Bancelin:** None. **J. Angibaud:** None. **K.V.V.G. Inavalli:** None. **K. Keppler:** None. **M. Mittag:** None. **V.U. Nägerl:** None. **M. Fuhrmann:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.05

Topic: B.07. Synaptic Plasticity

Title: A deformation-based morphometry on exercise-induced effects in hippocampal subregions

Authors: *Y. CHEN[1], A. BECKE[2], A. CARDENAS-BLANCO[2], E. DUZEL[3]
[1]Inst. of Cognitive Neurol. and Dementia Res., Otto-von-guericke-University Magdeburg, Magdeburg, Germany; [2]DZNE, Magdeburg, Germany; [3]Inst. Cognitive Neurol. and Dementia Res., Magdeburg, Germany

Abstract: The hippocampus (HC) is as one of the brain regions most sensitive to the effects of aerobic exercise. Numerous studies in animals and humans suggest that such effects could be associated with vascular/neuro-genesis related hippocampal plasticity and may prevent age-related decline with various improvements in cognitive performance. The morphometric changes of this critical brain region, however, have often a very small effect size (<2%) over the plausible time-span of most studies. While previous studies have heavily relied on direct comparison of segmentations across different time points, the reported effects are strongly influenced by the segmentation procedures thus often appear to be equivocal. Here we address this problem by combining ultra-high field imaging and diffeomorphic deformation-based morphometry (DBM), aiming at a statistically sensitive and spatially specific analyzing approach.
41 subjects participated in a 4-month physical exercise intervention and were scanned 3 times (at 0, 1 and 4 months) in a 7T scanner. Ultra-high resolution (0.44x0.44x1.1 mm), T2-weighted coronal slabs were acquired at each time points, covering the whole HC region. Bilateral HC subregions from all the time points were segmented manually to calculate CA1-3, DG and Subiculum volumes for later comparison. For each subject, rigid transformations between T2 images at different time points were first estimated and symmetrically applied to the image pairs to minimize subsequent estimation bias [1]. The Symmetric Normalization algorithm from ANTs package [2] was then used to determine the diffeomorphic deformation between the images. Morphometric changes of the HC subregions from the deformation were computed in both volumetric and surface-based ways, by integrating the deformation Jacobian determinant and the deformation flow through subregion surfaces.
Our results from DBM showed a similar trend as the volumetric changes calculated from manual segmentation. However, the variance of volume change across subjects from DBM is significantly smaller, leading to improved statistical power. Moreover, the volumetric and surface-based morphometric analyses provided spatially specific information on how subregions of HC are differentially affected by exercise.
In summary, our study demonstrated the great potential of diffeomorphic DBM in analyzing

exercise-induced effects on HC, and with the spatially specific morphometry, promises a detailed understanding of the HC plasticity induced by aerobic exercise.

Reference

[1] Yushkevich, P., et al., 2010. NeuroImage.
[2] Avants, B.B., et al., 2008. Med. Image Analysis.

Disclosures: Y. Chen: None. **A. Becke:** None. **A. Cardenas-Blanco:** None. **E. Duzel:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.06

Topic: B.07. Synaptic Plasticity

Support: Swedish Brain Foundation research fellowship
Swiss National Science Foundation SNF171978
Burroughs Wellcome Fund Career Awards at the Scientific Interface
the Searle Scholars Program
Packard award in Science and Engineering
NARSAD Young Investigator Award
the JBP Foundation

Title: Npas4 is a critical regulator of learning-induced plasticity at mossy fiber-CA3 synapses during contextual memory formation

Authors: *F.-J. WENG[1], R. I. GARCIA[1], S. LUTZU[2], K. ALVINA[2,3], Y. ZHANG[1], M. DUSHKO[1], T. KU[1], K. ZEMOURA[1], D. RICH[1], D. GARCIA-DOMINGUEZ[1], M. HUNG[1], T. D. YELHEKAR[1], A. T. SORENSEN[1,4], W. XU[1], K. CHUNG[1], P. E. CASTILLO[2], Y. LIN[1]
[1]Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA; [2]Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY; [3]Dept. of Biol. Sci., Texas Tech. Univ., Lubbock, TX; [4]Dept. of Neurosci., Univ. of Copenhagen, Copenhagen, Denmark

Abstract: Synaptic connections between hippocampal mossy fibers (MFs) and CA3 pyramidal neurons are essential for contextual memory encoding, but the molecular mechanisms regulating MF-CA3 synapses during memory formation and the exact nature of this regulation are poorly understood. Here we report that the activity-dependent transcription factor Npas4 selectively regulates the structure and strength of MF-CA3 synapses by restricting the number of their functional synaptic contacts without affecting the other synaptic inputs onto CA3 pyramidal neurons. Using an activity-dependent reporter, we identified CA3 pyramidal cells that were activated by contextual learning and found that MF inputs on these cells were selectively strengthened. Deletion of Npas4 prevented both contextual memory formation and this learning

induced synaptic modification. We further show that Npas4 regulates MF-CA3 synapses by controlling the expression of the polo-like kinase Plk2. Thus, Npas4 is a critical regulator of experience-dependent,structural, and functional plasticity at MF-CA3 synapses during contextual memory formation.

Disclosures: F. Weng: None. **R.I. Garcia:** None. **S. Lutzu:** None. **K. Alvina:** None. **Y. Zhang:** None. **M. Dushko:** None. **T. Ku:** None. **K. Zemoura:** None. **D. Rich:** None. **D. Garcia-Dominguez:** None. **M. Hung:** None. **T.D. Yelhekar:** None. **A.T. Sorensen:** None. **W. Xu:** None. **K. Chung:** None. **P.E. Castillo:** None. **Y. Lin:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.07

Topic: B.07. Synaptic Plasticity

Support: Simons Foundation Award #: 345485

Title: Regulation of Homeostatic Plasticity by Shank3

Authors: *V. TATAVARTY[1], C.-H. WU[1], H. K. LIN[1], K. B. HENGEN[3], A. TORRADO PACHECO[1], N. J. MISKA[2], G. TURRIGIANO[1]
[2]Neurosci., [1]Brandeis Univ., Waltham, MA; [3]Biol., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: Firing rates in the rodent visual cortex remain remarkably stable through various state transitions (Hengen at al 2016). How this stability is maintained in the face of dramatically changing stimulus is not known. It has been proposed that if neocortical firing rates are not maintained in an ideal regime, networks become susceptible to catastrophic failure due to run away activity (e.g. epileptic state) or complete silencing (catatonic state). Homeostatic mechanisms in the brain are critical regulators of network stability that prevent networks from entering these extreme regimes. Homeostatic control over firing rates is realized via the exquisite control of synaptic and intrinsic properties of individual neurons. In fact, deficits in homeostasis have been proposed to contribute to pathogenesis of Autism Spectrum Disorders (ASDs) (Valakh and Nelson 2015). Here we investigate the hypothesis that aberrant homeostatic plasticity may contribute the pathogenesis of Autism Spectrum Disorders (ASDs). We first delineated the role of Shank3 (a gene linked to ASDs) in homeostasis in cultured neurons. Our electrophysiological as well as immunostaining data demonstrate that a transient knockdown of Shank3 with Short Hairpin (SH) expression, leads to dramatic deficits in intrinsic and synaptic homeostatic mechanisms in cultured neurons. Using awake behaving animal multi electrode array recording from the visual cortex in Shank3 knockout mice, we further demonstrate that the lack of Shank3

also leads to deficits in firing rate homeostasis in vivo. We are investigating the mechanistic basis of these homeostatic deficits caused by a lack of Shank3 using phosphoproteomics as well other biochemical approaches to identify key signaling pathways. We find that treatment of Shank3 deficient cells with lithium is able to rescue deficits in synaptic as well as intrinsic homeostasis. These results support the idea that deficits in homeostatic mechanisms play an important role in the pathogenesis of ASDs.

Disclosures: V. Tatavarty: None. **C. Wu:** None. **H.K. Lin:** None. **K.B. Hengen:** None. **A. Torrado Pacheco:** None. **N.J. Miska:** None. **G. Turrigiano:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.08

Topic: B.07. Synaptic Plasticity

Support: NIH Grant NS093057

Title: Short-term brain network changes following repeated optogenetic M1 stimulation

Authors: *S. VAHDAT[1], M. CHENG[2], M. ITO[2], H. LEE[1], G. STEINBERG[2], J. LEE[1]
[1]Dept. of Neurol., [2]Dept. of Neurosurg., Stanford Univ., Stanford, CA

Abstract: Neural stimulation is often carried out through a block-design approach, in which repeated blocks of stimulation are delivered to specific brain areas. This approach has been utilized as a means to promote motor recovery and function following ischemic stroke or in Parkinson's disease. However, the effect of repeated blocks (in the order of tens of seconds) of stimulation on brain network dynamics is not well understood. Recently, optogenetic stimulation has been used an alternative approach to traditional deep brain stimulation, allowing cell-type-specific activation of different neural populations with high temporal resolution. Here, we used a technique called optogenetic functional magnetic response imaging (ofMRI) to examine large-scale brain network changes associated with repeated blocks of optogenetic stimulation.
We performed ofMRI experiments targeting M1 layer V excitatory neurons in 11 mice by injecting AAV1-CamKIIa-ChR2-eYFP viral vector, and investigated pattern of brain activation changes over repeated runs of stimulation in a block-design paradigm. Moreover, in order to identify persistent changes in brain connectivity that outlast the period of stimulation, we examined changes in functional connectivity between the stimulation site and the rest of the brain during resting-state periods before and after optogenetic stimulation.
Our results show that 1) M1 layer V excitatory neurons stimulation activates a widespread network of cortical and subcortical areas including the ipsilateral M1, M2 S1, and thalamus and the contralateral M1. 2) Repeated runs of stimulation potentiate activation locally in the

stimulation site (M1) and remotely in the ipsilateral thalamus (VL, and VPL, and VPM nuclei), while suppress activation in the ipsilateral striatum. 3) Over the first stimulation run activation increases linearly in ipsilateral thalamus. 4) Functional connectivity between the stimulation site and both ipsilateral striatum and thalamus is increased during resting-state periods following stimulation as compared to baseline pre-stimulation periods.
These findings indicate that repeated blocks of M1 optogenetic stimulation result in potentiation and depression of activity in local and remote brain areas that are known to be the targets of M1 pyramidal neurons projections. Additionally, our results reveal that the potentiation of the cortico-thalamic pathway outlasts the periods of M1 stimulation for at least the next 10 minutes during the resting-state periods. These findings should be considered when designing optogenetic stimulation parameters in preclinical studies.

Disclosures: S. Vahdat: None. **M. Cheng:** None. **M. Ito:** None. **H. Lee:** None. **G. Steinberg:** None. **J. Lee:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.09

Topic: B.07. Synaptic Plasticity

Support: The Hartwell Foundation
NIH Grant R01 MH099114

Title: Extracellular vesicle release facilitates rapid synaptic strengthening

Authors: *Y.-Z. WANG[1], C. PIOCHON[2], Q. HE[3], S. MARSHALL[4], S. SMUKOWSKI[4], E. T. BARTOM[4], A. SHILATIFARD[4], A. CONTRACTOR[4], J. N. SAVAS[5]
[1]Neurol., [2]Dept. of Physiol., Northwestern Univ., Chicago, IL; [3]Physiol., Northwestern Univ. Dept. of Physiol., Chicago, IL; [4]Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [5]Northwestern University, Feinberg Sch. of Medici, Chicago, IL

Abstract: Extracellular vesicles (EVs, including exosomes) are newly identified vesicles bud from cell surface and considered as novel ways for cell communication. Until now, our understanding of the importance of EVs has been limited to pathological contexts such as cancer or neurodegeneration. Although neuronal EVs (NEVs) were identified nearly a decade ago, their physiological significances remain largely unknown. Here we report that, NEVs are released shortly after the induction of synaptic strengthening and are required for the establishment of it. Through bioinformatic analysis of transcriptome and quantitative proteomic data, we found a panel of EV proteins that exhibited high dynamic shortly after glycine (Mg^{2+}-free) treatment. This process reflected rapid NVE dynamics, which was confirmed by immunocytochemistry and

real-time monitoring release. We identified many postsynaptic proteins in purified NEVs by mass spectrometry and detected key EV proteins enriched in purified postsynaptic density (PSD) fraction. This findings strongly suggested that postsynapses are important NEV release sites. Interestingly, blocking NEV synthesis or trafficking greatly impaired AMPAR trafficking in postsynaptic membranes. Furthermore, potentiation of miniature excitatory postsynaptic current (mEPSC) amplitudes was largely abolished by pre-incubation of neurons with an EV synthesis inhibitor. The mechanisms that regulate the post-synaptic proteome to cause plasticity of synapses are not well defined. Therefore, rapid NEV release potentially provides one such mechanism to unlock synapses and facilitate rearrangement of discrete synaptic proteins, which is a necessary step for rapid synaptic strengthening. Overall, we reveal a critical physiological role of NEVs, and discover a key cellular process underlying synaptic potentiation that may be fundamental to regulating synaptic efficacy.
Terms: Extracellular vesicle, Long-term potentiation, Proteomics, Mass spectrometry, RNA sequencing

Disclosures: Y. Wang: None. **C. Piochon:** None. **Q. He:** None. **S. Marshall:** None. **S. Smukowski:** None. **E.T. Bartom:** None. **A. Shilatifard:** None. **A. Contractor:** None. **J.N. Savas:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.10

Topic: B.02. Ligand-Gated Ion Channels

Support: 5R01DA022727-11
1R01NS106906-01
5 R01 MH100093-05

Title: Molecular mechanisms of the EphB-NMDAR interaction

Authors: H. R. WASHBURN[1], N. XIA[1], W. ZHOU[1], S. HASSLER[3], T. J. PRICE[3], *M. B. DALVA[2]
[2]Neurosci., [1]Thomas Jefferson Univ., Philadelphia, PA; [3]Sch. of Behavioral and Brain Sci., UTD, Richardson, TX

Abstract: Crucial for proper synaptic development is the EphB family of receptor tyrosine kinases and their membrane bound ligands, the ephrin-Bs. The binding of ephrin-B2 to the ligand binding domain (LBD) of EphB2 drives a direct extracellular interaction between the EphB2 receptor and the N-methyl-D-aspartate receptor (NMDAR), an ionotropic glutamate receptor required for synaptic plasticity. Normal brain function requires that NMDARs are properly

localized to synaptic sites, whereas absence of the NMDAR is lethal in mice. EphB2 is necessary for the correct localization and function of NMDAR at synapses. However, because the mechanisms enabling extracellular interactions have not been well studied, the mechanisms of interaction between EphB2 and the NMDAR have yet to be determined.We demonstrated that EphB2 undergoes post-translational modification of its extracellular domain that enables it to interact with the NMDAR. Unbiased mass spectrometry data showed that a specific tyrosine reside, Y504, in the fibronectin type III (FN3) repeat domain of the extracellular region of EphB2 undergoes ephrin-B2 ligand-dependent phosphorylation. Furthermore, functional analysis of EphB2 phosphorylation mutants indicated that Y504 is necessary and sufficient for the EphB-NMDAR interaction.Here we identify a specific group of amino acids in the hinge region of the N-terminal domain of the GluN1 subunit of the NMDAR that is necessary for the EphB-NMDAR interaction. Our data suggest that this interaction may be mediated by charge, as model-based mutational analysis indicate that a positive surface charge in this region is required for interaction with the negatively charged phospho-site in EphB2. Loss of the NMDAR-EphB interaction, by either mutating GluN1 to be more negatively charged in the hinge region or knocking down endogenous EphB2, increases NMDAR mobility. These findings define a novel mechanism for extracellular interaction mediated by charged domains.

Disclosures: H.R. Washburn: None. **N. Xia:** None. **W. Zhou:** None. **S. Hassler:** None. **T.J. Price:** None. **M.B. Dalva:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.11

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH R01MH085666
NIH/NINDS F99NS105185

Title: PSD-95 deficiency alters afferent-specific projections in the mPFC

Authors: *A. A. COLEY[1], S. YANG[3], B. XING[2], W.-J. GAO[4]
[1]Dept. of Neurobio. and Anat., [2]Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [3]Drexel Univ. Sch. of Med., Philadelphia, PA; [4]Dept Neurobiol & Anat., Drexel Univ. Col. Med., Philadelphia, PA

Abstract: Postsynaptic density protein-95 (PSD-95) is a major scaffolding protein involved in the maturation of excitatory synapses by interacting and trafficking NMDARs and AMPARs to the postsynaptic membrane of the dendritic spine during neurodevelopment. The medial prefrontal cortex (mPFC)—a brain region responsible for cognition and sociability—contains

major reciprocal connections with the mediodorsal thalamus (MD), and this connectivity is severely disrupted in psychiatric disorders such as schizophrenia and autism. Coincidently, PSD-95 disruption has been linked to both disorders, but how PSD-95 deficiency affects the MD-mPFC connectivity remains unknown. Using PSD-95 deficient mouse models (PSD-$95^{+/-}$ & PSD-$95^{-/-}$) combined with electrical and/or optogenetic simulation, we compare corticocortical versus thalamocortical connections in the mPFC. *We hypothesize that there will be afferent-specific alterations in NMDAR/AMPAR-mediated transmission in in the mPFC of PSD-$95^{-/-}$*. Our results reveal a significant increase in NMDAR/AMPAR-mediated current amplitude ratio in corticocortical connection, indicating an increase in silent synapses in PSD-95 deficient mice. In contrast, there is a significant reduction in NMDAR/AMPAR-mediated transmission in MD-mPFC connection in the PSD-$95^{+/-}$ and PSD-$95^{-/-}$ mice. This data suggests afferent specific alterations within the mPFC in response to PSD-95 deficiency. Future experiments will test projections from the controlateral hemisphere and the ventral hippocampus (vHPC), by optically stimulating these cortical afferents that project on layer V pyramidal neurons of the mPFC. These studies would indicate which projections are susceptible to PSD-95 deficiency and thus may contribute to the pathologies associated with psychiatric disorders.

Disclosures: A.A. Coley: None. **S. Yang:** None. **B. Xing:** None. **W. Gao:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.12

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant RO1 NS097016 03

Title: Both GluN2A and GluN2B NMDA receptors undergo Ca^{2+}-dependent inactivation by accumulating in desensitized states

Authors: *G. IACOBUCCI[1], G. K. POPESCU[2]
[1]Biochem., Univ. At Buffalo, Buffalo, NY; [2]Biochem., Univ. at Buffalo, SUNY, Buffalo, NY

Abstract: NMDA receptors are Ca^{2+}-permeable channels gated by glutamate and are essential for excitatory synaptic transmission during physiologic and pathologic brain processes. Ca^{2+}-dependent inactivation (CDI) by calmodulin is a regulatory mechanism that reduces NMDA receptor gating in an activity-dependent manner. Although the obligatory GluN1 subunit directly mediates CaM binding and is required for CDI, the present literature suggests that GluN2B receptors are insensitive to CDI. We used electrophysiological recordings of recombinant NMDA receptors, to examine the mechanism of CDI subtype-dependency. Whole-cell currents recorded in the presence of 2 mM external Ca^{2+} showed that CDI is robust for GluN2A channels

(CDI_{2A} = 0.51 ± 0.05) but appears absent for GluN2B (CDI_{2B} = 0.04 ± 0.07), as previously reported. However, when we dialyzed Ca^{2+} intracellularly, we detected robust CDI for both GluN2A and GluN2B channels (CDI_{2A} = 0.80 ± 0.06; CDI_{2B} = 0.52 ± 0.06), indicating that GluN2B channels are susceptible to CDI. To investigate this apparent discrepancy, we used patch clamp fluorometry to record single-channel activity from individual NMDA receptors (as Na^{+} influx) and simultaneously monitor intracellular Ca^{2+}elevations upon ionomycin treatment. We found upon Ca^{2+}entry, the gating kinetics of both GluN2A and GluN2B channels decreased by a common kinetic mechanism, reflecting the accumulation of channels in long-lived closed (desensitized) states. Moreover, the derived kinetic models suggested that the apparent subtype-dependent susceptibility to CDI of NMDA receptors by external Ca^{2+} reflects differences in equilibrium open probability (P_o) which correlate with the amount of receptor-fluxed Ca^{2+}. To test this hypothesis, we measured CDI by external Ca^{2+} using whole cell recordings from GluN2B channels carrying a Lurcher (Lc) mutation, $GluN1^{A652Y}$, which dramatically increases channel P_o ($P_{o,\,2Bwt}$ = 0.19 ± 0.07; $P_{o,\,Lc}$ = 0.81 ± 0.08). We found that 2 mM external Ca^{2+} produced robust CDI for these high-P_o GluN2B channels (CDI_{Lc} = 0.54 ± 0.06). Together, these results show that Ca^{2+} flux produces activity-dependent CDI for both GluN2A and GluN2B receptors and that the extent of CDI varies with channel P_o. These results are consistent with CDI as a neuroprotective mechanism against excessive Ca^{2+} load during high-P_o activation.

Disclosures: G. Iacobucci: None. **G.K. Popescu:** None.

Nanosymposium

539. Postsynaptic Organization and Structure

Location: SDCC 31C

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 539.13

Topic: B.02. Ligand-Gated Ion Channels

Support: R33DA041876
R21DA041876
K01NS073700

Title: Regulation of NMDA receptor phosphorylation by PP1 targeting protein, spinophilin

Authors: *A. BEIRAGHI SALEK[1], V. OLFOUSI[2], M. C. EDLER, JR[4], J. MCBRIDE[3], A. J. BAUCUM II[5]
[1]Biol., IUPUI, Indianapolis, IN; [2]Biol., Indiana university-Purdue university- Indianapolis, Indianapolis, IN; [3]Biol., Indiana university-Purdue university- Indianapolis, INDIANAPOLIS, IN; [4]Biol., Indiana Univ. Purdue Univ. Indianapolis, Indianapolis, IN; [5]Biol., Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN

Abstract: Excitotoxicity is a result of cerebral ischemic insult that is associated with accumulation of glutamate in the extracellular space. Excitotoxicity requires activation of glutamate receptors such as the N-methyl-D-Aspartate (NMDA) receptors. Excessive influx of calcium as a result of receptor activation, will eventually activate apoptotic pathways and is the most widely recognized correlative factor leading to loss of neurons. Regulation of NMDA receptor subunit composition, localization, surface expression, and activity strongly determine the activation of pro-death or pro-survival pathways after a course of an ischemic insult. Differential subunit phosphorylation of NMDA receptors define receptor activity, downstream signaling pathways, and localization. GluN2B, one of the main subunits of NMDARs, is known to particularly play a role in ischemic neuronal toxicity such that GluN2B KO neurons show more resistance to ischemic insults. However, this effect of GluN2B containing NMDARs is highly dependent on localization such that activation of synaptic NMDA receptors demonstrate more neuroprotective role whilst extrasynaptic receptors induce more neurotoxic effects. Mechanistically, NMDA receptor subunit phosphorylation regulates many properties of these channels. However, the phosphatase-dependent mechanisms in modulating NMDA receptor phosphorylation has not been well characterized. Spinophilin, the main postsynaptic-enriched protein phosphatase 1 (PP1) targeting protein, regulates both PP1 activity and PP1 targeting. Various subunits of NMDA receptor interacts with spinophilin and this interaction regulates PP1-dependent NMDA receptor function. Our data show that spinophilin decreases both PP1γ1 and PP1α binding to the GluN2B subunit of the NMDAR in a heterologous cell system. We also demonstrate that, overexpression of spinophilin attenuated PP1-induced decreases in Ser-1284 phosphorylation on GluN2B, a site known to be hyperphosphorylated in animal models of ischemia. Our data also suggest that activation of endogenous PKA and/or overexpression of PKA catalytic subunit in a heterologous cell system robustly increased the association between spinophilin and the GluN2B subunit of the NMDAR. Conversely, CDK5 along with its activator, p35, decrease the interaction when overexpressed. Taken together, our data demonstrate a unique mechanism by which spinophilin attenuates PP1γ1-dependent dephosphorylation of GluN2B at Ser-1284, a site that has altered phosphorylation in ischemia.

Disclosures: A. Beiraghi Salek: None. **V. Olfousi:** None. **M.C. Edler:** None. **J. McBride:** None. **A.J. Baucum II:** None.

Nanosymposium

540. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways

Location: SDCC 24

Time: Tuesday, November 6, 2018, 1:00 PM - 2:30 PM

Presentation Number: 540.01

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

Title: ApoE receptor sortilin affects brain lipid homeostasis in an apoE isoform-specific manner

Authors: *T. WILLNOW[1], A. ASARO[2], A.-S. CARLO[2]
[1]Max-Delbrueck-Center, Berlin, Germany; [2]Max-Delbrueck Ctr. for Mol. Med., Berlin, Germany

Abstract: Sortilin is a member of the VPS10P domain receptor gene family, a class of sorting receptors with central roles in control of neuronal viability and function. Previously, we showed that sortilin acts as a neuronal receptor for apolipoprotein E (APOE), the main apolipoprotein to deliver lipids to neurons and major risk factor for sporadic AD (Carlo et al., J Neurosci 2013). To investigate the APOE isoform-specific contribution of sortilin to brain lipid homeostasis, we introduced the sortilin gene defect into mice carrying a targeted replacement (TR) of the murine Apoe locus with the human APOE3 or APOE4 genes. Subsequently, we performed lipidomics analyses in the brain of APOE3 and APOE4 TR animals either wild-type or deficient for sortilin. Major differences in the brain lipidome were detected comparing APOE3 and APOE4 TR mice wild-type for sortilin, supporting distinct functions for APOE3 and APOE4 in brain lipid metabolism. Interestingly, we also noted profound lipid changes in the brain of sortilin-deficient compared to wild-types on a APOE3 TR background, but only minor differences between the two genotype groups in APOE4 TR mice. These findings suggest distinct functions for APOE3 in the brain that are dependent on sortilin. In contrast, no sortilin-dependent activities in neuronal lipid metabolism can be assigned to APOE4. Current studies aim at further elucidating the molecular mechanisms whereby sortilin impacts isoform-specific functions of APOE in the brain and potentially impacts the risk of AD associated with APOE4.

Disclosures: T. Willnow: None. **A. Asaro:** None. **A. Carlo:** None.

Nanosymposium

540. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways

Location: SDCC 24

Time: Tuesday, November 6, 2018, 1:00 PM - 2:30 PM

Presentation Number: 540.02

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

Support: NIH F30 AG051327
NIH T32 AG20506
NIH T32 GM008152

Title: Neuronal APOE modulates a sporadic Alzheimer's disease phenotype in patient-derived induced neurons

Authors: *A. R. WADHWANI[1], J. A. KESSLER[2]
[2]Davee Dept Neurol, [1]Northwestern Univ., Chicago, IL

Abstract: The apolipoprotein E (APOE) E4 isoform is the strongest genetic risk factor for sporadic Alzheimer’s disease (sAD). While APOE is predominantly expressed by astrocytes in

the central nervous system, neuronal expression of APOE is of increasing interest in age-related cognitive impairment, neurological injury, and neurodegeneration. The human and murine APOE promoter sequences contain distinct regions that control expression in a species-specific, cell-type specific manner, and consequently, neuronal APOE has not been implicated directly in neurotoxicity. Here we show that endogenous expression of E4 weakens neurons and contributes to the sAD cellular phenotype. Genetic correction of E4 to the risk-neutral E3 isoform in three patient lines reduces tau phosphorylation and phosphoactivation of a specific kinase in excitatory neurons. Moreover, E4 promotes secretion of proaggregatory species of amyloid ß, and E4 exacerbates the neurotoxic effects of a calcium ionophore. Our results demonstrate that neuronal APOE is an upstream modulator of multiple cellular pathways that in turn predisposes neurons to synapse deterioration, calcium dysregulation, and ultimately, cell death. Importantly, these effects are independent of, but likely compounded by, glial APOE by distinct mechanisms. These findings demonstrate the utility of a reductionist human stem-cell derived system for *in vitro* modeling of disease and emphasize a heretofore underappreciated, cell-autonomous role of APOE in neurons. Because of this, novel therapeutic strategies to control neuronal APOE expression in a cell-type specific manner will likely protect neurons in the aging brain.

Disclosures: A.R. Wadhwani: None. **J.A. Kessler:** None.

Nanosymposium

540. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways

Location: SDCC 24

Time: Tuesday, November 6, 2018, 1:00 PM - 2:30 PM

Presentation Number: 540.03

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

Title: New paradigms in treating apoE4-associated Alzheimer’s disease; Proof of concept and translational finding from studies with the ABCA1 agonist therapeutic CS6253

Authors: H. N. YASSINE[1], *J. JOHANSSON[2], D. SVIRIDOV[3], H. ZETTERBERG[4], B. WINBLAD[5], J. K. BIELICKI[6], D. M. MICHAELSON[7]
[1]USC, Los Angeles, CA; [2]Artery Therapeutics, Inc, San Ramon, CA; [3]Baker Inst., Melbourne, Australia; [4]Inst. of Neurosci. and Physiol., the Sahlgrenska Academy at the University of Gothe, Sweden; [5]Karolinska Institute, Dept NVS, Div. of Neurogeriatrics, Huddinge, Sweden; [6]UC Berkeley, Berkeley, CA; [7]Tel Aviv Univ., Tel Aviv, Israel

Abstract: Background: The apolipoprotein E (*APOE*) ε4 allele is the strongest risk factor for Alzheimer’s disease (AD), but until recently, the mechanism of action responsible for its adverse effects was not known. Apolipoprotein E protein (apoE) in cerebrospinal fluid (CSF) and brain in men and mice, respectively, is hypolipidated in ε4 compared to non-ε4 carriers. The ATP Binding Cassette A1 (ABCA1) transfers polar lipids (free cholesterol and phospholipids) across the cell membrane to the apoE acceptor particle thereby regulating the cholesterol composition

and lipid raft configuration of the cell membrane. In the brain, this most notably occurs in glial cells.
Methods: *In vitro* and *in vivo* studies were performed to study ABCA1 - apoE interaction in the context of *APOE* ε4 AD.
Results: From the C-terminal of apoE we invented CS6253, a synthetic ABCA1 agonist that crosses the BBB. CS6253 shows an 8-fold higher binding affinity to ABCA1 compared to apoE. CS6253 incubation at therapeutic concentrations increase cholesterol efflux from apoE4 astrocytes 6-fold. Incubation of CS6253 in macrophage cells showed increased total and cell surface ABCA1 concentrations and reductions in lipid rafts. In male, female, homo- and heterozygous apoE4 TR on C57B6 background lacking α-synuclein, a model accentuating early brain pathogenesis and cognition decline (Bar 2017), CS6253 increased ABCA1 protein levels, increased apoE4 particle size/lipidation and increased apoE Receptor 1 (LRP1) and 2 (LRP8) protein levels. Concomitantly in apoE4 TR mice, hippocampal AD phenotype was reversed with lowering of intraneuronal Aβ and P-tau levels as well as increases in neurotransmitter vesicle proteins VGlut1 (glutamineric) and VGAT (GABAminergic) (all $p<0.05$). Reversal of cognition decline was observed as assessed by Morris water test and novel object recognition. CS6253 added to CSF in culture with ABCA1 expressing cells showed dose-response increase for cholesterol efflux. CS6253 ABCA1 agonist treatment in apoE4 mice lowered plasma apoJ/Clusterin and neurofilament-light (NFL) concentrations. In addition, specific apoE size and phospholipid changes were seen in brain and in plasma consistent with enhanced ABCA1-apoE cooperation.
Conclusions: The ABCA1 agonist CS6253 shows reversal of apoE4-driven AD phenotype and cognition decline in apoE TR mice with concomitant lowering of plasma apoJ/Clusterin and NFL concentrations. Targeting the ABCA1 - apoE functionality holds promise in the prevention and treatment of apoE4-driven AD and provides a signature set of biomarkers supporting translation into human studies and eventually defining optimal dose-regimen.

Disclosures: H.N. Yassine: None. **J. Johansson:** A. Employment/Salary (full or part-time):; Artery Therapeutics, Inc.. **D. Sviridov:** None. **H. Zetterberg:** None. **B. Winblad:** None. **J.K. Bielicki:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder, minor ownership. **D.M. Michaelson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); minor shareholder.

Nanosymposium

540. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways

Location: SDCC 24

Time: Tuesday, November 6, 2018, 1:00 PM - 2:30 PM

Presentation Number: 540.04

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

Support: NIH Grant 5R01NS034467

Title: Amyloid-independent cerebrovascular dysfunctions in aged humanized APOE4 targeted replacement mice

Authors: *A. MONTAGNE[1], S. BARNES[2], E. LAWSON[1], A. P. SAGARE[1], M. T. HUUSKONEN[1], A. M. NIKOLAKOPOULOU[1], D. LAZIC[1], S. REGE[1], C.-J. HSU[1], E. ZUNIGA[1], M. LADU[3], R. E. JACOBS[1], B. V. ZLOKOVIC[1]
[1]USC, Los Angeles, CA; [2]Loma Linda Univ., Loma Linda, CA; [3]Univ. of Illinois, Chicago, IL

Abstract: The apolipoprotein E-ε4 (*APOE4*) gene is associated with an early age of onset and increased risk of Alzheimer's disease (AD), a debilitating dementia with early neurovascular dysfunction that is being increasingly documented. The role of apoE in the pathogenesis of AD is not fully understood but a hypothesis gaining widespread support is that *APOE4* is involved in early impairment of the cerebrovascular system, resulting in accelerated capillary dysfunction associated with blood-brain barrier (BBB) breakdown. Cerebrovascular changes in AD have been typically attributed to amyloid-β (Aβ) and/or tau vasculotoxicity. However, neurovascular dysfunction is present in normal *APOE4* carriers before cognitive decline and Aβ accumulation occur. To address the effect of apoE4 on the spatiotemporal progression of AD, we used transgenic mice carrying 5 familial-AD mutations (*5xFAD*) that overexpress human Aβ, crossed with targeted replacement (TR) mice expressing human *APOE3* or *APOE4* (*TR-APOE3/3* or *TR-APOE4/4*). Using high-field magnetic resonance imaging (MRI) and advanced pre-/post-processing techniques, we show that aged *5xFAD; TR-APOE4* mice have an increased regional BBB permeability compared to age-matched *5xFAD; TR-APOE3* mice, which correlates with the magnitude of mural cell and tight junction losses, fibrinogen extravascular and hemosiderin deposits, as seen on post-mortem tissue sections. Most importantly, independently of amyloid pathology, aged *TR-APOE4* mice develop a comparable vascular phenotype, *i.e.*, BBB breakdown and cerebral blood flow and volume reductions, compared to age-matched *TR-APOE3* mice. Of note, behavioral testing outcomes reflect deficits in the regional neural pathways that are primarily affected by vascular defects. In addition, positive correlations between regional MR diffusion metrics and vascular dysfunction measures are also found, suggesting changes in tissue water content and connectivity, which are exacerbated in mice expressing human apoE4. Finally, using structural MR scans, we found reduced cortical thickness and hippocampal shrinkage, predominantly in mice expressing human apoE4. We validated all our MR findings with histology and biofluid biomarkers. These results corroborate our recent study in humans showing that individuals carrying the *APOE4* allele may be predisposed to accelerated vascular defects and greater BBB damage. We provide further evidence that apoE4 worsens regional brain microcirculation and BBB integrity by driving the pathological changes in the living brain leading to neuronal loss and cognitive decline independently of Aβ.

Disclosures: A. Montagne: None. **S. Barnes:** None. **E. Lawson:** None. **A.P. Sagare:** None. **M.T. Huuskonen:** None. **A.M. Nikolakopoulou:** None. **D. Lazic:** None. **S. Rege:** None. **C. Hsu:** None. **E. Zuniga:** None. **M. LaDu:** None. **R.E. Jacobs:** None. **B.V. Zlokovic:** None.

Nanosymposium

540. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways

Location: SDCC 24

Time: Tuesday, November 6, 2018, 1:00 PM - 2:30 PM

Presentation Number: 540.05

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

Support: NIH Grant U01 AG024904

Title: Effect of APOE and ABCA7 on memory decline in individuals with African ancestry

Authors: *K. D. DETERS[1], V. NAPOLIONI[2], M. D. GREICIUS[2], E. C. MORMINO[3]
[1]Neurol., Stanford, Stanford, CA; [2]Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA; [3]MGH, Boston, MA

Abstract: The APOE4 allele is *more frequent* in blacks versus whites, but, the APOE4 effect on risk of Alzheimer's disease (AD) may be *reduced* in blacks compared to whites. Although variants in ABCA7 are consistently implicated in AD, the frequency and risk across these variants also varies by race. Thus, it is critical to understand the impact of established AD risk factors across different genetic backgrounds. Linear mixed models were used to examine relationships between a priori AD genetic risk variants (APOE4, ABAC7 rs3764650) with longitudinal cognitive decline as a function of genetic ancestry, controlling for age, education, and diagnosis. Individual genetic ancestry was determined using ancestry informative markers from the 1000 Genomes Project for 1,669 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants. Finally, we determined the extent to which associations between genetic risk factors and cognition were mediated by Amyloid (measured with CSF or PET). Whereas most participants showed high European ancestry (>80%; N=1334; "EUR"), a subset of individuals showed clear admixture between European and African ancestry (N=78; "EUR+AFR") which varied continuously. Interestingly, 100% of EUR self-identified as white, whereas 84.6% of EUR+AFR identified as black. APOE4 was associated with significant memory decline in EUR (β=-0.04, $p<0.0001$) and EUR+AFR (β=-0.12, $p<0.0001$). In EUR+AFR, the APOE4 effect was modified by ancestry, such that the association between APOE4 and memory was diminished at higher levels of African ancestry (β=0.35, $p=0.019$). ABCA7 was significantly associated with decline in memory for EUR+AFR (β=-0.095, $p<0.0001$), but not EUR (β=0.016, $p=0.009$). The effect of ABCA7 was not modified by ancestry in EUR+AFR, suggesting similar decline in carriers of the ABCA7 risk variant irrespective of African ancestry. There was no association between ABCA7 and Amyloid in either group. The APOE4 effect on memory decline was mediated by Amyloid in the EUR group, whereas no mediation was present in EUR+AFR. Established genetic risk factors of AD have different effects on cognitive decline across different genetic backgrounds. The finding that continuous levels of ancestry modifies the relationship between APOE4 and memory in an admixed population further implies that self-identified black

populations do not represent a homogenous group, and instead show a continuum of genetic admixture that should be considered in estimates of AD risk. Finally, the Amyloid-independent effect of APOE4 on memory decline in the EUR+AFR admixed group suggests that additional pathways related to this genotype are present and warrant further investigation.

Disclosures: K.D. Deters: None. **V. Napolioni:** None. **M.D. Greicius:** None. **E.C. Mormino:** None.

Nanosymposium

540. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways

Location: SDCC 24

Time: Tuesday, November 6, 2018, 1:00 PM - 2:30 PM

Presentation Number: 540.06

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

Support: Flinn Foundation
Mueller Family Charitable Trust

Title: First degree family history of alzheimer’s disease influences paired associates performance and is modified by apolipoprotein e genotype, heart disease, and smoking

Authors: *J. S. TALBOOM[1,2], A. K. HÅBERG[3,4], M. DE BOTH[1,2], M. NAYMIK[1,2], A. L. SINIARD[1,2], L. RYAN[3,2], E. L. GLISKY[3,2], M. J. HUENTELMAN[1,2]
[1]Neurogenomics, The Translational Genomics Res. Inst., Phoenix, AZ; [2]Arizona Alzheimer’s Consortium, Phoenix, AZ; [3]Evelyn F. McKnight Brain Inst., Univ. of Arizona, Tucson, AZ; [4]NTNU, Trondheim, Norway

Abstract: Background A first-degree family history Alzheimer’s disease (FH) can be a proxy for heritable and non-heritable risk factors of dementia. However, the exact influence of FH on cognition across the lifespan is poorly understood. Further, the presence of FH specific interactions with lifestyle choices, medical conditions, and genetics on cognition remains largely unexplored. We examined the influence of FH on paired associate learning (PAL) task performance and the interaction with modifiable and non-modifiable factors. **Methods** We developed a web-based PAL task (at www.mindcrowd.org) and tested over 75,000 individuals between the ages of 18-85. Next, we developed a follow-up health and lifestyle factor survey that was completed by over 7,000 individuals from the cohort. Lastly, we examined the well-known Alzheimer’s disease genetic risk factor, the apolipoprotein E (APOE) epsilon 4 allele, in over 500 FH positive individuals via dried blood spot collection from the cohort. **Results** FH was associated with significantly decreased performance on PAL. This difference was larger in participants under the age of 60. Propensity score matching analysis revealed an effect size of approximately half a word pair deficit in FH individuals. Next, we identified factors modifying the FH effect. We found that a history of heart disease or smoking significantly interacted with

FH and elevated an individual's risk of lowered PAL performance. Of note, the smoking interaction was only significant in females. Lastly, FH positive carriers of the APOE E4 allele also demonstrated a higher risk for decreased PAL performance. **Conclusions** This study suggests that FH, APOE genotype, heart disease, and smoking are important factors that modify the trajectory of an individual's cognitive performance across their lifespan.

Disclosures: J.S. Talboom: None. **A.K. Håberg:** None. **M. De Both:** None. **M. Naymik:** None. **A.L. Siniard:** None. **L. Ryan:** None. **E.L. Glisky:** None. **M.J. Huentelman:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.01

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Gray matter volume is more strongly associated with multiple sclerosis symptomatology compared to white matter volume

Authors: *N. CHERBUIN, M. E. SHAW, C. J. LUECK, T. MADDESS
Australian Natl. Univ., Canberra, Australia

Abstract: Introduction:
Multiple sclerosis (MS) is an auto-immune demyelinating disease characterised by inflammation of the Central Nervous System and neurodegeneration. Because of its pathophysiology much research to date has focused on identifying and measuring white matter changes and their association with treatment, progression, and functional impact. However, limited recent findings suggest that substantial neurodegeneration occurs in the gray matter. These changes may make substantial contributions to symptomatology and functional losses. This study aims to extend the evidence base on structural gray relative to white matter changes in MS and to investigate their cross-sectional association with disease stage, Glatiramer treatment, and symptoms.
Methods:
81 MS patients (50.9 years, 73% female) fulfilling the revised McDonald criteria and 30 matched controls (50.4 years, 67% female) were included in this study. Of the MS patients, 10 were stable, 70 relapsing-remitting (RR), and one progressive, while 24 were on Glatiramer treatment. Symptomatology was assessed with the Expanded Disability Status Scale (EDSS). All participants were imaged with a 1.5T Siemens Avanto scanner for a T1-weighted 3-D axial structural scan (TR/TE/TI=4.17ms/1160ms/600ms). Brain scans were segmented with Freesurfer 5.3 Group differences were tested with multiple regression analyses controlling for age, sex, and ICV.
Results:
MS patients were found to have smaller total gray (3.5%, $p<0.01$) and white matter (9.3%,

p<0.01) as well as total brain (4.3%, p<0.01) volumes and larger white matter hypointensities (234%, p<0.01) volumes. Higher symptom scores on the MDSS were associated with significantly lower gray matter and total brain volume and higher white matter hypointensities volumes. No differences associated with Glatiramer treatment were detected. Stable MS was associated with larger brain volumes compared to RR.
Conclusions:
In this clinical sample significantly lower brain volumes were detected in MS patients compared to controls. While this difference was proportionally greater for white matter, it was also substantial in gray matter. Moreover, MS symptomatology was significantly associated with gray but not white matter volume. These findings suggest that more attention should be paid to gray matter changes in MS which may provide important information relating to disease progression.

Disclosures: N. Cherbuin: None. **M.E. Shaw:** None. **C.J. Lueck:** None. **T. Maddess:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.02

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: board of directors, Tisch MS center of NY

Title: The nexus of methionine and phosphatidylcholine metabolism in multiple sclerosis

Authors: *F. MIR[1], M. MENDELSOHN[2], S. A. SADIQ[3]
[1]Tisch MS Res. Ctr. of NY, New York, NY; [2]Tisch MS Res. center of NY, NY, NY; [3]Tisch MS Res. Ctr., New York, NY

Abstract: In the current study, we used a targeted quantitative metabolomic screening of the cerebrospinal fluid (CSF) of multiple sclerosis (MS) patients (Absolute IDQ p180 assay from Biocrates, Austria). Age- and sex-matched MS patients (n = 120) and control CSF (N = 30) were screened for more than 186 endogenous metabolite classes including amino acids, biogenic amines, acylcarnitines, glycerophospholipids, sphingolipids, ceramides, and monosaccharides. Rigorous statistical analysis was done to identify the significantly altered metabolites. The results revealed 40 metabolites and 11 markers/ratios that are altered more than a fold in the MS population as compared to the control CSF. The significantly altered metabolic pathways include those involved in aromatic amino acid, branched chain amino acid, phosphatidylcholine, sphingomyelin and methionine metabolism among others. Furthermore, the metabolite changes clearly show correlations with disease stage and activity. Several phosphatidylcholine species including PCaaC38:1/C34:3/C32:2/C36:5 were found to be significantly decreased in MS patients. Methionine levels were found to be decreased while there was a significant increase in

its oxidized form i.e., methionine sulfoxide. Independent studies have since shown that the levels of S-adenosyl-methionine (SAM) are significantly reduced in the CSF of MS patients as compared to controls. We have also seen reductions in the level of taurine as well as lower total anti-oxidant levels in active MS patients. Taken together, our results indicate the methionine metabolic pathway is significantly altered in MS and warrant further investigation of its effects on the synthesis of phosphatidylcholine and generation of the anti-oxidant glutathione, and on MS pathogenesis and progression.

Disclosures: F. Mir: None. **M. Mendelsohn:** None. **S.A. Sadiq:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.03

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: U57GM10494
P30GM103488
P20GM109098
P20GM103434
P20RR016440
P30RR032138/P30GM103488.
NIH T32 GA052375

Title: Neuroinflammation-related cytokine exposure alters extracellular vesicle secretion, microRNA profiles, and mitochondrial function in a neuronal cell line

Authors: *A. RUSSELL[1], S. SARKAR[1], S. JUN[2], S. RELLICK[1], S. LEWIS[1], J. SIMPKINS[1]
[1]West Virginia Univ., Morgantown, WV; [2]Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Extracellular vesicles (EVs) are small (40 – 1000 nm) membrane-bound vesicles released from most, if not all cell types, and present in all bodily fluids. EVs can carry functionally active cargo (proteins, nucleic acids) that can be taken up by neighboring cells and mediate physiologically relevant effects. In this capacity, EVs are being regarded as novel cell-to-cell communicators, and may play an important role in the progression of neurological diseases by spreading pathological proteins or RNAs from diseased to healthy cells. Many neurodegenerative diseases are associated with chronic neuroinflammation, characterized by increased levels of immunomodulatory molecules, such as tumor necrosis factor-alpha (TNF-α). In the current study, we investigated how exposure to TNF-α influenced the production of EVs from a hippocampal neuronal cell line (HT-22 cells). Additionally, we assessed the RNA content of the purified EVs for changes in levels of three microRNAs (miR-34a, -146a, and -155), which

have been shown to be associated with neuroinflammation. We observed significant increases in EV concentration after a 24-hour exposure period to TNF-α, especially at the highest concentration (10 ng/ml), along with dose-dependent increases in all three neuroinflammatory microRNAs. Our lab has previously shown that miR-34a targets mRNAs which encode for several proteins of the mitochondrial electron transport chain; we hypothesized that exposing naïve cells to these exosomes would induce mitochondrial dysfunction. Interestingly we observed significant mitochondrial enhancement on several parameters measured by the Agilent Seahorse mitochondrial bioanalyzer. We have detected the presence of cAMP in cytokine-induced EVs and belive this effect is being mediated by vesicular transfer of cAMP, subsequent PKA activation in recipient cells, followed by downstream phosphorylation of electron transport chain proteins. Increased phosphorylation of these proteins may be the driving force behind the observed enhancement in mitochondrial function after exposure to cytokine-induced EVs.

Disclosures: A. Russell: None. **S. Sarkar:** None. **S. Jun:** None. **S. Rellick:** None. **S. Lewis:** None. **J. Simpkins:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.04

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant UH2NS100608-01
NIH Grant 5R01AG032289-08
Larry L Hillblom Foundation 2014-A-004-NET

Title: Peripheral inflammatory serum biomarkers associate with white matter injury

Authors: *M. ALTENDAHL[1], S. WALTERS[1], A. WOLF[1], E. FOX[1], M. YOU[1], D. COTTER[1], J. KRAMER[1], C. DECARLI[2], J. HINMAN[3], F. ELAHI[1]
[1]Neurol., Univ. of California, San Francisco, San Francisco, CA; [2]Univ. of California, Davis, Davis, CA; [3]UCLA, Los Angeles, CA

Abstract: Objective and Rationale:
System chronic sterile inflammation has been associated with cerebrovascular disease and white matter degeneration and injury, which are considered critical contributors to neurodegeneration and cognitive decline. Nevertheless, we lack non-invasive blood markers for risk stratification and dissection of inflammatory molecular substrates *in vivo*. We investigated the relationship between select systemic inflammatory markers in serum and neuroimaging measures of white matter integrity in a cross-sectional cohort design.
Methods:

163 deeply-phenotyped older adults (mean age: 77, SD 7.1, 82 females) with normal cognition (n=104; CDR 0) or mild cognitive impairment (n=59; CDR 0.5) underwent brain MR imaging and blood draw within a six-month period. Participants also completed a cognitive battery, physical examination, and health questionnaire. Global cerebral white matter hyperintensities (WMH) were quantified using structural T2 Flair imaging and diffusion tensor imaging (DTI) was used to measure global free water (FW), global fractional anisotropy (FA), and global mean diffusivity (MD). Serum levels of MPO, GDF-15, RAGE, ST2, IL-18, and MCP-1 were measured in duplicate using a custom assay on the Luminex platform (R&D Systems). Inflammatory markers were log transformed and a composite z-score was calculated. Linear regressions were used to investigate the association of the inflammatory composite score (ICS) with measures of white matter integrity, co-varying for age and total intracranial volume.

Results:

ICS was significantly associated with FW (β=0.488, *p*=0.005) and WMH (β=0.409, *p*=0.031), but not global FA (β=0.054, *p*=0.710) or MD (β=-.088, *p*=0.527).

Conclusion:

ICS showed a significant positive association with FW and WMH, but not MD and FA. Although not fully specific, FW and WMH are hypothesized to have higher specificity for changes in white matter integrity due to cerebrovascular disease. Our findings suggest that peripheral inflammation is associated with subclinical or antecedent white matter injury resulting from cerebrovascular disease and that ICS may be a promising peripheral biomarker of white matter injury of vascular etiology.

Disclosures: M. Altendahl: None. **S. Walters:** None. **A. Wolf:** None. **E. Fox:** None. **M. You:** None. **D. Cotter:** None. **J. Kramer:** None. **C. DeCarli:** None. **J. Hinman:** None. **F. Elahi:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.05

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant K01MH115819
NIH grant R41NS105177

Title: Targeting immunometabolic mechanisms in astroglia to enhance neuronal bioenergetics

Authors: *J. A. FIELDS[1], C. L. ACHIM[2], M. SWINTON[3], E. QVALE[5], A. B. SANCHEZ[4]
[1]Pathology, [2]Psychiatry, UCSD, La Jolla, CA; [3]UCSD, LA Jolla, CA; [4]UCSD, La Jolla, CA; [5]Univ. of California San Diego, San Diego, CA

Abstract: Mitochondrial dysfunction is associated with many neurodegenerative diseases including NeuroHIV and AD. Healthy mitochondria are crucial to neuronal function due to the massive energy requirement, but also because glia require the metabolic flexibility to react to the bioenergetic needs of neurons. Reduced mitochondrial biogenesis, altered mitochondrial dynamics, or reduced mitochondrial bioenergetics in neurons often coincides with inflammatory gene expression and reactive gliosis. Despite these findings, the mechanisms by which activated astroglia may contribute to bioenergetic deficits in neurons is unknown. Astroglia regulate metabolism, inflammation, and neuronal function in the brain; however, little is known about metabolic changes regulating astroglia function in AD and NeuroHIV. Recent studies show that cannabinoid receptor (CB) agonists may be protective in animal models for neurodegenerative diseases. Therefore, targeting immunometabolic mechanisms in astroglia through CB to reduce neuroinflammation may represent a promising therapeutic strategy for NeuroHIV and AD. To test this, we exposed astroglial cultures to a CB agonist and then to AD and NeuroHIV-relevant stimuli (Amyloid beta and interleukin-1beta) and then assayed for alterations in respirometry, ATP levels, mitochondrial gene expression, inflammatory gene expression, and neuroprotective potential. We also assayed postmortem brains from HIV+ individuals for mitochondrial gene expression and CB expression. Stimulated astroglia make a metabolic switch before exhaustion, at which point they may rely on glycolysis. These changes coincide with increased inflammatory and mitochondrial gene expression and the secretion of neurotoxic molecules. All of these effects are reversed by treating with a CB agonist. Moreover, expression of mitochondrial biogenesis related genes and copies of mtDNA/cell are reduced in brain tissues from HIV+ individuals that were diagnosed with neurocognitive impairment. CB 1 and 2 protein levels were increased in brain lysates and these increases were represented in both neurons and glia in the frontal cortex. In conclusion, targeting immunometabolic mechanisms in astroglia with CB agonists may represent a novel therapeutic strategy for neurodegenerative diseases.

Disclosures: J.A. Fields: None. **C.L. Achim:** None. **M. Swinton:** None. **E. Qvale:** None. **A.B. Sanchez:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.06

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIAAA K08 AA024829
NIAAA AA011605
NIAAA AA020024

Title: Trail mediates tlr7 neuroimmune-mediated cell death

Authors: *L. G. COLEMAN, JR[1], J. Y. ZOU[2], L. QIN[3], C. J. LAWRIMORE[4], F. T. CREWS[5]
[1]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Univ. North Carolina, Chapel Hill, Chapel Hill, NC; [3]Bowles Ctr. Alcohol Studies, Univ. North Carolina, Sch. Med., Chapel Hill, NC; [4]UNC Chapel Hill, Chapel Hill, NC; [5]Prof Pharmacol & Psychiat, Skipper Bowles Ctr. Alcohol, Chapel Hill, NC

Abstract: Neuroimmune activation is a hallmark feature of numerous neurodegenerative diseases. Toll-like Receptor 7 (TLR7) is a single-strand RNA viral neuroimmune receptor. TLR7 activation via its endogenous agonist (miRNA let-7) has been implicated in neurodegeneration associated with Alzheimer's and Alcoholism (Lehmann et al 2012 and Coleman et al 2017). We investigated the mechanism of TLR7 mediated neurodegeneration. TRAIL is a TNF-superfamily protein that activates Death Receptor (DR) signaling leading to cell death. Using hippocampal-entorhinal (HEC) slice culture we found the TLR7 agonist imiquimod (IMQ) induced TRAIL expression (5-fold, $p<0.001$). IMQ also induced expression of the TRAIL receptor DR5. CRISPR/Cas9 knockdown of TLR7 prevented IMQ-induced cell death. To assess the role of TRAIL in TLR7-mediated neurotoxicity a TRAIL neutralizing antibody (αTRAIL) was used. αTRAIL completed blocked propridium-iodine (PI) labeled cell death due to the TLR7 agonist IMQ, implicating TRAIL in TLR7-mediated neurodegeneration. MK801 also blunted TRAIL-induced cell death identifying a role of excitotoxicity in TRAIL toxicity. We then assessed the role of TLR7-TRAIL signaling in models of alcohol use disorders. In mice, acute alcohol (6g/kg, i.g.) induced TLR7 (4-fold at 6 hours), TRAIL (2-fold at 12-24h), and cleaved caspase-3 in mouse brain. Fluorescent microscopy found that TRAIL was localized in neurons (NeuN) and Astrocytes (GFAP) in the hippocampus, with little expression in microglia. In the frontal cortex, TRAIL was nearly 100 colocalized to neurons. In the SH-SY5Y neuronal cell line, alcohol induced TLR7 mRNA (2.5-fold) with secretion of TRAIL into the media at 6 hours (2-fold increase, ELISA). TRAIL receptors DR4 and DR5 were each increased by ethanol (25-50%, by western blot). IMQ also induced TRAIL in a similar manner to ethanol. TRAIL was similarly induced and secreted from U373 astrocytes by ethanol, but not BV2 microglia. Pretreatment of HEC with ethanol for 24 hours, increased TRAIL sensitivity, with PI-labeled cell death enhanced by 3-fold. Assessment of postmortem human alcoholic hippocampal tissue found a strong correlation between TRAIL and TLR7 protein levels ($R=0.75$, $p<0.0001$). Both TRAIL and TLR7 protein levels correlated with BAC at death ($R=0.77$ and 0.71 respectively). TRAIL was negatively correlated with BDNF ($R=-0.51$, $p<0.03$) suggesting a shift in the trophic/neurotoxic balance. Thus, TRAIL activation is a critical feature of TLR7-mediated neurodegeneration. This pathway is involved in alcohol use disorders and may underlie the hippocampal neurodegeneration seen in alcoholics and other neurodegenerative diseases.

Disclosures: L.G. Coleman: None. **J.Y. Zou:** None. **L. Qin:** None. **C.J. Lawrimore:** None. **F.T. Crews:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.07

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: TLR7 and imiquimod: Taking a toll on the blood-brain barrier

Authors: *N. C. DERECKI[1], S. RAO[2], Y. HE[1], S. CAMPBELL[1], M. HESSE[2], A. BHATTACHARYA[1]
[1]Neurosci., [2]Immunol., Janssen Res. and Develop. La Jolla, San Diego, CA

Abstract: The toll-like receptors (TLRs) comprise a family of proteins critical in pathogen recognition. Thirteen unique TLRs have been identified to date. TLR ligands are commonly utilized as inducers of immune response in both periphery and CNS. By far the best investigated are TLR4 agonist Lipopolysaccharide (LPS), a bacterial mimic, and TLR3 agonist Poly I:C, a double-stranded RNA viral mimic. Accordingly, their effects are best understood. Much less is known, however, about the remaining TLRs, yet most are expressed not only by peripheral cells, but also on neurons, glia, and brain-associated vascular cells. Of particular interest is TLR7, which recognizes single-stranded viral RNA. TLR7 is most highly expressed in periphery by plasmacytoid dendritic cells (PDC) and in B lymphocytes; in brain, significant TLR7 expression is specific to microglia and CNS macrophages. TLR7 is critical in several peripheral inflammatory pathologies that show strong comorbidity with mood disorders, e.g. lupus, psoriasis, and, accordingly, in release of immune factors shown to be associated with mood disorders, including interleukin (IL)-1B, IL-6, and interferon (IFN)-a. For these reasons, we have chosen to more deeply interrogate the CNS response to TLR7 agonism by adapting a model already used to study psoriasis, i.e. topical application of the TLR7/8 agonist Imiquimod. Here, we show that topical application of Imiquimod is sufficient to potentiate a cascade of immune responses from periphery to brain. We confirm frank infiltration of brain by classical (pro-inflammatory) monocytes, TH17 (IL-17-producing) T cells, and several other immune subsets. We show that this immune response is dose-dependent, and examine both peripheral and CNS aspects of the ‘inflammatory chain’ over a time-course of several days. We present FACS, Luminex, and transcriptome analysis of key pathways and factors associated with TLR7 engagement, including IL-6, IL-17, IL-23, and IFN-a, in peripheral immune cells, immune cells at the borders of the brain, i.e. meninges, and within the brain, i.e. microglia. We believe that a better understanding of the brain response to engagement of less well-studied TLRs associated with peripheral inflammation will help us to unravel the specific mechanisms underlying the observed comorbidity of inflammatory diseases with mood disorders and provide rational targets at which to intervene in order to ameliorate—or even prevent—CNS pathology.

Disclosures: S. Rao: None. **Y. He:** None. **S. Campbell:** None. **M. Hesse:** None. **A. Bhattacharya:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.08

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Role of astrocytes in western pacific parkinsonism-dementia complex

Authors: *Y. HONG[1], X. DONG[1]
[1]Western Univ. of Hlth. Sci., Pomona, CA

Abstract: Western Pacific Parkinsonism-Dementia Complex (PDC) is a largely sporadic neurodegenerative disease with clinical and neuropathological relationships with Parkinson's disease and Alzheimer's disease among Chamorro's on Guam. This disorder has been linked etiologically to exposure to neurotoxic substances, notably naturally occurring chemicals in a plant (cycad) used for food. The role of environmental factors in chronic neurodegenerative disorders is poorly understood. Patient-derived induced pluripotent stem cells (iPSCs) have significantly advanced our understanding of the underlying pathogenesis of neurodegenerative disorders and thus, provide a more relevant *in vitro* model system to explore the environmental causes of neurodegenerative disease. iPSCs have been derived from lymphoid cells of age- and gender-matched PDC-affected and unaffected subjects and then the iPSC-derived neurons and astrocytes have examined for biomarkers of PDC, notably the accumulation of pathological proteins (i.e., tau, amyloid) and astrocyte activation in the presence or absence of Guam cycads, including methylazoxymethanol (MAM), *β-N*-methylamino-L-alanine (BMAA)**.** Our studies showed that astrocytes play an important role in altering tau, *β*-amyloid accumulation in response to the suspect chemical agent's exposure.

Disclosures: Y. Hong: None. **X. Dong:** None. **G. Kisby:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.09

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Swedish Alzheimer Foundation
Swedish Brain Foundation
Swedish Research Council

Title: Dysregulation of TGF-beta signaling in monocyte-derived macrophages results in fatal neurodegeneration

Authors: *H. LUND[1], M. PIEBER[1], R. PARSA[1], D. GROMMISCH[1], E. EWOUD[1], L. KULAR[1], J. HAN[1], J. NIJSSEN[1], E. M. HEDLUND[2], M. NEEDHAMSEN[1], S. RUHRMANN[1], A. O. GUERREIRO-CACAIS[1], R. BERGLUND[1], M. J. FORTEZA[1], D. F. J. KETELHUTH[1], O. BUTOVSKY[3], M. JAGODIC[1], X. ZHANG[1], R. A. HARRIS[1]
[1]Karolinska Institutet, Stockholm, Sweden; [2]Dept. of Neuroscience, Karolinska Institutet, Stockholm, Sweden; [3]Neurology/ARCND, Brigham and Women's Hosp., Boston, MA

Abstract: Microglia are CNS resident phagocytes with pleiotropic functions including regulation of neuronal wiring, myelination and astrocyte activation. The homeostatic gene signature and function of microglia is maintained by the cytokine TGF-β. Under defined host conditions circulating monocytes can compete for the microglial niche and give rise to long-lived monocyte-derived macrophages residing in the central nervous system (CNS). Whether monocytes require TGF-β for colonization of the microglial niche and maintenance of CNS integrity is unknown. We made use of a mouse model of microglia ablation, resulting in partial repopulation from circulating Ly6C^{hi} monocytes, to address this question. In the CNS, monocyte-derived macrophages responded to TGF-β, as evidenced by their high expression of *Tgfbr1* and upregulation of TGF-β induced genes. To determine the functional consequence of niche colonization, we abrogated TGF-β signaling in CX3CR1^{+} monocyte-derived macrophages. This resulted in a rapid onset of a progressive and fatal demyelinating motor disease characterized by myelin-laden giant macrophages throughout the spinal cord. *Tgfbr2*-deficient macrophages were characterized by high expression of genes encoding proteins involved in antigen presentation, inflammation and phagocytosis. TGF-β is thus crucial for the functional integration of monocytes into the CNS microenvironment.

Disclosures: H. Lund: None. **M. Pieber:** None. **R. Parsa:** None. **D. Grommisch:** None. **E. Ewoud:** None. **L. Kular:** None. **J. Han:** None. **J. Nijssen:** None. **E.M. Hedlund:** None. **M. Needhamsen:** None. **S. Ruhrmann:** None. **A.O. Guerreiro-Cacais:** None. **R. Berglund:** None. **M.J. Forteza:** None. **D.F.J. Ketelhuth:** None. **O. Butovsky:** None. **M. Jagodic:** None. **X. Zhang:** None. **R.A. Harris:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: BrightFocus A2016501S
NIH grant AG023695
NIH grant NS079858
NIH grant P50 AG025688 pilot
NIH grant NS095269

Title: Phosphorylation of ULK1 by p38α MAPK promotes microglial inflammatory response

Authors: *H. SHE, Y. HE, T. ZHANG, H. XU, Y. ZHAO, Z. MAO
Emory Univ., Atlanta, GA

Abstract: Inflammation and autophagy are two intertwined processes vital for immune cells to perform their functions. Under resting condition, autophagy acts as a brake to suppress inflammation in microglia. Upon signal stimulation, their fine-tuned interplay is pivotal for proper response to stress. However, the signaling mechanisms that relieve this autophagy-mediated inhibition of inflammation to permit a beneficial inflammatory response remain unknown. Our work revealed that LPS triggered a p38α MAPK-dependent phosphorylation of ULK1 in microglial cells. Phosphorylation of ULK1 by p38α MAPK inhibited its kinase activity, prevented it from binding to its downstream effector ATG13, and reduced autophagy flux in microglia. In addition, LPS-induced microglial morphology change and the production of IL-1β in vitro and in the brain was mediated through p38α MAPK activation, which closely followed the p38α MAPK-dependent inhibition of autophagy. Furthermore, inhibition of ULK1 alone was sufficient to elevate the basal level of inflammation in the absence of any overt inflammatory stimulation. Thus, our findings establish a mechanism that functions to relieve the immune suppressive activity of autophagy upon stimulation and allows the full induction of inflammatory process during microglial activation. This mechanism may play an important role in regulating innate immune response in the central nervous system.

Disclosures: H. She: None. **Y. He:** None. **T. Zhang:** None. **H. Xu:** None. **Y. Zhao:** None. **Z. Mao:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01NS093491
NIH Grant R01CA161056

NIH Grant P30MH075673

Title: Dendrimer-PMPA decreases neuroinflammation in a rabbit model of cerebral palsy

Authors: *Z. ZHANG[1], A. SHARMA[2], A. G. THOMAS[3], C. ROJAS[1], B. S. SLUSHER[4], R. KANNAN[2], S. KANNAN[5]
[1]Johns Hopkins Sch. of Med., Baltimore, MD; [2]Ctr. for Nanomedicine, [3]Johns Hopkins Drug Discovery, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [4]Johns Hopkins Drug Discovery, Baltimore, MD; [5]Anesthesiol. and Critical Care Med., Johns Hopkins Univ., Baltimore, MD

Abstract: Neuroinflammation and glutamate excitotoxicity mediated by activated glia are two major pathophysiologic mechanisms involved in the brain injuries. We have previously demonstrated that glutamate carboxypeptidase II (GCPII) is upregulated in activated microglia in newborn rabbits exposed to maternal inflammation in utero. There are several GCP-II inhibitors including phosphonate- (e.g. 2-(phosphonomethyl)-pentanedioic acid, 2-PMPA), thiol- (e.g. 2-(3-mercaptopropyl)pentane-dioic acid; 2-MPPA) and urea-based inhibitors (e.g. (N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-L-cysteine; DCMC). 2-PMPA is extremely potent and selective; however, 2-PMPA is highly hydrophilic, which limits its bioavailability. Hence, we synthesized and characterized dendrimer-2-(phosphonomethyl)-pentadioic acid (D-2-PMPA) conjugate for CNS transport of 2-PMPA and evaluated the *in vivo* efficacy in a rabbit model of cerebral palsy. Timed-pregnant New Zealand rabbits underwent laparotomy on gestation day 28 (G28). LPS (Endotoxin group) was injected along the uterus as previously described. Endotoxin kits from the same litter were randomly divided into three groups, and intravenously injected with PBS, 2-PMPA (40mg/kg) and D-2PMPA (40 mg/kg) at postnatal day 1(PND1). Neurobehavioral assessment were done at 24, 48 and 96 h post-treatment. Rabbits were sacrificed at PND5 and the periventricular regions of brains were micro-dissected, and analyzed for pro- and anti-inflammatory cytokines and microglia activation. To determine the D-2PMPA bio-distribution in the brain of CP rabbits, Cy5-D-2-PMPA was administered (i.v.) at PND1 and rabbits were sacrificed 24h post-injection. We found that Cy5-D-2-PMPA co-localizes with activated microglia and astrocytes at the periventricular white matter area in endotoxin rabbit kits, which indicates that D-2PMPA can cross the blood brain barrier and specifically target the activated microglia/astrocytes. Rabbit treated with D-2PMPA had more prominent increase of body weight and improvement of suck and swallow at 96 h post-treatment, compared with PBS and free 2-PMPA groups. D-2PMPA is more effective than free 2PMPA at decreasing pro-inflammatory cytokines levels in vivo, indicated by decreased pro-inflammatory cytokine levels, such as TNF-α and IL-1β, as well as TSPO (glial cell activation marker). Therefore, dendrimer mediated targeted and selective delivery of 2-PMPA to activated microglia and astrocytes can be highly beneficial to improve efficacy, reduce the off-site effects.

Disclosures: Z. Zhang: None. **A. Sharma:** None. **A.G. Thomas:** None. **C. Rojas:** None. **B.S. Slusher:** None. **R. Kannan:** None. **S. Kannan:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 5P01AI073693-09

Title: ACE inhibitors in the treatment of microglial inflammation in neuropsychiatric systemic lupus erythematosus

Authors: *J. NESTOR[1], Y. ARINUMA[2], T. HUERTA[1], C. KOWAL[1], Y. FUJIEDA[3], E. NASIRI[1], N. KELLO[1], A. BIALAS[4], T. R. HAMMOND[5], U. SRIRAM[7], B. A. STEVENS[6], P. HUERTA[1], B. VOLPE[1], B. DIAMOND[1]
[1]Feinstein Inst. for Med. Res., Manhasset, NY; [2]Kitasato Univ. Sch. of Med., Kanagawa, Japan; [3]Hokkaido Univ., Sapporo, Japan; [4]Boston's Children's Hosp., Boston, MA; [6]Harvard Med. Sch. Neurobio., [5]Boston Children's Hosp., Boston, MA; [7]Temple Univ., Philadelphia, PA

Abstract: Systemic Lupus Erythematosus (SLE) is an autoimmune disorder, which when it attacks the brain is called Neuropsychiatric Systemic Lupus Erythematosus (NSPLE). NPSLE covers a variety of symptoms, from cognitive impairment to mood disorders. There is no consensus regarding the pathophysiology of NPSLE and no definitive treatment currently exists. Our previous research shows that SLE patients carry autoantibodies, which are reactive to not only dsDNA, but also the N-methyl-D-aspartate receptor (NMDAR). These autoantibodies are found in both the CSF and serum of many NPSLE patients. Production of these cross-reactive antibodies can be induced in mice by immunization with a peptide sequence from the NMDAR. When lipopolysaccharide opens the blood brain barrier, autoantibodies enter the brain and cause both acute excitotoxic neuronal death and chronic loss of dendritic complexity. This loss of complexity enlarges hippocampal placefields, and results in poor performance on behavioral tasks correlating to deficits seen in NPSLE patients. The acute neuronal damage induced by the autoantibodies creates a chronic neuro-inflammatory state characterized by increased complement protein C1q and activated microglia. These characteristics are shared by other neurodegenerative disorders, such as Alzheimer’s Disease. In order to determine the roles of C1q and microglia in this inflammatory state, we used C1q knockout mice and mice who were depleted of microglia using CSF1R inhibitors in their chow. The lack of C1q or microglia, did not prevent the initial neuronal damage, but were protective in preventing the loss of dendritic complexity and spatial memory deficits. These results make anti-C1q antibodies and CSF1R inhibitors potential new therapeutics for NPSLE. ACE inhibitors have been beneficial in Alzheimer’s Disease management. In our model, ACE inhibitors prevented the loss of dendritic complexity and spatial memory deficits. We hypothesize that ACE inhibitors may function by

modifying the effects of C1q or microglia. Future studies are required to understand the exact mechanism behind ACE inhibitors' benefits in managing neurodegenerative pathology, but also make them a possible target for clinical trials.

Disclosures: J. Nestor: None. **Y. Arinuma:** None. **T. Huerta:** None. **C. Kowal:** None. **Y. Fujieda:** None. **E. Nasiri:** None. **N. Kello:** None. **A. Bialas:** None. **T.R. Hammond:** None. **U. Sriram:** None. **B.A. Stevens:** None. **P. Huerta:** None. **B. Volpe:** None. **B. Diamond:** None.

Nanosymposium

541. Neurotoxicity, Neuroinflammation, and Neurodegeneration

Location: SDCC 7

Time: Tuesday, November 6, 2018, 1:00 PM - 4:15 PM

Presentation Number: 541.13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Involvement of the complement system in the SAH-induced hippocampal abnormalities

Authors: *E. V. GOLANOV, E. I. BOVSHIK, M. A. SHARPE, A. S. REGNIER-GOLANOV, D. S. BASKIN, G. W. BRITZ
Neurosurg., The Houston Methodist Hosp., Houston, TX

Abstract: Up to 95% subarachnoid hemorrhage (SAH) survivors experience permanent disabilities, which include cognitive and emotional disturbances, impaired memory and executive functions, language complications. These observed atrophy of temporomesial area indicate hippocampal abnormalities following SAH. The underlying mechanisms of hippocampal damage following SAH are still not completely understood. Recently it was established that reactive astrocytes are capable to exert the negative effects on neurons through activation of the complement system. We hypothesize that SAH-induced cytokine release activates astrocytic complement system, which may exert negative effect on the hippocampal neurons. To test this hypothesis we explored changes in complement expression in human astrocytic culture and expression of complement components in the post-SAH hippocampus. Normal human astrocytes (NHA) were obtained from Lonza and grown to confluency in Astrocyte Cell Basal Medium in 96-well plates. TNFα (124 nM), C3 (85 nM) and TNFα combined with C3 were applied to the cultured cells, and 24 hours later NHAs were fixed in ice-cold 4% PFA, washed/permeabilized, and immunohistochemical (IHC) analysis of expression of C1qb, CfB and C3 was carried out using quantitative fluorescent microscopy. TNFα and C3 increased C3 ($p=0.005$) and CfB ($p=0.007$) expression, but failed to do so when applied simultaneously. We explored changes in the levels of C1qB, C3 and CfB in the dentate gyrus in the mice circle of Willis perforation model of SAH. Four days following the perforation mice were intracardially perfused, brains were extracted, sliced and processed for IHC. Quantification of immunofluorescence in the hippocampal granular layer revealed increased levels of CfB ($p=0.04$) and C1qB ($p=0.05$), while levels of C3 decreased ($p=0.008$) compared to sham perforation. Our data suggest that in

agreement with the previous observation astrocytes are capable of expression/release of complement components in response to cytokine stimulation. Interestingly, C3 when applied simultaneously with TNFα was capable to decrease expression of C1qb and CfB, suggesting the existence of feedback mechanism. Observations *in vivo* are in line with the proposed role of complement in post-SAH processes in hippocampus. Importantly, in subacute period following SAH levels of C3 in granular layer decreased suggesting dynamic role of complement system. Further exploration of the role of astrocytes and complement system in the hippocampal damage following SAH will allow to develop new therapeutic approaches to the treatment of long-term consequences of SAH.

Disclosures: E.V. Golanov: None. **E.I. Bovshik:** None. **M.A. Sharpe:** None. **A.S. Regnier-Golanov:** None. **D.S. Baskin:** None. **G.W. Britz:** None.

Nanosymposium

542. Transplantation and Regeneration: PNS

Location: SDCC 25

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 542.01

Topic: A.04. Transplantation and Regeneration

Title: Promoting functional recovery after peripheral nerve injury by alteration of macrophage phenotype using exogenous interleukin10 delivery

Authors: *M. GOLSHADI[1], E. F. CLAFFEY[1], T. P. MOORE[1], M. SLEDZIONA[1], J. CHEETHAM[2]
[2]Dept. of Clin. Sci., [1]Cornell Univ., Ithaca, NY

Abstract: Peripheral nerve injury (PNI) produces a well-orchestrated series of events that are essential for successful regeneration and functional recovery. In the first three days after injury Schwann cells (SC) remove fragmented axonal segments and break down the nerve-blood barrier. Denervated SC then recruit macrophages to the site of repair. Increased macrophage recruitment can promote endothelial and Schwann cell migration and axonal regrowth. Since functional recovery are very dependent upon the macrophage response to the nerve injury, macrophages are the major cell type in the first few days after injury. In this presentation, we show that altering the phenotype of macrophages at the injury site promotes functional recovery after PNI. We investigated the effect of exogenous interleukin10 (IL10), a potent immunoregulatory and anti-inflammatory cytokine, on the modulation of macrophage response during the period of macrophage migration. The ability of exogenous IL10 to alter macrophage phenotype was studied in both mouse (C57BL/6) and rat (Thy1-GFP) animal models. Initially, we established a dose range for IL10 by loading a 5 mm silicon conduit with 0.7% agarose gel and a range of IL10 concentrations, and the number of motor axons reaching their target was determined. Unloaded agarose and empty conduits were used as negative controls. Following an

8 week repair period and using a technique called retroDISCO, the number of axons crossing the repair site was determined by confocal microscopy. We then used the IL10 dose that produces the greatest number of axons and isolated macrophages and SC during the period of cytokine release (day 3) to evaluate early changes in gene expression with and without IL10. This was done by using a novel flow cytometry approach to isolate individual cell types, allowing precise interrogation of gene expression and function for each cell type. Results indicate a dose-dependent increase in the numbers of regenerating axons crossing the repair site following addition of exogenous IL10 at the site of sciatic nerve transection in both mice and rats. Gene expression analysis indicates that delivery of IL10 as an exogenous ligand manipulates the phenotype of macrophages early after repair. Axon extension and innervation of neuromuscular junctions were improved by exogenous IL10, and showed dose-dependent increase. In conclusion, we identified IL10 as an effective therapeutic target for peripheral nerve repair and demonstrated the modulation of macrophage response using exogenous IL10.

Disclosures: M. Golshadi: None. **E.F. Claffey:** None. **T.P. Moore:** None. **M. Sledziona:** None. **J. Cheetham:** None.

Nanosymposium

542. Transplantation and Regeneration: PNS

Location: SDCC 25

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 542.02

Topic: A.04. Transplantation and Regeneration

Support: Grant of Japan Orthopaedics and Traumatology Research Foundation, Inc.
Medical research grant on traffic accident from The General Insurance Association of Japan

Title: Mature Schwann cells but not developing Schwann cells support axon regeneration after peripheral nerve injury

Authors: *T. ENDO, K. KADOYA, Y. SUZUKI, Y. MATSUI, Y. RUFEI, Y. NAGANO, D. KAWAMURA, N. IWASAKI
Hokkaido University, Grad. Sch. of Med., Sapporo-Shi, Japan

Abstract: Despite of the fact that peripheral nerve can regenerate, clinical outcomes after peripheral nerve injuries (PNI) are still unsatisfactory, especially in severe and proximal injury cases. Accumulated evidences show that Schwann cell (SC) graft is one of potential approaches for regenerative therapy after PNI. While the graft of glial precursors supports axon regeneration in adult central nervous system, it remains to be elucidated that SCs at developmental stages promote regeneration of adult axons after PNI. The purpose of the current study is to elucidate the axon promoting effects of developing SCs after PNI. Total of 4 types of SCs were tested,

including 1) SC precursors (SCPs), 2) immature SCs (ISCs), and 2 types of mature SCs, which were 3) repair SCs (RSCs) and 4) non-RSCs (n = 6 / group). All cells were prepared from RFP transgenic Lewis rats. SCPs, ISC, and non-RSCs were harvested from intact sciatic nerves at embryonic day 14 (E14), E18, and postnatal 10-12 weeks. RSCs were isolated from transected adult sciatic nerves at 1 week after injury. One million cells were grafted into 25 mm long cell-free area between crush injuries in a sciatic nerve of syngenic Lewis rat. Cell-free area was achieved by repeated freeze and thaw procedures with liquid nitrogen. Crush alone (no decellularization) and no cell graft groups were used as positive and negative controls. Two weeks after injury and grafts, RSCs group showed the greatest axon regeneration among all cell graft groups, although its extent was still significantly reduced compared to a positive control. Non-RSCs was the next effective cell type. Surprisingly, SCPs and ISCs failed to support axon regeneration at all, even though they maintained proliferative ability after grafting. Further, in vitro culture of dorsal root ganglion (DRG) neurons at adult and embryonic (E14) stages in combination with RSCs and SCPs demonstrated that RSCs but not SCPs promoted neurite outgrowth of adult DRG neurons and that neither of RSCs and SCPs stimulated neurite outgrowth of E14 DRG neurons. These findings indicate that, unlike CNS, SCs at developmental stages don't support regeneration of adult axons after PNI and that mature SCs, especially RSCs, are good candidates as a graft cell type for regeneration therapy after PNI.

Disclosures: T. Endo: None. **K. Kadoya:** None. **Y. Suzuki:** None. **Y. Matsui:** None. **Y. Rufei:** None. **Y. Nagano:** None. **D. Kawamura:** None. **N. Iwasaki:** None.

Nanosymposium

542. Transplantation and Regeneration: PNS

Location: SDCC 25

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 542.03

Topic: A.04. Transplantation and Regeneration

Title: Age-dependent macrophage defects in peripheral nerve injury repair

Authors: *A. P. BRUNSON[1], K. SAGAR[2], J. CHEETHAM[3]
[1]Biol. and Biomed. Sci., [3]Clin. Sci., [2]Cornell Univ., Ithaca, NY

Abstract: Age related changes in the immune system are responsible for dysfunctional recovery and repair after peripheral nerve injury (PNI). These changes involve systemic stress and stimulation resulting in inflammation, reshaping the aged immune response. A major player in systemic inflammation is the macrophage (Mφ). They are highly reactive to their microenvironment due to sensitivity to cytokines, chemokines, and other stimuli, which in turn alter their function. Mφs play a wide range of roles during PNI and are intimately involved in the process of homeostasis, tissue repair, and regeneration. The Mφ response to tissue injury is plastic and heavily dependent on their ability to respond to microenvironmental cues, which

generate a spectrum of heterogeneous Mφ sub-populations, phenotypes, and functions. In the context of PNI, Mφs play a crucial role in the orchestration of the events which are essential for successful regeneration and functional recovery to occur, yet an understanding aging's affect on the relationship between Mφ function and nerve regeneration is not clear. It has been hypothesized that the delay in nerve regeneration in aged animals is due to defects in chemokine production of the nerve after injury to recruit Mφs. However, once Mφs migrate to the site of injury in aged animals, there is an additional defect in their phagocytic function, during Wallerian degeneration, that creates delayed and disorganized nerve regeneration. Here, we test the hypothesis that the PNI microenvironment in old mice regulates specific defects in Mφ function. We performed phagocytosis assays using unstimulated peritoneal Mφs that were harvested from young and old C57Bl6 mice. These Mφs were analyzed for phagocytosis in a naïve environment and after incubation with homogenized sciatic nerve of young (6-12 weeks) or old (18+ months) C57Bl6 mouse. Our *in vitro* assay showed that exposure to homogenized nerve increased the phagocytic function in both young and old Mφs, independent of the nerve's age. Interestingly, old Mφs exposure to old nerve homogenate, significantly diminished Mφ phagocytosis, while young Mφs showed no change in phagocytosis in the presence of young or old nerve. The culture media was also analyzed by Luminex for chemokines, cytokines, and growth factors before and after phagocytosis. Results showed that old Mφs had undetectable levels of IL-6, TNF-α, S100A9, and PDGF-BB independent of age of nerve homogenate while young Mφ showed significant differences in expression before and after phagocytosis. This lead us to conclude that while the microenvironment can effect phagocytic activity, aged Mφ have defects in function independent of microenvironment.

Disclosures: A.P. Brunson: None. **K. Sagar:** None. **J. Cheetham:** None.

Nanosymposium

542. Transplantation and Regeneration: PNS

Location: SDCC 25

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 542.04

Topic: A.04. Transplantation and Regeneration

Support: NIH Grant R01DC016892

Title: Cellular dynamics of Sonic hedgehog transport and release in neurons

Authors: *W.-J. LU, A. S. BAGHEL, P. A. BEACHY
Stem Cell Inst., Stanford Univ., Stanford, CA

Abstract: How organs maintain and restore functional integrity during ordinary tissue turnover or following injury represents a central biological problem. The maintenance of taste sensory organs in the tongue was shown 140 years ago to depend on innervation from distant ganglion

neurons, but the underlying mechanism has remained unknown. We found that Sonic hedgehog (Shh), which encodes a secreted protein signal, is expressed in these sensory neurons, and that experimental ablation of neuronal Shh expression causes loss of taste receptor cells (TRCs). TRCs are also lost upon pharmacologic blockade of Hedgehog pathway response, accounting for the loss of taste sensation experienced by cancer patients undergoing Hedgehog inhibitor treatment. We found that TRC regeneration following such pharmacologic ablation requires neuronal expression of Shh and can be substantially enhanced by pharmacologic activation of Hedgehog response. Although the functional importance of SHH in TRC regeneration is demonstrated genetically, it is still unknown mechanistically how the regenerative SHH signal is delivered to the stem and progenitor cells in the taste buds, which are located far away from the nuclei and cell bodies of the neurons. We aim to further investigate how the neuronal source of Shh regulates regenerative capabilities of epithelial cells by examining the distribution and activities of neuronal Shh. We have generated new reagents and are applying imaging techniques to monitor the distribution and signaling activities of Shh produced from sensory neurons.

Disclosures: W. Lu: None. **A.S. Baghel:** None. **P.A. Beachy:** None.

Nanosymposium

542. Transplantation and Regeneration: PNS

Location: SDCC 25

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 542.05

Topic: A.04. Transplantation and Regeneration

Support: NIH Grant DC014261
NIH Grant DC014089

Title: ErbB family signaling drives supporting cell proliferation *in vitro* and supernumerary hair cell formation *in vivo* in the neonatal mouse cochlea

Authors: *P. WHITE[1], J. ZHANG[1,2], Q. WANG[2], D. ABDUL-AZIZ[2], A. S. B. EDGE[2,3], J. MATTICIAO[3]
[1]Univ. of Rochester Sch. of Med. and Dent., Dept. of Neurosci., Rochester, NY; [2]Dept. of Otolaryngology, Harvard Med. Sch., Boston, MA; [3]Biol., St. John's Fisher Col., Rochester, NY

Abstract: In mammals, cochlear hair cells are not regenerated once they are lost, leading to permanent hearing deficits. In other vertebrates, the adjacent supporting cells act as a stem cell compartment, that proliferates and generates *de novo* cochlear hair cells. In other epithelial systems ERBB2 signaling can act as a stretch receptor for damage, and early investigations implicated ERBB2 signaling in inner ear regeneration. Here we test the hypothesis that ERBB2 activation can drive regeneration in the neonatal mouse cochlea. We drive ERBB2 signaling in cochlear supporting cells, using viruses, transgenic expression, and small molecule interventions.

Induction was conducted on mice of both sexes prior to 3 days of age without inducing hair cell death. Sex differences were not assessed. Viruses and transgenic expression include the use of lineage tracers to follow the fates of ERBB2 activated cells. *In vitro*, individual supporting cells harboring constitutively active ERBB2 receptors appear to signal to their neighboring supporting cells, inducing them to proliferate. Comparisons were made between cochleae infected with a CA-ERBB2 virus, a kinase-dead ERBB2 virus, and a GFP virus. Supporting cells were identified with JAG1 (n>8 per condition), SOX2 (n>3 per condition) and a SOX2-Tomato lineage marker (n>8 per condition). JAG1+ and SOX2-lineage marker+ supporting cells had significantly increased incorporation of EdU. Interestingly, supporting cells appeared to down-regulate SOX2 prior to initiating cell division. *In vivo*, we find significantly more supernumerary MYO7+ cells near supporting cells that express ERBB2 receptors compared to control animals (n=5-8 per genotype). As we activate ERBB2 signaling at P0, and ectopic MYO7+ cells are seen in the basal cochlea at P8 and P14, this effect is likely due to transdifferentiation, as convergent extension is complete prior to the initiation of the experiment. Both supporting cell proliferation and ectopic MYO7+ cell production were largely reproduced *in vitro* using small molecules that activate ERBB signaling by interfering with endogenous negative regulators (n=5). All samples were blinded and randomized prior to quantification by a different individual. Our data indicates that ERBB signaling may drive the activation of secondary signaling pathways to regulate regeneration. We further investigate the effects of ERBB signaling in the adult mouse utricle after hair cell ablation, replicate the non-cell autonomous relationship between cells that initiate ERBB2 signaling and neighboring cells that divide. We propose a model wherein inner ear regeneration is regulated by an interplay of signaling pathways.

Disclosures: P. White: None. **J. Zhang:** None. **Q. Wang:** None. **D. Abdul-Aziz:** None. **A.S.B. Edge:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Decibel Therapeutics. **J. Matticiao:** None.

Nanosymposium

542. Transplantation and Regeneration: PNS

Location: SDCC 25

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 542.06

Topic: A.04. Transplantation and Regeneration

Support: Musculoskeletal Transplant Foundation
NIGMS 2P20GM103432

Title: Regeneration of complex peripheral nerve defects using allografts treated with localized and temporary immunosuppressive therapy

Authors: *J. S. BUSHMAN[1], S. DHUNGANA[2], K. ROBALLO[2], R. CZAIKOWSKI[2]
[1]Pharm., [2]Univ. of Wyoming, Laramie, WY

Abstract: Peripheral nerve regeneration after segmental defects occurs naturally, but is often sub-optimal. The most effective current clinical option is a sensory autograft of a freshly removed nerve, with degradable biomaterial conduits and decellularized grafts of lesser efficacy. Allografting of freshly isolated live nerves is as or more effective than autografts, but is not widely practiced due to the serious risks of systemic immune suppression. Our group has been developing methods to localize the immune response surrounding only the graft in an effort to reduce risks and enable use of this highly effective strategy to regenerate peripheral nerves. Data shows that localized immune suppression achieved with drug and cell based strategies allow for full regeneration equivalent or superior to mixed nerve autografts in critical sized defects in the rat model. This strategy has also proven effective for regenerating critical sized defects that encompass bifurcations and complex nerve structures. Allografts are uniquely positioned to address this critical aspect of peripheral nerve injury.

Disclosures: J.S. Bushman: None. **S. Dhungana:** None. **K. Roballo:** None. **R. Czaikowski:** None.

Nanosymposium

542. Transplantation and Regeneration: PNS

Location: SDCC 25

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 542.07

Topic: A.04. Transplantation and Regeneration

Support: NIH Grant NS095046

Title: Effect of Neuregulin 1 in repairing a 4 cm gap injury in the rabbit common peroneal nerve

Authors: G. S. BENDALE, B. T. TRAN, J. RYAN, F. RAHMAN, E. SHIMIZU, S. ANAND, *M. I. ROMERO-ORTEGA
Bioengineering, Univ. of Texas at Dallas, Richardson, TX

Abstract: The surgical repair of nerve gap lesions longer than 3 cm from severe traumatic injuries, remain a significant clinical challenge. Off-the-shelf alternatives such as decellularized allografts and hollow conduit, which are viable options for short gap nerve repairs, often fail in bridging longer gaps, likely due to the lack of trophic support normally provided by Schwann cells. Our preliminary data indicated that supplementing multiluminal nerve conduits with pleiotrophin (PTN) is an effective strategy in bridging a 4 cm gap injury in the rabbit peroneal nerve. However, while PTN support was able to mediate axonal regeneration and moderate recovery in toe- spread index, electron microscopy showed signs of late radial sorting arrest, and

delayed or arrested re-myelination. Given that Neuregulin-1 plays a critical role in promoting radial sorting and myelination, we reasoned that adding this signaling molecule to the multi-luminal nerve conduits, would promote re-myelination and functional recovery in long gap nerve injuries. We hypothesize that sustained release of recombinant Neuregulin 1 type-III (NRG1-III) encapsulated in PLGA microparticles, would increase Schwann cell differentiation enhancing axonal sorting and myelination, and that combined with PTN, would increase axon number and functional recovery. In this study, twenty-four adult NZW rabbits underwent a peroneal nerve transection, where a 4 cm long gap was repaired either by a control nerve autograft, or by a multiluminal nerve conduit containing NRG1-III, PTN-NRG1-III or empty PLGA microspheres. After 5 weeks of recovery, toe-spread behavior was video analyzed weekly for a 6.5 months. At the end of the study the repaired nerve was re-exposed to evaluate nerve conduction properties of the regenerated tissue. Force measurements and EMG activity from the re-innervated muscles were evaluated. Gross tissue examination showed robust nerve regeneration across the 4 cm gap, including extensive angiogenesis. The results of toe-spread index, muscle recruitment, immunohistochemistry and electron microscopy morphometric analysis of the regenerated nerve will be presented.

Disclosures: G.S. Bendale: None. **B.T. Tran:** None. **J. Ryan:** None. **F. Rahman:** None. **E. Shimizu:** None. **S. Anand:** None. **M.I. Romero-Ortega:** None.

Nanosymposium

543. Somatosensation: Peripheral Mechanisms and Spinal Circuits

Location: SDCC 5

Time: Tuesday, November 6, 2018, 1:00 PM - 4:00 PM

Presentation Number: 543.01

Topic: D.04. Somatosensation: Touch

Support: DFG Grant SCHM 2533/2-1
DFG Grant GO 2481/2-1
Max Planck Society
DFG, CRC889, Project A9

Title: Piezo2 mechanotransduction is regulated by the interplay of Mtmr2 and $PI(3,5)P_2$

Authors: *M. SCHMIDT[1], P. NARAYANAN[1], M. HUETTE[1], F. REHFELDT[2], G. KUDRYASHEVA[2], S. LECHNER[3,2], F. TABERNER[3], D. GOMEZ-VARELA[1]
[1]Somatosensory Signalling and Systems Biol., MPI of Exptl. Med., Goettingen, Germany; [2]3rd Inst. of Physics - Biophysics, Goettingen, Germany; [3]Inst. of Pharmacol., Heidelberg, Germany

Abstract: The ability to sense force is vital for an organism to interact with its physical environment, and mechanotransduction represents a key aspect in this process. Accordingly, immense research efforts have been invested to gain molecular insights into

mechanotransduction relevant for vertebrate somatosensation. Piezo2 ion channels have emerged as major somatosensory mechanotransducers and mediate rapidly adapting mechanically activated (RA-MA) currents in primary afferent sensory neurons of dorsal root ganglia (DRG). By now it has been established that Piezo2 channels are crucially involved in vertebrate light touch and proprioception. In view of this, elucidating the molecular mechanisms that regulate native Piezo2 channels in sensory neurons is of high importance.
Our previous work has revealed a protein network associated with native Piezo2 in murine DRG. Among identified candidates, the phosphoinositide phosphatase myotubularin related protein 2 (Mtmr2) is a significantly enriched and prominent member of the Piezo2 interactome. Here, we show that Mtmr2 indeed controls Piezo2-mediated mechanotransduction by suppressing its function in cultured sensory neurons of murine DRG and upon heterologous expression. In contrast, heterologous Piezo1 or other MA current subtypes in DRG are not altered by Mtmr2. Mechanistically, our pharmacological and mutational experiments strongly suggest that changes in the enzymatic activity of Mtmr2 regulate Piezo2 mainly via $PI(3,5)P_2$ availability. In fact, we uncovered a previously unknown polybasic motif in Piezo2 that can bind $PI(3,5)P_2$. We further used osmotic stress paradigms to establish the (patho)physiological significance of $PI(3,5)P_2$ for RA-MA currents in vitro and also for behavioral hypersensitivity to tactile, but not thermal, stimuli in male mice.
Thus, we elucidated a novel mechanism by which Mtmr2 activity and $PI(3,5)P_2$ availability can locally control Piezo2-mediated mechanotransduction in peripheral sensory neurons. In summary, our study revealed Mtmr2 and its substrate $PI(3,5)P_2$ as part of the complex cellular machinery regulating mechanotransduction in the somatosensory system of vertebrates.

Disclosures: M. Schmidt: None. **P. Narayanan:** None. **M. Huette:** None. **F. Rehfeldt:** None. **G. Kudryasheva:** None. **S. Lechner:** None. **F. Taberner:** None. **D. Gomez-Varela:** None.

Nanosymposium

543. Somatosensation: Peripheral Mechanisms and Spinal Circuits

Location: SDCC 5

Time: Tuesday, November 6, 2018, 1:00 PM - 4:00 PM

Presentation Number: 543.02

Topic: D.04. Somatosensation: Touch

Support: NINDS F31NS103439-01
NINDS 5T32NS064928-07
NINDS R01NS073119
NINDS F31NS094023

Title: Maintenance and postnatal development of peripheral neuronal endings requires Sarm1

Authors: *R. CLARY[1], B. A. JENKINS[1], E. A. LUMPKIN[2]
[1]Neurosci., [2]Neuroscience, Physiol. and Cell. Biophysics, Dermatol., Columbia Univ., New York, NY

Abstract: Skin, our largest sensory organ, is innervated by diverse sensory afferents that encode thermal, noxious, itchy and tactile stimuli. These afferents must maintain neuronal architecture despite the continuous postnatal renewal of target tissues. For example, slowly adapting Aβ afferents that innervate epidermal Merkel cells and respond to gentle touch stimuli exhibit structural plasticity in adult mice. Merkel cell-neurite complexes are thus a tractable model system to test whether Wallerian degeneration pathways contribute to afferent maintenance in healthy tissue.
Sterile alpha and TIR motif-containing 1 (SARM1) is an intracellular protein required after injury to induce Wallerian degeneration. Mutations in *Sarm1* lead to protection from injury-induced degeneration of axons. Although SARM1's role in axonal degeneration in injury and disease models is well documented, a role for SARM1 in neural development and maintenance has not been examined. To test whether SARM1 is required for afferent maintenance in healthy tissue, we performed quantitative immunohistochemistry on cryosections and whole-mount preparations in postnatal *Sarm1-/-* and wild-type mice. Afferents were labeled with antibodies against neurofilament heavy (NFH), beta-III tubulin (βIII), and myelin basic protein (MBP), and Merkel cells were labeled with keratin-8 (K8). Branching parameters and Merkel-cell counts were analyzed by tracing neuronal arbors in Neurolucida. At P0, Merkel-cell numbers were indistinguishable between genotypes, indicating that SARM1 is not required for their embryonic development. At P21 however, *Sarm1-/-* mice showed a significant decrease in the number of Merkel cells compared with control mice, with many arbors lacking Merkel cells altogether. By contrast, the gross morphology of Merkel cell-afferents did not differ across genotypes. These data show that SARM1, an effector of Wallerian degeneration, is required for postnatal maintenance of Merkel cell-neurite complexes, which opens questions about the role of neurodegenerative signaling in the development and maintenance of sensory neurons. Ongoing studies seek to determine whether SARM1 is required for maintenance of function or morphology in other somatosensory neuron subtypes.

Disclosures: R. Clary: None. **B.A. Jenkins:** None. **E.A. Lumpkin:** None.

Nanosymposium

543. Somatosensation: Peripheral Mechanisms and Spinal Circuits

Location: SDCC 5

Time: Tuesday, November 6, 2018, 1:00 PM - 4:00 PM

Presentation Number: 543.03

Topic: D.02. Somatosensation

Title: Identification of spinal neurons contributing to both the dorsal column projection mediating fine touch and corrective motor movements

Authors: *S. PAIXAO, L. LOSCHEK, L. GAITANOS, R. KLEIN
Max Planck Inst. of Neurobio., Martinsried, Germany

Abstract: The dorsal spinal cord is the integrative center that processes and transmits a variety of somatosensory information, including a wide range of tactile stimuli that provide us with the capacity for texture discrimination, object recognition and fine motor control. The molecular identity and specific function of dorsal horn interneurons and projection neurons in touch-related spinal cord circuits is still largely unknown. We have previously identified a population of interneurons located in laminae III-V marked by the co-expression of the transcription factor Zic2 and the axon guidance receptor EphA4, which we hypothesized to receive tactile stimuli and to send their axons into an ascending pathway towards the brain (Paixao et al., Neuron, 2013). We have recently generated a Zic2 inducible-cre line and, using a trans-synaptic rabies virus approach, we have confirmed that Zic2 neurons receive sensory inputs from cutaneous afferents. Retrograde and genetic tracing experiments also revealed that at least a subset of Zic2 neurons sends projections to the cuneate nucleus in the medulla, indicating that Zic2 represents a molecular marker of projection neurons forming the postsynaptic dorsal column pathway (PSDC). Using an intersectional genetics approach, we have observed that the ablation of spinal Zic2 neurons specifically reduces light touch sensitivity and the ability of textural discrimination. Moreover, these mice show an impairment in fine motor control when challenged to cross thin elevated beams. In a complementary approach, chemogenetic activation of spinal Zic2 neurons leads to a higher sensitivity to light touch stimuli without affecting nociceptive behaviors. Furthermore, Zic2 neurons receive monosynaptic inputs from several descending brain centers mainly involved in motor control, like the motor cortex, red nucleus and numerous brainstem nuclei. In turn, Zic2 neurons seem to have synaptic outputs to spinal motor neurons raising the interesting possibility that Zic2 neurons could play a role in the integration of sensory and motor spinal circuits. We are currently addressing the functional significance of the Zic2 cell's ascending projection to the cuneate nucleus. Preliminary behavioral analysis points to the relevance of this pathway in the processing of light touch. Our data is suggests a model in which Zic2 neurons specifically participate in processing of light touch information and in controlling fine motor performance.

Disclosures: S. Paixao: None. **L. Loschek:** None. **L. Gaitanos:** None. **R. Klein:** None.

Nanosymposium

543. Somatosensation: Peripheral Mechanisms and Spinal Circuits

Location: SDCC 5

Time: Tuesday, November 6, 2018, 1:00 PM - 4:00 PM

Presentation Number: 543.04

Topic: D.03. Somatosensation: Pain

Support: NIH K08NS101064
NIH 2T32DA007261
NIH R01NS42595
NIH RO1NS101704
NIH RO1NS038253
Adelson Medical Research Foundation

Title: Molecular characterization of nerve injury and regeneration by single-nucleus RNA sequencing

Authors: *W. RENTHAL[1], I. TOCHITSKY[2], E. LI[1], M. A. NAGY[1], L. MCILVRIED[3], R. W. GEREAU, IV[4], C. J. WOOLF[5]
[1]Harvard Med. Sch., Boston, MA; [2]Neurobio., Boston Children's Hosp. and Harvard Med. Sch., Boston, MA; [3]Anesthesiol., Washington Univ. at St. Louis, Saint Louis, MO; [4]Anesthesiol., Washington Univ. Sch. Med., Saint Louis, MO; [5]Neurobio., Children's Hosp. Boston, Boston, MA

Abstract: Summary:
Sensory nerve injury initiates a massive transcriptional response that simultaneously leads to both pain and nerve regeneration, but the heterogeneity of primary sensory neurons has made it difficult to study the underlying molecular events within individual neuronal subtypes. Leveraging recent advances in single-nuclei transcriptomics, we have characterized the neuronal subtype-specific changes in gene expression that occur within hours of sciatic nerve injury in the mouse and how they evolve during the subsequent months.
Aims:
To characterize the cell-type-specific patterns of gene expression in mouse and human dorsal root ganglia (DRG) and the transcriptional changes that occur in mouse models of sensory neuron injury.
Methods:
Single-nuclei RNA sequencing was performed on DRG tissue from naïve or injured (sciatic nerve transection, sciatic nerve crush, or spinal nerve ligation) C57/Bl6 mice. Multiple time points were conducted after these injury models (hours to months). Cell types were determined by graph clustering and marker gene identification. Single-nuclei RNA sequencing was also performed on human lumbar DRG that were collected from three organ donors. After human DRG cell types were identified by graph clustering, the expression level of the closest gene(s) to pain-associated human single nucleotide polymorphisms were assayed in each human DRG cell type.
Results:
We observe that within hours of peripheral axonal injury, all DRG neuronal subtypes (e.g. peptidergic nociceptors, mechanoreceptors) initiate a conserved transcriptional program that results in an entirely new injured cell state that no longer resembles their previous neuronal identity. While the injury-induced transcriptional program is similar across sensory neuron subtypes, the recovery from injury is largely cell-type-specific as the neuron regains its original

transcriptional identity. Ongoing experiments are characterizing the role of injury-induced transcription factors in the induction of and recovery from this injured cell state. Finally, we have created a single-nuclei atlas of the human DRG and will use these data to characterize human sensory neuron subtypes and to localize single nucleotide polymorphisms associated with human pain disorders.
Conclusions:
Single-nuclei RNA sequencing has enabled the molecular characterization of sensory neuron injury in each neuronal subtype and has provided a rich resource of the injury-induced gene expression changes that contribute to both pain sensitization and nerve regeneration.

Disclosures: W. Renthal: None. **I. Tochitsky:** None. **E. Li:** None. **M.A. Nagy:** None. **L. McIlvried:** None. **R.W. Gereau:** None. **C.J. Woolf:** None.

Nanosymposium

543. Somatosensation: Peripheral Mechanisms and Spinal Circuits

Location: SDCC 5

Time: Tuesday, November 6, 2018, 1:00 PM - 4:00 PM

Presentation Number: 543.05

Topic: D.03. Somatosensation: Pain

Title: A point missense mutation in nerve growth factor (NGF^{R100W}) results in hereditary sensory and autonomic neuropathy type v

Authors: *K. J. SUNG[1], W. YANG[2], C. WU[3]
[1]Univ. of California San Diego, LA Jolla, CA; [2]Dept. of Neurology, Ruijin Hosp., Shanghai City, China; [3]Neurosciences MC0624, UCSD Sch. of Med., La Jolla, CA

Abstract: A missense point mutation in nerve growth factor (NGF^{R100W}) is associated with hereditary sensory autonomic neuropathy V (HSAN V), originally discovered in a Swedish family. These patients develop severe loss of perception to deep pain but with apparently normal cognitive functions. To better understand the disease mechanism, we have generated the first knockin mouse model of HSAN V. Mice homozygous for the NGF^{R100W} mutation (fln/fln) showed severe absence of intra-epidermal nerve fibers (IENFs) at birth, and severe loss of pain perception at ~2 months of age, and often failed to survive to full adulthood. The heterozygous mice (+/fln) developed a progressive degeneration of small sensory fibers both behaviorally and functionally: they showed a progressive loss of IENFs starting at the age of 4 months accompanied with progressive loss of perception to painful stimuli such as noxious temperature. We carried out detailed behavioral and histological studies of the +/fln mice and our quantitative analysis of lumbar dorsal root ganglia (DRG) showed the +/fln mice had a significant reduction in small size neurons positive for calcitonin gene-related peptide, while the number and profile of myelinated nerve fibers exhibited no significant difference from their +/+ littermate age-matched controls. Interestingly, the heterozygous mice showed no apparent structural alteration

in the brain including the NGF-dependent basal forebrain cholinergic neurons. Accordingly, they did not develop appreciable deficits in a battery of tests for functions of the central nervous system. Our study has thus provided novel insights into the selective impact of the NGF^{R100W} mutation on the development and function of the peripheral sensory system, which results in peripheral sensory degeneration in HSAN V.

Disclosures: K.J. Sung: None. **W. Yang:** None. **C. Wu:** None.

Nanosymposium

543. Somatosensation: Peripheral Mechanisms and Spinal Circuits

Location: SDCC 5

Time: Tuesday, November 6, 2018, 1:00 PM - 4:00 PM

Presentation Number: 543.06

Topic: D.02. Somatosensation

Support: NINDS 1 ZIA NS003153 02
NIDCD 1 ZIA DC000059 18

Title: Massively parallel single nucleus transcriptional profiling defines spinal cord neurons and their activity during behavior

Authors: *A. SATHYAMURTHY[1], K. R. JOHNSON[1], K. J. E. MATSON[1], C. I. DOBROTT[1], L. LI[1], A. R. RYBA[1], T. B. BERGMAN[1], M. KELLY[2], M. KELLEY[3], A. J. LEVINE[1]
[1]NINDS, NIH, Bethesda, MD; [2]Natl. Cancer Inst., Bethesda, MD; [3]Natl. Inst. on Deafness and Other Communication Disorders, Bethesda, MD

Abstract: Coordinated motor movements require the integrative action of diverse, yet specialized spinal networks. However, the neural substrates underlying the rich repertoire of motor behaviors is not well understood, owing to the lack of a comprehensive inventory of cell types within the mammalian spinal cord. To gain a deeper understanding of the cellular diversity within the spinal cord, we sought to create a molecular atlas of spinal cells. We performed massively parallel single-nucleus RNA sequencing (snRNA-seq) of the adult mouse lumbar spinal cord and identified 7 major groups of cells - neurons, oligodendrocytes, meningeal and Schwann cells, astrocytes, vascular cells, oligodendrocyte precursor cells, and microglia. To delve deeper into the transcriptional basis of functional heterogeneity among spinal neurons, we further analyzed these neurons and identified 43 distinct neuronal populations. While dorsal neurons formed discrete clusters, ventral neurons displayed overlapping gene expression patterns, suggesting the latter could have a continuum of phenotypes. Furthermore, by performing this technique immediately following formalin-injection and locomotion and mapping transient molecular signatures of neuronal activity onto single neurons, we identified both previously known and novel populations of spinal neurons that were active during these tasks. Ongoing studies are aimed at linking the transcriptional characterization of neuronal

populations to their functional repertoires to illuminate the molecular basis of spinal cord neuronal diversity. Together, this technique will enable us to probe dynamic changes in gene expression, thereby opening a new path to understanding the cellular basis of behavior.

Disclosures: A. Sathyamurthy: None. **K.R. Johnson:** None. **K.J.E. Matson:** None. **C.I. Dobrott:** None. **L. Li:** None. **A.R. Ryba:** None. **T.B. Bergman:** None. **M. Kelly:** None. **M. Kelley:** None. **A.J. Levine:** None.

Nanosymposium

543. Somatosensation: Peripheral Mechanisms and Spinal Circuits

Location: SDCC 5

Time: Tuesday, November 6, 2018, 1:00 PM - 4:00 PM

Presentation Number: 543.07

Topic: D.02. Somatosensation

Support: ERC Grant DHISP 250128 (previously)
ETH Research Grant 0-20157-15

Title: Gene expression profiling of four interneuron populations in the dorsal spinal cord

Authors: *R. R. DAS GUPTA[1,2], L. SCHEURER[1], H. WILDNER[1], H. U. ZEILHOFER[1,2]
[1]Inst. of Pharmacol. and Toxicology, Univ. of Zurich, Zurich, Switzerland; [2]Inst. of Pharmaceut. Sci., ETH Zurich, Zurich, Switzerland

Abstract: A complex network of excitatory and inhibitory interneurons located in the spinal dorsal horn serves critical functions both, in the maintenance of a physiological level of pain sensitivity and in the induction and maintenance of pathological pain states. The interneurons of this network are highly heterogeneous and fall into different subtypes that likely serve distinct functions in sensory processing. An unbiased classification based on genome-wide analyses of gene expression is urgently needed to allow targeted manipulations of the different neuron types. Here, we have employed the translating ribosome affinity purification (TRAP) technology in four lines of BAC transgenic mice expressing an eGFP tagged ribosomal subunit L10a under the transcriptional control of the Gad67, GlyT2, vGAT or vGluT2 genes. We identified 214 and 163 genes with specific expression in excitatory (vGluT2) and inhibitory (vGAT) spinal cord neurons, respectively (FDR ≤ 0.05, ratio ≥ 2). Amongst the most strongly enriched genes, many encoded for transcription factors, neuropeptides or other extracellular signalling molecules and their receptors. We selected 40 highly enriched genes for analysis of their expression patterns in the spinal cord by *in situ* hybridization (ISH). Out of these genes, we identified 23 genes with spatially restricted expression patterns in the spinal dorsal horn. We used multiplex, fluorescent ISH to determine the overlap in expression of the identified genes with each other and with known marker genes of excitatory and inhibitory dorsal horn interneurons. These genes may serve as potential marker genes expressed in functional distinct interneuron populations.

Disclosures: R.R. Das Gupta: None. **L. Scheurer:** None. **H. Wildner:** None. **H.U. Zeilhofer:** None.

Nanosymposium

543. Somatosensation: Peripheral Mechanisms and Spinal Circuits

Location: SDCC 5

Time: Tuesday, November 6, 2018, 1:00 PM - 4:00 PM

Presentation Number: 543.08

Topic: D.04. Somatosensation: Touch

Support: NIH grant AR059385
NIH grant NS07224

Title: The neuronal basis of chronic itch

Authors: *R. Z. HILL[1], Z. RIFI[1], R. B. BREM[2], D. BAUTISTA[1]
[1]Mol. and Cell Biol., UC Berkeley, Berkeley, CA; [2]Buck Inst. for Res. on Aging, Novato, CA

Abstract: Atopic dermatitis a highly prevalent chronic itch disorder for which few effective treatments exist. While much work has been done to understand the multifaceted interactions between immune cells, keratinocytes, and sensory neurons that drive atopic dermatitis in the skin, little is known regarding the molecular changes that occur in somatosensory neurons after onset of atopic dermatitis. It is known that immune cells, glia, and sensory neuronal cell bodies in the trigeminal and dorsal root ganglion (TG/DRG) undergo vast changes in chronic inflammatory pain models, and that these changes help drive the course of the disease. However, it is unknown whether similar changes occur in chronic itch. Here, we used RNA-seq of whole tissue to ask whether gene expression changes occur in somatosensory ganglia in the MC903 mouse model, a widely studied model of chronic itch, which mirrors many molecular and morphological hallmarks of human atopic dermatitis. We collected total RNA from TG and treated cheek skin from male C57BL/6 mice at various time points in the MC903 model: from 24 hours after the first treatment, when no skin lesions are present, through the twelfth day of treatment, when lesions are mature. These samples were subjected to sequencing, read mapping, and differential expression analysis in which each time point was compared to samples isolated from corresponding vehicle control animals. We additionally collected spinal cord samples from mice that were treated with MC903 on the back skin in order to study its potential effects on the central nervous system. We found that MC903 treatment induces profound changes in the TG by the fifth day of the model, when behavioral data shows mice begin to scratch, consistent with selective hyperinnervation of pruriceptors. Analysis of the skin samples showed profound dysregulation of axon guidance molecules. We also observed an increase in markers for several immune cell subtypes in the TG by the eighth day. Evidence for demyelination, another hallmark of chronic pain that is relatively unstudied in chronic itch, was present in the TG by later time points. Additionally, by the eighth day, transcriptional changes in the skin and TG consistent

with neuroinflammation were reflected in the spinal cord. Spinal cord also displayed changes consistent with demyelination, lipid dysregulation, aberrant axonal growth, and altered excitability. We are now performing additional experiments to validate these findings and to complete our characterization of the neuronal basis of atopic dermatitis.

Disclosures: R.Z. Hill: None. **Z. Rifi:** None. **R.B. Brem:** None. **D. Bautista:** None.

Nanosymposium

543. Somatosensation: Peripheral Mechanisms and Spinal Circuits

Location: SDCC 5

Time: Tuesday, November 6, 2018, 1:00 PM - 4:00 PM

Presentation Number: 543.09

Topic: D.04. Somatosensation: Touch

Support: Howard Hughes Medical Institute
NIH Grant AR059385
NIH Grant NS07224
NIH Grant AI072429
NIH Grant AI063302
NIH Grant AI104914
NIH Grant AI105184

Title: Neuro-immune interactions drive itch in early eczema development

Authors: *C. M. WALSH[1], J. SCHWENDINGER-SCHRECK[1], J. DEGUINE[1], N. KUCIREK[1], E. BROCK[1], J. WEI[2], K. GRONERT[2], G. BARTON[1], D. BAUTISTA[1]
[1]MCB, [2]Vision Sci., UC Berkeley, Berkeley, CA

Abstract: Eczema is one of the most common chronic itch disorders. Both immune cell infiltration and neuronal activation are required for the development of itch in this disease. However, the distinct molecular and cellular players that contribute to the development of eczema have not been systematically studied. Here we set out to examine the neuro-immune interactions that occur in the skin during eczema pathogenesis using the Vitamin D mouse model of atopic dermatitis. We used a variety of techniques including calcium imaging, qPCR, FACS and mouse behavior to define the molecular interactions between immune cells and sensory neurons that drive itch behaviors in the development of atopic dermatitis. We find that although a variety of cytokines and innate immune cells infiltrate the skin at different stages of the model, neutrophils are early key players required for the onset of itch during the first week of eczema pathogenesis.

Disclosures: C.M. Walsh: None. **J. Schwendinger-Schreck:** None. **J. Deguine:** None. **N. Kucirek:** None. **E. Brock:** None. **J. Wei:** None. **K. Gronert:** None. **G. Barton:** None. **D. Bautista:** None.

Nanosymposium

543. Somatosensation: Peripheral Mechanisms and Spinal Circuits

Location: SDCC 5

Time: Tuesday, November 6, 2018, 1:00 PM - 4:00 PM

Presentation Number: 543.10

Topic: D.02. Somatosensation

Support: NIH R37HD091856

Title: Precise levels of PTF1A are required to generate itch-modulating neurons

Authors: *B. MONA, J. VILLARREAL, R. K. KOLLIPARA, J. E. JOHNSON
Neurosci., UT Southwestern Med. Ctr., Dallas, TX

Abstract: Touch, pain, itch and proprioception are somatosensory modalities that allow us to perceive our environment. Sensory input from the periphery via sensory neurons is modulated by an intricate network of interneurons in the spinal cord, then this information is relayed to the brain or motor circuits for an appropriate response. The diversity of neurons generated during development that form these networks is dependent on spatio-temporally controlled expression of transcription factors required for neuronal subtype specification. Here, we focus on the regulation of one such factor, PTF1A, and its function in specification of spinal inhibitory interneurons required for processing somatosensory input. We generated mutant mice using CRISPR-Cas9 to target mutations to three distinct regulatory elements in the *Ptf1a* gene locus. These experiments test the in vivo contribution of each element individually and in combination in directing *Ptf1a* transcription. Mutations in an auto-regulatory enhancer, specifically disrupting both PTF1-complex binding sites, causes reduced levels of PTF1A and alters the generation of subsets of PAX2 positive inhibitory neurons during dorsal neural tube development. In contrast to *Ptf1a* nulls, these enhancer mutant animals survive postnatally, but exhibit a severe scratching phenotype post-weaning. Behavioral analysis of the *Ptf1a* enhancer mutants revealed they have increased sensitivity to itch but sensitivity to mechanical or thermal pain is not different from wildtype littermates. Examination of spinal cords in 3-5 week old animals reveals a reduced number of *Gad1* positive inhibitory neurons, with a notable decrease in the *Penk* positive subpopulation. We are currently determining other neuronal subsets affected in these mouse models to gain insight into inhibitory contributions to the itch circuit, and how PTF1A levels encode diversity in the dorsal spinal cord.

Disclosures: B. Mona: None. **J. Villarreal:** None. **R.K. Kollipara:** None. **J.E. Johnson:** None.

Nanosymposium

543. Somatosensation: Peripheral Mechanisms and Spinal Circuits

Location: SDCC 5

Time: Tuesday, November 6, 2018, 1:00 PM - 4:00 PM

Presentation Number: 543.11

Topic: D.02. Somatosensation

Support: ERC Advanced Investigator Grant DHISP 250128
SNF grant 176398

Title: Neurons and pathways of stress-induced analgesia in mice

Authors: *K. HAENRAETS[1,2], R. GANLEY[1], S. SCHALBETTER[1], F. LUZI[1], L. YANG[2], H. C. JOHANNSSEN[1], H. WILDNER[1], H. U. ZEILHOFER[1,2]
[1]Univ. of Zurich, Inst. of Pharmacol. and Toxicology, Zurich, Switzerland; [2]ETH Zurich, Inst. of Pharmaceut. Sci., Zurich, Switzerland

Abstract: Stress-induced analgesia (SIA) is an important physiological mechanism that allows higher organisms to react properly to acute life-threatening situations. Descending projections from the rostral ventromedial medulla (RVM) to the superficial dorsal horn are key players of SIA. The precise cellular substrates of SIA in the brainstem and spinal cord have hitherto remained unknown. We have identified a population of inhibitory dorsal horn neurons (characterized by the expression of the gastrulation brain homeobox gene Gbx1) as key effectors of SIA. Pharmacogenetic inhibition of spinal Gbx1 neurons had little effect on acute pain, whereas their activation induced strong analgesia to noxious mechanical, cold and heat stimuli. Inhibition of these same neurons completely prevented SIA for all pain modalities in response to the forced swim test. We employed monosynaptic rabies tracing, and opto- and chemogenetics to establish a comprehensive model of the underlying circuit. More than 70% of medullary neurons that innervate Gbx1 neurons of the superficial dorsal horn were inhibitory. Strong descending inhibitory input onto Gbx1 neurons was confirmed by optogenetic experiments, in which light-evoked IPSCs were recorded from Gbx1 neurons after local RVM injection of AAVs carrying a ChR2-expression cassette. Using optogenetics, we also established that Gbx1 neurons provide monosynaptic inhibitory input onto spinal nociceptive output neurons located in lamina I, while they only scarcely contribute to presynaptic inhibition of primary sensory fiber terminals. First behavioral experiments employing intersectional gene transfer to target specifically glycinergic RVM neurons with terminals in the spinal cord revealed that inhibition of these neurons mimics SIA. Our results support a model of SIA in which GABA/glycinergic neurons descending from the RVM tonically inhibit spinal Gbx1 neurons under baseline conditions. During exposure to stressful conditions, Gbx1 neurons become disinhibited and subsequently inhibit lamina I projection neurons to interfere with the spinal relay of nociceptive signals.

Disclosures: K. Haenraets: None. **R. Ganley:** None. **S. Schalbetter:** None. **F. Luzi:** None. **L. Yang:** None. **H.C. Johannssen:** None. **H. Wildner:** None. **H.U. Zeilhofer:** None.

Nanosymposium

543. Somatosensation: Peripheral Mechanisms and Spinal Circuits

Location: SDCC 5

Time: Tuesday, November 6, 2018, 1:00 PM - 4:00 PM

Presentation Number: 543.12

Topic: D.03. Somatosensation: Pain

Support: Department of Biotechnology, Ministry of Science and Technology, Government of India (BT/PR14279Med/30/452/2010) for the financial support.
Indian Council of Medical Research for Senior Research Fellowship to MG

Title: Role of neuropeptide Y in post-incisional pain in rats: An immunohistochemical and behavioral study

Authors: *M. GAUTAM[1], P. PRASOON[2], S. B. RAY[2]
[2]Anat., [1]All India Inst. of Med. Sci. (AIIMS), New Delhi, India

Abstract: Background: Neuropeptide Y (NPY) is a 36 amino acid molecule distributed widely in the central and peripheral nervous system. It belongs to the pancreatic polypeptide family including peptide YY. NPY binds to several G-protein-coupled receptors and decreases calcium ion concentration in neurons. Its involvement in neuropathic pain is well established. However, its role in postoperative pain is still not fully elucidated. Therefore, we aimed to evaluate the expression of NPY in the dorsal horn and assess the antinociceptive effect of intrathecal NPY in a rat model of postoperative pain. **Materials and methods:** Adult male Sprague-Dawley rats were subjected to hind paw incision and the spatiotemporal expression of NPY in the affected region of the spinal cord was studied. Thereafter, rats were implanted with an intrathecal catheter (PE-5) and NPY (30 μg/10 μl) was administered. Morphine (30 μg) and normal saline were also administered in different groups. 15 minutes later, these rats were subjected to paw incision. Post-incisional pain behaviour was studied for 7 days. Guarding behaviour was evaluated from 2 h post-incision until postoperative day 4, while mechanical allodynia and thermal hyperalgesia were assessed until day 7. The antinociceptive effect of NPY was compared with morphine (30 μg). **Results:** Immunohistochemical localization of NPY in laminae I and II of dorsal horn showed its presence in the primary sensory afferents. Many could be seen ending around lamina I neurons. NPY expression in the deeper part of the dorsal horn was more discrete and present in neuronal cell bodies of varying sizes. Expression was also noted around blood vessels. The expression in the superficial laminae almost disappeared between 1-6 h after incision. At 12 h, the expression reappeared but again disappeared at day 1. Finally, increased expression was noted between days 3-5 when its distribution was similar to that of the control group. Intrathecal administration of NPY significantly attenuated guarding behaviour up to day 2 and this was

comparable to morphine. Thermal hyperalgesia was decreased between 2 h to day 2 but this was less effective than morphine. Allodynia was unaffected. **Conclusion:** The sudden disappearance of NPY from dorsal horn including Rexed's laminae I and II signifies its release from presynaptic terminals. Relief of post-incisional pain behaviour indicated its role in antinociception. This information may have clinical significance.

Disclosures: M. Gautam: None. **P. Prasoon:** None. **S.B. Ray:** None.

Nanosymposium

544. Neuro-Oncology

Location: SDCC 1

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 544.01

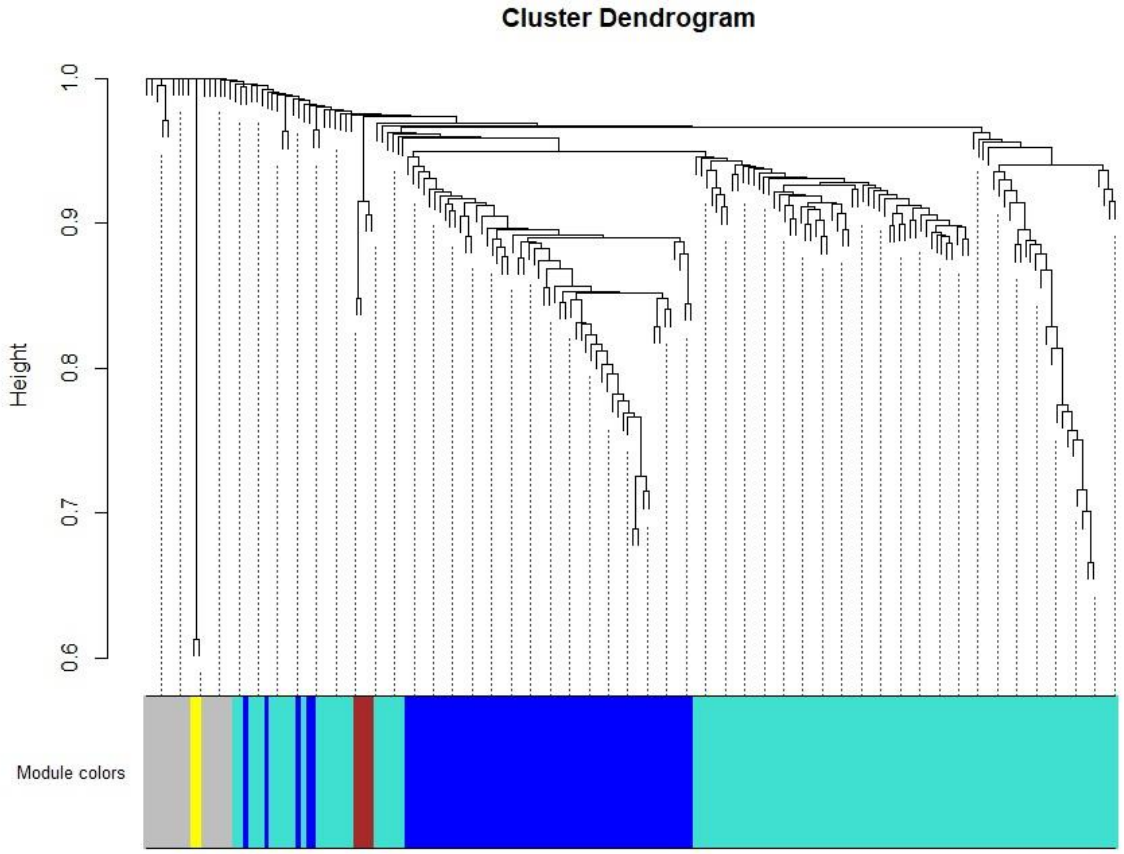
Topic: B.13. Neuro-Oncology

Title: Fusion detection analysis of public single cell RNA sequencing datasets reveals natural selection of chimeric transcripts in tumor evolutionary microenvironment

Authors: *M. CHUKHMAN[1], J.-L. GU[2], H. LU[3]
[1]Univ. of Illinois, Chicago, Chicago, IL; [2]Shanghai Jiaotong Univ., Shanghai, China; [3]Univ. of Illinois at Chicago, Chicago, IL

Abstract: Gene Fusions have been shown to have potential for successful targeted cancer therapies but have often eluded exploitation due to their inconsistency in disease penetrance. The currently accepted gold standard for identifying driver fusions in cancer is their rate of recurrence among the patient population. However, many fusions are "private" to individual patients and are usually thus excluded from driver candidacy. With the recent reduction in sequencing costs and the advent of new high throughput single cell RNA sequencing techniques it is now possible to trace cancer cell lineage within a single tumor and explore the evolutionary processes that selectively amplify some mutations and chimeras over others, identifying conserved lesions that are more likely to drive cancer growth and drug resistance.
A single cell RNA-Seq dataset containing a total of over 6TB of 25bp paired end reads from 5 primary Glioblastoma tumors and two GBM cell lines. This dataset contains millions or transcriptomic reads from 96 to 192 cells from each tumor, which the publishing authors used to profile the various cell types in the tumors based over 8000 gene expression levels in each cell. Our research augmented their results by searching for gene fusions harbored by multiple cell clones within each tumor. Open Source FusionCatcher software was run on the transcript fastq files from each cell and the final fusion candidates were sorted by harboring clone and aggregated by fusion identity using a Python script, tracking which cells harbored each fusion. Our findings indicate several significantly conserved fusions including, most notably, a CDK6 chimera with KIAA0895L, involved in the cell replication cycle through the RetinaBlastoma (RB) pathway and harbored in 8 of 192 cells in a freshly resected tumor and 11 of 192 cells in a

cultured GBM cell line. Hierarchical Cluster was done on these sample datasets with 5 clusters detected. This CDK6-KIAA0895L fusion localized to the two biggest clusters (blue and turquoise), (P=0.048) suggesting that it may be driving the cell division process in these tumors.



Disclosures: M. Chukhman: None. **J. Gu:** None. **H. Lu:** None.

Nanosymposium

544. Neuro-Oncology

Location: SDCC 1

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 544.02

Topic: B.13. Neuro-Oncology

Title: Specific inhibition of gsk-3β by tideglusib: Potential therapeutic target for neuroblastoma and glioblastoma cancer stem cells

Authors: *H. F. BAHMAD, R. M. CHALHOUB[1], T. ARAJI[1], S. ASSI[1], P. GHANEM[1], Z. ABOU MRAD[1], F. CHAMAA[1], H. KADARA[2], H. HARATI[3], W. ABOU-KHEIR[1]

[1]Dept. of Anatomy, Cell Biol. and Physiological Sciences, Fac. of Med., [2]Dept. of Biochem. and Mol. Genetics, Fac. of Med., American Univ. of Beirut, Beirut, Lebanon; [3]Neurosci. Res. Center, Fac. of Med. Sci., Lebanese Univ., Beirut, Lebanon

Abstract: Nervous system tumors represent some of the highly aggressive cancers in both children and adults, particularly neuroblastoma and glioblastoma. The standard care of treatment comprises of surgical resection, radiotherapy, and chemotherapy; yet, tumors often recur regardless of the given treatment. Thus, there is ultimate need to come up with novel effective therapies that uniquely target the slowly dividing cancer stem cells (CSCs) within those tumors, which are believed to be the main reason behind therapy resistance. Glycogen synthase kinase (GSK)-3β is an active proline-directed serine/threonine kinase, well-known to be involved in different signaling pathways entangled in the pathophysiology of neuroblastoma and glioblastoma. Therefore, we aimed in our study to assess the potency of an irreversible GSK-3β inhibitor drug, Tideglusib, in suppressing proliferation, viability, migration, and CSCs population of human neuroblastoma and glioblastoma cell lines. We studied the *in vitro* anti-tumor effect of Tideglusib on human neuroblastoma SH-SY5Y and glioblastoma U-251 MG cells, in 2D culture, using MTT assay (cell proliferation), trypan blue assay (cell viability), wound healing assay (cell migration), and western blotting (different pathways' targeting), and in 3D culture using neurospheres formation assay (targeting CSCs). Our results showed that treatment with Tideglusib significantly reduced cell proliferation, viability, and migration of SH-SY5Y and U-251 cells, in a dose- and time-dependent manners. Tideglusib also significantly inhibited neurospheres formation capability in both cells, eradicating the self-renewal ability of highly resistant CSCs. Besides, since anti-tumorigenic activity of Tideglusib was much more prominent on glioblastoma cells than neuroblastoma cells, we surveyed an online publicly-available database (Ramaswamy Multi-cancer Statistics) to determine and compare between mRNA expression patterns of GSK-3β in human glioblastoma tissues and other body tumor tissues. Interestingly, GSK-3β was significantly overexpressed in glioblastoma tissues relative to other tumor tissues, with a fold change of 51.733, which explains why U-251 cells were much more sensitive to this drug treatment. In conclusion, Tideglusib proved to be an effective *in vitro* treatment for neuroblastoma and glioblastoma cell lines and may hence serve as a potential therapeutic target for both nervous system tumors.

Disclosures: R.M. Chalhoub: None. **T. Araji:** None. **S. Assi:** None. **P. Ghanem:** None. **Z. Abou Mrad:** None. **F. Chamaa:** None. **H. Kadara:** None. **H. Harati:** None. **W. Abou-Kheir:** None.

Nanosymposium

544. Neuro-Oncology

Location: SDCC 1

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 544.03

Topic: B.13. Neuro-Oncology

Support: NIH R21CA191846

Title: A role for hypocretin/orexin in metabolic and sleep abnormalities in a mouse model of non-metastatic breast cancer

Authors: *W. H. WALKER[1], J. C. BORNIGER[3], K. M. EMMER[2], R. J. NELSON[4], A. C. DEVRIES[5]
[1]Neurosci., [2]Vet. Preventative Med., The Ohio State Univ., Columbus, OH; [3]Stanford Univ., Stanford, CA; [4]Neurosci., [5]Med., West Virginia Univ., Morgantown, WV

Abstract: Among cancer patients, metabolic and sleep abnormalities are significant problems that are associated with decreased quality of life and increased mortality. Specifically, breast cancer patients frequently display aberrant sleep and elevated blood glucose levels at the time of diagnosis, both of which are associated with worsened outcomes. In spite of the abundance of metabolic and sleep abnormalities in cancer patients, the mechanisms by which tumors alter metabolism and sleep remain unknown. Utilizing a non-metastatic murine breast cancer model, we investigated the relationships among immune, metabolic, and sleep abnormalities. Tumor bearing mice displayed increased serum interleukin-6 concentrations, concurrent with hyperglycemia, altered gluconeogenesis/glycolysis gene expression, dysregulated satiety hormones (leptin and ghrelin), and sleep abnormalities. Previous research using a genetic model of metastatic lung adenocarcinoma hypothesized that tumor induced elevations in IL-6 promote hepatic insulin resistance and increase hepatic glucose production (Masri et al., 2016). To test whether tumor induced elevations in IL-6 were responsible for the metabolic and sleep abnormalities observed in our study, we reduced IL-6 signaling by administering a monoclonal antibody against IL-6. Despite successfully suppressing IL-6 signaling, metabolic and sleep abnormalities remained. Next, we investigated hypocretin/orexin (HO) signaling in the lateral hypothalamus as this population of neurons is known to regulate both metabolism and sleep, and observed increased HO activity. HO neurons directly regulate glucose secretion via autonomic signaling. Therefore, we administered a dual HO receptor antagonist (almorexant) or peripheral sympathetic neurotoxin (6-OHDA) to test whether the increased HO signaling via peripheral sympathetics was driving the altered hepatic glucose production and hyperglycemia. Notably, administration of almorexant or peripheral sympathetic denervation rescued the tumor-induced deficits in hyperglycemia and hepatic glucose production, independent of IL-6. Together, our data demonstrate a novel mechanism by which non-metastatic tumors can promote energy availability, and suggest that targeting HO system may represent a potential intervention for breast cancer patients with metabolic dysfunctions.

Disclosures: W.H. Walker: None. **J.C. Borniger:** None. **K.M. Emmer:** None. **R.J. Nelson:** None. **A.C. DeVries:** None.

Nanosymposium

544. Neuro-Oncology

Location: SDCC 1

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 544.04

Topic: B.13. Neuro-Oncology

Support: Field Neuroscience Institute
CMU Department of Chemistry and Biochemistry
John G Kulhavi Professorship in Neuroscience
CMU College of Medicine
CMU Neuroscience Program

Title: Potential application of the novel dendrimer-cystamine-curcumin nanoparticle technology for treatment of glioblastoma

Authors: *M. FANA[1,2], N. MUNRO[3,2], B. SRINAGESHWAR[3,2], B. KATHIRVELU[3,2], D. SWANSON[4,2], G. L. DUNBAR[5,2,6,8], A. SHARMA[4], J. ROSSIGNOL[7,1,3]
[1]Col. of Med., [2]Field Neurosci. Inst. Lab. for Restorative Neurol., [3]Neurosci., [4]Dept. of Chem. & Biochem., Central Michigan Univ., Mount Pleasant, MI; [5]Neurosci., Central Michigan Univ., Central Michigan University, MI; [6]Dept. of Psychology, [7]Field Neurosciences Inst. Lab. for Restorative Neurol., Central Michigan Univ., Mount Pleasant, MI; [8]Field Neurosciences Inst., Saginaw, MI

Abstract: Glioblastoma multiforme (GBM) is a grade IV astrocytoma localized in various structures of the brain with an unclear pathogenic origin. Malignancy is a common prognosis of the tumor with complications in treatment due to the blood-brain barrier (BBB) preventing drug penetration, tumor resistance to oncogenic therapies, and self-repair mechanisms limited in the brain. The median survival rate following diagnosis is 12 months post-diagnosis. Curcumin (Cur; a natural phytochemical), commonly consumed in turmeric, is known to inhibit tumor growth. However, Cur is water insoluble and, though it is able to penetrate the BBB, has minimal bioavailability in the brain. Entrapping Cur into a cystamine dendrimer (D-Cys; w/w 1:10) can carry the drug across the BBB and will make Cur more soluble and increase its bioavailability in the brain. The D-Cys is a G4 90/10 dendrimer (90%OH and 10%NH2 surface functional group) with a Cys-core (S-S). D-Cys is cleaved intracellularly in the presence of glutathione, an antioxidant greatly produced in cancer cells, to allow for greater release of Cur from D-Cys dendrimer complexed with Cur (D-Cys-Cur). This study tested the D-Cys-Cur efficacy in mouse-derived glioblastoma cells (Gl261) using an MTT assay by administering the nanoparticles at various concentrations (0.2-0.8mg/mL). MTT assay was also performed on splenocytes and mesenchymal stem cells (MSCs) to observe its effect on other cells in the body. An IFN-γ ELISA test was performed on activated splenocytes to determine the anti-

inflammatory effects of D-Cys-Cur.
Results: The UV absorbance spectrum shift data confirmed entrapment of Cur into D-Cys compared to only D-Cys and Cur. Furthermore, release kinetics showed steady linear increase in absorbance at 425nm over 24 hours indicating release of Cur from D-Cys. To confirm the anti-oxidant property of D-Cys-Cur, PAGE showed blue bands in gels loaded with D-Cys-Cur proportionate to the concentration of D-Cys-Cur whereas D-Cys alone did not show bands. The MTT assay results demonstrated that administration of D-Cys-Cur concentrations between 0.2mg/mL to 0.8mg/mL to be detrimental to Gl261 cell viability when compared to primary cortical neurons and MSCs. This shows that *in vitro*, the D-Cys-Cur caused cell death in the glioblastoma cells while sparing the other cell types.
The ELISA showed that D-Cys-Cur had a significant anti-inflammatory effect, even at very small concentrations (0.1/0.01). The amount of IFN-γ that was observed after the D-Cys-Cur treatment was close to the level of non-activated cells.
This significant effect of D-Cys-Cur may provide a new avenue for treating GBM.

Disclosures: M. Fana: None. **N. Munro:** None. **B. Srinageshwar:** None. **B. Kathirvelu:** None. **D. Swanson:** None. **G.L. Dunbar:** None. **A. Sharma:** None. **J. Rossignol:** None.

Nanosymposium

544. Neuro-Oncology

Location: SDCC 1

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 544.05

Topic: B.13. Neuro-Oncology

Title: Determining the elastic moduli and cellular properties of brain and gbm organoids to develop a biofabricated gbm model

Authors: *T. RIGGINS[1], H. MCNALLY[2], L. SMITH[5], S. HARBIN[3], J. L. RICKUS[4]
[1]Biomed. Engin., Purdue Univ., Lafayette, IN; [2]Knoy Sch. of Engin. Technol., [3]Weldon Dept. of Biomed. Engin., Purdue Univ., West Lafayette, IN; [4]Biomed Engr/Ag&Biol Engr/Bindley Biosci, Purdue Univ., W Lafayette, IN; [5]3D Bioprinting Core, IU Sch. of Med., IU Sch. of Med., Indianapolus, IN

Abstract: Glioblastomas (GBM) are the most aggressive and common brain tumor, accounting for 55% of all central nervous system tumors. Brain organoids are an emerging brain cancer model system that offer advantages of as a complex, multicellular system of human cells that can recapitulate key features of the human brain. Literature provides a wide range of mechanical properties of brain and brain tumor tissue due to varying tissue preparation methods, testing methods, temperature conditions, and post-mortem analysis time intervals. The morphology and proliferation rate of GBMs can be influenced by the mechanical properties of its environment, in particular, many of the of these 3D cultured systems utilize ECM components such as collagen,

laminin, and fibronectin, which are not major components of the proteoglycan- and glycosaminoglycan-rich brain parenchyma. Since GBM tumors are derived from the connective and supportive cells that compose the parenchyma, the mechanical properties of the brain are reliant on these cell-to-cell connections. Furthermore, tumors communicate through gap junctions to take nutrients, vasculature and recruit monocytes from stromal cells meaning that cell-to-cell connections and mechanical properties influence tumor signaling, behavior and metabolism. To develop and characterize GBM models representing natural GBM constitution, we use a scaffold free biofabrication process that results in an *in vitro* organoid model with the desired heterogeneous cell-to-cell properties. We will confirm change in physiological stiffness of GBM models by measuring elastic modulus using atomic force microscopy, and also confirm the presence of a functioning ECM with a quantitative glycosaminoglycan assay. We determine cellular heterogeneity by imaging change in cytoarchitecture over time using cell tracker dyes, and the presence of gap junctions using antibody connexin 43. By creating a GBM model replicating native cell and ECM composition and tissue mechanical properties, potential research findings and therapeutics derived using this model may lead to better clinical outcomes.

Disclosures: T. Riggins: None. **H. McNally:** None. **L. Smith:** None. **S. Harbin:** None. **J.L. Rickus:** None.

Nanosymposium

544. Neuro-Oncology

Location: SDCC 1

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 544.06

Topic: B.13. Neuro-Oncology

Title: Modulation of TLR-4/Wnt pathways as new therapeutic strategy in the treatment of glioblastomas

Authors: *E. ESPOSITO[1], G. CASILI[1], M. CAFFO[2], M. CAMPOLO[1], S. M. CARDALI[2], M. LANZA[1], A. FILIPPONE[1], A. CONTI[2], A. GERMANÒ[2], S. CUZZOCREA[1]
[1]Dept Chem. Biol. Pharmaceut. and Envrn. Scences, [2]Dept Biomed. and Dent. Sci. and Morphofunctional Imaging, Unit of Neurosurg., Univ. of Messina, Messina, Italy

Abstract: Glioblastomas (GBMs) are highly aggressive brain tumors. Despite recent improvements in surgical treatment, radiotherapy and chemotherapy, the 5-year survival rate for patients with GBM remains low and novel and tailored therapies are needed. Various pathways are involved in gliomagenesis, among which the Wingless (Wnt) signaling. Dickkopf protein-related protein 3 (Dkk-3) interacts with proteins of Wnt pathways inhibitor. The Wnt signaling contributes to activity of the claudins, that are critical components of tight junctions (TJ), whose expression was altered selectively in cerebral microvessels of GBM. The mutations of this pathway show clinical implication, because they lead to the onset of several cancers, including

brain tumors, being also involved in tumor angiogenesis. The aim of this study was to determine the role of Wnt pathway in directly regulating tumor grown, apoptosis process by targeting Dkk-3, TJ alteration and claudin-5, and to suggest possible therapeutic interactions involving Wnt/Toll-like receptors (TLRs) pathways. In the present study we investigated the expression of Dkk-3, claudin-5, apoptosis markers and TLR-4 receptor protein levels in in vitro studies on U-138MG, A-172, LN-18 and LN-229 human glioblastoma cell lines, in in vivo study with TLR-4 -/- mice and in GBM human biopsies. We showed a significant Dkk-3 and claudin-5 downregulation, with apoptosis process involvement and with an interesting TLR-4/Wnt modulation. We concluded that combined modulation of Wnt/Dkk-3/claudin-5 and TLR-4 pathways, simultaneously targeting apoptosis and survival signaling defects, might shift the balance from tumor growth stasis to cytotoxic therapeutic responses, flowing in greater therapeutic benefits.

Disclosures: E. Esposito: None. **G. Casili:** None. **M. Caffo:** None. **M. Campolo:** None. **S.M. Cardali:** None. **M. Lanza:** None. **A. Filippone:** None. **A. Conti:** None. **A. Germanò:** None. **S. Cuzzocrea:** None.

Nanosymposium

544. Neuro-Oncology

Location: SDCC 1

Time: Tuesday, November 6, 2018, 1:00 PM - 2:45 PM

Presentation Number: 544.07

Topic: B.13. Neuro-Oncology

Support: NIH/NINDS R01NS088648

Title: Fyn kinase is a novel interactor of the central nervous system-specific protein Olig2

Authors: *S. V. MEHTA[1], A. DEROGATIS[2], F. RAUF[3], R. KUPP[4], C. LOCASCIO[2], E. LUNA MELENDEZ[2], J. LABAER[3]
[1]Barrow Neurolog. Inst., Phoenix, AZ; [2]Neurobio., Barrow Neurolog. Inst., Phoeinx, AZ; [3]Biodesign Inst., Arizona State Univ., Tempe, AZ; [4]Cancer Res. UK, Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Olig2 is a multifunctional basic helix loop helix (bHLH) transcription factor with critical roles during brain development and gliomagenesis. Recent studies have shown that phosphorylation of Olig2 at Serine and Threonine residues regulate the recruitment of distinct partner proteins, which in turn dictate its function. We utilized a novel *in vitro* Nucleic Acid Programmable Protein Array (NAPPA) platform to identify direct interactors of Olig2. Here, we report the identification of Fyn kinase, a Src-family non-receptor tyrosine kinase as a novel interactor of Olig2. While Olig2 plays a critical role in cell fate determination of oligodendrocyte lineage cells, Fyn has been shown to play a key role in the oligodendroglial differentiation and

maturation. We confirmed the interaction by co-immunoprecipitation of endogenous proteins in normal and oncogenic murine neural progenitor cells as well as in patient-derived glioblastoma stem cells. Furthermore, we find that Olig2 is phosphorylated at the tyrosine residues in a Fyn-dependent manner. Mutating the tyrosine residues in Olig2 to inactive phenylalanine affects cell migration and the ability of glioma stem cells to differentiate into astrocytes and neurons. In summary, we have unraveled additional post-translational modification of Olig2 through its interaction with Fyn kinase which regulates Olig2-mediated cell migration, invasion, and differentiation in glioma stem cells.

Disclosures: S.V. Mehta: None. **A. DeRogatis:** None. **F. Rauf:** None. **R. Kupp:** None. **C. LoCascio:** None. **E. Luna Melendez:** None. **J. LaBaer:** None.

Nanosymposium

545. Human Cognition and Behavior: Human Long-Term Memory Representations: Network and Circuit Mechanisms

Location: SDCC 33

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 545.01

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant RII Track-2 FEC 1539067

Title: Measuring the relationship between memory performance and hippocampal structure/function in periadolescent children: A longitudinal investigation from the Dev-CoG project

Authors: *D. E. WARREN, N. CHRISTOPHER-HAYES[1], A. RANGEL[2], J. M. STEPHEN[3], V. D. CALHOUN[4], Y.-P. WANG[5], T. W. WILSON[2]
[2]Neurolog. Sci., [1]Univ. of Nebraska Med. Ctr., Omaha, NE; [3]Mind Res. Network, Albuquerque, NM; [4]The Mind Res. Network, Albuquerque, NM; [5]Tulane Univ., New Orleans, LA

Abstract: The hippocampus is necessary for normal declarative memory, but effects of adolescent brain development on hippocampal volume, function, and related memory processes are not well characterized. Despite this knowledge gap, adolescence is predicted to be associated with significant changes in the volume and/or functional connectivity of hippocampus because of substantial differences in declarative memory performance between children and adults. The Developmental Chronnecto-Genomics project (Dev-CoG) is an ongoing NSF-funded effort to better understand adolescent brain changes which is conducting repeated MRI scans of the brains of 230 children (9-15 years of age). Here, we report preliminary findings from the current Dev-CoG dataset which provides an opportunity to investigate adolescent changes in hippocampus and cognition. Based on longitudinal neuroimaging and cognitive assessment data collected from children and adolescents (N=80, age=9-15 years) at two timepoints separated by one year, we

analyzed the developmental trajectory of hippocampal volume and resting-state functional connectivity (rs-FC) as well as behavioral performance on a measure of declarative memory (NIH Toolbox Picture Sequence Memory Test). Hippocampal volume was measured through manual tracing of the hippocampus from T1 MRI (1×1×1 mm). Hippocampal masks were next used as seed regions for an exploratory whole-brain analysis of hippocampal rs-FC. Resting-state fMRI (rs-fMRI) data were collected using two identical multiband sequences (one eyes-open, one eyes-closed): voxel size, 3.3×3.3×3.0 mm; TR, 460 ms.; TE, 29 ms.; duration, 306 s (i.e., 650 measurements). Standard functional MRI preprocessing was applied to the rs-fMRI data followed by best-practices processing for rs-FC analyses (Power et al., 2014). We evaluated developmental changes in memory performance, hippocampal volume, and seed-based hippocampal rs-FC as well as the interrelated changes in these measures with development. The results provide evidence that adolescent brain development exerts selective effects on memory, hippocampus, and a broader network of brain regions supporting memory and depends on several factors. By evaluating the volumetric, functional, and behavioral consequences of adolescent brain development in the hippocampus, this study addresses an important gap in our current understanding of how memory systems develop and further motivates the longitudinal collection of large datasets from child and adolescent populations.

Disclosures: N. Christopher-Hayes: None. **A. Rangel:** None. **J.M. Stephen:** None. **V.D. Calhoun:** None. **Y. Wang:** None. **T.W. Wilson:** None.

Nanosymposium

545. Human Cognition and Behavior: Human Long-Term Memory Representations: Network and Circuit Mechanisms

Location: SDCC 33

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 545.02

Topic: H.02. Human Cognition and Behavior

Support: Ministry of Education of PRC Humanities and Social Sciences Research grant 16YJC190006
STCSM Shanghai Pujiang Program 16PJ1402800
STCSM Natural Science Foundation of Shanghai 16ZR1410200
European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC grant agreement n.242809

Title: Right lateralized frontoparietal network subserves task-independent temporal context recollection

Authors: *Q. YE[1], E. MACALUSO[2], S. KWOK[1]
[1]Sch. of Psychology and Cognitive Sci., East China Normal Univ., Shanghai, China; [2]Univ. Claude Bernard Lyon 1, Lyon, France

Abstract: Temporal context is instrumental for the recall of episodic events. However, the elucidation of neural mechanisms underlying temporal context has been constrained by individual tasks (e.g., recency judgment task), rather than by some overarching processes. To tackle this, we used multivariate decoding to investigate the extent to which common neural patterns within the same cortices may carry temporal-contextual information under two different retrieval tasks: temporal order judgment (TOJ) and temporal duration estimation (TDE). 19 subjects watched a 42-min TV episode, and 24 hours later, completed the two tasks during fMRI. In the TOJ, subjects were presented with two frames of either same- or different-storylines from the episode, and required to choose the frame that happened earlier (2 runs); in the TDE, the same subjects were required to indicate how far apart in time the two frames were: "very near", "near", "far", "very far" (2 runs). We first ran GLM analyses to model the subject's BOLD response separately for same- and different-storylines in all runs and searchlight the whole cortex using a sphere of 251 voxels (4-voxel radius) to extract the beta-estimates for the 2 distinct contexts. We then trained a SVM classifier to distinguish the neural patterns associated with same- versus different-storylines in TOJ and applied this classifier to predict the temporal context on the neural data obtained from TDE, and vice versa. We revealed above-chance accuracy in the across-task prediction in right inferior frontal gyrus and angular gyrus, extending into superior temporal gyrus (all $P_{FWE} < 0.05$; Fig. 1A). The decoding accuracy of across- and within-task (average of TOJ_{within} and TDE_{within}) was significantly above chance in these ROIs but not for the visual cortex (Fig. 1B), confirming the frontoparietal's role in representing temporal-context memory irrespective of tasks. MVPA results delineated the signature of context recollection and prompted us to put forward a novel notion that the computation implicated in temporal context abstraction is independent of task demands.

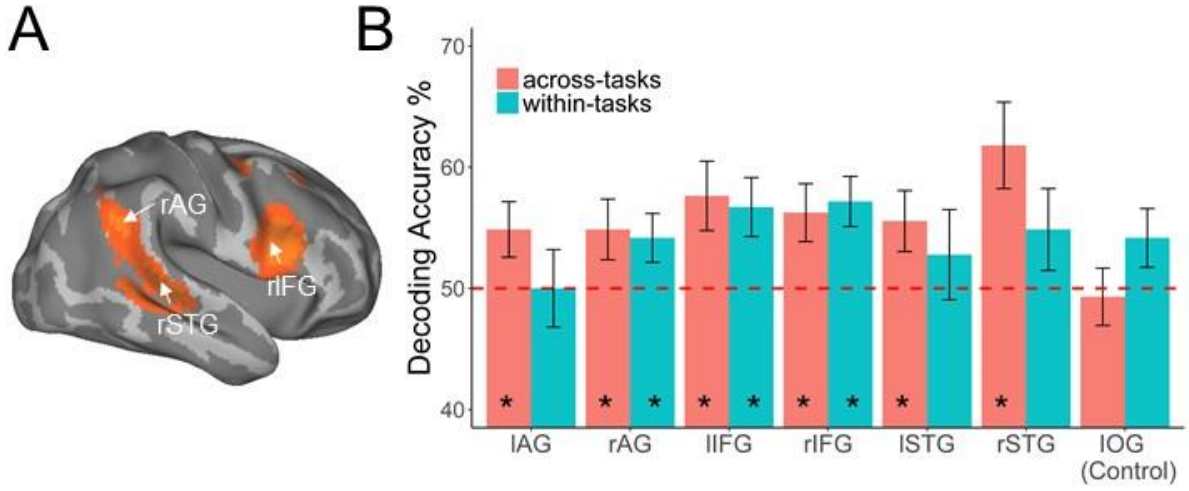


Figure 1. (A) Searchlight decoding brain map. Across-tasks memory signals decoded for temporal-contexts (voxel level at $P < 0.001$; $P_{FWE\text{-}cluster} < 0.05$). For cross-validation, this procedure was also repeated the other way round (i.e., trained SVM classifier using TDE data and tested on TOJ data). (B) Decoding accuracy comparison. Mean decoding accuracy for across-tasks (TOJ <->TDE) and within-task (average of TOJ and TDE). Dashed line = chance at 50%. Error bars = standard error of the mean. AG = angular gyrus, IFG = inferior frontal gyrus, STG = superior temporal gyrus, IOG = inferior occipital gyrus (bilateral); l = left, r = right. * denoted $P_{FDR} < 0.05$.

Disclosures: Q. Ye: None. **E. Macaluso:** None. **S. Kwok:** None.

Nanosymposium

545. Human Cognition and Behavior: Human Long-Term Memory Representations: Network and Circuit Mechanisms

Location: SDCC 33

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 545.03

Topic: H.02. Human Cognition and Behavior

Support: NIMH RO1MH60941

Title: Reinstatement of event details during episodic simulation in the hippocampus

Authors: *P. P. THAKRAL[1], K. P. MADORE[2], D. ADDIS[3], D. L. SCHACTER[1]
[1]Psychology, Harvard Univ., Cambridge, MA; [2]Psychology, Stanford Univ., Stanford, CA; [3]Sch. of Psychology & Ctr. for Brain Res., The Univ. of Auckland, Auckland, New Zealand

Abstract: According to the constructive episodic simulation hypothesis, episodic simulation (i.e., imagining specific novel future episodes) draws on the same neural processes that support episodic memory (i.e., recalling specific past episodes). Episodic retrieval supports the ability to simulate future experiences by providing access to episodic details (e.g., the people and locations that comprise memories) that can be recombined in new ways. In the current functional magnetic resonance imaging study, we test this hypothesis by examining whether the hippocampus, a region implicated in the reinstatement of episodic information during successful memory, also supports the reinstatement of episodic information during simulation. Participants recalled past episodes each comprising two event details, a personally familiar location and person. Participants also simulated novel future episodes using recombined pairs of person and location details taken from different recalled episodes. Participants rated the vividness of each location and person in their memory and simulation. Behaviorally, the vividness of the remembered details co-varied with the vividness of the simulated details. Employing a multi-voxel pattern similarity analysis, we interrogated the similarity between neural patterns during memory and simulation at the level of individual event details. Using a hippocampal voxel set identified with a univariate analysis, we calculated for each participant the similarity between memory and simulation trials when matched as a function of a shared event detail (i.e., matching correlations). Critically, to assess the specificity of reinstatement, these matching correlations were compared to their mismatching counterparts (i.e., where each memorial detail was correlated to all other simulations not containing that detail). Both matching and mismatching correlations were computed for details as a function of high and low vividness during episodic simulation. Across participant analyses of the resulting mean correlations revealed a significant correlation type (match, mismatch) by vividness (high, low) interaction: the magnitude of the matching correlations was greatest for simulated details associated with high vividness relative to all other

correlations (i.e., match-low, mismatch-high, and mismatch-low). This pattern was common to both location- and person-specific details. These findings indicate that the hippocampus supports the reinstatement of detail-specific information from memory during episodic simulation, with the level of reinstatement mediating the subjective experience of simulated details.

Disclosures: P.P. Thakral: None. **K.P. Madore:** None. **D. Addis:** None. **D.L. Schacter:** None.

Nanosymposium

545. Human Cognition and Behavior: Human Long-Term Memory Representations: Network and Circuit Mechanisms

Location: SDCC 33

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 545.04

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R37NS21135

Title: Frontotemporal network temporally encodes emotional sequences in humans

Authors: *J. ZHENG[1], L. MNATSAKANYAN[2], S. VADERA[3], R. T. KNIGHT[5], J. LIN[4]
[1]Dept. of Biomed. Engin., [2]Comprehensive Epilepsy Program, Dept. of Neurol., [3]Dept. of Neurolog. Surgery, [4]Dept. of Neurol., Univ. of California, Irvine, Irvine, CA; [5]Helen Wills Neurosci. Institute; Dept. of Psychology, Univ. of California Berkeley, Berkeley, CA

Abstract: How are events sequentially coded to shape our perception of environment and guide our behavior? An influential theory is that theta oscillations facilitate the temporal coding and integration of sequential information via spike-timing-dependent plasticity. In particular, rodent electrophysiology studies have shown that past, current and future spatial locations are represented at distinct theta phases. Recent studies suggest that this phase precession may be not only restricted to spatial coding but extend to temporal coding of sequential events. Whether theta-phase precession provides a mechanism to integrate emotional sequences in humans has not been investigated. To test the generalizability of theta-phase precession for emotional processing in humans, we use a decision-making task that integrates the temporal sequence of emotional context to face perception. Each trial started with an emotional context image, followed by a short delay period (0.5s) and then a neutral face presentation. Subjects were instructed to rate the emotional valence of each neutral face after seeing the emotional context. We conducted the experiment on 8 patients with epilepsy undergoing surgical evaluations. Local field potentials were simultaneously recorded from intracranial electrodes while subjects performed the task. We found that the preceding emotional context biases subjects' subsequent valence rating of the neutral face, indicating an information binding from past emotional context to the face perception. Next, we investigated the underlying neural dynamics and focused on the interactions among the amygdala, hippocampus and orbitofrontal cortex, a core circuit for

emotional processing and sequential learning. Since the temporal structure of this task sequenced the encoding (i.e. context display period), maintenance (i.e. delay period) and integration (i.e. face display period) of the context, we were able to decode the emotional information from the context at different task stages using Bayesian decoding technique. We observed a transient phase precession when switching from the delay period to the face display, with temporal coding of contextual information shifted from late theta phases (180º - 360º) to early theta phases (0º - 180º). In the meanwhile, the late theta phases were updated with the information of subjects' subsequent face ratings. Moreover, this phase advancement only occurred in the trials demonstrating strong contextual modulation. These findings highlight that theta-phase precession, may serve as a common neural mechanism across species, bridges temporal coding of spatial and temporal sequences.

Disclosures: J. Zheng: None. **L. Mnatsakanyan:** None. **S. Vadera:** None. **R.T. Knight:** None. **J. Lin:** None.

Nanosymposium

545. Human Cognition and Behavior: Human Long-Term Memory Representations: Network and Circuit Mechanisms

Location: SDCC 33

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 545.05

Topic: H.02. Human Cognition and Behavior

Support: NSFC Grant31730038

Title: Transformation of association- and item-specific neural representations across different memory stages

Authors: *J. LIU[1,2], H. ZHANG[2], N. AXMACHER[2], G. XUE[1]
[1]Beijing Normal Univ., Beijing, China; [2]Dept. of Neuropsychology, Ruhr-University Bochum, Inst. of Cognitive Neurosci., Bochum, Germany

Abstract: Memory has long been considered as a dynamic and transformative process. Recent evidence from both fMRI and EEG suggests that stimulus-specific representations can be identified during perception and tracked during consecutive memory stages including short-term memory maintenance and long-term memory retrieval. However, the electrophysiological mechanisms underlying the transformation of perceived representations into stable long-term memory traces have remained elusive. Here, we implemented a novel paradigm that allowed us to probe the representational basis of short- and long-term memory as well as their interactions while recording intracranial EEG from the hippocampus and wide-spread neocortical areas of presurgical epilepsy patients. Participants learned associations between Chinese words and pictures, maintained these stimulus-specific associations for a few seconds, and were later tested

for their item and associative memory of these stimuli. We applied representational similarity analysis across electrodes and frequencies during various stages of information processing. Our preliminary results suggest that item- and association-specific information can indeed be identified and that they rely on different distributions of activity patterns. Both types of representations predominantly depend on activity in the low-frequency range (3-15Hz). These results underline the utility of multivariate analysis methods to directly track the role of stimulus-specific representations for memory.

Disclosures: J. Liu: None. **H. Zhang:** None. **N. Axmacher:** None. **G. Xue:** None.

Nanosymposium

545. Human Cognition and Behavior: Human Long-Term Memory Representations: Network and Circuit Mechanisms

Location: SDCC 33

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 545.06

Topic: H.02. Human Cognition and Behavior

Support: European Research Council (Grant Agreement no 647954) awarded to SH
Deutsche Forschungsgemeinschaft (HA 5622/1-1) awarded to SH
Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (107672/Z/15/Z) awarded to BS
SH is further supported by the Wolfson Society and the Royal Society

Title: Forward and time-compressed replay of human episodic memories flexibly changes its speed

Authors: *S. MICHELMANN[1], B. STARESINA[1], H. BOWMAN[1,2], S. HANSLMAYR[1]
[1]Univ. of Birmingham, Birmingham, United Kingdom; [2]Univ. of Kent, Canterbury, United Kingdom

Abstract: When we remember episodes from our past, we can do this oftentimes in a highly detailed manner and with temporal precision. On the other hand, we are able to go through wide-ranging time intervals in our memory without having to recall every sub-event completely. This implies that our memory system can flexibly guide us through the past at varying speeds. We here track the replay of continuous episodes in memory. These episodes were continuous videos that consisted of distinct sub-events (i.e. scenes). In two experiments subjects learned associations between unique word-cues and one of three distinct scenes within the video-episodes. In a behavioral experiment we could show that the speed of memory replay is forward and compressed: We compared the time that participants took to recall associations that were learned early in these video-episodes to the time that it took to recall associations that were learned in later scenes. Using Magnetencephalography (MEG), we then tracked the replay of

these continuous episodes with a method that combines representational similarity analysis and oscillatory phase coherence. This allowed us to directly observe the unfolding of continuous representations from memory. This neural replay took place in a forward direction and operated at flexible compression levels. Specifically participants were faster to skip between distinct boundaries in the video-episodes (i.e. distinct scenes) than they were in replaying the detailed individual sub-events. These results identify memory replay as a flexible process that operates at different speeds.

Disclosures: S. Michelmann: None. **B. Staresina:** None. **H. Bowman:** None. **S. Hanslmayr:** None.

Nanosymposium

545. Human Cognition and Behavior: Human Long-Term Memory Representations: Network and Circuit Mechanisms

Location: SDCC 33

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 545.07

Topic: H.02. Human Cognition and Behavior

Support: Volkswagen AZ 86 507-3
DFG SFB 1089

Title: Concept neurons in the human medial temporal lobe reflect relational processing

Authors: *M. BAUSCH[1], J. NIEDIEK[1], T. P. REBER[1,3], S. MACKAY[1], J. BOSTRÖM[2], C. E. ELGER[1], F. MORMANN[1]
[1]Dept. of Epileptology, [2]Dept. of Neurosurg., Univ. of Bonn Med. Ctr., Bonn, Germany; [3]Fac. of Psychology, Swiss Distance Learning Univ., Brig, Switzerland

Abstract: The human medial temporal lobe is important for relational processing and memory. It contains “concept neurons” that represent semantic rather than perceptual features of presented stimuli. The activity of such neurons has been shown to reflect whether or not their preferred stimulus is kept in working memory. Here we asked whether concept cells could play a role in relational processing.
During 38 experimental sessions, we recorded from 2512 neurons in the amygdala, parahippocampal cortex, entorhinal cortex, and hippocampus of 12 neurosurgical patients performing perceptual or semantic comparisons of visual stimuli. Before the experiment, four images were chosen based on a screening procedure to maximize the likelihood of eliciting selective visual responses. In each trial of the main experiment, subjects viewed one of five possible questions, followed by a sequence of two of the four images that had to be compared. Subjects indicated the sequential position of the stimulus that best answered the question by pressing keys “1” or “2”. Four questions required semantic processing of the stimuli (”Bigger?”,

“Last seen in real life?”, “More expensive”/”Older?”, “Which do you like better?”), one question only required perceptual processing (“Brighter image?”). Two control conditions with the same structure but different questions were additionally included in the task.
We detected 61 semantic concept neurons with increased firing during the presentation of one of the images relative to baseline (significant binwise-signed-rank, alpha level of 10^{-5}) and higher firing for both the preferred image and its written name relative to other images and written names, respectively (Hedges’ g greater than 0.3). About half of these concept units responded to the non-preferred stimuli with a delayed but well-defined onset (about 400 ms later) whenever the task required a comparison to the response-eliciting concept. Firing patterns of 22 local pairs of concept neurons resulted in asymmetric population cross correlation peaks on short (<25 ms) as well as longer (200-700ms) time scales if and only if their preferred concepts had to be compared semantically.
For the first time we could directly monitor the activity of concept cells as a neuronal correlate of relational processing. Task-imposed ordered relations of concepts were expressed in ordered firing patterns of concept neurons. Their sequential activity holds the potential to store concept relations in memory via spike-time dependent or behavioral time scale plasticity and should be the topic of further investigation.

Disclosures: M. Bausch: None. **J. Niediek:** None. **T.P. Reber:** None. **S. Mackay:** None. **J. Boström:** None. **C.E. Elger:** None. **F. Mormann:** None.

Nanosymposium

545. Human Cognition and Behavior: Human Long-Term Memory Representations: Network and Circuit Mechanisms

Location: SDCC 33

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 545.08

Topic: H.02. Human Cognition and Behavior

Title: Time course of the development of episodic memory signals in the human hippocampus

Authors: *J. T. WIXTED[1], L. R. SQUIRE[2], M. H. PAPESH[3], S. D. GOLDINGER[4], P. N. STEINMETZ[5]
[1]Psychology, UC San Diego, La Jolla, CA; [2]VA Med. Ctr., San Diego, CA; [3]Louisiana State Univ., Baton Rouge, LA; [4]Arizona State Univ., Tempe, AZ; [5]NeurTex Brain Res. Inst., Dallas, TX

Abstract: In prior work, we reported evidence that episodic memory in the human hippocampus is supported by a sparse code such that (1) a small percentage of recorded neurons responded to any one previously seen target and (2) a small percentage of previously seen targets elicited a strong response in any one neuron. These findings accord with the predictions of long-standing neurocomputational models. In the current study, we tested memory using a continuous

recognition procedure in which spoken words were presented in a continuous stream and were sometimes repeated. Throughout the task, patients were asked to classify each word as “novel” upon its first presentation and as “repeated” upon its second presentation. A correct "repeated" decision in response to a repeated word is an instance of successful episodic memory. The hippocampus is known to support episodic memory, and hippocampal lesions impair performance on continuous recognition tasks for words. Our goal was to trace the development of the episodic memory signal in the hippocampus from the moment a word was presented to the ultimate behavioral decision. Each session consisted of 760 trials involving 380 pairs of spoken words. Baseline single-unit activity was recorded over an 800 msec period prior to the presentation of each word, and trial-specific activity was measured over an 800 msec period at various points after the onset of the spoken word. In total, we gave 30 tests to 27 subjects, recording from 191 well-isolated neurons in the hippocampus (115 left, 76 right). We examined the full distributions of normalized spike counts (pooled across single units recorded from all patients) from trials involving novel items and, separately, from trials involving repeated items. In accordance with prior work, the distribution of single-neuron activity in left hippocampus, measured 200 to 800 msec after word offset indicated that only a small fraction of neurons exhibited strong responding to a given repeated word and that each repeated word elicited strong responding in a different small fraction of neurons. By contrast, the distribution of single-neuron activity measured 200 to 800 msec after word onset exhibited a sharp reduction in firing relative to baseline.

Disclosures: J.T. Wixted: None. **L.R. Squire:** None. **M.H. Papesh:** None. **S.D. Goldinger:** None. **P.N. Steinmetz:** None.

Nanosymposium

545. Human Cognition and Behavior: Human Long-Term Memory Representations: Network and Circuit Mechanisms

Location: SDCC 33

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 545.09

Topic: H.02. Human Cognition and Behavior

Support: NRF of Korea Grant 2018M3C7A1022317
NRF of Korea Grant 2018M3C1B8013690

Title: Characterized neural correlates of successful memory in the hippocampus induced by direct stimulation in the lateral temporal cortex

Authors: *S. JUN[1], J. KIM[1], S. RYUN[2], C. CHUNG[1,2,3]
[1]Brain and Cognitive Sci., [2]Interdisciplinary Program in Neurosci., Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Neurosurg., Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of

Abstract: Direct electrical stimulation of the brain has emerged as a powerful treatment for multiple neurological diseases, and as a potential technique to enhance human cognition. However, the evidence for the effects of stimulation on memory performance is empirical; hence, its underlying electrophysiological activities remain to be explored. Particularly, it is unclear that the degree to which memory performance can be determined by neural processing characterized in encoding and retrieval via stimulation. To identify the mechanism of stimulation, which may underwrite successful memory, here we investigated the contribution of neural processes engaged in different memory processes. Drug-refractory epilepsy patients with intracranial electrodes were given direct electrical stimulation in the brain region known to support declarative memory: the lateral temporal cortex. The stimulation was delivered during the presentation of words in encoding. Intracranial EEG with or without stimulation during encoding and during verbal recognition were recorded. We found that the lateral temporal cortex stimulation led to improvement in memory performance. In the hippocampus, both encoding and retrieval, neural oscillations of correctly recognized trials showed distinct pattern changes between stimulation “on” and “off”. The stimulation induced positive modulation of high frequency (> 30 Hz) activities when trials were encoded correctly and recognized. Interestingly, frequency specific pattern during successful encoding, the hippocampus consistently showed relatively increased theta activity (3 - 8 Hz) from both “on” and “off”. However, during recognition, the pattern was different from stimulation that induced high frequency activity but not theta activity. Our results show that specific patterns of stimulation induced neural activity were linked to successful memory formation and retrieval. These results may envision useful intrinsic brain states and dynamics, which take into account their role in memory enhancement. Given that these physiologic changes were correlated with the effect of stimulation on task performance, these findings indicate the engagement of core memory features. Furthermore, different patterns of neural activity between encoding and recognition may suggest that positive high frequency modulation in retrieval determines the fate of the studied information.

Disclosures: S. Jun: None. **J. Kim:** None. **S. Ryun:** None. **C. Chung:** None.

Nanosymposium

546. Human Cognition and Behavior: Working Memory III

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 1:00 PM - 3:00 PM

Presentation Number: 546.01

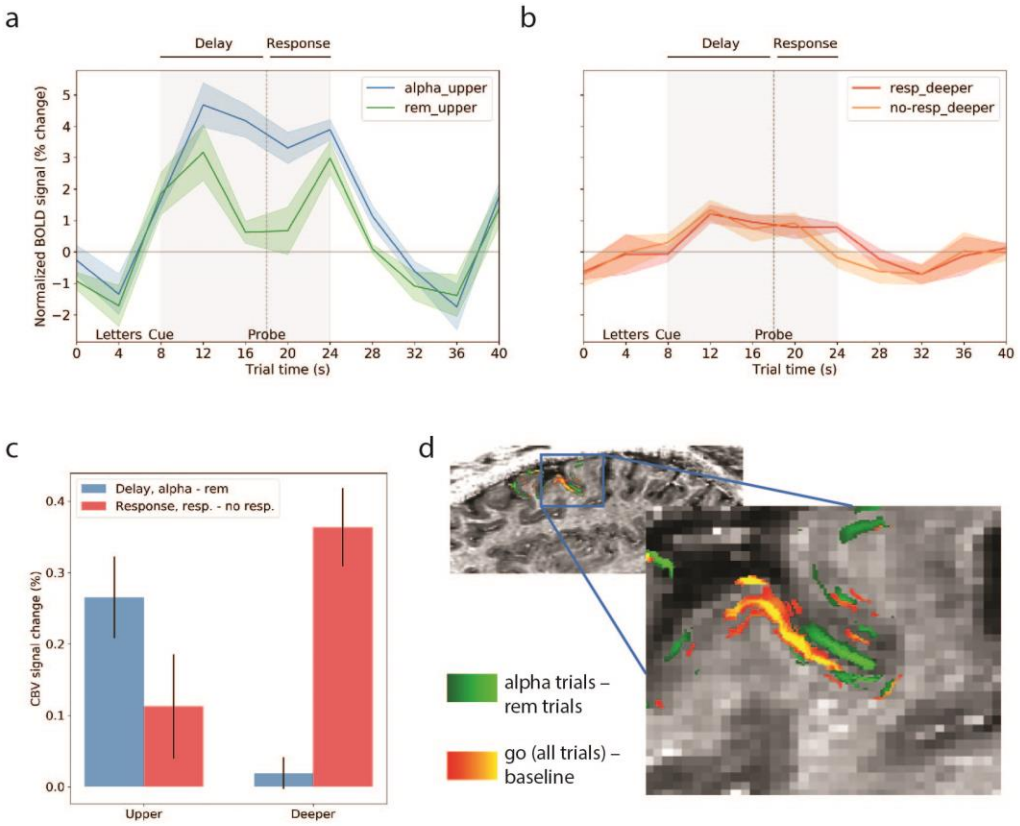
Topic: H.02. Human Cognition and Behavior

Support: NIH IRP ZIAMH002783

Title: High-resolution fMRI reveals layer-specific activity in human prefrontal cortex during working memory

Authors: *E. S. FINN, L. HUBER, D. C. JANGRAW, P. A. BANDETTINI
Lab. of Brain and Cognition/Section on Functional Imaging Methods, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Working memory (WM) involves a series of functions: encoding a sensory stimulus, maintaining its representation over a delay, and finally making a response. WM tasks engage dorsolateral prefrontal cortex (DLPFC) in both monkeys and humans. It has been hypothesized that WM's constituent functions localize to distinct cortical layers within this region: delay-period activity relies on recurrent excitatory connections among pyramidal cells in layers II and III, while response-related output stems from layer V. However, few studies have directly investigated WM-related activity as a function of cortical depth, and none have done so in humans. Here, we use state-of-the-art methods in high-resolution fMRI to interrogate the layer specificity of neural activity during different epochs of a WM task in DLPFC.
Participants (n = 6) saw a string of 5 letters followed by a cue telling them to either alphabetize the letters (manipulation condition) or remember them in their original order (maintenance condition). Following a delay period, on some trials participants responded to a probe letter by indicating its position within the string (response); on other trials they saw a dummy probe that did not require a response (no-response).
Using blood oxygen level-dependent (BOLD) imaging of DLPFC, we replicated findings that manipulation evokes greater delay activity than maintenance (Fig. 1a) and response trials evoke greater response period activity than no-response (Fig. 1b). Using cerebral blood volume (CBV) imaging, we show that these condition differences follow the hypothesized layer-specific patterns: superficial layers show preferential delay activity during manipulation vs maintenance trials, while deeper layers show preferential activity during the response period (Fig. 1c,d). As one of the first reports of layer-specific fMRI in a non-primary region, these results demonstrate the possibility of using high-resolution fMRI to map cognitive cortical circuitry in humans at the mesoscale by tracking input, recurrent local activity and output in higher-order brain regions.



Disclosures: E.S. Finn: None. **L. Huber:** None. **D.C. Jangraw:** None. **P.A. Bandettini:** None.

Nanosymposium

546. Human Cognition and Behavior: Working Memory III

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 1:00 PM - 3:00 PM

Presentation Number: 546.02

Topic: H.02. Human Cognition and Behavior

Support: NIH R01-EY022229
NSF SMA-0835976
NIH F31-NS103306
NIH F32-EY026796
NSF DGE-1247312

Title: Combined visual, auditory and tactile working memory fMRI reveals the topography of human sensory-selective and sensory-independent cerebral cortex

Authors: *S. M. TOBYNE[1], J. A. BRISSENDEN[2], A. L. NOYCE[2], D. C. SOMERS[2]
[1]Grad. Program for Neurosci., [2]Psychological and Brain Sci., Boston Univ., Boston, MA

Abstract: Our laboratory and others have recently reported that selectivity for sensory modality characterizes distinct subregions of the human brain, even outside of primary sensory cortices. We previously used fMRI to identify cortical regions that are preferentially recruited for visual vs. auditory attention and working memory (WM; Michalka et al., 2015; Noyce et al., 2017). Here, we extend our approach to include tactile cognition. While prior tactile studies have been reported, the joint organization of visual-, auditory- and tactile-selective WM recruitment within individual subjects remains to be investigated. Ten subjects participated in a blocked fMRI task requiring them to perform *N*-back WM judgements in auditory (animal vocalizations), visual (face photos), and tactile (raised dot textures) modalities. To identify sensory-selective regions, we contrasted each WM modality against the other two modalities. We observed several bilateral tactile-selective regions abutting previously described visual- and auditory-selective regions, including dorsal and ventral precentral sulcus, the postcentral sulcus, and the anterior intraparietal sulcus. Contrasting tactile WM with a sensorimotor control showed functional differentiation between regions of this tactile-selective network. We also observed recruitment of visual-selective frontal regions during tactile WM, suggesting these regions may be recruited for WM in a sensory-independent manner. To quantify this, we projected auditory, tactile and visual WM recruitment into a 3D space and developed a continuous measure of sensory independence. We observed several regions with high sensory independence, including within precentral sulcus, anterior and middle inferior frontal sulcus, intraparietal sulcus, anterior insula and medial superior frontal gyrus. We also noted several regions of visual/tactile multisensory-selectivity; auditory-selective cortex showed lower levels of multisensory recruitment. Lastly, resting-state analyses revealed differing profiles of functional connectivity across sensory-selective and sensory-independent regions, both across and within sensory modality. A hierarchical cluster analysis showed that auditory, visual and tactile WM regions segregate into networks based upon their connectivity profiles. Our results reveal the regional and network-level topography of sensory influences on working memory processes. Together, these results shed light on the complexity of sensory-selective and sensory-independent regions supporting higher-order cognition.

Disclosures: S.M. Tobyne: None. **J.A. Brissenden:** None. **A.L. Noyce:** None. **D.C. Somers:** None.

Nanosymposium

546. Human Cognition and Behavior: Working Memory III

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 1:00 PM - 3:00 PM

Presentation Number: 546.03

Topic: H.02. Human Cognition and Behavior

Support: NSF OIA 1632738
NSF OIA 1632849

Title: When less is more: Frontoparietal neurostimulation targets the cross-frequency neural code for working memory

Authors: *E. L. JOHNSON, K. T. JONES[1,2], M. E. BERRYHILL[1]
[1]Psychology, Univ. of Nevada Reno, Reno, NV; [2]Psychology, Colorado State Univ., Fort Collins, CO

Abstract: There is considerable interest in maintaining or enhancing working memory (WM), the neurocognitive horsepower behind ecologically valid measures of daily living. However, research and commercial interventions attempting to increase WM capacity have been met with mixed results. One emerging approach is to pair WM training with transcranial direct current stimulation (tDCS) to improve training gains. Twenty-four healthy young adults were trained and assessed on a difficult visuospatial WM task over one week, with or without active tDCS. The high-density electroencephalogram (EEG) was recorded during the initial WM assessment, prior to tDCS, and again after completing the training + tDCS program (24 hours post-tDCS). Previously, we found that only participants who received active anodal tDCS to the right frontoparietal network demonstrated WM gains, concomitant with enhanced low-frequency oscillatory synchronization. Here, we took a data-driven approach to further elucidate the neural basis of WM gains. EEG data were spatial-filtered using the Laplacian transformation, analyzed for local and long-range cross-frequency phase-amplitude coupling (PAC) between a broad range of spectral pairs, and validated using a bootstrapping approach. PAC outputs were submitted to mixed models by subsequent memory (correct vs. incorrect responses), training session, and tDCS group, and tested using a Monte Carlo method with cluster-based correction for multiple comparisons. Strikingly, we found that spatially and spectrally distributed reductions in PAC predicted superior WM performance at the post-training session with near-perfect accuracy, challenging prevailing theories of PAC and cognition. Furthermore, training-related WM gains were inversely predicted by changes in left PFC delta-modulated PAC, locally and across the frontoparietal network - and tDCS selectively reduced delta-gamma PAC at the left PFC, explaining the observed behavioral gains. These results demonstrate that the relationship between WM and PAC is not unidirectional, and reveal for the first time that tDCS targets the cross-frequency neural code in the service of WM.

Disclosures: E.L. Johnson: None. **K.T. Jones:** None. **M.E. Berryhill:** None.

Nanosymposium

546. Human Cognition and Behavior: Working Memory III

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 1:00 PM - 3:00 PM

Presentation Number: 546.04

Topic: H.02. Human Cognition and Behavior

Support: NRF-2016R1C1B2016039
NRF-2016R1E1A2A01939949

Title: Resource overwrite model for sequential working memory in human

Authors: *H. LEE[1], W. CHOI[1,2], Y. PARK[1], S.-B. PAIK[1,2]
[1]Dept. of Bio and Brain Engin., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of; [2]Program of Brain and Cognitive Engin., Daejeon, Korea, Republic of

Abstract: Human can memorize items given serially, such as phone numbers, as a form of sequential working memory. One of the interesting features of sequential working memory is the serial-position effects that the quality of memory varies by presented order. In particular, it has been reported that subjects memorize better the first and last items in a sequence, referred to as the primacy and recency effects (Hurlstone et al., 2014; Gorgoraptis et al., 2011). However, the underlying mechanism of the serial-position effects remains unclear. Here, we suggest a model to explain the mechanism of the serial-position effects using sequential overwrite and non-uniform allocation of memory resources. We hypothesized that a recent item overwrites the resource of previous items (sequential overwrite) so that the memory performance of the recent item is higher than previously shown items. We also assumed that the amount of allocated resources decreases sequentially (non-uniform allocation) to explain the primacy effect. To validate our hypotheses, we designed a human psychophysical experiment in which subjects were asked to memorize visual patterns presented sequentially and recall them freely. First, we found that memory performance for previous items was decreased when a new item was added, which could be quantitatively modeled by resource overwrite. Next, we found that the memory performance for the last item in a sequence decreases as the number of items increases. Since the last items are not affected by other memorized items, the memory performance of the last item reveals how much resources are allocated sequentially. This decreasing resource allocation accounts for the observed primacy effect. Taken together, our model with the sequential overwrite and decreasing resource allocation well explained the observed serial-position effects. Furthermore, we predicted that pre-allocation of memory resources will improve memory performance by reducing the degree of sequential overwrite. To test our idea, three types of pre-allocation condition were examined: prior to the memory task, the number of items to be presented was 1) correctly given, 2) not given or 3) wrongly given. The memory performance

was improved when the correct number of items was given, while it was worsened when the wrong number of items was given. Our model well described the three conditions by assuming that the overwrite ratio is minimal when the correct number is given and that it is maximal when the wrong number is given. In summary, our model proposes the mechanism of the serial-position effects in working memory and suggests that pre-allocation of memory resources can modulate memory performance.

Disclosures: H. Lee: None. **W. Choi:** None. **Y. Park:** None. **S. Paik:** None.

Nanosymposium

546. Human Cognition and Behavior: Working Memory III

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 1:00 PM - 3:00 PM

Presentation Number: 546.05

Topic: H.02. Human Cognition and Behavior

Support: Mark Diamond Research Fund Grant
National Multiple Sclerosis Society Pilot Research Grant

Title: Event-related potential evidence for verbal and spatial modality-dependent brain activity during visual working memory

Authors: *T. J. COVEY[1], D. W. SHUCARD[2], X. WANG[3], J. L. SHUCARD[2]
[2]Neurol., [3]Neurosci. Program, [1]Univ. at Buffalo, Buffalo, NY

Abstract: Working memory (WM) involves the short-term storage and manipulation of information, and enables many aspects of goal-directed behavior. There is theoretical support and empirical evidence indicating that information in the verbal and spatial modalities is maintained in distinct subcomponents of WM (i.e., phonological loop and visual-spatial sketchpad, respectively). We examined differences in neuronal activity between phonological (visual-verbal) and visual-spatial WM using event-related potentials (ERPs). ERPs were compared between these two stimulus categories at different stages of processing, from initial perceptual discrimination to stimulus categorization. Young adult participants (n = 37) completed verbal and spatial conditions of a visual 3-back task of WM. Letter stimuli were used in the verbal condition (match based on letter identity); solid square stimuli were used for the spatial condition (match based on stimulus location). Three trial types were analyzed: Matches (e.g., with letter stimuli, the following item sequence: t-b-r-t); Non-Matches (e.g., t-b-r-h); and Lures (e.g., t-b-r-b). Dense-electrode electroencephalographic (EEG) activity was recorded for each condition, and ERPs were derived for each trial type. Task performance was better (higher accuracy, faster reaction time) for the spatial compared to verbal condition, regardless of trial type; and for Non-Match trials compared to other trial types, regardless of condition. With respect to ERPs, the N1 (component at 120 msec post-stim) and P2 (180-200 msec) components

had greater amplitude for the spatial compared to verbal condition, regardless of trial type, reflecting differences between modalities in initial attention and perceptual discrimination processes. A higher amplitude, shorter latency P3 (320-450 msec) was also observed for the spatial compared to verbal condition, regardless of trial type, reflecting differences in the allocation of neural resources during stimulus categorization. However, frontal N2 amplitude (280-320 msec) was greater for the verbal compared to spatial condition. This effect was most pronounced for Non-Match trials. This finding could reflect the engagement of conflict monitoring processes that aid subvocal articulatory rehearsal, a process unique to phonological WM. The results indicate that the allocation of neural resources differs between visual-verbal and visual-spatial WM as early as 120 msec after stimulus onset, and persists through stimulus categorization. Furthermore, visual-verbal WM may engage conflict monitoring processes that are unique to phonological WM functions (i.e., articulatory rehearsal).

Disclosures: T.J. Covey: None. **D.W. Shucard:** None. **X. Wang:** None. **J.L. Shucard:** None.

Nanosymposium

546. Human Cognition and Behavior: Working Memory III

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 1:00 PM - 3:00 PM

Presentation Number: 546.06

Topic: H.02. Human Cognition and Behavior

Support: Veritas Fund

Title: Comparison of spike sorting methods shows distributed coding of visual objects by single neurons in the human brain

Authors: *P. N. STEINMETZ
NeurTex Brain Res. Inst., Dallas, TX

Abstract: The fraction of neurons in the human medial temporal which code for visual objects is a fundamental determinant of how these objects are represented in human cognition and memory. Yet present estimates of this fraction range between 1% and 24%, which have rather different functional implications. A variety of explanations for these differences have been advanced, including differences in the number of presentations of visual objects and technical differences between techniques, such as spike sorting.
To better understand these different estimates, I performed spike sorting of the intracranial microwire recordings from a previous experiment using two previously described methods: the Brain Modeling Laboratory (BML) method and WaveClus (WC). During the experiment, 4 views of 11 visual objects were presented six times to each subject. Large voltage fluctuations in the extracellular recordings were detected and then sorted into clusters of similar waveform shape.

In total, spike sorting using both methods was performed on 2752 recordings in 51 experiments in 4 brain areas: the amygdala (A), anterior cingulate cortex (AC), hippocampus (H), and ventromedial prefrontal cortex (PF). The fractions of single unit activity (SUA) with a significant response to the object presented (1-way ANOVA, $p<0.05$) in each brain area using the BML method were: A - 0.23, AC - 0.20, H - 0.21, PF - 0.12. Using the WC method the fractions were: A - 0.31, AC - 0.16, H - 0.32, PF - 0.19. There was a significant effect (ANOVA, $p<0.05$) of brain area and type of spike sorting on the fraction of clusters with a significant response.
The level of agreement between spike sorting methods, computed using mututal information, was low, with average AMIall = 0.04 (possible 0-1 range), though comparable to that found in simulations of SUA in similar noise levels (typical SNR 2.5).
These results confirm that there is a distributed coding of visual objects by neurons in the human medial temporal lobe which is independent of the spike sorting method being used. Thus differences in spike sorting are unlikely to account for disparate prior findings. Additionally, agreement on which specific aspects of the high frequency (300-3000 Hz) signal best represents visual object coding and single unit activity is low.

Disclosures: P.N. Steinmetz: None.

Nanosymposium

546. Human Cognition and Behavior: Working Memory III

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 1:00 PM - 3:00 PM

Presentation Number: 546.07

Topic: H.02. Human Cognition and Behavior

Support: NIMH Grant MH63901

Title: Feature-based attentional control over the contents of visual working memory

Authors: *J. M. SCIMECA, Y. VAFAI, W. HUERTA, J. A. MILLER, M. D'ESPOSITO
Helen Wills Neurosci. Inst., UC Berkeley, Berkeley, CA

Abstract: Given the limited capacity of visual working memory (WM), control processes that manage the contents of memory are critical to successful WM performance. WM performance can be enhanced by a retrospective cue (retrocue) that indicates a high-priority item in WM, typically a spatial-retrocue to a single item. However, the cognitive and neural mechanisms that support prioritization within WM remain vigorously debated. One prominent account proposes that internally-directed attention biases competing mnemonic representations in favor of prioritized items, whereas recent theories propose instead that a limited focus of internal attention prioritizes an item without biasing mnemonic representations or imposing costs on non-prioritized information. The current study addresses this debate using a combination of behavior and fMRI. Male and female human participants completed a WM task in which they memorized

complex visual items from two categories (bodies and scenes) and then a categorical feature-retrocue directed attention to multiple items in WM (e.g. “prioritize both scene items”). Across three experiments, we found that participants use feature-retrocues to prioritize multiple items within memory and improve performance relative to neutral cue trials, and that prioritization incurs clear costs to non-prioritized items. We next collected fMRI data while participants completed the retrocue task and a task in which they only memorized items from a single category (bodies or scenes) on each trial. Motivated by the biased competition model of visual attention, we hypothesized that the neural representation for remembering items from multiple categories could be modeled as a weighted sum of the representations for remembering each category in isolation. We further predicted that retrocues would bias the representation for multiple categories in favor of the prioritized category. We used the single-category task to train a forward encoding model on multivariate activity patterns across visual cortex during the WM delay, then we inverted the model and applied it to activity patterns from the retrocue task. We found that the representation for remembering multiple categories is initially an equally-weighted combination of the single-category representations, and that the retrocues bias the representation in favor of the retrocued category. Together, these findings challenge recent theories proposing a single-item focus of internal attention and cost-free prioritization within WM, and instead support a model in which internal feature-based attention can flexibly bias competing mnemonic representations in favor of multiple high-priority items.

Disclosures: J.M. Scimeca: None. **Y. Vafai:** None. **W. Huerta:** None. **J.A. Miller:** None. **M. D'Esposito:** None.

Nanosymposium

546. Human Cognition and Behavior: Working Memory III

Location: SDCC 30B

Time: Tuesday, November 6, 2018, 1:00 PM - 3:00 PM

Presentation Number: 546.08

Topic: H.02. Human Cognition and Behavior

Support: NRSA fellowship NIMH F31MH107157
NIMH grant MH63901

Title: Respective roles of frontoparietal and stimulus-selective visual regions in visual working memory for complex objects

Authors: *E. S. LORENC[1,2], M. D'ESPOSITO[2]
[1]Dept. of Psychology, Univ. of Texas at Austin, Austin, TX; [2]Helen Wills Neurosci. Inst., Univ. of California Berkeley, Berkeley, CA

Abstract: There is considerable variability, both between and within individuals, in the precision with which complex images are maintained in visual working memory (VWM). Here, we test the

hypothesis that precise VWM relies upon the continued maintenance of perception-related activity in stimulus-selective regions like the fusiform face area (FFA). We acquired functional MRI data while 20 human participants (7 males, mean age 23 years) performed a delayed-estimation task for faces from a continuous face space. Then, we used an inverted encoding model face reconstruction approach to examine VWM representations in the FFA, early visual areas, and delay-active regions of frontoparietal cortex.
On each trial, participants were presented with a randomly-chosen face, followed by a post-cue which indicated whether to store the item through a 10s delay period ('store") or discard it from memory ("drop"). Importantly, we found that an encoding model trained on perception-related FFA activity patterns allowed successful reconstruction of faces maintained in VWM ("store" trials), but not faces dropped from memory ("drop" trials). In contrast, despite successful *perceptual* reconstructions in the early visual areas, we did not find reliable face information from these regions during the delays of either "store" or "drop" trials. Finally, although the left inferior frontal sulcus (IFS) and intraparietal sulcus (IPS) both showed elevated delay activity during VWM maintenance, we were unable to reconstruct reliable face information from these regions. However, we did find preliminary evidence that greater sustained IPS activity during VWM maintenance may be related to higher-fidelity VWM representations in the FFA.
This pattern of results is consistent with a sensory recruitment model of VWM, in which a stimulus-selective region like the FFA is involved in maintaining the precise details of a face in VWM, and regions of the frontal and parietal cortices exert top-down control over these representations. In addition, our use of an inverted encoding model trained on face perception and used to reconstruct VWM representations provides further evidence for a common coding scheme underlying both perception/encoding and VWM maintenance.

Disclosures: E.S. Lorenc: None. **M. D'Esposito:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.01

Topic: H.02. Human Cognition and Behavior

Support: SNF

Title: Early life shapes our brain: Prematurity and low birth weight

Authors: *P. S. HUPPI[1], L. LORDIER[2], L. FREITAS[4], D. MESKALDJI[2], D. VAN DE VILLE[3], D. GRANDJEAN[5]
[1]Geneva Univ. Hosp., Geneva, Switzerland; [2]Pediatrics, [3]Univ. of Geneva, Geneva, Switzerland; [4]Pediatrics, Universtiy of Geneva, Geneva, Switzerland; [5]Neurosci. of Emotion and Affective Dynamics Lab., Geneva, Switzerland

Abstract: Early life events such as premature birth and low birth weight due to poor fetal environment are important modulators of brain development with neurological and neuropsychiatric consequences through childhood and into adult life. 7-12% of all birth worldwide occur prematurely, 1% are born very premature and 35% of them develop neurodevelopmental impairments. Since 2000 we have established longitudinal cohorts of preterm infants that are followed-up both with newly developed neuroimaging tools combined with motor, cognitive and behavioral evaluations. These studies have allowed to identify altered global brain tissue growth rates in preterm infants and have identified microstructurally altered brain white matter networks in the associative and limbic cortico-basal ganglia-thalamocortical circuits, involving the dorsolateral prefrontal cortex, the orbitofrontal cortex and the amygdala. These brain structural changes were coupled with deficits in early emotion processing and emotion regulation, as well as attention, executive control and social reasoning difficulties. From our more recent cohort of preterm newborns we have evidence for altered salience (anterior insula to anterior cingulate) network functionality already in the newborn period, a network that allows to adapt behavior according to the predictive value of stimuli, positive (reward) or negative (punishment). Predictive relations between stimuli and outcome are learned through experience and preterm infants clearly have very different early life experiences with extreme situations of non-predictability. Salience has been shown to be crucially involved in neuropsychiatric disorders seen in adults born preterm.
These findings raise the question of how to induce resilience through more predictable stimuli in the newborn period or specific cognitive training in childhood. Our recent research project has engaged in introducing interventions, both in the newborn period (Music) and in childhood (socio-emotional cognitive training (VAV) and mindfulness (MBI)) specifically aimed at reducing these structural and functional consequences of preterm birth. Results from these brain activity modulating intervention studies will be presented.

Disclosures: P.S. Huppi: None. **L. Lordier:** None. **L. Freitas:** None. **D. Meskaldji:** None. **D. van de Ville:** None. **D. Grandjean:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.02

Topic: H.02. Human Cognition and Behavior

Support: NSF GRFP DGE-114747
NIH Grant 1RO1EY02231801A1
NRSA 1F31EY027201-01

Title: Receptive field development in human visual cortex impacts viewing behavior and spatial coding

Authors: *J. GOMEZ[1], A. DRAIN[3], V. S. NATU[2], B. L. JESKA[2], M. BARNETT[4], K. GRILL-SPECTOR[2]
[2]Psychology, [1]Stanford Univ., Stanford, CA; [3]California State Fullerton, Fullerton, CA; [4]Univ. of Pennsylvania, Philadelphia, PA

Abstract: A fundamental property of neurons in the visual system is that they have receptive fields that process visual information in spatially restricted regions of visual space. How RFs develop in humans, however, is unknown. While high-level visual areas involved in reading and face recognition show a protracted development in humans, it is unknown if this development is associated with changes to receptive fields, and if so, at what stages of the visual hierarchy they occur. To answer these questions, we estimated the population receptive field (pRF) of all voxels in the visual system in 26 typical children (5-12 years) and 26 adults (22-27 years) and compared across age groups. Participants took part in two fMRI experiments: (1) retinotopic mapping with bars containing flickering black and white checkerboards to delineate retinotopic areas and estimate pRFs, and (2) a functional localizer containing faces, words, bodies, places, and objects to map high-level regions. We find that while early retinotopic regions are developmentally stable after age 5, ventral and lateral visual streams demonstrate unique forms of receptive field development. In the ventral stream, receptive fields in category-selective regions differentially develop across hemispheres in terms of size and eccentricity, affecting visual field coverage. Face-selective regions in the right hemisphere, and word-selective regions in the left are more foveally-biased in the way their pRFs tile the visual field in adults than children. Furthermore, we discovered a strong link between pRF development and viewing behavior. Developmental differences in the visual field coverage of face and word regions predict how children look at face and word stimuli differently form adults. In the lateral stream, we find that the visual field coverage by pRFs in lateral occipital (LO) and temporal occipital (TO) field maps increases with age, extending into the periphery and ipsilateral visual field. This development enhances the precision of spatial coding of visual information from childhood to adulthood. This work demonstrates differential development of pRFs across processing streams in human visual cortex, and has important implications for understanding developmental deficits such as dyslexia and autism that entail atypical fixation patterns on visual stimuli.

Disclosures: J. Gomez: None. **A. Drain:** None. **V.S. Natu:** None. **B.L. Jeska:** None. **M. Barnett:** None. **K. Grill-Spector:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.03

Topic: H.02. Human Cognition and Behavior

Support: NIH EY018875

Title: Development of 3D vision in infants and children

Authors: *A. M. NORCIA, P. J. KOHLER, W. J. MEREDITH
Dept. of Psychology, Stanford Univ., Stanford, CA

Abstract: The lateral separation of our two eyes creates differences in the two retinal images - horizontal disparities - that are a robust cue for depth. The adult perceptual system is extremely sensitive to retinal disparity relationships or “relative” disparity. Relative disparity is first extracted in extra-striate visual areas that are likely to undergo substantial post-natal maturation under the influence of environmental cues. Here we used high-density EEG recordings to measure 4-7 month-old infants’ and 4-7 year-old childrens’ sensitivity to relative disparity. Random dot stereograms were used to isolate time-locked, disparity-specific activity in the Visual Evoked Potential. To relate disparity sensitivity to perceptual sensitivity, we compared evoked responses to horizontal disparities that support a percept of depth from disparity (stereopsis) to otherwise equivalent vertical disparities that do not. Adults and 4-7 year old children have much better sensitivity to horizontal disparities, but infant sensitivity is equal and substantially poorer, overall. By manipulating the availability of disparity and motion references in the stimulus, we show that infants fail to use referential cues for either disparity or motion. Taken together our results indicate that while infants are quite sensitive to isolated, absolute disparity information, their sensitivity to relative disparity is rudimentary at 4-7 months of age, but develops to near adult levels by 4-7 years of age.

Disclosures: A.M. Norcia: None. **P.J. Kohler:** None. **W.J. Meredith:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.04

Topic: H.02. Human Cognition and Behavior

Support: Fondation de France
Fondation NrJ-Institut de France
Fondation Fyssen
Erc Adv Grant

Title: Cerebral bases of face perception during the first semester of life

Authors: *G. DEHAENE-LAMBERTZ[1], P. ADIBPOUR[2], J. DUBOIS[2]
[1]INSERM U992, Gif Sur Yvette, France; [2]INSERM U992, Saclay, France

Abstract: The ontogeny of the human brain functional asymmetries is poorly understood. Are they a consequence of differential development based on competition mechanisms, or are they constitutive of the human brain architecture from the start? Using structural MRI and a face discrimination EEG paradigm with lateralized presentation of faces, we studied face perception in infants over the first postnatal semester. We showed that the corpus callosum is sufficiently mature to transfer visual information across hemispheres, but the inter-hemispheric transfer time of early visual responses is modulated by callosal fibers myelination. We also revealed that only the right hemisphere shows evidence for face discrimination when presented in the left visual-hemifield. This capability improved throughout the first semester with no evidence of discrimination in the left hemisphere. Face processing lateralization is thus a characteristic of the infant's extra-striate visual cortex, highlighting the differential left-right organization of the human brain already established in infanthood.

Disclosures: G. Dehaene-Lambertz: None. **P. Adibpour:** None. **J. Dubois:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.05

Topic: H.02. Human Cognition and Behavior

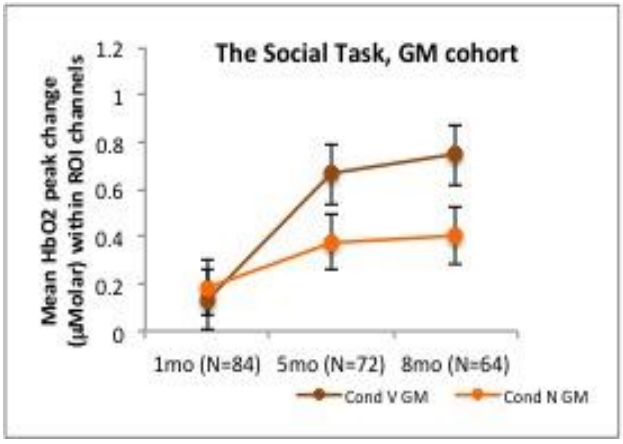
Support: Bill & Melinda Gates Foundation Grants OPP1061089 and OPP1127625
Core funding MC-A760-5QX00 to the International Nutrition Group by the Medical Research Council UK

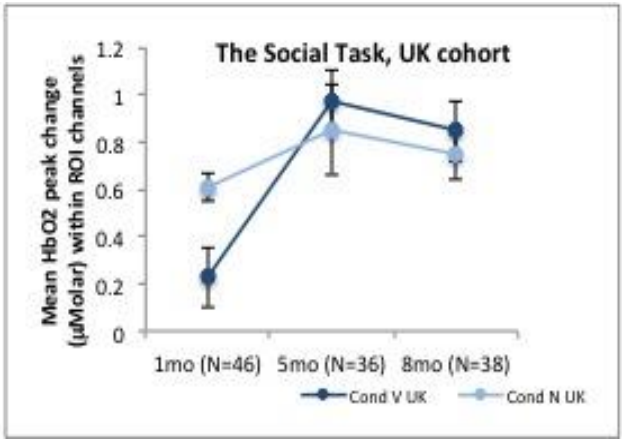
Title: Development of social and attentional fnirs responses in infants in their first year in the uk and the gambia

Authors: *A. BLASI[1], S. L. LLOYD-FOX[3], L. MASON[3], S. MCCANN[4], M. ROZHKO[1], L. KISCHKEL[2], C. E. E. ELWELL[1]
[2]Great Ormond Street Inst. of Child Hlth., [1]Univ. Col. London, London, United Kingdom; [3]Ctr. for Brain and Cognitive Development, Birkbeck, Univ. of London, London, United Kingdom; [4]3Medical Res. Council, The Gambia, Keneba, Gambia

Abstract: During the the first 1000 days of life, the brain is highly susceptible to external influences, and exposure to socio-economic and health challenges (such as under-nutrition or poverty) can have lasting effects. This work is part of the Brain Imaging for Global Health (BRIGHT) project, a longitudinal study with infants in the UK and The Gambia (GM) that aims

to chart brain development during this period. Here we present our first wave of results from a *Social* and *Novelty* (*Attention*) fNIRS tasks at 1, 5 and 8 months.
For the *Social Task*, participants listened to human vocal (Cond V) or non-vocal sounds (Cond N) during sleep (1mo) or while watching visual social stimuli (from 5mo).
The *Novelty* (*Attention*) task assesses repetition suppression and detection of novelty. Participants were exposed to 15 repetitions of the same sentence by one speaker, 5 repetitions with a different speaker and 5 repetitions of the first condition.
Preliminary results indicate that (i) at 1mo, infants tend to respond more strongly to non-vocal sounds in the temporal regions; (ii) by 5mo, this trend appears to reverse; (iii) profiles of responsiveness to the Novelty task differ across age with the younger infants showing continued suppression of their response after presentation of the novel stimuli, while older infants exhibit a novelty response (iv) and although similar in overall profile, differences between the UK and GM samples suggest greater variance in the GM group, suggesting they may be representing a population exposed to a wider range of challenges.





Disclosures: A. Blasi: None. **S.L. Lloyd-Fox:** None. **L. Mason:** None. **S. McCann:** None. **M. Rozhko:** None. **L. Kischkel:** None. **C.E.E. Elwell:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.06

Topic: H.02. Human Cognition and Behavior

Support: NIH grant RC2DA029475
NIH grant R01HD061414
NIH R24HD075489

Title: Brain development in childhood: Longitudinal relationships between regional cortical area, global motion sensitivity and numerical/visuospatial cognition

Authors: *O. J. BRADDICK[1], J. ATKINSON[2], W. ZHAO[3], W. THOMPSON[6], E. NEWMAN[4], C. A. AZAMA[7], H. BARTSCH[8], N. AKSHOOMOFF[6], C.-H. CHEN[6], A. M. DALE[5], T. L. JERNIGAN[7]
[1]Exptl. Psychology, Univ. Oxford, Oxford, United Kingdom; [2]Univ. Col. London, London, United Kingdom; [3]Cognitive Sci., UCSD, San Diego, CA; [4]Ctr. for Human Develop., [5]Neurosciences and Radiology, UCSD, La Jolla, CA; [7]Ctr. for Human Develop., [6]Univ. of California San Diego, La Jolla, CA; [8]Univ. of California San Diego, LA Jolla, CA

Abstract: Sensitivity to global motion can be measured from 4 years of age using the 'Ball in the Grass' test (Atkinson & Braddick, *Curr Psy Cog*, 2005; Braddick et al, 2016), with results from this test showing large individual differences in childhood. Global motion sensitivity has been taken as a signature of cortical dorsal stream function in contrast to global static form sensitivity, with motion sensitivity deficits found across many neurodevelopmental disorders, both genetic and acquired (Braddick et al, *Neuropsychologia*, 2003; Atkinson, *J Vis*, 2017) Research with children aged 4-12 years in the San Diego PLING cohort (Pediatric Longitudinal Imaging, Neurocognition and Genetics) has shown that individual global motion sensitivity is associated with variations in surface area of the parietal lobe, particularly around the intraparietal sulcus, measured from automatic parcellation of structural MR images. It also correlates with fractional anisotropy of the SLF defined by TBSS (Braddick et al, *Vision Res* 2017) Motion sensitivity also correlates with measures of visuospatial (VMI test) and numerical cognition (Woodcock-Johnson & Panamath) (Braddick et al, *J Cog Neuro*, 2016).
Data is now available from the longitudinal follow-up examinations of this cohort (N=4ensitivity 11 observations between 4-14 years on 126 children). These results show substantial correlations between successive measurements of individual differences of both motion sensitivity and parietal area across this age range. However, the relation between motion and parietal area, while consistently correlated up to 9 years of age, is no longer significant in 9-14 year old children. This does not simply reflect the reduced variance in the older group, since the correlation of motion sensitivity with math abilities and visuo-motor integration remains in this age group, showing the presence of functionally meaningful variation.
These results suggest that in early to mid childhood, individual cortical variations are important determinants of global motion processing, probably through parietal decision processes acting on global motion information. However, once these cognitive differences are established, they are maintained independently of cortical area differences. The dynamics of area differences in later childhood and adolescence may reflect developmentally overlapping processes of initial regional expansion and the later area contraction which appears through adolescence and adulthood (Jernigan et al, *Dev Cog Neuro*, 2016). This raises the question of whether this sequence may be delayed in atypical development, where motion coherence sensitivity is reduced.

Disclosures: O.J. Braddick: None. **J. Atkinson:** None. **W. Zhao:** None. **W. Thompson:** None. **E. Newman:** None. **C.A. Azama:** None. **H. Bartsch:** None. **N. Akshoomoff:** None. **C. Chen:** None. **A.M. Dale:** None. **T.L. Jernigan:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.07

Topic: H.02. Human Cognition and Behavior

Support: Leverhulme Trust
Castang Foundation
SPARKS
Nutricia Ltd

Title: Brain development in children with perinatal brain injury: Relation of severity from MRI to dorsal stream deficits in attention and motion sensitivity

Authors: *J. ATKINSON[1], M. ANDREW[2], C. MONTAGUE-JOHNSON[2], J. PARR[3], P. SULLIVAN[2], O. J. BRADDICK[4]
[1]Univ. Col. London, London, United Kingdom; [2]Paediatrics, Univ. of Oxford, Oxford, United Kingdom; [3]Inst. of Neurosci., Univ. of Newcastle, Newcastle-on-Tyne, United Kingdom; [4]Exptl. Psychology, Univ. Oxford, Oxford, United Kingdom

Abstract: *Background:* We have identified a cluster of deficits, across many genetic disorders (e.g. Williams syndrome, autism) and acquired developmental disorders (e.g.perinatal brain injury) in tasks underpinned by dorsal stream networks, including poor motion coherence sensitivity, visuospatial cognition and visual attention (Atkinson *J Vis*, 2017). *Methods*: Here we test relationships between attention deficits, motion sensitivity and the severity of perinatal brain injury (PBI) identified on neonatal MRI, in a cohort (N=54), including children born prematurely <32 weeks, in the Oxford Dietary Supplement Trial (Andrew et al, *BMC Paed*, 2015). Brain injury was graded for each child from neuroimaging as severe, moderate or mild on the extent of PVH, cystic PVL, basal ganglia lesions, ventricular enlargement or focal infarcts. We measured attention at age 4-7 months with the Fixation Shift Paradigm (FSP-Atkinson & Braddick *Dev Med Child Neurol, 2012*), shown to be sensitive to severity of neonatal MRI abnormality in HIE and very preterm-born infants (Atkinson & Braddick, *Prog Brain Res* 2007; Atkinson et al *Arch Dis Child*, 2008). At 4-6 years, subtests from the Early Child Attention Battery (ECAB, Breckenridge et al, *Brit J Dev Psy* 2013) were used to measure selective attention, sustained attention and attentional control, subsystems with distinct neural circuitry in adult brain (Petersen & Posner *Ann Rev Neuro, 2012*). Global motion and form coherence sensitivity were measured using the child-friendly 'Ball in the Grass' test as signatures of relative dorsal and ventral stream function (Atkinson & Braddick, *Curr Psy Cog* 2005; Atkinson, 2017). Cognitive abilities were assessed using the Kaufman KABC-II. *Results:* (a) The MRI index of PBI severity is significantly correlated with deficits of infant attention on FSP, all components of the later

ECAB and motion and form coherence (b) deficits in all components of attention, and in form and motion sensitivity are greater than predicted from KABC-II mental age, and greatest in sustained attention (c) motion coherence deficits correlate with attention deficits across the cohort (d) motion coherence deficits exceed those for form coherence. *Discussion:* These results will be related to our MRI findings that children's motion coherence sensitivity is correlated with differential brain growth in specific parietal areas and fibre tracts (Braddick et al, 2016, 2017), to recent findings on anomalies in the connectome following preterm birth (Karolis et al, 2016), and to the hypothesis that these dorsal stream deficits are markers of an abnormally developing 'multiple demand' brain network (Duncan 2011).

Disclosures: J. Atkinson: None. **M. Andrew:** None. **C. Montague-Johnson:** None. **J. Parr:** None. **P. Sullivan:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Nestec, Danone. **O.J. Braddick:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.08

Topic: H.02. Human Cognition and Behavior

Title: Development of early structural connectivity in autism spectrum disorder

Authors: *E. CONTI
IRCCS Stella Maris, Pisa, Italy

Abstract: Autism spectrum disorder (ASD) is behaviorally defined by the presence of social communication deficits and restricted and repetitive behaviors emerging within the third year of life. ASD expression is the result of a cascade of "gene x environment" factors likely beginning in utero, responsible for atypical development of brain connectivity. Thanks to MRI advanced techniques, many studies assessing brain connectivity in ASD have been recently published. As part of an on-going project started in 2012, we recruited subjects aged below 36 months referred to Tertiary Care Stella Maris Institute, receiving a clinical diagnosis of neurodevelopmental disorder according to DSM-IV (ASD or other developmental disorder, e.g. language disorder or developmental delay). All recruited patients performed diffusion MRI, to perform whole brain probabilistic and anatomically constrained tractography; network connectivity matrices were then built encoding the diffusion indexes (such as number of streamlines (D_{NUM}) or tract-averaged fractional anisotropy (D_{FA}))connecting each pair of cortical and subcortical regions. In our first study, we analysed 20 ASD toddlers, focussing on the correlation of laterality index of brain diffusion indexes and clinical severity, in terms of ADOS-Severity. We found a loss of left lateralization of fronto-temporal circuits in the most impaired subjects (presenting with higher ADOS total score) highlighting a precocious altered brain organization of circuits involved in

social-communication skills. In our second study, we collected 36 ASD toddlers and 16 other-DD toddelers to compare their connectivity patterns: the network differences resulted in an over-connectivity pattern in the ASD group and no contra-comparison results were found. The over-connectivity pattern in ASD occurred in networks primarily involving the fronto-temporal nodes, known to be crucial for social-skill development and basal ganglia, related to restricted and repetitive behaviours in ASD. Our results are in line with previous findings and with the "early over-connectivity theory" formulated by Solso and colleagues (2015). Brain-imaging research has significantly advanced our knowledge of the early development of autism and potential sources of vulnerability for the disorder. Further studies (comprising multimodal brain assessment, multifunctional correlation with brain indexes, inclusion of different control groups) are needed to confirm these developmental trajectiories of brain networks in ASD and detect early neural signs of the disorder, thus potentially supporting early diagnosis and early tailored intervention.

Disclosures: E. Conti: None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.09

Topic: H.02. Human Cognition and Behavior

Support: CIHR-INMHA Bridge Grant
NSERC Discovery Grant

Title: Longitudinal functional connectivity changes in attention networks in early childhood

Authors: *S. L. BRAY, C. ROHR, D. DIMOND, A. WEBBER, D. DEWEY
Univ. of Calgary, Calgary, AB, Canada

Abstract: Attention skills undergo rapid maturation in early childhood, laying a foundation for learning complex skills such as reading. Despite the importance of this developmental stage, relatively little is known about how functional brain networks involved in attention mature in early childhood. Here we acquired longitudinal measures of attention and brain function from 47 typically developing children aged 4-7 years, at baseline and 12-month follow-up. Functional magnetic resonance imaging (fMRI) was collected while children watched an 18-minute video comprised of clips from a children's television show. Volume censoring was applied at a framewise displacement threshold of 0.2mm and signal change amplitude of 0.3%; we retained for analysis only data from children with at least 10 minutes of usable fMRI (N=35). Attention skills were measured using an adaptation of the Early Childhood Attention Battery, based on a multi-component model of attention and including selective, sustained and executive tests. We

found significant changes in selective ($p = 0.009$) and sustained ($p = 0.006$), but not executive ($p > 0.05$) attention across this age range. In the neuroimaging data, we examined both consistency and differences in functional connectivity across time, using models seeded from regions involved in the dorsal attention network: left and right intraparietal sulcus (IPS) and left and right putative human frontal eye fields (FEF). Intraclass correlation (ICC) values for unweighted global connectivity of the seeds ranged from 0.3 to 0.6, suggesting fair consistency across timepoints. We found evidence for increasing segregation of the dorsal attention and default mode networks as left IPS and precuneus ([-2 -52 36], k=266, Z=4.13) showed significantly greater functional connectivity at baseline than at follow-up. We similarly found greater segregation over time between the left FEF and motor/premotor regions ([-46 -8 56], k=530, Z=4.4). However, we did not find evidence for a longitudinal increase in integration between dorsal attention network regions. Functional network changes are important to study longitudinally as they may help to explain the profound cognitive maturation occurring in early childhood, while controlling for inter-individual variability. Our work suggests that increasing segregation between brain networks in early childhood may play an important role in the maturation of attention skills.

Disclosures: S.L. Bray: None. **C. Rohr:** None. **D. Dimond:** None. **A. Webber:** None. **D. Dewey:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.10

Topic: H.02. Human Cognition and Behavior

Support: NSF BCS #1551330

Title: Automaticity in the reading circuitry

Authors: *S. J. JOO[1,2], K. TAVABI[2], J. D. YEATMAN[1,2]
[1]Speech and Hearing Sci., [2]Inst. for Learning & Brain Sci., Univ. of Washington, Seattle, WA

Abstract: Skilled reading requires years of practice with learning to associate visual symbols (graphemes) with speech sounds (phonemes). Over the course of the learning process, this association becomes almost effortless and automatic. Here, we hypothesize that automatic activation of the phonological processing circuit in response to a visually presented word is a hallmark of skilled reading. We used magnetoencephalography (MEG) to measure cortical responses to printed words while (1) children conducted a lexical decision task and (2) children engaged in an attention-demanding fixation task in which their attention was directed away from the words. A minimum norm estimate (MNE) was used to reconstruct source localized responses

on the cortical surface, allowing us to examine the source time course within cortical regions involved in reading. The lexical decision task was used to define cortical regions activated during children were actively reading words. Then, in the same regions, we isolated automatic, stimulus-driven responses to words in the absence of attention based on the independent dataset from the fixation task. We found strong activation in the core brain region involved in speech sound processing, the superior temporal gyrus (STG), irrespective of whether children were actively reading the words or ignoring them. This automatic response to the visually presented words in a canonical language region was indicative of good reading skills: the visual stimulus-driven STG response was only present in fluent readers, but not in struggling readers and children with dyslexia. Additionally, we found that for the best readers, this automaticity was present even for visually degraded text that is presented at low contrast, or with noise. Our results suggest that automatic recruitment of the phonological processing circuit is a hallmark of skilled reading; with practice, reading becomes effortless as the brain learns to automatically translate letters into sound and meaning.

Disclosures: S.J. Joo: None. **K. Tavabi:** None. **J.D. Yeatman:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.11

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant HD075865

Title: Regional differences in cortical thickness associated with numerosity and math skills in 5 year-old children born very preterm

Authors: *N. AKSHOOMOFF[1], F. HAIST[1], H. M. HASLER[1], J. STILES[2], T. L. JERNIGAN[2], T. T. BROWN[3], A. M. DALE[4]
[1]Psychiatry, [2]Cognitive Sci., [3]Neurosciences, [4]Radiology, Univ. of California San Diego, La Jolla, CA

Abstract: When children are born very preterm (VPT), there is an increased risk of disrupted perinatal brain development and later neurodevelopmental impairments. Even “healthy preterm” children with relatively benign neonatal courses and the absence of focal brain injury are at risk for diffuse changes in white matter development. Less is known about the impact on cortical development. VPT children are at particular risk for low math abilities but how this is related to earlier developing cognitive skills and vulnerable brain regions is not clear. In our FMRI pilot study of 10-year-old VPT and age- and IQ-matched full term (FT) children, we found correlations between math achievement and a BOLD signal measure of nonsymbolic numerosity

that differed significantly between groups in occipital and parietal regions, suggesting the groups differed in the neural systems supporting basic skills associated with early math achievement. Here, we examined cortical thickness in those regions and associations with nonsymbolic numerosity and early math skills in younger children to establish the foundation of disrupted math skills. MRI data were collected from 55 children born VPT (24-32 weeks gestation; mean=30 weeks; mean birthweight=1300g) and 40 children born FT who were within 6 months of kindergarten entry (mean age 5.3 years) and had no serious neurological problems or history of significant neonatal intracranial abnormalities or hemorrhage. Groups did not differ in age, sex, parents' age at birth, or SES. T1-weighted MRI images at 3.0 Tesla were analyzed using FreeSurfer methods and the Desikan-Killiany atlas to obtain estimates of cortical thickness. Controlling for sex, the right lateral occipital, right and left cuneus and pericalcarine regions were significantly thicker in the VPT group and thinner in the right and left supramarginal gyrus. Performance on a nonsymbolic numerosity task and the Test of Early Mathematics Ability (TEMA) was significantly lower in the VPT group. In the VPT group, performance on the nonsymbolic numerosity task was significantly correlated with thickness in the left supramarginal gyrus, right lateral occipital and right and left pericalcarine regions while performance on the TEMA was correlated with thickness in the right and left cuneus and right pericalcarine region. These results suggest very preterm birth in the absence of significant neonatal injury is associated with altered development of cortical regions associated with numerosity and early math skills. Longitudinal data are needed to determine how these differences are associated with later math achievement.

Disclosures: N. Akshoomoff: None. **F. Haist:** None. **H.M. Hasler:** None. **J. Stiles:** None. **T.L. Jernigan:** None. **T.T. Brown:** None. **A.M. Dale:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.12

Topic: H.02. Human Cognition and Behavior

Support: NICHD Grant F31HD086957
Harvard Mind Brain Behavior Grant
NSF Division of Research on Learning Grant 164450

Title: Cerebellar contributions to children's language processing

Authors: *A. M. D'MELLO[1], R. R. ROMEO[2], J. LEONARD[1], A. MACKEY[3], J. D. E. GABRIELI[1]
[1]Brain and Cognitive Sci., MIT, Cambridge, MA; [2]Div. of Med. Sci., Harvard Univ., Cambridge, MA; [3]Psychology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Clinical and neuroimaging studies suggest that the cerebellum is involved in multiple aspects of language including articulation and comprehension. Importantly, distinct cerebellar regions are engaged during motor versus non-motor language functions. The anterior cerebellum is functionally and anatomically connected to somatomotor cerebral networks and is active during overt speech and articulation. The posterior cerebellum is connected to higher-order language regions and is active during semantic processing. Across both motor and non-motor realms, the cerebellum contributes to the acquisition of new skills via error-based learning. Thus, the cerebellum may be particularly important during development, when skill acquisition and learning are at their highest levels. Unlike motor skills, language development is contingent upon instruction. However, little is known about how the cerebellum contributes to growing language skills, or how children's environment impacts neural substrates of language processing.
We examined cerebellar contributions to language processing in a group of pre-kindergarten/kindergarten, typically-developing, native English-speaking children (n=32; mean age=5.86). Children completed standardized behavioral assessments of their verbal abilities, and a functional magnetic resonance imaging (fMRI) session during which they listened to simple stories presented forwards, backwards, and dichotically, during which children had to attend to stories in one ear or the other. Families also completed two full days of real-world audio recordings via a child-worn audio recorder, allowing for measurement of the child's linguistic environment (e.g. number of adult words spoken, number of child vocalizations).
Cerebellar activation was highest when linguistic stimuli were nonsensical, consistent with the role of the cerebellum in error-monitoring (FWE cluster correction<0.05). Across all types of linguistic stimuli, increased right lateralized posterior cerebellar activation was associated with better verbal skills. Lastly, we found a positive relationship between number of adult words heard and activation in left posterior cerebellar during dichotic listening.
Together, these findings support a role for the cerebellum in language processing and auditory attention early in development, and suggest that language exposure is associated with both behavior and neural activation in regions known to support language.

Disclosures: A.M. D'Mello: None. **R.R. Romeo:** None. **J. Leonard:** None. **A. Mackey:** None. **J.D.E. Gabrieli:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.13

Topic: H.02. Human Cognition and Behavior

Support: NSF Career Award #1122374
Whitaker Health Sciences Fund Fellowship

Title: How language facilitates theory of mind development: Behavioral and fMRI evidence in children with delayed access to language

Authors: *H. RICHARDSON[1], J. KOSTER-HALE[1], N. CASELLI[2], R. MAGID[1], R. BENEDICT[2], H. OLSON[1], J. PYERS[3], R. SAXE[1]
[1]MIT, Cambridge, MA; [2]Boston Univ., Boston, MA; [3]Wellesley Col., Wellesley, MA

Abstract: From ages three to ten years, children develop an increasingly sophisticated understanding of minds, including how beliefs, desires, and emotions predict other people's actions and reactions. Similar to adults, this Theory of Mind (ToM) in children appears to rely on distinct brain regions from other high level cognitive capacities like language or executive function. When children listen to stories or watch movies that evoke a character's thoughts and feelings, hemodynamic activity increases selectively in the "Theory of Mind network", including regions in right temporo-parietal junction (RTPJ) and medial prefrontal cortex (MPFC). Moreover, cognitive development of ToM appears to correspond to increasingly selective responses, especially in the RTPJ. Similar to the development of specialized regions for other functions (like face perception or reading alphabets), increasing selectivity occurs by the suppression of responses to non-preferred stimuli (e.g. non-mentalistic social information). One key open question concerns the cause of this increasing selectivity. In particular, how do children's experiences or environment influence the development of a selective brain region for ToM?
Prior behavioral studies have established that linguistic experience is clearly related to ToM reasoning. Children's ToM is correlated with their own linguistic abilities, and with their parents' use of mental-state vocabulary. In d/Deaf signing children, delayed access to sign language is correlated with subsequent delays on behavioural measures of ToM. We therefore used fMRI to investigate the development of ToM brain regions among proficient ASL-speaking d/Deaf children (n=33, ages 4-12), as a function of age of first exposure to a sign language (birth – 7 years). In these children, delayed access to sign language was correlated with delayed performance only on the most difficult verbal ToM tasks (e.g. verbal questions about accidents and non-literal speech). All children showed robust recruitment of ToM brain regions during both verbal and non-verbal tasks, independent of linguistic history. However, delayed access to language was specifically correlated with reduced selectivity, i.e. delayed suppression of responses to the social stories, in the RTPJ of children. In a comparison group of adults, we found no enduring effects of early language delay. These results suggest that early linguistic experiences or abilities facilitate the development of a selective (i.e. domain specific) brain region for thinking about minds.

Disclosures: H. Richardson: None. **J. Koster-Hale:** None. **N. Caselli:** None. **R. Magid:** None. **R. Benedict:** None. **H. Olson:** None. **J. Pyers:** None. **R. Saxe:** None.

Nanosymposium

547. Human Cognition and Behavior: Neurocognitive Development

Location: SDCC 23

Time: Tuesday, November 6, 2018, 1:00 PM - 4:30 PM

Presentation Number: 547.14

Topic: H.02. Human Cognition and Behavior

Support: Excellent youth project of the National Natural Science FoundationNo.31522028

Title: Neurocognitive development of risky-decision making in young children

Authors: *Y. ZHAO[1,2,3,4], L. ZHUANG[1,2], S. TAN[3,4], J. XU[1,2], J. WANG[1,2], L. HAO[1,2], M. CHEN[1,2], J. GAO[5,6], Y. HE[1,2], Q. DONG[1,2], S. TAO[1,2], S. QIN[1,2]
[1]State Key Lab. of Cognitive Neurosci. and Learning, Beijing Normal Univ., Beijing, China; [2]IDG/McGovern Inst. for Brain Research, Beijing Normal Univ., Beijing, China; [3]Psychiatry Res. Center, Beijing Hui-Long-Guan Hosp., Beijing, China; [4]Peking Univ. Huilongguan Clin. Sch., Beijing, China; [5]Ctr. for MRI Research, Acad. for Advanced Interdisciplinary Studies,Peking Univ., Beijing, China; [6]McGovern Inst. for Brain Res., Peking Univ., Beijing, China

Abstract: The ability to make incentive-based risk decisions can not only affect children's immediate motivation and impulsive behavior, but also can be linked to mental health outcomes in late life during adolescence and adulthood. Alterations in the brain's incentive circuitry and prefrontal executive systems in risk decision making are often reported in individuals with emotional and behavioral disorders even during childhood and adolescence. However, little is known about the developmental trajectories of these incentive-related brain circuitry and systems underlying adaptive risk decision-making. Using event-related functional magnetic resonance imaging with Balloon Analogue Risk Task, we investigated the neurodevelopmental bases of risky-decision making in a large sample of children (N=251, 6-12 years old) and young adults (N=93, 18-28 years old). Behaviorally, children demonstrated significantly lower average number of adjusted pumps, less money earned and longer time to make risky-decision. On neuroimaging level, children showed decreased activation during risky-decision making in dorsolateral prefrontal cortex (DLPFC), ventral medial prefrontal cortex (vmPFC), caudate, putamen, the amygdala and thalamus. Furthermore, we observed increased activation during receipt of reward in children in the left caudate and thalamus than adults. Finally, children showed increased activation in the bilateral insular but decreased activation in the thalamus during receipt of punishment. Between-group comparisons of connectivity strength during risky-decision making revealed weaker functional coupling between the ventral striatum (VS) and the right DLPFC and the right super parietal cortices in children compared to adults. Both of the functional coupling of the VS with the right superior parietal cortices, and that of the VS and the right DLPFC were positively correlated with risk-taking tendency. Further mediation analysis

revealed that age-related changes in functional coupling of the VS with prefrontal-related regions and the left insular during risky-decision making explain the link between age and increases in risk-taking behavior. Our findings suggest that children show immature adaptive risk-taking decision, characterized as more sensitivity to both reward and loss but weaker prefrontal cognitive control over the VS. With the increase of age, children tend to make more adaptive risk-taking decision as the maturation of prefrontal cognitive control systems.
Keywords: risky-decision making, children, fMRI, Balloon Analogue Risk Task

Disclosures: Y. Zhao: None. **L. Zhuang:** None. **S. Tan:** None. **J. Xu:** None. **J. Wang:** None. **L. Hao:** None. **M. Chen:** None. **J. Gao:** None. **Y. He:** None. **Q. Dong:** None. **S. Tao:** None. **S. Qin:** None.

Nanosymposium

548. Physiological Methods: Electrophysiology: Stimulating Neurons and Electrode Arrays

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 1:00 PM - 3:30 PM

Presentation Number: 548.01

Topic: I.04. Physiological Methods

Support: GRF Grant 15102417

Title: Non-invasive and selective brain stimulation by ultrasound via activation of mechanosensitive ion channels

Authors: *Z. QIU[1], J. GUO[2], S. KALA[2], J. ZHU[2], Q. XIAN[2], T. ZHU[2], X. HOU[2], Y. YANG[2], L. SUN[2]
[1]The Interdisciplinary Div. of Biomed. Engin., [2]The Hong Kong Polytechnic Univ., Hung Hom, Hong Kong

Abstract: Understanding brain functions and treating brain disorders requires modulating the activity of well-defined neuronal populations with high spatiotemporal resolution. To achieve this, diverse modalities have been developed in the past few decades. Among these modalities, 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 mechanisms are still unclear and it lacks of cell type selectivity. Here we explored the mechanism of US brain stimulation and demonstrate the feasibility of non-invasive and selective brain stimulation by US *in vivo*. On gating mechanosensitive ion channels by US was verified on HEK293t cells and primary cultured neurons overexpressing Piezo1, MscL and CFTR by calcium imaging and downstream molecular assays. In addition, Piezo1 and MscL were packaged into virus particles and injected in the mice brain. C-fos staining and behavior testing were utilized to test the selective neural activation in vivo. Experimental results

demonstrated that US can activate Piezo1- and MscL- cells while no response can be detected at the same stimulation energy for the control cells. The induced calcium influx and the downstream signals are US pressure dependent and can be partially blocked by specific blocker. The in vivo experiments validated the selective stimulation strategy as most of the C-fos signals were co-localized with neurons overexpressing Piezo1 and MscL, and the mechanosensitive ion channel overexpressed mice exhibited significant higher sensitivity to US both on free moving and strict conditions.Taking together, we conclude that mechanosensitive ion channels is a mediator for initiating neural activation upon ultrasound stimulation. Engineering of the expression of Piezo1and MscL can increase the ultrasonic sensitivity in the targeted neurons for subsequent activation by ultrasound and selective inhibition of neurons expressing CFTR by ultrasound is feasible.

Disclosures: Z. Qiu: None. **J. Guo:** None. **S. Kala:** None. **J. Zhu:** None. **Q. Xian:** None. **T. Zhu:** None. **X. Hou:** None. **Y. Yang:** None. **L. Sun:** None.

Nanosymposium

548. Physiological Methods: Electrophysiology: Stimulating Neurons and Electrode Arrays

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 1:00 PM - 3:30 PM

Presentation Number: 548.02

Topic: I.04. Physiological Methods

Support: NIH Grant R01NS089679

Title: A microscale, printable device for recording and manipulating activity in small peripheral nerves

Authors: *T. M. OTCHY, C. MICHAS, B. LEE, K. GOPALAN, D. SEMU, J. GLEICK, A. E. WHITE, T. J. GARDNER
Boston Univ., Boston, MA

Abstract: Chronic implantation of high-precision, multi-channel probes into the brain for stable in vivo mapping and precise modulation of neuronal activity has been critical for the advance of both neuroscience research and medicine. However, the deployment of similarly advanced probes in the peripheral nervous system has been hindered by the challenges of access, miniaturization, and environmental robustness. We recently reported a microscale 3D-printed probe carrier that can be tailored to fit precisely the geometry of small (<250μm) peripheral nerve targets and surgically implanted with minimal disturbance to the nerve or surrounding tissue. Here we report a new, versatile instantiation of this device that integrates a flexible polyimide thin-film probe, and we demonstrate device efficacy and precision in recording and modulating behaviorally-linked nerve activity at acute and chronic timescales. The device is fabricated using a novel two-photon direct laser writing lithography technique (developed for

this application) that enables the seamless integration of a complexly structured acrylic photopolymer with a thin-film probe or other instrumentation (here: a polyimide multi-channel array). This fabrication method offers the ability to easily tailor, with micron-resolution, the geometry of the nerve retention mechanism to that of the targeted nerve, ensuring proper device fit and operation. Device performance was assayed in acute and chronic (5+ weeks) in vivo preparations in songbird. In acute preparations, we demonstrate recording and precise modulation of small (~150μm) peripheral nerve activity. In addition, we made stable multiunit recordings from whole nerves in freely behaving songbirds, finding singing-related activity to be stable at chronic timescales. Notably, we show in a novel fictive singing preparation the ability to use current-steering-based stimulation in a small diameter nerve to achieve a high degree of modulatory and behavioral specificity. These results, which include some of the longest continuous stable recordings from peripheral nerves of this size, indicate that this device is a uniquely robust, reliable, and manufacturable interface for fine nerves. The simplicity of implantation and stability of the preparation offer advantages over other interfacing approaches, enabling new understanding the nervous system's interactions with the tissues of the body and spurring the advance of a new class of bioelectronic therapies for chronic disease and injury. Future research aims at adapting the carrier design for a variety probe types and nerve targets.

Disclosures: T.M. Otchy: None. **C. Michas:** None. **B. Lee:** None. **K. Gopalan:** None. **D. Semu:** None. **J. Gleick:** None. **A.E. White:** None. **T.J. Gardner:** None.

Nanosymposium

548. Physiological Methods: Electrophysiology: Stimulating Neurons and Electrode Arrays

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 1:00 PM - 3:30 PM

Presentation Number: 548.03

Topic: I.04. Physiological Methods

Support: NIDA Intramural Research Program

Title: Focal transcranial magnetic stimulation(TMS) of the rat and mouse brains

Authors: *H. LU[1], Q. MENG[2], L. JING[1,3], S. UKANI[1], E. A. STEIN[1], Y. YANG[1], F.-S. CHOA[2]
[1]Natl. Inst. on Drug Abuse, Baltimore, MD; [2]Univ. of Maryland, Baltimore County, Baltimore, MD; [3]Tianjin Med. Univ., Tianjin, China

Abstract: TMS is emerging as a therapeutic tool for several neuropsychiatric disorders. However, its underlying mechanisms remain largely unknown. Preclinical rodent studies are of great value in understanding the neurobiological mechanism of TMS.Which brain region and network are stimulated and how the stimulation is delivered temporally will likely affect TMS outcomes. To draw spatially translatable neurobiological conclusions, and ultimately to inform

clinical interventions to improve efficacy, it is critical that animal studies mimic human TMS conditions. Unfortunately, there is no commercial rodent TMS coil that can mimic the spatial focality of human TMS. We report here a novel system capable of inducing a brief twitch of a single limb when a TMS pulse is delivered to the motor cortex of the mouse and rat brain. Based on known cortical representation of the motor cortex, we estimate the focality of the TMS system is about 1 mm. A key strategy in our coil design is the use of long magnetic core. Theoretically, the Maxwell equation $\nabla \times \boldsymbol{E} = \partial \boldsymbol{B}/\partial t + \mu_0 \boldsymbol{J}$ dictates that the induced $\boldsymbol{E}$ field is a function of how fast the $\boldsymbol{B}$ field changes over time. $\boldsymbol{B(x,y,z)} = \mu_r(x,y,z) \times \mu_0 \times \boldsymbol{H(x,y,z)}$, here μ_0 is a constant; $\mu_r(x,y,z)$ is relative permeability of the core material. $\mu_r(x,y,z)=1$ for air; the theoretical value of μ_r is 5000 for silicon steel, but practically it depends on the shape and content of the material. $\boldsymbol{H}$ is the magnetic field strength produced by a coil in free space (air core). It is apparent that the intensity and spatial distribution of the $\boldsymbol{B}$ field of the coil in relation to the $\boldsymbol{H}$ field is shaped by $\mu_r(x,y,z)$. By properly designing a silicon steel magnetic core, one can not only drastically ***enhance*** the $\boldsymbol{B}$ field, but can also ***guide and focus*** the magnetic flux to the region of interest, depending on the spatial distribution of $\mu_r(x,y,z)$. Based upon this insight, we have developed a TMS coil and impedance-matched driver circuits specific for rats and mice. Experiments were performed on 6 mice anesthetized with sodium pentobarbital (I.P. 50 mg/kg) and on 6 awake rats. The coil was carefully adjusted to the motor cortex representation of the hindlimb region. We consistently observed contralateral hindlimb twitch to a single TMS pulse. We also measured motor evoked potential (MEP) in some of the animals via implanted microwires into the lateral gastrocnemius of the left hindlimb muscle. We observed MEP signal with the delay, duration and amplitude consistent with the literature. The development of a rodent-specific focal TMS system opens novel opportunity to investigate the neurobiological basis of TMS. This work was partially supported by NIDA IRP of the NIH.

Disclosures: H. Lu: None. **Q. Meng:** None. **L. Jing:** None. **S. Ukani:** None. **E.A. Stein:** None. **Y. Yang:** None. **F. Choa:** None.

Nanosymposium

548. Physiological Methods: Electrophysiology: Stimulating Neurons and Electrode Arrays

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 1:00 PM - 3:30 PM

Presentation Number: 548.04

Topic: I.04. Physiological Methods

Support: NIH Grant EY01234
Stanford FIDL Research 1027995-191-EAFGT
Stanford SIP Funds from OTL 1185084-100-DBIRD

Title: Teasing apart the desired and unwanted effects of anesthetics at $GABA_A$ receptors

Authors: *N. S. CAYLA[1], M. F. DAVIES[1], E. R. GROSS[1], B. D. HEIFETS[1], M. B. MACIVER[1], E. J. BERTACCINI[1,2]
[1]Anesthesia, Stanford Sch. of Med., Stanford, CA; [2]DVA, VA Hlth. Care Syst., Palo Alto, CA

Abstract: GABA receptors ($GABA_AR$) are important targets for anesthetics, but it remains unclear how they are involved in producing unconsciousness or contributing to side effects. Our group has developed anesthetic agents that specifically act on $GABA_A$ receptors by targeting the same binding site as etomidate without producing the common side effect of adrenal suppression. The most promising compounds were tested on tadpoles, then in rat brain slice electrophysiology experiments. Finally, *in vivo* experiments were conducted with propofol, etomidate, and the best candidate (BB) to compare their hemodynamic effects.
For the *in vivo* studies, the compounds were pipetted into the amphibians' water and rats were administered drugs by intravenous bolus. For electrophysiology, rat brain slices were submerged in artificial cerebrospinal fluid (ACSF). In the hippocampal CA1 region, bipolar stimulating electrodes were used to evoke field potentials which were recorded by a microelectrode placed near the pyramidal cell body. Control recordings were acquired with brain slices in ACSF before and after drug exposure. Additionally, we compared BB to propofol and etomidate, agents known to selectively increase $GABA_AR$-mediated inhibition, and picrotoxin, a chloride channel blocker coupled to $GABA_ARs$.
When exposed to BB, tadpoles and rats quickly lost consciousness, then fully recovered. Also, rats' heart rate and blood pressure appeared more stable compared to propofol's exposure. Our electrophysiology results show that BB and etomidate produced a reversible enhancement of $GABA_AR$-mediated inhibition that appeared to be more selective than propofol. All of BB's effects occurred through the specific $GABA_A$-slow receptors, like etomidate. Propofol, in contrast, clearly enhanced other forms of $GABA_AR$-mediated inhibition. The effects of both agents were fully reversed by picrotoxin.
BB has an anesthetic effect via $GABA_ARs$ as predicted. BB were more selective than propofol, which acts mainly on $GABA_A$-fast and -tonic receptors, instead of the $GABA_A$-slow receptors that are most sensitive to BB. This $GABA_AR$ selectivity could account for the observed decrease in undesirable side effects on hemodynamics compared to propofol. Thus, our results suggest that anesthetic action on subtypes of $GABA_ARs$ contributes to both desired and undesired effects, so more selective targeting holds great promise for developing safer anesthetics.

Disclosures: N.S. Cayla: None. **M.F. Davies:** None. **E.R. Gross:** None. **B.D. Heifets:** None. **M.B. MacIver:** None. **E.J. Bertaccini:** None.

Nanosymposium

548. Physiological Methods: Electrophysiology: Stimulating Neurons and Electrode Arrays

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 1:00 PM - 3:30 PM

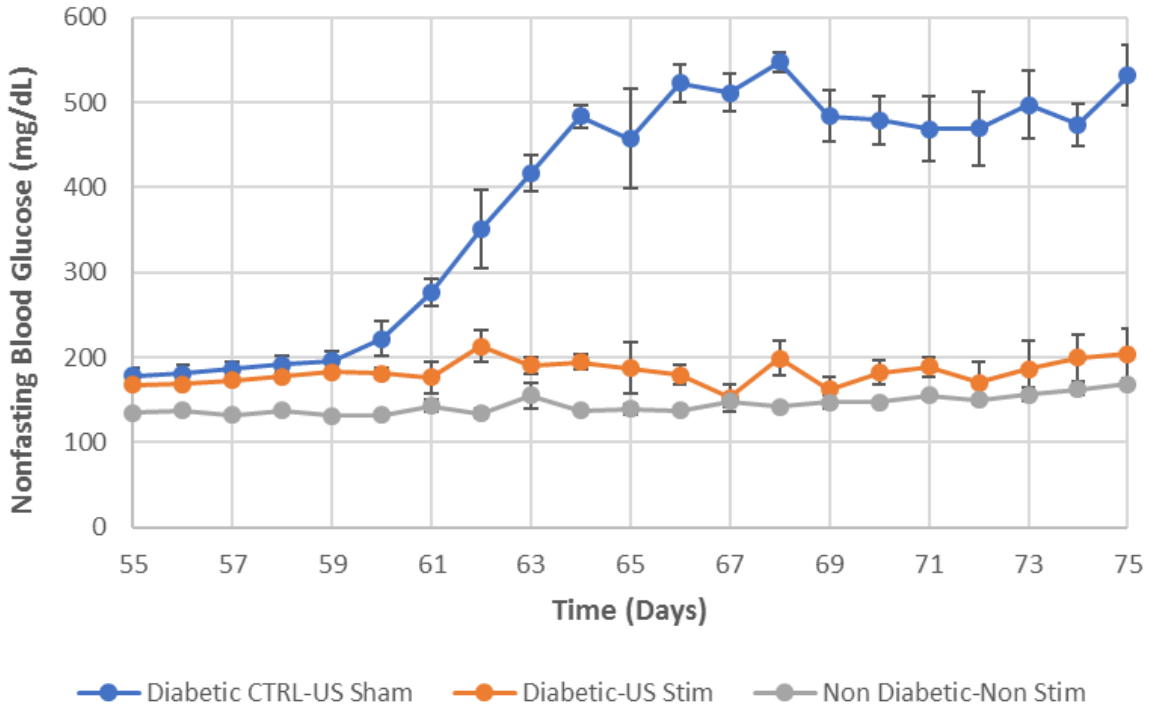
Presentation Number: 548.05

Topic: I.04. Physiological Methods

Title: Non invasive hepatic ultrasound improves insulin sensitivity and metabolic glucose status in animal models of insulin resistance

Authors: *V. E. COTERO[1], C. PULEO[2], Y. FAN[2], S. KAANUMALLE[2], J. ROBERTS[2], J. ASHE[2]
[1]Biochem. and Biol. Engin., [2]Gen. Electric- Global Res. Ctr., Niskayuna, NY

Abstract: Obesity and type 2 diabetes mellitus (T2DM) are associated with dysfunctional insulin signaling. Moreover, both central and peripheral glucose sensing mechanisms are impaired in these diseases. This is supported by findings suggesting that dysfunctional insulin signaling, leading to insulin resistance, predates the development of hyperglycemia (Hunter and Garvey, 1998; Cotero, Routh and Zhang, 2009). Furthermore, glucose sensing neurons residing both in the periphery and in key brain areas are critical in the maintenance of glucose and energy homeostasis, and alterations in these neurons occur under pathologies where glucose homeostatic mechanisms are disturbed (Spanswick et al., 2000; Levin et al., 1999; Cotero et al., 2008). We hypothesized that ultrasound stimulation of the hepatic nervous system is sufficient to activate pathways associated with insulin signaling and glucose responsiveness eliciting an improvement in peripheral insulin sensitivity and glucose metabolism. To test this hypothesis, we applied ultrasound (U/S) stimulation to a region of the liver known to contain a high density of nerve terminals. U/S stimulus was applied daily in both acute and chronic models of insulin resistance. Animals receiving U/S treatment showed a significant decrease in circulating glucose, insulin and triglycerides which persisted throughout the course of treatment. These changes in circulating metabolic markers occurred in parallel to a change in hypothalamic, but not hepatic, activity and biochemistry as compared to untreated control animals. No direct enhancement in glycolytic activity was seen in the liver and no change in food and water intake was observed, suggesting that U/S ability to improve metabolic status is due to a change in hypothalamic neuronal activity and signal transduction. Further, we provide a mechanism to explain the reported beneficial effect of therapeutic U/S on metabolic regulation.



Disclosures: **V.E. Cotero:** A. Employment/Salary (full or part-time):; General Electric-Global Research. **C. Puleo:** A. Employment/Salary (full or part-time):; General Electric-Global Research. **Y. Fan:** A. Employment/Salary (full or part-time):; General Electric-Global Research. **S. Kaanumalle:** A. Employment/Salary (full or part-time):; General Electric-Global Research. **J. Roberts:** A. Employment/Salary (full or part-time):; General Electric-Global Research. **J. Ashe:** A. Employment/Salary (full or part-time):; General Electric-Global Research.

Nanosymposium

548. Physiological Methods: Electrophysiology: Stimulating Neurons and Electrode Arrays

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 1:00 PM - 3:30 PM

Presentation Number: 548.06

Topic: I.04. Physiological Methods

Title: A non-invasive non-contact MEMS sensor for electric vector field encephalography

Authors: J. BICKFORD, S. GOLMON, W. LENK, P. KUMAR, W. SAWYER, J. LEBLANC, *J. J. WHEELER
Draper Lab., Cambridge, MA

Abstract: Traditional non-invasive methods of measuring neural activity (e.g., fNIR, fMRI, MEG, EEG) suffer from a variety of limitations, including large size, poor spatial- or temporal-resolution, and sensitivity to changing electrical contact with the scalp. Additionally, these methods are not practical for mobile applications, which limits their use to stationary and well-controlled environments. Here we present the design and initial testing of our novel electric field encephalography (EFEG) sensor that addresses the shortcomings of traditional non-invasive methods. Our sensor is based upon a torsional MEMS system that measures the torque generated by an external electric field interacting with a polymer electret. Unlike EEG, which measures 1-dimensional scalar potentials, our approach is capable of measuring full 3-dimensional vector fields. This novel approach combines high spatiotemporal resolution, miniaturization to millimeter size, and does not require direct contact with the scalp, enabling future mobile applications with a wearable head-worn system.

Disclosures: J. Bickford: None. **S. Golmon:** None. **W. Lenk:** None. **P. Kumar:** None. **W. Sawyer:** None. **J. LeBlanc:** None. **J.J. Wheeler:** None.

Nanosymposium

548. Physiological Methods: Electrophysiology: Stimulating Neurons and Electrode Arrays

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 1:00 PM - 3:30 PM

Presentation Number: 548.07

Topic: I.04. Physiological Methods

Support: R43MH104170

Title: Automated perfusion and electrophysiological measurements for drug studies in iPS derived epileptic neurons

Authors: C. COLLINS[1], H. WONG[2], J. KOHANA[2], A. RANGEL[3], P. SCHWARTZ[3], *J. COLLINS[2]
[1]Univ. High Sch., Irvine, CA; [2]Biopico Systems Inc, Irvine, CA; [3]Children's Hosp. of Orange County, Orange, CA

Abstract: We developed a microfluidic perfusion system for feeding media/drug reagents to neural stem cells and observed them through 10 weeks of differentiation to neurons. The neural stem cells are derived from normal controls and patients with epilepsy. At 4th and 5th week the neural cells show high activity under microelectrode array electrophysiological measurements. The field potential spikes are analyzed for electrical stimulation results from different drug concentration experiments.
Epilepsy is a chronic neurological disorder in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally and cause seizures. Many drugs called anti-epileptic drugs are used to prevent and control seizures. Till this day there has not been a cure for epilepsy

because epilepsy affects every person differently and each person needs different medications. Two drugs are used in this experiment. One drug called Carbamazepine is used to prevent and control seizures. Another dug called minocycline is used to treat bacterial infections. Minocycline can reduce inflammation in the central nervous system. We have applied these drugs on neural stem cells after 4 and 5 weeks of differentiation. Spontaneous spikes and stimulus spikes are measured and analyzed.

The combined effect of Carbamazepine drug and electrical stimulation makes the height of the valleys increases thereby the ratio of the height of the peaks to valleys of the spikes decreases as in Fig. 1. The combined effect of Minocycline drug and electrical stimulation decreases the ratio of the height of peaks to valley of the spikes as in Fig. 2. Carbamazepine drug shows larger response than the Minocycline drug.

Fig. 1. Effect of Carbamazepine drug on neural stem cells of 4 weeks of differentiation (a) Control (b) drug concentration 1uM (c) drug concentration 10uM

Fig. 2. Effect of Minocycline drug on neural stem cells of 4 weeks of differentiation (a) Control (b) drug concentration 10uM (c) drug concentration 100uM

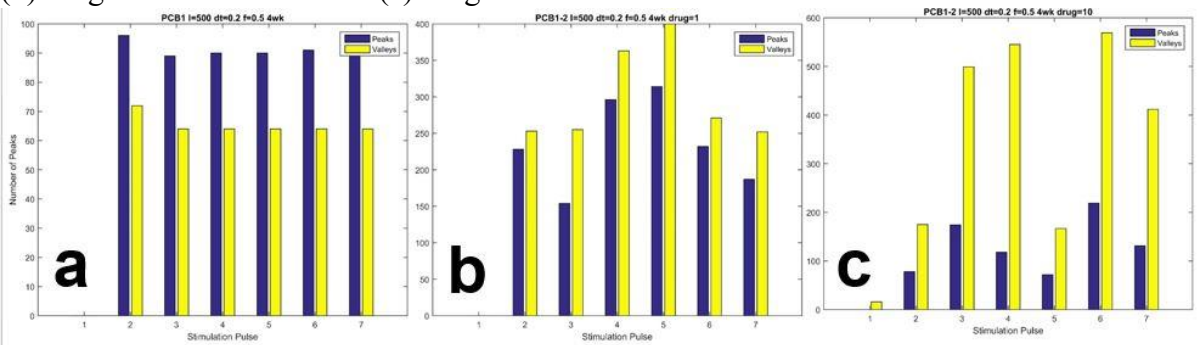


Fig. 1. Effect of Carbamazepine drug on neural stem cells of 4 weeks of differentiation (a) Control (b) drug concentration 1uM (c) drug concentration 10uM

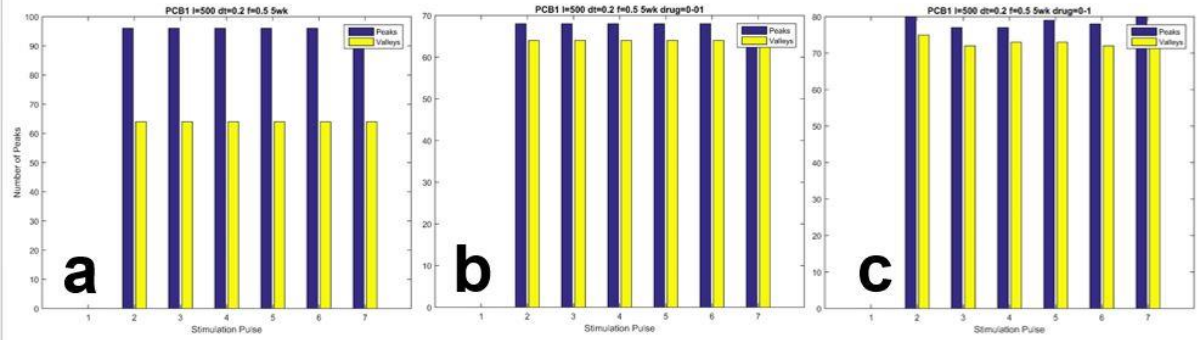


Fig. 2. Effect of Minocycline drug on neural stem cells of 4 weeks of differentiation (a) Control (b) drug concentration 10uM (c) drug concentration 100uM

Disclosures: C. Collins: None. **H. Wong:** A. Employment/Salary (full or part-time):; Biopico Systems Inc. **J. Kohana:** None. **A. Rangel:** None. **P. Schwartz:** A. Employment/Salary (full or part-time):; children's hospital of orange county. **J. Collins:** A. Employment/Salary (full or part-time):; Biopico Systems Inc, Children's Hospital of Orange County.

Nanosymposium

548. Physiological Methods: Electrophysiology: Stimulating Neurons and Electrode Arrays

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 1:00 PM - 3:30 PM

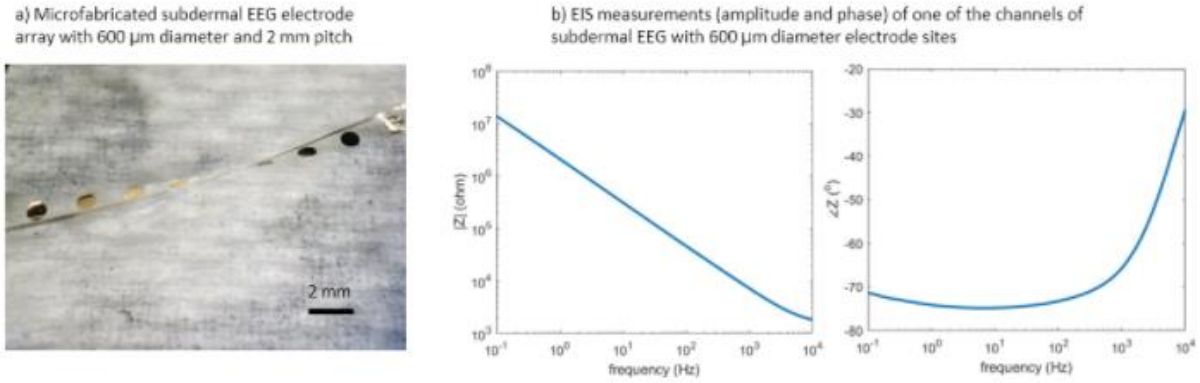
Presentation Number: 548.08

Topic: I.04. Physiological Methods

Title: Flexible, ultra-resolution, subdermal eeg probes

Authors: *K. DESHPANDE, Z. AHMED, J. REDDY, A. KRISHNAN, P. VENKATESH, S. KELLY, P. GROVER, M. CHAMANZAR
Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Electroencephalogram (EEG) is a popular, noninvasive method to record neural activity. Commonly used in the clinical setting as a gold-standard for diagnosing many disorders, including epilepsy, EEG's spatial resolution is of critical concern for targeting surgical interventions and resultant patient outcomes. However, high-resolution spatial information is filtered and obscured by noise as electrical signals propagate through layers of tissue. We present a novel paradigm of subdermal EEG arrays, capable of being implanted under the scalp to increase spatial resolution of EEG recordings while minimizing invasiveness compared to traditional implantable recording electrode arrays such as electrocorticography (ECoG) cortical surface electrodes. In addition, our device can be chronically implanted for a long period of time, as opposed to traditional EEG electrodes that need to be removed periodically for re-application of conductive electrode gel. We demonstrate the design, fabrication and electrical characterization of high-density subdermal EEG arrays realized in Parylene C polymer platform using our optimized microfabrication techniques. Devices are realized in a range of electrode diameters (200 microns - 1000 microns) and pitch (1 mm - 3.5 mm), to characterize the effects of electrode size and spacing on the spatial frequency content and redundancy of recorded neural signals. The Electrochemical Impedance Spectroscopy (EIS) measurements show an impedance of <10 kΩ (for 600 micron diameter) at 1 kHz. We will discuss testing and validation of the presented subdermal EEG probes and will compare their performance to traditional EEGs based on recording of stimulated evoked potentials.



Disclosures: K. Deshpande: None. **Z. Ahmed:** None. **J. Reddy:** None. **A. Krishnan:** None. **P. Venkatesh:** None. **S. Kelly:** None. **P. Grover:** None. **M. Chamanzar:** None.

Nanosymposium

548. Physiological Methods: Electrophysiology: Stimulating Neurons and Electrode Arrays

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 1:00 PM - 3:30 PM

Presentation Number: 548.09

Topic: I.04. Physiological Methods

Title: High-density microfabricated stainless steel neural probes for high-resolution recording in primates

Authors: *Z. AHMED[1], J. REDDY[1], K. DESHPANDE[1], T. TEICHERT[2], R. S. TURNER[3], M. CHAMANZAR[1]
[1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Dept. of Psychiatry, [3]Dept. of Neurobio., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Significant research effort has been expended for development of high density probes in rigid (e.g., Silicon) and flexible polymer platforms for rodents. However, these technologies are not easily translatable to developing neural probes for studying non-human primate brain. This is mainly due to the larger size of brain in non-human primates (NHP), which requires longer neural probes. While silicon is a common choice for designing neural probes for rodents, the brittleness and fragility of silicon makes it difficult to implement long probes with large aspect ratio. Different prosthetic devices including commercially available neural probes are realized in stainless steel because of its higher durability, higher modulus of resilience, bio-compatibility, and its corrosion-resistant properties. While micromachining techniques are well-developed for silicon, micromachining of stainless steel has not been explored much. Therefore, existing stainless steel probes are mostly manually assembled, which significantly limits the channel density, and makes them very expensive. In this work, we demonstrate high-density

flexible clinical neural probes monolithically fabricated on stainless steel shuttles. Leveraging our previously developed process to realize high-density neural probes in Parylene-C, we designed 5-10 cm long and 260 μm wide neural probes with 30-64 channels in a hybrid stainless steel and Parylene C platform. Our EIS measurements proved that we can achieve high-yield (~70%) functional probes with stable performance over 6 weeks. We will discuss how these neural probes can be tested and validated in rhesus macaques. Our highly scalable, high-throughput process in the hybrid Parylene-stainless steel platform enables large-scale high-resolution recordings across different brain areas in NHPs, paving the way for implementing high-density clinical neural probes for acute intraoperative recording as well as future chronic recordings.

Disclosures: Z. Ahmed: None. **J. Reddy:** None. **K. Deshpande:** None. **T. Teichert:** None. **R.S. Turner:** None. **M. Chamanzar:** None.

Nanosymposium

548. Physiological Methods: Electrophysiology: Stimulating Neurons and Electrode Arrays

Location: SDCC 30E

Time: Tuesday, November 6, 2018, 1:00 PM - 3:30 PM

Presentation Number: 548.10

Topic: I.04. Physiological Methods

Support: NIH R21NS084492-01

Title: Robotic, head-mountable intracellular systems (RHeMIS) for *in vivo* applications

Authors: *S. SAMPATH KUMAR[1], M. BAKER[2], M. OKANDAN[2], J. MUTHUSWAMY[1]
[1]Arizona State Univ., Tempe, AZ; [2]Sandia Natl. Labs., Albuquerque, NM

Abstract: Conventional intracellular recording electrodes and associated positioning systems for steering the electrodes to single neurons *in vivo* are large and bulky, which has largely limited their use to single-channel recording in anesthetized animals. Further, the process of *in vivo* intracellular recording requires: 1) extraordinary skill and training, which hinders adoption of technique by novice neurophysiologists, and 2) a high degree of mechanical precision and stability, which has limited typical recording durations with the conventional system to less than 2 hrs. Here, we present the latest results of our development of a MEMS-based, robotic head-mountable intracellular system (RHeMIS) for fully autonomous intracellular recording *in vivo*. This system combines 3 unique technologies: 1) novel microscale, glass-polysilicon penetrating electrode for intracellular recording, 2) electrothermal microactuators for precise microscale navigation of each electrode in the brain tissue and 3) closed-loop control algorithm for autonomous positioning of electrode inside single neurons. Previously, we had demonstrated the ability of our glass-polysilicon electrodes to record high fidelity intracellular potentials from *Aplysia* ganglion neurons and validated the performance of our closed-loop controller after

integration of our electrodes with a conventional hydraulic microdrive. Here, we demonstrate the fully autonomous, MEMS-based RHeMIS system that integrates the intracellular electrode, microscale actuators and closed-loop control for obtaining intracellular recordings from single neurons in the abdominal ganglion of *Aplysia* (n=10 cells). Good quality resting potentials (< -35mV) and action potentials (> 60mV) were consistently recorded after each controller trial. Further, we also demonstrate the ability of the glass-polysilicon electrode to reliably record good quality intracellular potentials (< -55mV resting potential, >60 mV action potentials) from the motor cortex of rats *in vivo* (n=3 animals). We are currently testing the ability of our fully integrated RHeMIS system to obtain autonomous intracellular recordings from somatosensory cortex of rats *in vivo*. This system offers significant advantages: 1) reduction in overall size for potential use in behaving animals, 2) scalable approach to potentially realize multi-channel (>100 channels) recordings and, 3) a viable mechanism to improve stability of intracellular recordings.

Disclosures: S. Sampath Kumar: None. **M. Baker:** None. **M. Okandan:** None. **J. Muthuswamy:** None.

Nanosymposium

549. Computation, Modeling, and Simulation: Network Models: Theory and Experimentation

Location: SDCC 2

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 549.01

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant MH096093
NIGMS P50 GM085273
NIGMS K12 GM088021
Harvey Family Endowment (ELB)

Title: Witnessing the evolution of functional anatomy across the whole brain of living mice by MEMRI: Lessons for Alzheimer's disease, early life stress, and post-traumatic stress disorder

Authors: *E. L. BEARER[1,2], D. BARTO[1], A. R. H. REVIERE[1], C. S. MEDINA[1], R. E. JACOBS[3]
[1]Dept. of Pathology, UNM Sch. of Med., Albuquerque, NM; [2]Div. of Biol., Caltech, Pasadena, CA; [3]Zilkha Neurogenetic Inst., USC Keck Sch. of Med., Los Angeles, CA

Abstract: Electrophysiology and optical imaging have produced detailed information about the brain, yet are limited by dimensions in vivo, and by sacrifice for whole brain anatomy. Emerging technologies allow whole brain imaging of the living brain and are changing our concepts of how various brain regions integrate for coordinated processing. We have pioneered one of these

emerging technologies: Manganese-enhanced magnetic resonance imaging (MEMRI). Mn2+, a cation, enters neurons via voltage-gated Ca2+ channels giving hyper-intense signals in MRI--thus highlighting active neurons. Manganese is non-toxic at concentrations used for imaging by histopathology, electrophysiology and behavioral criteria. Mn2+ is a direct indicator of neuronal activity unlike BOLD. Uptake requires minutes to hours to be detectable, which allows neural activity in awake, behaving animals to be detected after the experiment. We have developed computational processing to extract statistically significant information from cohorts of genetically identical mice experiencing similar experimental procedures. Non-toxic, non-destructive MEMRI permits repeated imaging session. The brain is transparent to MR, hence the whole brain can be imaged live tho with slightly lower resolution (50-100μm3) than optical imaging. While capture times preclude detection of millisecond firing patterns, MEMRI identifies areas of activity. Companion studies acquire higher spatial and temporal resolution in areas identified by MEMRI. We perform microscopy on post-mortems of mice whose experiential history was documented by MEMRI. We also perform electrophysiology of circuits after Mn2+ stereotactic injection for tract tracing. We have applied these approaches to two validated experimental systems, one for Alzheimer's disease (AD) and the other for post-traumatic stress disorder (PTSD). In AD, we used time-lapse MEMRI after injection into CA3 of the hippocampus to measure axonal transport rates in the memory circuit to the septum. In PTSD we imaged activity throughout the brain after predator stress and discovered that activity increases and decreases in coordinated regions immediately and continues to evolve over time. This presentation will focus on MEMRI for whole brain functional imaging in pre-clinical studies.

Disclosures: E.L. Bearer: None. **D. Barto:** None. **A.R.H. Reviere:** None. **C.S. Medina:** None. **R.E. Jacobs:** None.

Nanosymposium

549. Computation, Modeling, and Simulation: Network Models: Theory and Experimentation

Location: SDCC 2

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 549.02

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant MH096093
NIGMS K12 GM088021
NIGMS P50 GM085273
Harvey Family Endowment (ELB)

Title: Acute and persistent anxiety in the presence of fear: An memri approach to compare invivo global brain changes between wt and sert-ko mice across multiple timepoints

Authors: *D. BARTO[1], A. R. H. REVIERE[1], R. E. JACOBS[2], E. L. BEARER[1,3]
[1]Dept. of Pathology, Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM; [2]Zilkha Neurogenetic Inst., USC Keck Sch. of Med., Los Angeles, CA; [3]Div. of Biol., Caltech, Pasadena, CA

Abstract: Why are some individuals sensitive to a traumatic event, with anxiety lasting even days after the event occurs? Additionally, why are other individuals, while exposed to the same traumatic event, resilient? How does the global brain activity of these individuals differ? We investigated these questions with manganese-enhanced magnetic resonance Imaging (MEMRI) of the whole brain in living mice before, immediately, and at 9 days after exposure to predator stress (PS) (2,3,5-Trimethly-3-thiazone, TMT). Post-traumatic stress disorder (PTSD) is believed to be modulated in part by dysfunction of the monoamine distribution network. Hence, we compared WT and serotonin reuptake transporter (SERT) KO mice (n=24). SERT KO and WT have similar neurological anatomy, while their functional anatomy based on Mn^{2+} transport differs. Our novel approach compares the uptake of Mn^{2+} by active neurons as a function of genotype and time, with acute and delayed responses to PS. TMT induced anxiety-like (PS) behavior as measured in the light-dark box. Both KO and WT mice explored at baseline, and both reacted to the TMT with statistically significant decrease in exploration compared to baseline ($p<0.001$ by Dunnett's test). While WT returns to baseline, KO does not ($p<0.0001$ at 24 days post PS). KO differed from WT significantly at all post PS time-points. Mice received intraperitoneal injections of Mn^{2+} (0.28 mL of 24 mM), which enters neurons through voltage-gated Ca^{2+} channels, producing a hyper-intense MR signal. Statistical parametric mapping within group detected differential activity throughout the brain at each time point, as well as global differences between genotypes immediately after PS and evolving 9 days later ($p<0.0001$). Alignment to a manually drawn MR atlas based on the Allen atlas followed by automated computational analysis of 92 segmented regions revealed that PS affected multiple regions (nucleus accumbens, dorsal raphe, dentate gyrus etc). Region of interest intensity measurements confirmed Mn^{2+} signal and c-Fos staining verified neural activity. By whole brain live imaging we discovered that the effect of life-long dis-regulation of the serotonergic modulatory system is dynamic, with functional differences in multiple regions, in part explaining the prolonged anxiety behavior after PS of the SERT-KO genotype

Disclosures: A.R.H. Reviere: None. **R.E. Jacobs:** None. **E.L. Bearer:** None.

Nanosymposium

549. Computation, Modeling, and Simulation: Network Models: Theory and Experimentation

Location: SDCC 2

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 549.03

Topic: I.06. Computation, Modeling, and Simulation

Support: Chinese NSF No. 81430010, 31627802, 81701774 and 61771423

Title: A novel connectome mapping method with infrared neural stimulation and ultra-high-field fMRI

Authors: *A. G. XU, M. QIAN, J. WANG, X. SONG, X. ZHANG, A. W. ROE
Interdisciplinary Inst. of Neurosci. and Technol. (ZIINT), Qiushi Acad. for Advanced Studies, Zhejiang Univ., Hangzhou, China

Abstract: INTRODUCTION
Mapping connection patterns is essential in understanding brain functions and diseases. However, existing methods are either very time-consuming or low in resolution. Previously, we reported that infrared neural stimulation (INS, wavelength 1875nm, radiant energy: 0.1-1.0 J/cm^2) can effectively and safely induce neuronal activity in cerebral cortex. Here, by combining INS with ultra-high-field functional magnetic resonance imaging (fMRI, 7-Tesla), we developed a method that can map connections rapidly, at sub-millimeter resolution, over the whole cat brain.
RESULTS
Our fMRI experiments in anesthetized cats (n=4) showed that INS produces focal intensity-dependent responses at stimulation site and at neurally connected sites. At stimulation site, the response magnitude increases monotonically with increasing laser energy. When stimulating area 17 (near 17/18 border) in visual cortex with laser energy $0.7J/cm^2$, we observed significant responses in ipsilateral lateral geniculate nucleus and both ipsilateral and contralateral visual cortex (area 17, 18, 19, 20, and 21). Other laser energies elicited similar cortical-cortical and cortical-subcortical connections. Overall, these connection patterns are consistent with known anatomical connections.
DISCUSSION
Our method (INS-fMRI) has several advantages over existing methods. Unlike anatomical dye tracing which requires animal sacrifice and time-consuming slice preparation and 3D reconstruction, INS-fMRI is *in vivo*, rapid and enables systematic point-by-point study of brain connections. The fMRI images presented here have resolution 1.0mm isotropic. By using multi-array coils and multi-shot scanning sequences, we can obtain connection data at sub-millimeter resolution and soon at cortical-column resolution.

Disclosures: A.G. Xu: None. **M. Qian:** None. **J. Wang:** None. **X. Song:** None. **X. Zhang:** None. **A.W. Roe:** None.

Nanosymposium

549. Computation, Modeling, and Simulation: Network Models: Theory and Experimentation

Location: SDCC 2

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 549.04

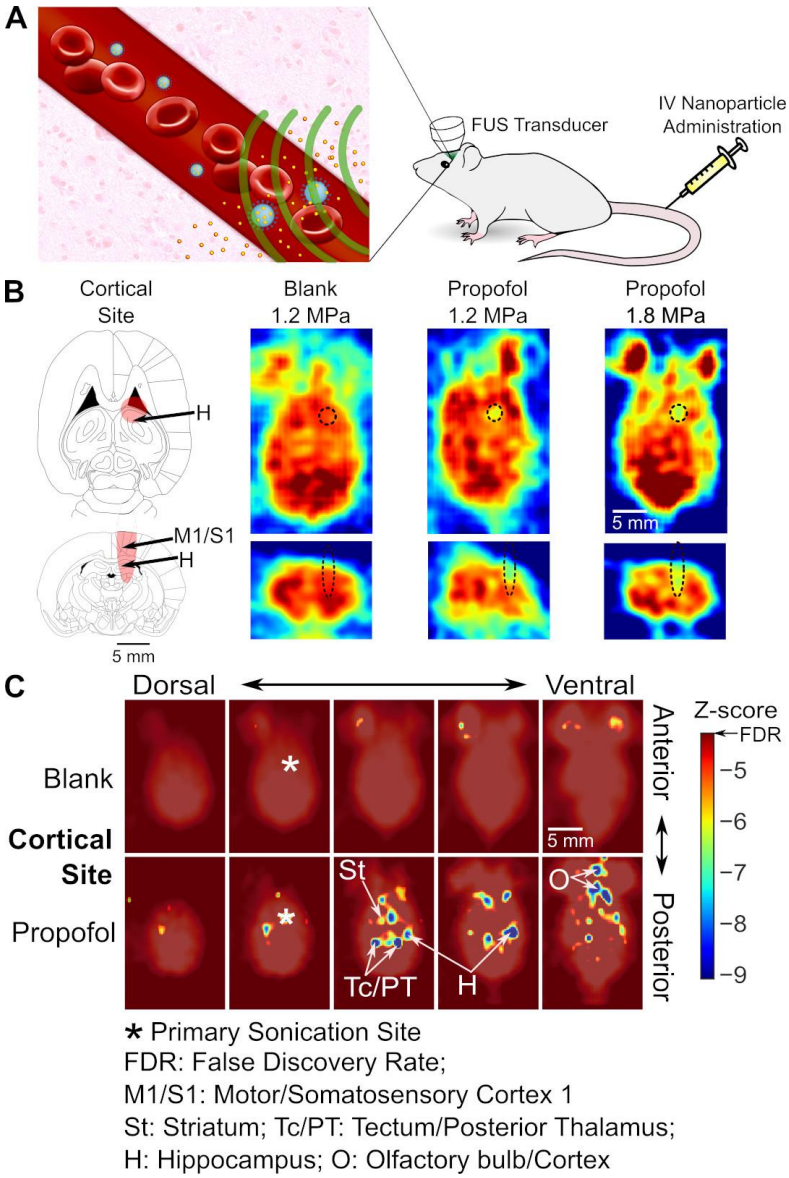
Topic: I.06. Computation, Modeling, and Simulation

Support: NIMH Grant (Brain Initiative RF1 MH114252)
American Society for Neuroradiology
Coulter Foundation
Dana Foundation

Title: Noninvasively mapping the neural functional connectome with ultrasonic drug uncaging

Authors: *J. B. WANG, M. R. ARYAL, Q. ZHONG, D. B. VYAS, R. D. AIRAN
Radiology, Stanford Sch. of Med., Stanford, CA

Abstract: A major goal of the neuroscience community is the development of noninvasive technologies to manipulate brain activity with clinically-relevant spatiotemporal resolution and without the need for irreversible procedures such as gene therapy.
Towards this end, we have developed a platform of biocompatible nanoparticles that uncage a drug payload specifically upon ultrasound application (Fig. A). With the model drug propofol, a GABA(A) agonist, we use [18-F] fluorodeoxyglucose positron emission tomography (PET) imaging to show that the anesthesia caused by ultrasonic uncaging of propofol is spatially limited to a 650 kHz, 1.2 MPa peak pressure sonication focus, with effect diameters of 1.2±0.3 mm axially and 4.0±0.9 mm longitudinally (N=5, Fig. B). Compared to our sonication focus (2.5 x 8.5 mm), we estimate an in vivo pressure threshold of 1.0 MPa. Electrophysiology confirms that brain activity recovers with a half-life of 8.8±3.5 seconds, depending on the sonication parameters. In contrast, sonication of blank nanoparticles causes no change in FDG avidity, indicating that this is specific to propofol release.
Furthermore, using statistical parametric maps of rat brains sonicated with a higher pressure of 1.8 MPa (N=5-7, Fig. C), we see secondary anesthetic effects in brain regions that are anatomically distinct from and functionally connected to the sonicated region, implying that this could be used to noninvasively map functional connectivity. Because these nanoparticles are generalizable to most neuromodulatory drugs, such as ketamine, our method holds promise as both a research tool to elucidate the functional connectome changes associated with pharmacologic activity and for clinical therapies using noninvasive neuromodulation via localized drug delivery.



Disclosures: J.B. Wang: None. **M.R. Aryal:** None. **Q. Zhong:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Applied for patent on nanoparticles for ultrasonic drug uncaging. **D.B. Vyas:** None. **R.D. Airan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Applied for patent on nanoparticles for ultrasonic drug uncaging.

Nanosymposium

549. Computation, Modeling, and Simulation: Network Models: Theory and Experimentation

Location: SDCC 2

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 549.05

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 5R01NS068409-08

Title: Fast objective coupled planar illumination microscopy

Authors: *C. J. GREER[1], T. E. HOLY[2]
[1]Washington Univ. in St. Louis, Saint Louis, MO; [2]Anat. & Neurobio., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: The immense scale and fast dynamics of the nervous system demand the development of commensurate techniques for recording the activity of large populations of neurons. We contribute to this effort with a novel light-sheet microscope designed to maximize the volume imaging rate of the Objective-Coupled Planar Illumination (OCPI) family of microscopes. OCPI microscopes, like Selective Planar Illumination (SPIM) microscopes, are rate-limited by two aspects of their design: the mechanics of scanning and the maximum framerate of modern cameras. We address these bottlenecks by optimizing scan mechanics and introducing Multi-Camera Image Sharing (MCIS), a technique that allows framerate to scale with the number of cameras used. Our design is unique among fast imaging methods in that it requires no sacrifice of image quality or photon efficiency when compared to conventional OCPI or SPIM microscopies. We demonstrate fast (10-20Hz) recordings of calcium dynamics in thousands of neurons throughout the larval zebrafish brain at 0.65μm x 0.65μm x 5μm resolution. We also provide a walkthrough of our preprocessing, cell segmentation, and analysis pipeline applied to these multi-terabyte datasets.

Disclosures: C.J. Greer: None. **T.E. Holy:** None.

Nanosymposium

549. Computation, Modeling, and Simulation: Network Models: Theory and Experimentation

Location: SDCC 2

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 549.06

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant MH098003

Title: Investigating individual variability in behavior, functional networks and inherent vulnerability using the predator scent model of PTSD

Authors: *D. DOPFEL, P. PEREZ, N. ZHANG
Bioengineering, Pennsylvania State Univ., University Park, PA

Abstract: Only a portion of individuals who experience a trauma subsequently develop post-traumatic stress disorder (PTSD). Specific biomarkers for PTSD have been considered through clinical trials, but there are complications when classifying these biomarkers into inherent vulnerabilities, trauma exposure outcomes, or consequences of PTSD development. These difficulties can be addressed by longitudinal assessment of animal models. We performed behavior and functional network measures in a longitudinal study of the predator scent stress rodent model of PTSD. We propose a novel method of separating vulnerable and resilient animals through behavioral assessment of the acute stress response that was found to be tightly linked to long term symptomology. This result was corroborated by corticosterone response that was performed in a subset of these animals. Brain-wide neural circuit function measured by awake rat resting state functional magnetic resonance imaging data was compared between vulnerable and resilient animals. The data revealed variability in resting state functional networks that reflect inherent vulnerabilities to PTSD. These results together demonstrate the role that inherent vulnerabilities play in long term outcomes after trauma and the importance of looking at this individual variability through a multifaceted longitudinal approach.

Disclosures: D. Dopfel: None. **P. Perez:** None. **N. Zhang:** None.

Nanosymposium

549. Computation, Modeling, and Simulation: Network Models: Theory and Experimentation

Location: SDCC 2

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 549.07

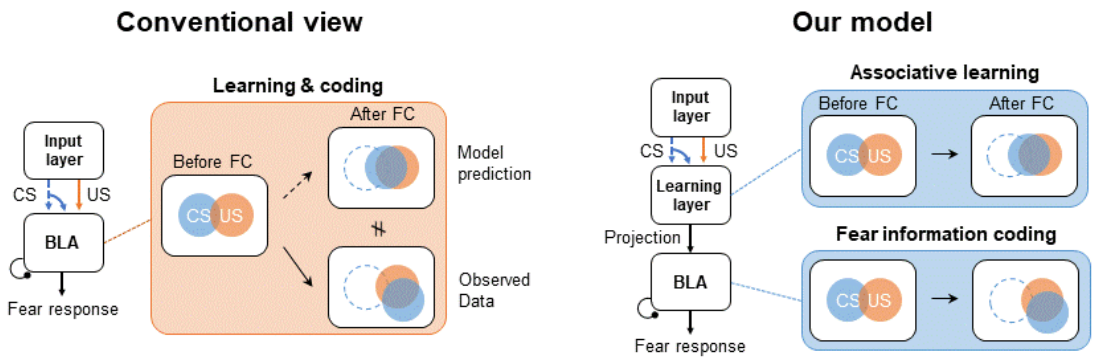
Topic: I.06. Computation, Modeling, and Simulation

Support: NRF-2016R1C1B2016039
NRF-2016R1E1A2A01939949

Title: Segregation of learning and coding layer is required to explain memory ensemble dynamics observed in the basolateral amygdala

Authors: *Y. PARK[1], S.-B. PAIK[1,2]
[1]Bio and Brain Engin., [2]Program of Brain and Cognitive Engin., KAIST, Daejeon, Korea, Republic of

Abstract: The basolateral amygdala (BLA) is known as a core brain region for fear memory, but how the memories are associated in the BLA remains elusive. Recently, Grewe et al. examined neural ensembles for conditioned stimulus (CS) and unconditioned stimulus (US) in the BLA during fear conditioning, and they found that the response changes of the individual neurons were contrary to the standard Hebbian model (Blair 2001). According to Hebbian predictions, the activity of neurons that simultaneously receive CS and US inputs should be increased, but in fact, those activities were half increased and half decreased. Thus Grewe et al. concluded there must be hidden elements, such as a hypothetical neuromodulator, that produce the observed result. Here, we suggest an alternative solution: a model with segregated learning and coding layers with the standard Hebbian rule. Since the previous model innately assumed that synaptic learning and ensemble coding occur simultaneously in the BLA, the bi-directional change could not be explained. However, if the BLA receives projections from a separate 'learning' layer, the observed non-Hebbian behavior might not be paradoxical. To test our idea, we designed neural network models for a computer simulation. CS and US inputs were introduced to the input layer, and the synaptic weights between the first two layers were updated by voltage-based STDP (Clopath 2010). Under this condition, two models were compared: the output layer receives CS and US input (1) directly, or (2) through the hidden 'learning' layer. As expected, the output response of the first model followed the Hebbian predictions; the response of neurons receiving both CS and US inputs increased, in contrast to the data. However, when these ensembles were projected to the next layer (second model), we could perfectly regenerate the non-Hebbian dynamics observed in the BLA. Our results suggest that the observed non-Hebbian behaviors could originate from the projection of pure Hebbian behavior, raising an issue about the role of each component in fear memory circuits (Kitamura 2017).



Disclosures: Y. Park: None. **S. Paik:** None.

Nanosymposium

549. Computation, Modeling, and Simulation: Network Models: Theory and Experimentation

Location: SDCC 2

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 549.08

Topic: I.06. Computation, Modeling, and Simulation

Support: NIA Grant U01-AG050618

Title: Network controllability predicts rTMS-induced benefits to working memory ability

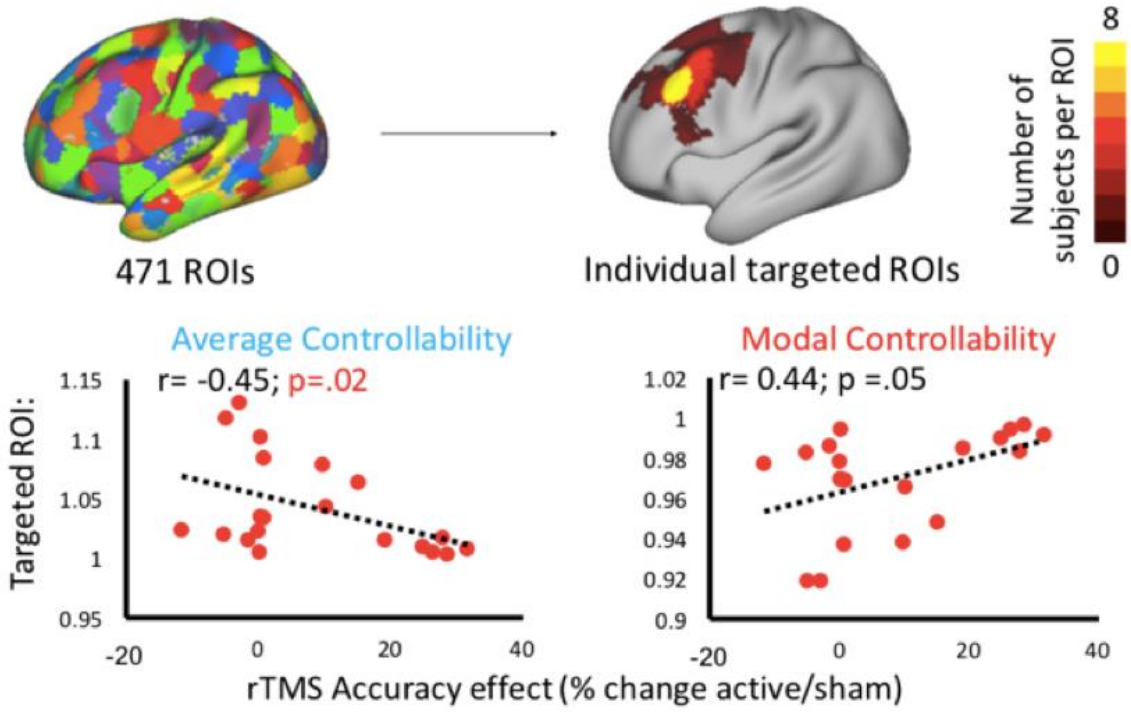
Authors: *S. W. DAVIS[1], L. BEYNEL[1], L. DENG[1], C. CROWELL[3], S. HILBIG[1], H. PALMER[1], A. BRITO[1], A. V. PETERCHEV[2], S. H. LISANBY[4], B. LUBER[5], L. G. APPELBAUM[1], R. E. CABEZA[1]
[2]Psychiatry & Behavioral Sci., [1]Duke Univ., Durham, NC; [3]Psychiatry, Duke Med., Durham, NC; [4]NIH, Bethesda, MD; [5]Exptl. Therapeut. and Pathophysiology Br., Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: ***Background***
The human brain is a complex dynamical system that transitions smoothly through states that directly supporting cognition. In a mathematical sense, these transitions can be thought of as paths through an underlying state space, from a baseline state of neuronal activity towards a desired brain state. Repetitive Transcranial Magnetic Stimulation (rTMS) represents an intriguing method for inducing these state transitions, but little is known about the ability of targeted stimulation at a single site in controlling the whole-brain dynamics. The approaches used in conventional rTMS applications remain limited in both the efficacy and theoretical application, due in large part on the reliance of a single brain region as a target for local rTMS.
Methods
The developing application of control theory to whole-brain networks represents an exciting technique for assessing the dynamic interactions between large-scale neural circuits. Here we utilize the Average and Modal Controllability, which defines control characteristics moving the brain in an easy- or hard-to-reach states, respectively. We apply these metrics to a structural connectivity dataset collected in 27 subjects who completed a rTMS-based intervention with a reliable improvement in working memory accuracy in active compared to sham stimulation.
Results
We found that the improvement in working memory accuracy due to rTMS was reliably predicted by control statistics at the stimulated node. While average controllability negatively predicted the accuracy improvement ($r = -0.45$, $p = 0.02$), Modal controllability was positively related to the same improvement ($r = 0.44$, $p = 0.05$). Furthermore, these network-TMS effect relationships were moderated by individual differences in behavioral state likely to affect brain

state transitions.

Conclusions

While these predictive techniques are in their infancy and many questions remain, the current analysis suggests a reliable, multivariate method for predicting the efficacy of stimulation targets for maximum cognitive effect.



Disclosures: S.W. Davis: None. **L. Beynel:** None. **L. Deng:** None. **C. Crowell:** None. **S. Hilbig:** None. **H. Palmer:** None. **A. Brito:** None. **A.V. Peterchev:** None. **S.H. Lisanby:** None. **B. Luber:** None. **L.G. Appelbaum:** None. **R.E. Cabeza:** None.

Nanosymposium

549. Computation, Modeling, and Simulation: Network Models: Theory and Experimentation

Location: SDCC 2

Time: Tuesday, November 6, 2018, 1:00 PM - 3:15 PM

Presentation Number: 549.09

Topic: I.06. Computation, Modeling, and Simulation

Support: Chinese 1000 Young Talent Program

Title: Controllability of functional brain networks

Authors: *S. GU[1], S. DENG[1], J. C. GEE[2]
[1]Dept. of Computer Sci. and Technol., Univ. of Electro. Sci. and Technol. of China, Chengdu, China; [2]Univ. of Pennsylvania, Philadelphia, PA

Abstract: In recent years, both network neuroscience and cognitive science have developed vigorously. The network approach provides an analytical perspective of understanding the brain structures and functions, and uncovers the intrinsic correlation between them. However, this family of methods pays more attention on the discovery and pattern recognition in the phenomenon, thus lack a mechanistic explanation of why and how this correlation happens. In this work, focusing on the core scientific problem of modeling the human cognitive control, we proceed from the functional MRI signals and study the following subproblems: 1) building the control theoretical dynamics model based on the blood oxygen level neural signals; 2) developing the framework of control theory analysis of human brain functional network; 3) investigating the relationship between functional control measures and the descriptive cognitive measurement. For the first target, we fit the stochastic linear system and adapt the noise term in the model into the control part to build the functional control frameworks. Next, based on the model setting, we investigate the minimal control sets for each person and further quantify each network's controllability, syncronizability and robustness w.r.t the control dynamics. Finally, we examine the distribution and relationships of these control measures, which are potential to be utilized as biomarkers correlated to the individual difference in cognitive performance.

Disclosures: S. Gu: None. **S. Deng:** None. **J.C. Gee:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.01

Topic: A.03. Stem Cells and Reprogramming

Support: CIHR
Ontario Brain Institute
NSERC

Title: Identifying the role of TAOK2 in brain development and the 16p11.2 CNV microdeletion

Authors: N. MURTAZA[1], S. H. WHITE[1], E. DENAULT[2], K. BRENNAND[3], J. ELLIS[2], S. SCHERER[2], *K. K. SINGH[1]
[1]Stem Cell and Cancer Res. Inst., McMaster Univ., Hamilton, ON, Canada; [2]Hosp. for Sick Children, Toronto, ON, Canada; [3]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: The 16p11.2 deletion is the most common CNV associated with autism spectrum disorder (ASD), found in ~1% of individuals with ASD. It is a deletion of 29 genes, including *KCTD13*, *MAPK3*, *MVP*, *SEZ6L2*, and *TAOK2*, however, there are still no direct studies to link the specific genes to the pathophysiology associated with the 16p11.2 CNV. Our recent publication, Richter M. and Murtaza N. et al. (*Mol. Psych.* 2018) showed similar phenotypes between *Taok2*Het and KO mice and 16p11.2del mouse, such as increased midbrain volume. *Taok2*Het and KO also have increased brain volume, which is not seen in the 16p11.2del mouse, however individuals with the 16p11.2 deletion do have increased head circumference and increased gray and white matter in the cortex and thalamus. In fact, a gain-of-function mutation in TAOK2 causes increased dendritic growth in cortical neurons similar to the 16p11.2 duplication mouse. Interestingly, investigation into the synaptic mechanism of TAOK2 identified altered RhoA levels and activity. Altered RhoA levels have previously been linked to the 16p11.2 deletion and duplication. Together these findings highlight the importance of *TAOK2*in the 16p11.2 locus; however the results seen in the mouse many not fully recapitulate the human context. For example, increase brain volume in the 16p11.2del mouse is not seen in individuals with the CNV. To study the direct link between TAOK2 and the 16p11.2 CNV, we ae using patient-derived iPSCs with heterozygous deletion of 16p11.2 and *TAOK2*Het iPSCs. These iPSCs have been differentiated into neurons to investigate how loss of TAOK2 and the 16p11.2 locus alters neuron development in cultured cortical neurons and in 3D cortical spheroids that mimic cortical development. This project will compare the *TAOK2*Het and 16p11.2del in a human neuron model to identify a disease-specific mechanism related to the pathophysiology of the 16p11.2 deletion and a major proportion of individuals with ASD.

Disclosures: N. Murtaza: None. **S.H. White:** None. **E. Denault:** None. **K. Brennand:** None. **J. Ellis:** None. **S. scherer:** None. **K.K. Singh:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.02

Topic: A.03. Stem Cells and Reprogramming

Support: Simons Foundation Grant 345469
NIMH Grant R01MH109885
NIMH Grant R01MH108528
NIMH Grant R01MH105524
NIMH Grant R21MH104766

Title: Cerebral organoid and animal models targeting the pathway dysregulated by 16p11.2 autism CNV

Authors: *L. M. IAKOUCHEVA[1], J. URRESTI[2], M. AMAR[2], P. MORAN LOSADA[2], P. ZHANG[2], P. NEGRAES[3], N.-K. YU[4], C. TRUJILLO[3], J. YATES III[4], A. R. MUOTRI[3]
[1]Univ. of California San Diego, LA Jolla, CA; [2]Psychiatry, [3]Pediatrics, Univ. of California San Diego, La Jolla, CA; [4]Scripps Res. Inst., La Jolla, CA

Abstract: Background: The 16p11.2 copy number variant is one of the most frequent CNVs involved in neurodevelopmental disorders. It is implicated in multiple psychiatric phenotypes, with deletions strongly associated with intellectual disability and autism, and duplications strongly associated with autism and schizophrenia. In addition, this CNV has opposing effect on the head size phenotype, i.e. deletion carriers have macrocephaly and duplication carriers have microcephaly. **Methods:** We previously hypothesized that dysregulation of the KCTD13-Cul3-RhoA pathway could be a potential mechanism contributing towards these phenotypes (Lin et al, Neuron, 2015). To test this hypothesis, we have developed human cerebral organoids from the skin fibroblasts of the patients with the 16p11.2 deletions and duplications. In addition, we created CRISPR/Cas9 mouse models with KCTD13 (16p11.2 gene) and Cul3 (its interacting partner) mutations to better understand the dysregulated pathway. **Results:** Cerebral organoids recapitulate 16p11.2 patient's head size phenotypes. RNAseq and proteomic profiling of 16p11.2 iPSCs confirmed the cis-effect of 16p11.2 CNV affecting dosage changes of 29 protein-coding genes. In addition, cytoskeleton organization proteins were detected as the most differentially expressed between deletion and duplication carriers. Gene co-expression analyses identified a unique cell adhesion/migration module upregulated in the duplication carriers, and a unique nucleosome/chromatin module upregulated in the deletion carriers. RNAseq analyses of cerebral organoid models is ongoing. In the KCTD13 and Cul3 mouse models, we observed upregulation of RhoA levels in the cortex, but not in the cerebellum at early postnatal developmental period. RNAseq of the cortex of KCTD13 mutant mice identified upregulation of the E2 ubiquitin conjugating enzyme responsible for neddylation and activation of Cul3. Cul3 mutant mice have lower birth weight compared to the wild type mice. Molecular and behavioral studies of these models are ongoing. **Conclusions:** Further studies of the cerebral organoid and mouse models would help to better understand the role of KCTD13-Cul3-RhoA pathways in autism.

Disclosures: L.M. Iakoucheva: None. **J. Urresti:** None. **M. Amar:** None. **P. Moran Losada:** None. **P. Zhang:** None. **P. Negraes:** None. **N. Yu:** None. **C. Trujillo:** None. **J. Yates III:** None. **A.R. Muotri:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.03

Topic: A.03. Stem Cells and Reprogramming

Support: NIH grant U19AI131130

Title: Modeling neurodevelopmental etiology of psychiatric disorders in human forebrain organoids

Authors: *X. QIAN[1,2], K. M. CHRISTIAN[3], G.-L. MING[3], H. SONG[3]
[1]Dept. of Neurosci., Perelman Sch. of Medicine, Univ. of Pennsyl, Philadelphia, PA; [2]Biomed. Engin. graduate program, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Dept. of Neurosci., Perelman Sch. of Medicine, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Neuropsychiatric disorders, including schizophrenia and major depression, are believed to have a neurodevelopmental etiology. Due to late onset and absence of apparent abnormalities in brain structures, the contribution of genetics towards the development of neuropsychiatric disorders during organogenesis remains elusive. Previously, our lab has demonstrated that a psychiatric disorder-relevant 4 base-pair deletion mutation of disrupted in schizophrenia 1 (DISC1) affects synaptic functions via transcriptional dysregulation in human induced pluripotent stem cells (hiPSC)-derived neurons. However, neurons produced from directed differentiation in 2D culture do not fully represent the developmental trajectories of neurons in vivo because external factors, rather than intrinsic signaling, cell-cell and cell-matrix interactions, play major role in their differentiation and maturation. Here, we developed novel method to generate human forebrain organoids that recapitulate human corticogenesis up to the third trimester at cellular, structural and transcriptional levels. These organoids exhibit specification of distinct cortical neuronal layers, and contain diverse cell types including neural progenitors, excitatory neurons, interneurons, astrocytes and oligodendrocytes. While DISC1 mutant hiPSC-derived organoids did not display striking structural abnormalities compared to control organoids, high-throughput single-cell transcriptional profiling revealed cell type-specific dysregulations of DISC1 mutant organoids at various developmental stages. Ongoing work focuses on further dissecting the single-cell transcriptomes to understand the dynamic progression of mutation-induced alterations in neuronal maturation and connectivity during cortical development, and the mechanisms by which they contribute to the later onset of psychiatric disorders.

Disclosures: X. Qian: None. **K.M. Christian:** None. **G. Ming:** None. **H. Song:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.04

Topic: A.03. Stem Cells and Reprogramming

Support: Maryland Stem Cell Research Fund Exploratory Grant-MSCRFD-3815

Hussman Foundation Pilot Grant-HIAS15004

Title: High throughput screening of hiPSC derived brain organoids to probe for phenotypes in idiopathic autism

Authors: A. W. PHILLIPS[1], J. NESTOR[2], *M. DURENS[3], M. W. NESTOR[4]
[1]The Hussman Inst. for Autism, Baltimore, MD; [2]Hussman Inst. For Autism, Baltimore, MD; [3]Hussman Inst. for Autism, Baltimore, MD; [4]The Hussman Inst. For Autism, Sykesville, MD

Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition demonstrating a wide spectrum of phenotypes, characterized by marked qualitative differences in social interaction, communication, and behavior. Factors impeding development of neurobiological diagnosis and treatment protocols include the lack of effective model systems from which pathobiology can be determined. 3-dimensional (3-D) cultures called generated from ASD patient-derived human induced pluripotent stem cells (hiPSCs) provide a platform whereby neural circuits can be functionally evaluated. The imbalance of excitatory and inhibitory inputs, partially driven by alterations in γ-Aminobutyric acid (GABA)ergic and glutamatergic circuits is a hypothesis put forth to explain behavioral phenotypes observed in individuals with autism. We interrogated a 3-D serum free embryoid body (SFEB) model based on Nestor et al., (2013) with respect to morphology and network-level function. High content screens were applied to this platform. Multi-electrode array recordings (MEA) on SFEBs were used to assess the role of various ASD-related variants in our cohort of individuals with idiopathic autism. Additionally we assessed calcium signaling using fluorescent reporters. 3-D SFEB cultures were generated by plating into a low adhesion V-bottomed 96-well plate for 14 days then switched to cell culture inserts for the duration of the culture. SFEBs were plated onto polyethyleneimine/laminin treated 12 and 48 well MEA plates and recordings taken at days 60 and 120 to determine spontaneous spiking across networks of neurons. SFEBs were transduced with the AAV-GCaMP6 calcium reporter and spontaneous calcium activity recorded after one week for up to three weeks. Calcium activity was captured and analyzed on the ThermoFisher ArrayScan XTi to evaluate the feasibility of the high content analysis platform for calcium imaging.
Our preliminary data revealed differences in GABA/glutamate ratios in SFEB cultures and show the utility of calcium signaling as a tool to assess functional differences. Spontaneous spike activity revealed less coordinated firing in many of the patient lines compared to controls. This difference increased as the cultures aged. These data demonstrate the utility of the 3-D in vitro platform as a tool in understanding the functional impact of genes in our cohort on the cellular and synaptic activity of developing neurons. The MEA and ThermoFisher ArrayScan XTi platforms are a useful combination as for high content analysis as a way to determine the effect of mutations on key cellular functions.

Disclosures: A.W. Phillips: None. **J. Nestor:** None. **M. Durens:** None. **M.W. Nestor:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.05

Topic: A.03. Stem Cells and Reprogramming

Support: Governor's Counsil for Medical Research and Treatment of Autism (CAUT3APS010, CAUT14APL031, CAUT15APL041)
Nancy Lurie Marks Family Foundation
Mindworks Charitable Lead Trust
Jewish community Foundation of Greater MetroWest NJ

Title: Idiopathic and 16p11.2 deletion autism neural precursor cells (npcs) exhibit common defects in neurite outgrowth, cell migration, and mTOR signaling

Authors: *S. PREM[1], C. C. PENG[1], B. DEV[5], X. ZHOU[1], R. J. CONNACHER[2], M. WILLIAMS[3], P. MATTESON[6], M. MEHTA[7], J. H. MILLONIG[6], E. M. DICICCO-BLOOM[4]
[2]Neurosci. and Cell Biol., [3]Neurosci., [4]Dept Neurosci & Cell Biol/ Pediatrics (Child Neurol. & Neurodevelopmental Disa, [1]Rutgers Robert Wood Johnson Med. Sch., Piscataway, NJ; [5]Rutgers Univ., New Brunswick, NJ; [6]Neurosci. and Cell Biol., [7]Dept. of Neurosci. and Cell Biol. – Robert Wood Johnson Med. Sch., Rutgers Univ., Piscataway, NJ

Abstract: Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impaired social interaction and presence of repetitive behaviors. Inability to directly study human neural cells, limitations of animal models, and disorder heterogeneity have thwarted discovery of cellular and molecular mechanisms. Fortunately, induced pluripotent stem cells (iPSCs) now allow for generation and study of live neural cells from patients with ASD. Genetic studies indicate that the mid-fetal period, when NPCs are proliferating, migrating, and differentiating, is important to ASD pathogenesis. Yet, most iPSC studies of ASD have focused on post-mitotic neurons and processes like synapse-formation which largely occur post mid-fetal development. Thus, we chose to assess neurite outgrowth, migration, and signaling pathways in NPCs derived from 6 individuals with ASD- 3 with idiopathic ASD (I-ASD) and 3 with genetically defined ASD, the 16p11.2 deletion (16pdel). Data from I-ASD NPCs were compared to sex-matched unaffected Sibs while 16pdel data was compared to averages of the 3 Sibs and 2 genetically normal newborns from NIH. Our studies also employ extracellular factors (EFs) that challenge NPCs to reveal deficits absent in control conditions. 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 were plated for 48h on Matrigel. Migration = total neurosphere area-inner mass area. Fascinatingly, our studies revealed common reductions in neurite outgrowth and cell migration in all 6 ASD patients! However, unlike NPCs of unaffected

individuals and 16pdel, NPCs of I-ASD failed to grow neurites under EF stimulation by PACAP, 5-HT, and NGF, suggesting differences between ASD subtypes. In addition, all 6 patients exhibited alterations in mTOR signaling as indicated by P-S6 protein levels. Two individuals (I-ASD-1&3) exhibited lower P-S6 while 4 individuals (I-ASD-2 and all three 16pdel) exhibited higher levels of P-S6. Excitingly, in low-mTOR patients (I-ASD-1) increasing P-S6 with SC-79 rescued neurite outgrowth, migration, and EF response. Likewise, decreasing P-S6 in high mTOR patients ameliorated neurite and migration defects showing that mTOR defects were central to developmental abnormalities in ASD NPCs. In summary, our studies demonstrate common defects in neurite outgrowth and cell migration in two distinct subtypes of ASD, idiopathic and 16pdel. Furthermore, ASD NPCs can be sub-typed based on EF responses, and categorized by mTOR dysregulation. In turn, targeting mTOR dysregulation allowed rescue of developmental deficits in ASD NPCs.

Disclosures: S. Prem: None. **C.C. Peng:** None. **B. Dev:** None. **X. Zhou:** None. **R.J. Connacher:** None. **M. Williams:** None. **P. Matteson:** None. **M. Mehta:** None. **J.H. Millonig:** None. **E.M. DiCicco-Bloom:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.06

Topic: A.03. Stem Cells and Reprogramming

Support: NINDS awards NS073596
NY state DOH award C32242GG

Title: Development and characterization of an innovative model of preterm hypoxic injury using cerebral organoids

Authors: *N. DAVIAUD[1], R. H. FRIEDEL[1], H. ZOU[1,2]
[1]Fishberg Dept. of Neurosci. and Friedman Brain Inst., Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Dept. of Neurosurg., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Preterm hypoxia-ischemia is a leading cause of long-term disability and mortality of infants with limited treatment options. Deprivation of oxygen and glucose causes immediate cellular damages as well as long-term dysfunction of neural progenitor cells, leading to developmental anomaly and increased risk of neurological disorders. Animal models are not ideal to study human corticogenesis, as human brain structure is much more complex, while studies of human fetal tissues have many limitations. Herein, we established cerebral organoid (C-organoid) cultures derived from human ESC to model preterm hypoxic injury (HI) in the developing human cortical tissue.

C-organoids provide an ideal paradigm to model prenatal HI. They contain ventricle-like structured aligned by progenitor cells, and cortical neurons in a stereotypical inside-out stratified layout. To study both short and long-term impact of non-lethal hypoxia, we developed a transient HI model, whereby C-organoids are subjected to low oxygen tension for 24 hours during maturation.
Immediately after HI, we observed an increased level of HIF-1α in C-organoids, which returned to baseline level at 7 or 14 days post-HI. An increase of double strand DNA damage marker was also observed at the same time-points. Importantly, even after one week and 2 weeks of recovery in normoxia condition, neural progenitor cells, as well as radial glia population, continue to exhibit decreased proliferation and increased apoptosis, indicating long-term effects of transient HI. EdU and BrdU pulse-chase studies have been performed to further characterize distinct responses of different isochronic progenitor cohorts to HI during corticogenesis. A higher vulnerability of neurons was observed compared to neural progenitor cells. Surprisingly progenitors that proliferates during hypoxic injury don't seem to suffer from the injury while cells that enter S phase right after the injury show a decrease of survival and migration 2 weeks after injury.
In conclusion, cerebral organoids represent an ideal model to understand the impact of hypoxic injury in the developing human cortex, thus shedding light into the underlying mechanisms of HI-induced developmental defects and neurological diseases later in life.

Disclosures: N. Daviaud: None. **R.H. Friedel:** None. **H. Zou:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.07

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant 1R35NS097370-01
University of Pennsylvania Medical Scientist Training Program

Title: Studying prenatal exposure to drugs of abuse using cerebral organoid models of early neural development

Authors: *D. ZHANG, F. JACOB, S. WONG, Y.-L. WENG, J. DANI, M. DE BIASI, K. CHRISTIAN, H. SONG, G.-L. MING
Perelman Sch. of Med. at the Univ. of P, Philadelphia, PA

Abstract: Prenatal exposure to drugs of abuse affects more than ten percent of children born in the U.S. and is a leading cause of birth defects and long-term deficits in cognitive and neurobehavioral function. Current treatment strategies focus on symptomatic management and

behavioral adaptations as no viable therapies targeted towards root cause mechanisms have yet been identified. Human iPSC derived cerebral organoids are advantageous *in vitro*models of early brain development through the second trimester and can be uniquely leveraged to further understand the pathophysiologic consequences of prenatal exposure to drugs of abuse. Cerebral organoids contain multiple different cell types, which is important for modeling brain development and disorders because they often involve these different cells types and their interactions. To model acute prenatal exposure to cocaine during the first trimester, day 56 forebrain organoids were treated for 12 h with 10 μM cocaine. A pilot single cell RNA-sequencing study revealed significant dysregulation of many genes across eight distinct cell populations. Notably, TAOK1 was upregulated in several neuronal populations but not in other cell types, such as progenitor cells. TAOK1 functions as a MEK kinase upstream of p38 MAPK, an important regulator of a stress sensitive pathway previously found to be activated in rat cortical neurons upon cocaine treatment. Activation of p38 MAPK leads to changes in adrenergic signaling, and has been linked to cocaine-induced behaviors. Furthermore, p38 MAPK plays important roles in cell fate decisions in the nervous system and in neuronal plasticity, and dysregulation of this pathway may contribute to some of the neurobehavioral sequelae of prenatal cocaine exposure. This preliminary study hints at potential mechanisms underlying the deleterious effects of cocaine on the early developing brain. Additional studies with organoids at different maturation stages with prolonged exposure to cocaine may reveal additional mechanistic insights. Importantly, these initial observations demonstrate the potential of using cerebral organoids as a tractable *in vitro* model to study the effects of prenatal exposure to drugs of abuse. Furthermore, this platform can be applied to investigating pharmacologic drugs, for which there is often an absence of a robust understanding of their effects on the developing fetus given the ethical and scientific challenges of these studies. Altogether, this approach can provide unique and complementary evidence to existing methodologies to further explore mechanisms of disease and to advance the drug discovery enterprise.

Disclosures: D. Zhang: None. **F. Jacob:** None. **S. Wong:** None. **Y. Weng:** None. **J. Dani:** None. **M. De Biasi:** None. **K. Christian:** None. **H. Song:** None. **G. Ming:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.08

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant GM111667-01
NIH Grant R01AA025080-01
NIH Grant R01CA203011-2
CSCRF 14-SCC-YALE-01

CSCRF 16-RMB-YALE-04
Kavli Foundation

Title: Modeling Rett syndrome using human brain organoids

Authors: *I.-H. PARK[1], Y. XIANG[3], Y. TANAKA[2], B. CAKIR[1], B. PATTERSON[1]
[2]Genet., [1]Yale Univ., New Haven, CT; [3]Dept. of Genetics, Yale Sch. of Med., New Haven, CT

Abstract: Rett syndrome (RTT) is a severe X-linked neurodevelopmental disorder caused by mutations in the transcriptional regulator methyl-CpG binding protein 2 (MeCP2). Cell-type-specific impairments caused by mutant MeCP2 contribute to RTT etiology. MeCP2 mutant cortical excitatory neurons generated from human pluripotent stem cells (hPSCs) have provided information about the function of MeCP2 in the projection neurons. However there is a gap in our knowledge about how MeCP2 functions in different neuronal cell types in human brain, including GABAergic interneurons that play a critical role in neural circuitry and activity. Additionally, no effective treatment for RTT has been developed yet. To address this, we engineered MeCP2 mutant human embryonic stem cells using CRISPR/Cas9 editing and generated cortical neurons. These were examined for molecular and cellular phenotypes. Single cell transcriptome analysis of human forebrain organoids further revealed that cell-type-specific transcription was impaired in MeCP2 mutant cells. Together, our data demonstrate that hESC-derived cortical neurons and organoids are useful model systems to study RTT.

Disclosures: I. Park: None. **Y. Xiang:** None. **Y. Tanaka:** None. **B. Cakir:** None. **B. Patterson:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.09

Topic: A.03. Stem Cells and Reprogramming

Title: Network and molecular changes during neuronal differentiation in iPSC derived from idiopathic autism patients

Authors: *Y. KIM[1], D. N. AMATYA[2], S. B. LINKER[5], C. MARCHETTO[3], F. H. GAGE[4]
[1]Child Adolescent Psychiatry, Natl. Ctr. for Mental Hlth., Seoul, Korea, Republic of; [2]Lab. of Genet., [4]LOG-G, [3]Salk Inst., La Jolla, CA; [5]Lab. of Genet., Salk Inst. For Biol. Studies, La Jolla, CA

Abstract: Autism spectrum disorder (ASD) is a condition characterized by deficits in social communication and social interaction as well as restricted and repetitive behaviors. It is a complex and heterogenous disorder and one of the features manifested by a subset of ASD is

macrencephaly. A network growth model that use an activity dependent rewiring rule was applied to investigate network complexity in neurons derived from induced pleuripotent stem cells of ASD patients with macrencephaly. Using multi-electrode array, the electrical activity of populations of developing neurons were measured in vitro. Examination of complexity, using minimum embedding dimension (MED) analysis, revealed a significant and transient difference between the ASD neurons and the normal developmental trajectory. During neuronal differentiation, the ASD group exhibits diminished network complexity, in comparison to controls in vitro. Differential expression analysis revealed expression differences with respect to the correlated MED variable. In conclusion, a transient difference between the ASD neurons and the normal developmental trajectory was observed in MED analysis, suggesting diminished neuronal network complexity may contribute to deficits in ASD patients with macrencephaly.

Disclosures: Y. Kim: None. **D.N. Amatya:** None. **S.B. Linker:** None. **C. Marchetto:** None. **F.H. Gage:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.10

Topic: A.03. Stem Cells and Reprogramming

Support: Ontario Brain Institute
Province of Ontario Neurodevelopmental Disorders
Canadian Foundation for Innovation
Colonel Harland Sanders Charitable Foundation
Medicine by Design
Canadian Institutes for Health Research

Title: Altered network connectivity in Rett syndrome stem cell-derived cortical neuron networks

Authors: *R. S. MOK[1], L. DUONG[2], M. MUFTEEV[1], D. C. RODRIGUES[1], L. DEJONG[1], W. WEI[1], A. PIEKNA[1], P. PASCERI[1], J. C. MARTINEZ-TRUJILLO[3], J. ELLIS[4]
[1]Developmental & Stem Cell Biol., Hosp. for Sick Children, Toronto, ON, Canada; [2]Robarts Res. Inst., London Ontario, ON, Canada; [3]Physiol. and Pharmacol., Univ. of Western Ontario, London, ON, Canada; [4]Developmental & Stem Cell Biol., The Hosp. for Sick Children, Toronto, ON, Canada

Abstract: The discovery of induced pluripotent stem cells (iPSCs) has facilitated the research of human disease by providing easily accessible and renewable sources of human cells for *in vitro* disease modeling. We use iPSCs from individuals with neurological disorders to generate neurons harbouring their specific genetic variants for morphological and electrophysiological

study. We investigate the rare neurodevelopmental disorder Rett syndrome (RTT), characterized by microcephaly and rapid regression in cognition and motor skills. The predominant genetic cause is heterozygous mutations in the X-linked gene methyl-CpG binding protein 2 (*MECP2*). MECP2 is an important transcriptional and translational regulator in neurons, and when dysfunctional leads to aberrant size and function. We previously reported that RTT neurons have reduced soma area and dendrite length, along with impaired action potentials and capacitance. Based on these findings in individual cells, we hypothesize that RTT neurons will exhibit a compromised ability to form connections with other neurons, leading to altered connectivity on the network level.

To examine neural circuit formation and network synchronicity, we used 64-channel micro-electrode arrays (MEAs; AxionBiosystems) to record extra-cellular action potential firing. We compared two isogenic pairs of control and *MECP2*-null excitatory cortical neurons differentiated using inducible expression of *Neurogenin-2* (7 days). Monolayer cultures were recorded by MEA daily for the initial 3 weeks to capture network formation information, followed by weekly for synchrony. We show that RTT neurons have reduced frequency and increased duration of network bursts at 6 weeks compared to controls (14-18 wells/line, 4 replicate plates). This network activity can be abolished at 9 weeks by treatment with AMPAR antagonist CNQX, indicating that synaptic transmission between neurons is responsible for the bursting phenotype. We piloted spiking analysis that demonstrates spatial-temporal mapping of connected nodes for evaluating the kinetics of network formation. The number of active nodes increases as a function of time (days) in both RTT and controls. We computed spike count correlations as a function of electrode position and distances, and preliminary results reveal that correlations decay faster as a function of distance in the RTT relative to control networks. Our results potentially identify changes in network development in RTT neurons that may account for features observed in the clinical phenotype. We are moving towards establishing a screening platform for assessments and interventions aimed at rescuing the observed changes.

Disclosures: R.S. Mok: None. **L. Duong:** None. **M. Mufteev:** None. **D.C. Rodrigues:** None. **L. Dejong:** None. **W. Wei:** None. **A. Piekna:** None. **P. Pasceri:** None. **J.C. Martinez-Trujillo:** None. **J. Ellis:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.11

Topic: A.03. Stem Cells and Reprogramming

Support: Canadian Institute of Health Research
Fonds de Research Sante Quebec

Title: Mutations in ACTL6B cause autism and epilepsy and lead to loss of dendrites in human neurons

Authors: *S. C. BELL[1], J. ROUSSEAU[2], H. PENG[1], M. JEFRI[1], H. WU[1], J.-F. THEROUX[1], Z. AOUABED[1], S. EHRESMANN[2], C. ERNST[1], P. CAMPEAU[2]
[1]Neurosci., McGill Univ., Montreal, QC, Canada; [2]Univ. of Montreal, Montreal, QC, Canada

Abstract: We identified nineteen families with neurodevelopmental disorders that all had mutations in ACTL6B, a member of the BAF complex and crucial regulator of dendrite formation that has not been previously identified in human genetic diseases. Ten families were found to have bi-allelic mutations in ACTL6B, and had epileptic encephalopathy and spasticity, and nine families were found to have de novo heterozygous missense mutations and presented intellectual disability, autism, and Rett-like phenotypes. Generating iPSC-derived neurons from an affected individual revealed that mutations in *ACTL6B* result in increased binding of the BAF complex to an enhancer of *SEMA4D*, an inhibitor of dendrite outgrowth. Patient neurons were observed to have abnormal morphology, including a profound loss of dendrites. Both the increased SEMA4D expression and aberrant morphology was reversible upon CRISPR/Cas9-mediated mutation correction of the patient line. To examine the effect of ACTL6B on human neuronal development, a CRISPR/Cas9-mediated ACTL6B expression knock out (KO) neuronal line was generated and was observed to also present a severe deficit in dendritogenesis and increased SEMAD4 expression. The introduction of *ACTL6B* mutations identified in patients into ACTL6B KO neurons led to further increases in *SEMA4D* expression, whereas re-introduction of wild-type ACTL6B resulted in downregulation of SEMA4D expression. This study provides both the first description of two novel genetic diseases caused by mutations in *ACTL6B*, and the first characterization of neural cells derived from patients affected by this disease. Furthermore, this study outlines a novel mechanism that causes dendritic deficits and may contribute to the neurodevelopmental symptoms observed in patients with mutations in *ACTL6B*.

Disclosures: S.C. Bell: None. **J. Rousseau:** None. **H. Peng:** None. **M. Jefri:** None. **H. Wu:** None. **J. Theroux:** None. **Z. Aouabed:** None. **S. Ehresmann:** None. **C. Ernst:** None. **P. Campeau:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.12

Topic: A.03. Stem Cells and Reprogramming

Support: U01MH114825
5 F32 NS103266-02

Title: Using single-cell rna sequencing to characterize the developing human neuroepithelia

Authors: *A. BHADURI[1], M. G. ANDREWS[4], T. NOWAKOWSKI[2], A. R. KRIEGSTEIN[3]
[2]Broad Ctr. of Regeneration Med. and Stem Cell Res., [3]Eli and Edythe Broad Ctr. for Regeneration Med. and Stem Cell Res., [1]Univ. of California San Francisco, San Francisco, CA; [4]UCSF, San Francisco, CA

Abstract: The human brain is comprised of a vast diversity of cells, regions, and substructures, including the cerebral cortex which has been significantly expanded during evolution. Many of these structures emerge as a product of radial glia that give rise to the bulk of the developing human cortex. Recent work has identified radial glia subtypes and even areal differences in these progenitor cells that may explain the cascading areal differences that emerge as the cortex develops and neurons mature. However, much less is known about how radial glia develop from what is thought to be a uniform neuroepithelia. Using single-cell RNA-sequencing, we sampled early stages of human development to identify novel markers of the neuroepithelia and to identify key signaling pathways that may regulate the fate specification to radial glia. These new markers suggest that key patterning pathways may utilize non-canonical signaling cascades to maintain the neuroepithelium and to signal the transition to radial glia. Moreover, we comprehensively identify similarities and differences between the radial glia at early stages and across cortical regions as well as across different brain regions. Finally, we explore the fidelity of mouse and organoid models to recapitulate the cell types and states of early stages of human development. Together, we promote a new understanding of human neuroepithelia and its role in giving rise to the human brain.

Disclosures: A. Bhaduri: None. **M.G. Andrews:** None. **T. Nowakowski:** None. **A.R. Kriegstein:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.13

Topic: A.01. Neurogenesis and Gliogenesis

Title: Primary cilia dysfunction in the mouse model of fragile X syndrome (FXS): A novel role of FMRP on primary ciliogenesis

Authors: *B. LEE, S. PANDA, H. LEE
UTHSCSA, San Antonio, TX

Abstract: The primary cilium is non-motile cilium present in most mammalian cell types, extending from cell surface which functions as antenna for cells to sense signals. Ablation of

primary cilia in adult-born neurons dentate granule cells results in shortening dendritic arborization and weakens synaptic strength, which are shown to be critical for regulating hippocampus-dependent learning and memory formation in adult brains. Therefore, it has been recently suggested that primary cilia might play critical roles in multiple brain disorders including psychiatric disorders. Since fragile X syndrome (FXS), a most common inherited form of mental disabilities with a high risk for autism spectrum disorder, is known to lose synaptic strength and to have a hippocampus-dependent learning and memory deficit, we wanted to check if primary cilia are involved in hippocampal phenotypes of FXS. To investigate the role of the FMRP, which is silenced in FXS, we analyzed primary cilia in the hippocampus of *Fmr1* knock out (KO) mouse in various ages. As a result, deficits in cliogenesis in *Fmr1* KO mice were observed in adult brains from postnatal day 30, specifically shown in NeuN positive cells. Primary cilia loss in adult dentate gyrus was brain region-specific since the number of primary cilia was not changed in CA1 or CA3 of hippocampus or somatosensory cortex. Taken altogether, our results implicate that FMRP might play a crucial role by regulating ciliogenesis of adult-born neurons given that dentate gyrus is one of a few places where neurons are differentiated after birth in adult. **Rigorous study design and reporting:** To provide maximal quality, reproducibility, and transparency in our data, we have designed our experiments to be randomized where possible and have adequate controls, and we will report all data. **Biological justification of using males:** The *FMR1* gene is present in the X chromosome and we can only produce male littermates of WT and *Fmr1* KO mice. Therefore, we justify that we need to use only male WT and *Fmr1* KO for all the tests in our study. Tests using primary cultured cells have been designed to incorporate sex as a biological variable; thus, equal numbers of male and female mice was utilized.

Disclosures: B. Lee: None. **S. Panda:** None. **H. Lee:** None.

Nanosymposium

624. Stem Cells and Disease Modeling: Neurodevelopment

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 624.14

Topic: A.03. Stem Cells and Reprogramming

Support: CIHR
Agilent Technologies
McMaster University
Brain Canada

Title: Cellular metabolic switches as checkpoints for tracking cellular transitions during sensory neuronal differentiation from iPSCs and neural precursors

Authors: K. SINGH[1], Y. KAM[4], S. MOHAMMAD[2], S. H. WHITE[2], K. K. SINGH[2,1], *E. SZABO[3,2,1]
[1]Biochem. and Biomed. Sci., [2]Stem Cell and Cancer Res. Inst., [3]McMaster Univ., Hamilton, ON, Canada; [4]Cell Analysis Div., Agilent Technologies, Boston, MA

Abstract: *In vitro* generation of peripheral sensory neuronal cells is critical for understanding pain biology and for developing robust and efficient drug screening strategies for identification of novel analgesic compounds. Current differentiation protocols require 30-45 days for generating fully mature and functional peripheral sensory neurons and hence it's crucial to identify checkpoints during the early neuronal differentiation that could serve as potential indicators of a successful differentiation protocol. Here, we describe a novel multistage differentiation protocol resulting in a pure sensory neuron population from human induced pluripotent stem cell (iPSCs), which exhibited the expression of peripheral sensory neuron markers and are functionally active. Furthermore, we performed continuous metabolic analysis during the differentiation timeline and observed metabolic switches at the different stages of the differentiation. Our results suggest that cellular metabolic analysis provides a checkpoint for tracing sensory neuronal differentiation at very early timepoints and through maturation to terminally differentiated sensory neurons. The iPSC derived sensory neuron model and the metabolic profiling provides a novel platform to evaluate peripheral neurodegenerative disorders and screen for drugs that regenerate or protect from neural degeneration.

Disclosures: K. Singh: None. **Y. Kam:** A. Employment/Salary (full or part-time):; Agilent Technologies. **S. Mohammad:** None. **S.H. White:** None. **K.K. Singh:** None. **E. Szabo:** A. Employment/Salary (full or part-time):; McMaster University. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Agilent Technologies.

Nanosymposium

625. Epilepsy: Human Studies

Location: SDCC 32

Time: Wednesday, November 7, 2018, 8:00 AM - 10:15 AM

Presentation Number: 625.01

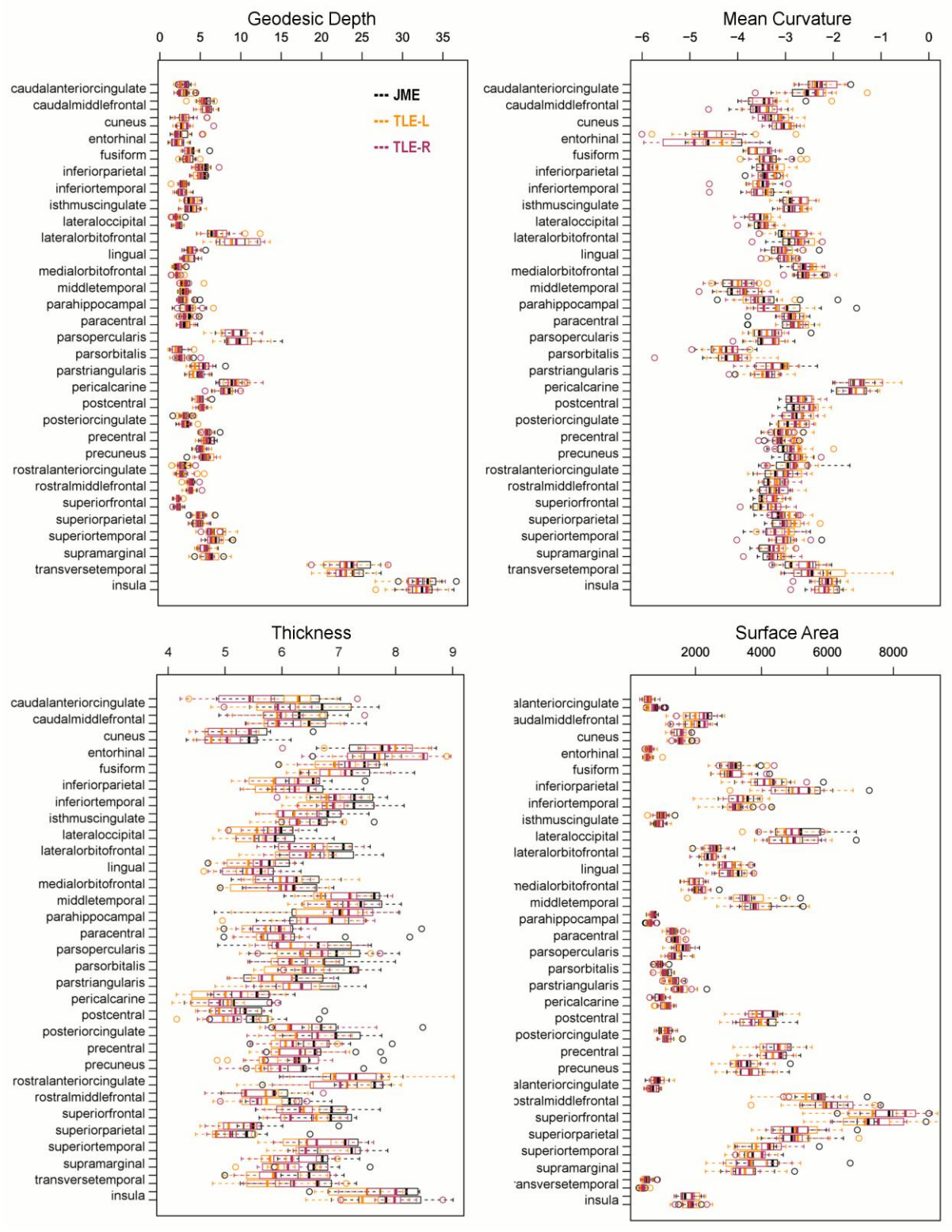
Topic: B.10. Epilepsy

Title: Comparison of brain MRI morphometry features in epilepsy

Authors: *C. SAIOTE, T. R. HENRY, M. C. PARK
Univ. of Minnesota, Minneapolis, MN

Abstract: Identification of anatomical or structural abnormality in the brain MRI can lead to localization of epileptogenic zone and successful surgical treatment of drug resistant epilepsy. But often, such abnormalities are not easily detected. Analysis of MRI brain morphological metrics such as cortical volumes and thickness can enhance the detection of epileptogenic zone

and potentially provide additional biomarkers for various epileptic disorders. Here, we characterized brain morphology in different epilepsy sub-types. Ten patients (3 males, mean age = 32.0 ± 11.6 y) with juvenile myoclonic epilepsy (JME), fourteen patients (9 males, mean age = 40.0 ± 14.0 y) with left temporal lobe epilepsy (TLE-L) and nine patients (4 males, mean age = 35.0 ± 7.4 y) with right temporal lobe epilepsy (TLE-R) were analyzed. Brain structure segmentation was performed with Freesurfer v6.0.0 using the 3T native resolution T1-weighted image (0.9x0.89x0.89 mm^3) and T2-weighted image (0.8 mm^3 isotropic) for improved pial surface reconstruction.The Mindboggle software package was used to calculate several summary morphological metrics - geodesic depth, mean curvature, travel depth, thickness, and surface area - for each cortical region defined in the Desikan-Killiany-Tourville protocol. All datasets were segmented successfully, often needing adjustments in orbitofrontal regions. We found that values for all calculated morphological metrics were not significantly different between epilepsy sub-types in all of the brain regions considered but there was a tendency for lower thickness in TLE-L and TLE-R (Fig 1). It is possible that subtle anatomical abnormalities do not manifest consistently and do not cause detectable differences at a group or sub-type level. Next, we will investigate how these morphological metrics compare to a healthy population, how they are associated with other clinical variables and how they can be utilized for pre-surgical evaluation in epilepsy patients.



Disclosures: C. Saiote: None. **T.R. Henry:** None. **M.C. Park:** None.

Nanosymposium

625. Epilepsy: Human Studies

Location: SDCC 32

Time: Wednesday, November 7, 2018, 8:00 AM - 10:15 AM

Presentation Number: 625.02

Topic: B.10. Epilepsy

Support: NIH Grant K01-ES026839
NIH Grant K08-NS069783
NIH Grant R01-NS094399
Doris Duke Clinical Scientist Award #2015096

Title: Properties of interictal background EEG are potential biomarkers of seizure onset zone

Authors: *B. HUNT[1], C. G. FINK[4], Z. T. IRWIN[2], C. A. CHESTEK[2], W. C. STACEY[1], S. V. GLISKE[3]
[1]Neurol., [2]Biomed. Engin., [3]Dept. of Neurol., Univ. of Michigan, Ann Arbor, MI; [4]Physics, Ohio Wesleyan Univ., Delaware, OH

Abstract: Objective. One goal of high resolution EEG is to improve clinical accuracy in epilepsy, but analysis has typically been limited to isolated events such as HFOs or ictal and preictal data. This work examines interictal background EEG signal as a potential biomarker of seizure onset zone.
Methods. Data were acquired from 23 patients, each with multiple days of intracranial EEG recording, sampled at over 4 kHz. Using only interictal data, we evaluated eleven features that were suggested by computational modeling to be indicative of epileptogenic tissue. Each feature was calculated in two frequency bands: gamma (30-80 Hz) and the high frequency (80-500 Hz). Features were evaluated in each 5 minute time interval of interictal patient data and then averaged over the full recording, resulting in a single value for each channel. These values were then compared within and without the region of resected tissue (using an asymmetry measure) in patients with good outcome to determine correlation with the epileptogenic zone. Results were compared with a similar analysis of HFO rate.
Results. Skewness of the interictal background signal was highly associated with the resected volume in 11 of 13 patients. Combining the skewness results with HFO rate was statistically superior than HFO rate alone (Wilcoxon signed rank test, $p < 0.01$). This result was found in both the low and high frequency band.
Conclusion. The interictal background (i.e. non-HFO) EEG contains information that can be used to localize the SOZ. Skewness of the background signal is one potential new biomarker of epilepsy. Further work is needed to determine the best way to utilize these tools in clinical work.
Significance. High resolution EEG contains potential epilepsy biomarkers even without

evaluating for HFOs. Skewness of the background EEG signal shows potential to identify and improve localization of the seizure onset zone.

Disclosures: B. Hunt: None. **C.G. Fink:** None. **Z.T. Irwin:** None. **C.A. Chestek:** None. **W.C. Stacey:** None. **S.V. Gliske:** None.

Nanosymposium

625. Epilepsy: Human Studies

Location: SDCC 32

Time: Wednesday, November 7, 2018, 8:00 AM - 10:15 AM

Presentation Number: 625.03

Topic: B.10. Epilepsy

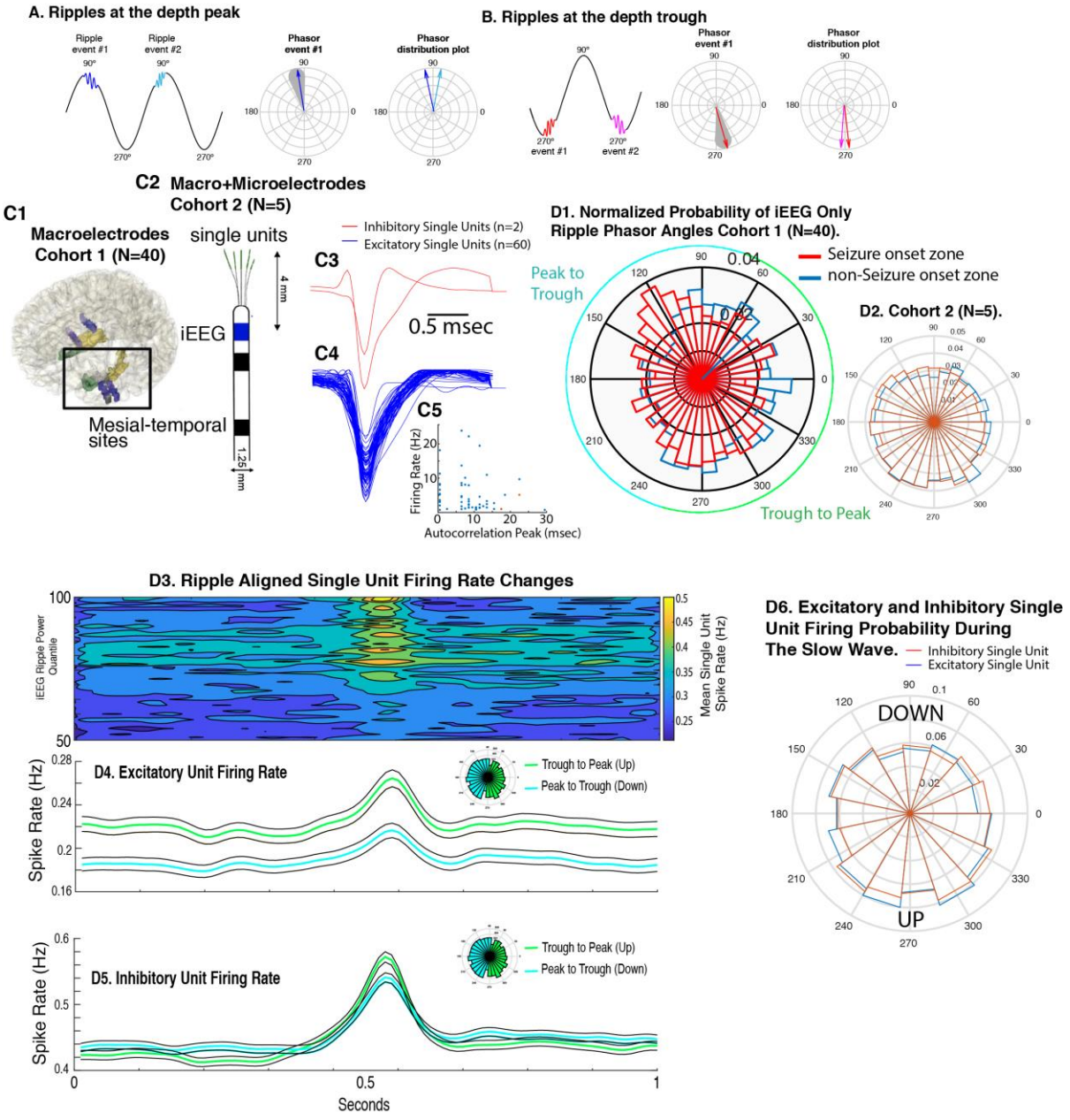
Support: NIH K23-NS094633

Title: Ripples (80-200 Hz) in the human mesial temporal lobe exhibit different profiles of phase-amplitude coupling in relation to slow waves

Authors: *S. A. WEISS[1], I. SONG[2], S. VANGALA[3], Z. J. WALDMAN[2], I. FRIED[5], M. R. SPERLING[1], A. BRAGIN[6], J. ENGEL, Jr.[4], Y. NIR[7], R. STABA[3]
[2]Neurol., [1]Thomas Jefferson Univ., Philadelphia, PA; [4]Neurobiology, and Psychiatry and Biobehavioral Sci., [3]UCLA, Los Angeles, CA; [5]UCLA Sch. Med., Los Angeles, CA; [6]Dept Neurol, David Geffen Sch. Med. UCLA, Los Angeles, CA; [7]Tel Aviv Univ., Tel Aviv, Israel

Abstract: The mechanisms that distinguish physiological from pathological ripples are not yet clear. Intracranial EEG (iEEG) was recorded from 40 patients with medically refractory epilepsy. Also, iEEG and local field potentials (LFPs) were simultaneously recorded from hybrid electrodes that were implanted in the MTL of five different patients during sleep. A custom pipeline was used to detect and quantify ripple oscillations in the iEEG, and measure the phase-amplitude coupling between the phase of the sleep slow wave (0.1-2 Hz) and ripple amplitude (A,B). We found a higher probability of MTL ripples (when MTL was within the SOZ) occurring around slow wave 'peak-trough' phases, in two cohorts on patients (C1,C2). We established statistically in the first cohort (N=40, n=399 seizure onset zone [SOZ], n=708 non-SOZ) that a ripple's preferred phase angle of coupling with respect to the slow wave depended on whether the electrode was within the SOZ (D1,D2, ANOVA, $p<0.001$, n=49,571). In the second cohort of five patients with hybrid electrode recordings we identified 60 excitatory single units, and two inhibitory single units from 19 mesial temporal electrode sites (C3-C5). Single unit firing rate increased during ripples (D3) associated with high power (above the median). Slow wave coupled ripple events and synchronized single unit activity were categorized as 'Trough to Peak' or 'Peak to Trough' depending on the ripple's preferred phase angle (D1,4-5). The mean baseline single unit activity corresponding with the ripple events in the 'Trough to Peak' ripple distribution was greater than that of the 'Peak to Trough' distribution, while the

'Peak to Trough' distribution included more of the DOWN-UP transition (D6). Ripples during the UP state were associated with a comparatively larger increase in single unit firing rates (D4-6). In the epileptogenic mesial temporal lobe pathological ripples occur during the DOWN-UP transition, while physiological ripples, that may be associated with memory consolidation, occur more often during the UP state.



Disclosures: S.A. Weiss: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Fastwave LLC. **I. Song:** None. **S. Vangala:** None. **Z.J. Waldman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Fastwave LLC. **I. Fried:** None. **M.R. Sperling:** None. **A. Bragin:** None. **J. Engel:** None. **Y.**

Nir: None. **R. Staba:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Fastwave LLC.

Nanosymposium

625. Epilepsy: Human Studies

Location: SDCC 32

Time: Wednesday, November 7, 2018, 8:00 AM - 10:15 AM

Presentation Number: 625.04

Topic: B.10. Epilepsy

Support: C. G. Swebilius Trust
Yale University Deans Fellowship for Undergraduate Research

Title: The intracranial EEG spike rate is inversely proportional to extracellular glutamate in patients with intractable epilepsy

Authors: *M. S. SANDHU[1], N. GANESH[2], I. I. GONCHAROVA[3], E. C. DAMISAH[4], C. ONG[5], E. L. PEREZ[5], O. PETROFF[3], L. STAIB[5], L. HIRSCH[3], D. D. SPENCER[4], T. EID[1], H. P. ZAVERI[3]
[1]Lab. Med., [2]Biomed. Engin., [3]Neurol., [4]Neurosurg., [5]Radiology and Biomed. Imaging, Yale Univ., New Haven, CT

Abstract: **Purpose:** Interictal EEG spikes are consistently observed in patients with epilepsy and rarely in others. EEG spikes have traditionally been considered to be a marker of excitability; though recent work has questioned this assumption. We correlated co-localized measurements of intracranially recorded interictal spikes and basal extracellular glutamate concentrations, a well-established marker of excitation, in patients with intractable epilepsy undergoing intracranial EEG (icEEG) monitoring for epilepsy surgery. **Methods:** EEG recordings and brain microdialysate were obtained from 37 combined depth icEEG electrode and microdialysis catheters placed in 17 patients with medically intractable focal epilepsy. Extracellular glutamate was quantified in the microdialysis samples. EEG spikes were documented using Persyst software, at the time when glutamate was documented, in three manners: (1) for the two icEEG electrode contacts on either side of the microdialysis catheter membrane, (2) for all contacts within 3 cm of the membrane, and (3) for all contacts within the region where the dialysis probe was located. **Results:** The basal glutamate and corresponding spike rates were plotted with respect to each other. Measures of high spike rates corresponded to low basal glutamate values and vice versa. The basal glutamate and spike rate values were also log transformed and plotted with respect to each other, and a straight line was fit to the log-transformed values in order to evaluate the relationship between glutamate and EEG spikes. The null hypothesis was that log(glutamate) and log (spike rate) were directly proportional. The null hypothesis was rejected for the measurement of spike rate both over 3 cm and for the larger brain region studied ($p < 0.05$). This suggests an inverse relationship between glutamate and EEG spikes. **Discussion:**

Spikes have traditionally been considered to be a marker of brain excitability. If spikes are markers of excitability we would expect a direct relationship between spike rate and glutamate. Our extensive study, rather showed an inverse relationship between glutamate and spike rates. The association of high spiking with low glutamate levels and vice versa supports the hypothesis that the relationship between basal glutamate and spike rate is best represented by an inverse function. **Conclusions:** This study suggests considerable value for in-vivo co-localized measurement of electrophysiology and neurochemistry to improve our understanding of the mechanisms underlying medically intractable epilepsy.

Disclosures: M.S. Sandhu: None. **N. Ganesh:** None. **I.I. Goncharova:** None. **E.C. Damisah:** None. **C. Ong:** None. **E.L. Perez:** None. **O. Petroff:** None. **L. Staib:** None. **L. Hirsch:** 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.; Dr. Hirsch's institution received funding from Eisai and Upsher-Smith (research support for investigator-initiated studies). D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Consultation fees for advising from Ceribell, Eisai, Monteris, Sun Pharma, and Engage Therapeutics, Neuropace (speaking honoraria). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UptoDate (royalties), Medlink (royalties), and Wiley (royalties). **D.D. Spencer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; The principal investigator of the FLARE study, which is funded by Monteris Medical.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US patents for the wireless transmission of intracranial electroencephalograms (8165684, 8738139, and 9326726 B2) and focal brain cooling (9849025).. F. Consulting Fees (e.g., advisory boards); A member of the scientific advisory board for Monteris Medical, a company which provides laser ablation for clinical purposes. **T. Eid:** None. **H.P. Zaveri:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US patents for the wireless transmission of intracranial electroencephalograms (8165684, 8738139, and 9326726 B2) and focal brain cooling (9849025).. F. Consulting Fees (e.g., advisory boards); A member of the scientific advisory board and is a cofounder of Alva Health, which uses wearable devices to monitor patients with neurological disorders other than epilepsy..

Nanosymposium

625. Epilepsy: Human Studies

Location: SDCC 32

Time: Wednesday, November 7, 2018, 8:00 AM - 10:15 AM

Presentation Number: 625.05

Topic: B.10. Epilepsy

Support: U01-NS090407-01
G0301067

Title: Altered modularity and local connectivity in sudden unexpected death in epilepsy

Authors: L. A. ALLEN[1], R. M. HARPER[2], M. GUYE[4], R. KUMAR[5], J. OGREN[6], S. B. VOS[1], L. LEMIEUX[1], S. D. LHATOO[7], *R. K. HARPER[8], C. L. WILSON[3], B. DIEHL[1]
[1]Clin. and Exptl. Epilepsy, Univ. Col. London, London, United Kingdom; [2]Neurobio., [3]Neurol., Univ. of California Los Angeles, Los Angeles, CA; [4]CNRS, CRMBM UMR, Aix Marseille Univ., Marseille, France; [5]Anesthesiol., [6]Neurobio., Univ. of California at Los Angeles, Los Angeles, CA; [7]Epilepsy Centre, Neurolog. Inst., Univ. Hosp. Case Med. Ctr., Cleveland, OH; [8]Neurobio., Univ. of California Los Angeles Dept. of Neurobio., Los Angeles, CA

Abstract: The processes underlying sudden unexplained death in epilepsy (SUDEP) remain unknown, but circumstances surrounding the fatal event suggest a sudden cardiovascular collapse or cessation of respiratory efforts; either outcome implies failure of central regulatory processes. Determining the interactions between brain areas mediating such processes using recently-developed resting-state functional magnetic resonance (rsfMRI) procedures has the potential to provide insights into those mechanisms and noninvasively reveal risk for SUDEP. We used graph theory to explore functional connectivity properties of a subnetwork of key autonomic and respiratory brain structures in a group of SUDEP (n=9) cases, healthy control subjects (n=18), and two groups at high and low risk for SUDEP (n=18 each), with risk based principally on history of frequent (high-risk) or no (low-risk) generalized tonic-clonic seizures (GTCS).
Modularity, an index which quantifies the extent to which networks form separate modules was significantly reduced in SUDEP ($p<.001$), high risk ($p=0.005$) and low-risk patients ($p=.04$), compared to healthy controls. Significantly increased participation, a measure of local inter-modular diversity, appeared in each patient subgroup, involving progressively more nodes in the direction of risk progression SUDEP>High-risk>Low-risk. Whole-brain modularity was also significantly reduced in patients, following the same pattern observed in the subnetwork. However, when participation of the selected regions was assessed with respect to the whole-brain, no significant differences appeared.
The findings indicate that patients at increased risk for SUDEP or who succumb show highly altered functional interactions between respiratory and cardiovascular brain sites, suggesting facilitation of seizure spread and exaggerated interchanges. Proposals for reducing SUDEP risk might include neuro-modulatory procedures to moderate afferent input to neural systems, disrupting abnormal network connectivity and remodeling neural responses to challenges.

Disclosures: L.A. Allen: None. **R.M. Harper:** None. **M. Guye:** None. **R. Kumar:** None. **J. Ogren:** None. **S.B. Vos:** None. **L. Lemieux:** None. **S.D. Lhatoo:** None. **R.K. Harper:** None. **C.L. Wilson:** None. **B. Diehl:** None.

Nanosymposium

625. Epilepsy: Human Studies

Location: SDCC 32

Time: Wednesday, November 7, 2018, 8:00 AM - 10:15 AM

Presentation Number: 625.06

Topic: B.10. Epilepsy

Support: OTKA-PD121123
OTKA-K119443

Title: An altered perisomatic innervation of principal cells contributes to the higher synchrony of population events in the epileptic human neocortical slice preparations

Authors: *E. Z. TÓTH[1,2], L. ERőSS[3], L. ENTZ[3], A. BAGÓ[3], D. FABÓ[3], I. ULBERT[1,4], L. WITTNER[1], K. TÓTH[1]
[1]Res. Ctr. For Natural Sciences, HAS, Budapest, Hungary; [2]Semmelweis Univ., Budapest, Hungary; [3]Natl. Inst. of Clin. Neurosci., Budapest, Hungary; [4]Dept. of Information Technol., , Pázmány Péter Catholic Univ., Budapest, Hungary

Abstract: Postoperative neocortical tissue of epileptic and non-epileptic (tumor) patients generates spontaneous synchronous population activity (SPA), *in vitro*. Our studies showed differences in the electrophysiological characteristics of SPAs generated by neocortical slices of epileptic or non-epileptic patients: Higher excitability and synchrony characterizes the neuronal circuits of the epileptic neocortex which might contribute to the initiation of epileptiform synchronies in these specimens. To reveal the possible structural basis of this hyperexcitability, the perisomatic innervation of pyramidal cells was examined (n=3 tumor- and n=3 epileptic specimens) and related to the generation of synchronies. The axo-axonic- and fast spiking basket cells were immunostained against parvalbumin (PV) and the perisomatic innervation of pyramidal cells were studied at the electron microscopic level in regions where SPA emerged, in vitro (layer 3). The synaptic coverage was determined as the sum of synaptic active zones (um) per 100 um soma perimeter. The number of PV-positive cells decreased in the human epileptic neocortex, while no considerable difference was seen in the axonal cloud. The total synaptic coverage of the perisomatic region of pyramidal cells was found to be increased in the epileptic tissue compared to tumor specimens, while the synaptic coverage provided by PV-immunolabelled axon terminals was significantly decreased. The increased perisomatic inhibitory innervation of principal cells suggest the sprouting of basket- and axo-axonic cell axons which may contribute to the elevated synchronization of the neocortical excitatory cells. The decreased number of PV-labelled interneurons as well as their reduced contribution to the synaptic coverage of pyramidal cells, however, may be the result of either the loss of PV-positive neurons or the lack of staining. Our results may shed light on how presumed structural differences may impact in the development of pathological synchronies.

Disclosures: E.Z. Tóth: None. **L. Erőss:** None. **L. Entz:** None. **A. Bagó:** None. **D. Fabó:** None. **I. Ulbert:** None. **L. Wittner:** None. **K. Tóth:** None.

Nanosymposium

625. Epilepsy: Human Studies

Location: SDCC 32

Time: Wednesday, November 7, 2018, 8:00 AM - 10:15 AM

Presentation Number: 625.07

Topic: B.10. Epilepsy

Support: Pathology Internal Funding for Academic Development (PIFAD)

Title: Inflammation and long-term epilepsy associated tumours (LEATs)

Authors: *R. R. HAMMOND[1], D. COSMA[2], E. M. CHAPMAN[3], M. J. MEYER[2], D. R. GORASSINI[4], A. PARRENT[2]
[1]Neuropathology, London Hlth. Sci. Ctr., [2]Western Univ., London, ON, Canada; [3]Univ. of Alberta, Edmonton, AB, Canada; [4]King's Univ. Col., London, ON, Canada

Abstract: Long term epilepsy associated tumours (LEAT) represent a heterogeneous group of low-grade neuroepithelial lesions amongst which gangliogliomas (GG), dysembryoplastic neuroepithelial tumours (DNT) and pilocytic astrocytomas (PA) figure prominently. These tumours have a predilection for the temporal lobe and, as the name implies, are frequently associated with long-term, pharmacoresistent epilepsy. Another common but under-appreciated feature of LEATs is inflammation. This is coupled with accumulating evidence that inflammatory elements in primary brain tumours may play a role in their epileptogenesis. For patients harboring LEATs, symptoms, morbidity and mortality are primarily related to seizures and the side-effects of anti-epileptic medications which are inherently less effective in this subpopulation. A better understanding of the nature of the inflammation in such tumours may identify new therapeutic options, especially for those patients where complete resection is delayed or not feasible. The objective of this study was to compare the inflammatory burden by immunohistochemistry in a variety of LEATs (GG, n=14; DNT, n=6; PA, n=6) to that of epileptic temporal lobe (TL, n=7). Oligodendrogliomas (OG, n=6) and glioblastomas (GBM, n=7) were examined as additional comparison groups. Inflammatory infiltrates are common and at times dramatic in LEATs. All LEAT subtypes revealed greater histopathological evidence of inflammation than TL. Of LEATs studied, GG and PA were the most inflamed. The dominant inflammatory element was microglial. While T-lymphocytic infiltrates were common, B-lymphocytic infiltrates were sparse with rare exceptions. Although inflammation can go relatively under-appreciated in their diagnosis and management, it may represent a greater symptomatic burden for the patient than the tumour itself. A better understanding of the nature and extent of inflammation in LEATs may serve to identify additional treatment strategies.

Disclosures: R.R. Hammond: None. **D. Cosma:** None. **E.M. Chapman:** None. **M.J. Meyer:** None. **D.R. Gorassini:** None. **A. Parrent:** None.

Nanosymposium

625. Epilepsy: Human Studies

Location: SDCC 32

Time: Wednesday, November 7, 2018, 8:00 AM - 10:15 AM

Presentation Number: 625.08

Topic: B.10. Epilepsy

Support: NIH R01-NS-49306-01
NIH R01-NS-064154-01
CMSRU Research Fund

Title: PADI4 protein expression in human brain from temporal lobe epilepsy patients

Authors: *S. N. WEISS, T. N. FERRARO, R. J. BUONO
Cooper Med. Sch. of Rowan Univ., Camden, NJ

Abstract: Genome-wide association studies (GWAS) in our laboratory seek to identify single nucleotide polymorphisms associated with common forms of human epilepsy including idiopathic or genetic generalized epilepsy (GGE) and focal temporal lobe epilepsy (TLE). GWAS was performed on a cohort of 2,220 epilepsy patients (964 GGE, 827 TLE and 429 idiopathic epilepsy) compared to 14,488 controls. Results identified variations at 1p36.13 that reached genome-wide significance (p &lt $5.0x10^{-8}$) in the *PADI4* and *PADI6* genes in patients with GGE and suggestive levels in patients with TLE (10^{-4}). *PADI* genes encode enzymes that deiminate arginine to citrulline as a protein post-translational modification. *PADI4* has been implicated by GWAS as associated with rheumatoid arthritis through possible autoantibody production. In addition, histone modifications via *PADI4*-mediated conversion of arginine to citrulline suggest that dysregulation of epigenetic mechanisms via *PADI4* mutations could be related to disease in humans. We collected samples of cortex from patients that had temporal lobectomy for remediation of drug resistant TLE and are currently testing the hypothesis that expression of *PADI4* protein is altered in TLE patients that harbor *PADI4* gene variations. In our preliminary studies, we surveyed commercial antibody reagents to optimize assays for studying *PADI4* protein expression in human brain via Western blot and immunohistochemistry. Preliminary immunohistochemistry results show *PADI4* staining in both neurons and glial cells of human temporal neocortex from TLE patients. Preliminary western blot results were generated using the Bio-Rad stain free gel-turbo blot technology and Chemidoc system with ImageLab software for imaging and quantification. *PADI4* protein signals were normalized against total protein per lane and reported as relative intensity units. Results show a consistent pattern of expression in controls (8.0 +/- 3.0, mean +/- SD, n=3) and a more variable pattern for TLE patients (15.0 +/- 3.0, n=6) with an overall trend for less expression in patients compared to

controls. These differences are not statistically significant (p=0.18 , two tailed t-test); however, additional samples remain to be analyzed. Results of these ongoing studies will help to clarify whether *PADI4* protein expression is altered in brain from patients with TLE.

Disclosures: S.N. Weiss: None. **T.N. Ferraro:** None. **R.J. Buono:** None.

Nanosymposium

625. Epilepsy: Human Studies

Location: SDCC 32

Time: Wednesday, November 7, 2018, 8:00 AM - 10:15 AM

Presentation Number: 625.09

Topic: B.10. Epilepsy

Support: SFI FUTURE-NEURO Research Centre 16/RC/3948
EpimiRNA (FP7) no 602130

Title: Plasma tiRNA fragments are elevated in advance of seizures in human epilepsy

Authors: J. H. M. PREHN[1], M. C. HOGG[1], R. RAOOF[1], N. MONSEFI[1], H. EL NAGGAR[1], N. DELANTY[2], S. BAUER[3,4], F. ROSENOW[3,4], *D. C. HENSHALL[1]
[1]Royal Col. Surgeons Ireland, Dublin, Ireland; [2]Beaumont Hosp., Dublin, Ireland; [3]Epilepsy Ctr. Hessen, Marburg, Germany; [4]Epilepsy Ctr. Frankfurt Rhine-Main, Frankfurt, Germany

Abstract: Stress-induced transfer RNA (tRNA) cleavage is preserved from single-celled organisms to humans indicating it represents part of a highly conserved stress response. In mammals, ribonucleases including angiogenin have been shown to cleave tRNAs during stress to produce ‘transfer-derived stress-induced RNAs’, or tiRNAs. tiRNAs have been found circulating in serum indicating they may act as a “read-out” for neuronal stress. We here investigated whether biofluid tiRNA levels indicated neuronal stress preceding or immediately following epileptic seizures in patients. We performed small RNA sequencing on plasma RNA from epilepsy patients pre- and post-seizure and healthy controls. We found that specific tiRNAs were significantly elevated pre-seizure and returned to control levels post seizure. RNA sequencing results were validated with Custom Taqman assays designed to recognise the tiRNA fragments, which do not detect the full-length tRNA. We could show that these fragments were also elevated 1 hour after seizures induced in mice via intra-amygdala kainic acid injection. This result suggested plasma tiRNA levels may be an early indicator of neuronal stress that are affected before there is evidence of more severe damage such as loss of neuronal markers (NeuN staining) or neurodegeneration (Fluorojade B staining), which are detected 4-8 hours after KA injection in this model. tiRNA levels returned to control levels at 48 hours post injection indicating this was a rapid, transient elevation of tiRNAs in plasma. We then used an *in vitro* model of epilepsy based on induction of epileptiform discharges following magnesium withdrawal from cultured hippocampal neurons to show that both intracellular and extracellular

tiRNA levels were decreased following epileptiform activity. Here we present a novel class of tRNA fragments generated in response to neuronal stress and present in circulation, which may be of use as a biomarker to predict onset of epileptic seizures.

Disclosures: J.H.M. Prehn: None. **M.C. Hogg:** None. **R. Raoof:** None. **N. Monsefi:** None. **H. El Naggar:** None. **N. Delanty:** None. **S. Bauer:** None. **F. Rosenow:** None. **D.C. Henshall:** None.

Nanosymposium

626. Alzheimer's Disease and Other Dementias: APP and Metabolites: Cleavage and Processing

Location: SDCC 33

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 626.01

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

Support: This work was supported by Award Number R01NS092497 (to GT) from National Institute of Health (NIH).

Title: Age-dependent elevation of APP is associated with reduced BACE1-mediated processing of CHL1 in both APP transgenic and knock-in mouse models of AD

Authors: *W. KIM[1], S. WU[2], T. SAITO[3], T. C. SAIDO[4], G. TESCO[1]
[1]Neurosci., [2]Tufts Univ. Sch. of Med., Boston, MA; [3]Brain Sci. Inst, RIKEN, Wako, Japan; [4]RIKEN Brain Sci. Inst., Saitama, Japan

Abstract: β-site amyloid precursor protein cleaving enzyme 1 (BACE1) is a prime drug target to inhibit the generation of toxic Aβ. However, it has been known that BACE1 cleaves not only APP but also other substrates including the cell adhesion molecule L1 like protein (CHL1) suggesting that it has roles in neuronal functions. We have previously shown that BACE1 and full-length APP levels are increased with age in 5XFAD mice. In contrast to increased BACE1-mediated APP processing, BACE1-mediated CHL1 processing was significantly decreased in 12 months old 5XFAD mice most likely due to substrate competition. Reduced BACE1-mediated cleavage of CHL1 was also observed in human brains from subjects affected by Down Syndrome (DS) carrying an extra copy of choromosome 21 encoding the APP gene, consistent with our studies in mouse.
We previously showed that increased BACE1 and APP levels with age were not only found in 5XFAD mice, but also in APPswe/PS1ΔE9 mice, indicating that APP elevation is independent of the promoter driving APP transgene expression. Next, we analyzed App^{NL-G-F} knock-in mice, which express APP harboring mutated (Swedish, Arctic, and Iberian) humanized Aβ sequence under the control of the endogenous promoter, and found that both BACE1 and APP levels are increased in 18 months old App^{NL-G-F} mice compared to 2 months old App^{NL-G-F} mice. These data

indicate that age-depended elevation of BACE1 and APP is not due to APP overexpression in 5XFAD and APPswe/PS1ΔE9 mice.
We have recently identified a novel BACE1 substrate by comparing its processing in BACE1-/- mice versus wild type and BACE1+/- mice. Using HEK cells, we found that overexpression of APP decreased BACE1-mediated processing of this novel substrate in cell culture, supporting our hypothesis that elevated APP levels are associated with reduced BACE1-mediated processing on other BACE1 substrates. Interestingly, we also found that production of the N-terminal fragment of the novel BACE1 substrate in DS human brain was inversely associated with APP levels within a group of subjects affected by DS.
We are currently investigating the extent to which APP elevation results in impaired processing of CHL1 and of the novel BACE1 substrate that we have identified in aged App^{NL-G-F} knock-in mice.
Taken together, these data indicate that age-dependent increase in APP levels is associated with reduced BACE1-mediated processing of other BACE1 substrates. Therefore, BACE1 inhibition could increase the chance of detrimental side effects in conditions associated with APP elevation (e.g. Down syndrome) owing to impairment of BACE1-mediated processing of substrates including CHL1.

Disclosures: W. Kim: None. **S. Wu:** None. **T. Saito:** None. **T.C. Saido:** None. **G. Tesco:** None.

Nanosymposium

626. Alzheimer's Disease and Other Dementias: APP and Metabolites: Cleavage and Processing

Location: SDCC 33

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 626.02

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

Support: NIA 1RF1AG057148-01
NINDS 5R01NS092497-08
Cure Alzheimer's Fund
BrightFocus Foundation

Title: GGA3 gene knock out and a novel AD-linked GGA3 gene mutation result in BACE1 accumulation in axonal swellings

Authors: *S. LOMOIO[1], R. WILLEN[1], K. Z. HO[1], W. KIM[1], E. K. ROBINSON[1], R. E. TANZI[2], G. TESCO[1]
[1]Neurosci., Tufts Univ. Sch. of Med., Boston, MA; [2]Genet. and Aging Res. Unit, MassGeneral Inst. for Neurodegenerative Dis., Massachusetts Gen. Hospital, Harvard Med. Sch., Charlestown, MA

Abstract: BACE1, the rate-limiting enzyme in the generation of amyloid-β peptide (Aβ), accumulates in dystrophic neurites in close proximity to Aβ-plaques. The mechanisms of BACE1 accumulation in peri-plaque dystrophic axons remain unknown. We have shown that clathrin adaptor GGA3 depletion results in BACE1 stabilization by impairing its sorting to lysosomes and that GGA3 levels are decreased and inversely correlated with BACE1 in Alzheimer's disease (AD) brains. Our current data demonstrate that GGA3 genetic deletion results in the accumulation of BACE1 in the axon of hippocampal neurons. Furthermore, we observed a general disruption of BACE1 axonal trafficking in GGA3 null neurons together with its accumulation in axonal swellings in live imaging experiments. These findings were confirmed in vivo. We found that endogenous levels of BACE1 are significantly elevated in the CA3 mossy fibers of the hippocampus in GGA3 null mice. Furthermore, Purkinje cells display a typical phenotype indicative of axonopathy, bearing numerous spheroids in the proximal part of their axons. In the same way some axons of the hippocampal CA1 area (most likely afferents from the entorhinal cortex) exhibit numerous axonal alterations accompanied by axonal degeneration. Inhibition of β- or γ-secretase was able to reduce axonal swellings and to ameliorate BACE1 axonal trafficking in vitro. These data suggest that axonal swellings are the results of a local toxicity, most likely mediated by increased production of Aβ. To test whether GGA3 genetic mutations play a role in human AD, we searched whole genome sequencing data for rare mutations in GGA3 that were present in any of the 410 pedigrees from the National Institute of Mental Health (NIMH) Alzheimer's Disease Genetics Initiative and found an AD-linked GGA3 gene mutation present in LOAD patients of 5 families. Rescue experiments revealed that the reintroduction of this AD-linked mutated GGA3, in contrast to GGA3 wild type, was not able to restore BACE1 axonal trafficking and prevent the swelling phenotype in GGA3 null neurons. These findings indicate that this AD-linked mutation results in GGA3 loss of function. Altogether our data demonstrate that GGA3 plays a central role in preserving BACE1 axonal trafficking. Thus, the depletion of GGA3 observed in AD brains and loss of function AD-linked GGA3 mutations are leading candidate mechanisms underlying BACE1 accumulation in dystrophic neurites. Our studies provide a proof-of-concept that drugs aimed to preserve GGA3 function could be beneficial for AD treatment and/or prevention.

Disclosures: S. Lomoio: None. **R. Willen:** None. **K.Z. Ho:** None. **W. Kim:** None. **E.K. Robinson:** None. **R.E. Tanzi:** None. **G. Tesco:** None.

Nanosymposium

626. Alzheimer's Disease and Other Dementias: APP and Metabolites: Cleavage and Processing

Location: SDCC 33

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 626.03

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

Support: NIH grant NS073512

Title: Disruption of endothelin-converting enzyme activity promotes the accumulation and aggregation of Aβ produced within endosomal-lysosomal vesicles and increases Aβ associated with exosomes

Authors: *E. A. ECKMAN[1], D. CLAUSEN[1], R. PEREZ-GONZALEZ[2], E. LEVY[3], J. PACHECO-QUINTO[1]
[1]Biomed. Res. Inst. of New Jersey, Cedar Knolls, NJ; [2]Ctr. for Dementia Res., Nathan S. Kline Inst. for Psychiatric Res., Orangeburg, NY; [3]Psychiatry, Biochem. & Mol. Pharmacology, and the Neurosci. Inst., NYU Langone Med. Center, Nathan S. Kline Inst. for Psychiatric Res., Orangeburg, NY

Abstract: The abnormal accumulation of amyloid β-peptide (Aβ) aggregates in the form of extracellular plaques in the brain is a defining feature of Alzheimer's disease. Converging lines of evidence suggest that Aβ aggregation may begin intracellularly, within vesicles of the endosomal/lysosomal pathway including late endosomes, multi-vesicular bodies and autophagosomes. We have recently described that endothelin-converting enzymes (ECEs)-1 and -2 reside within the membranes of endosomal/lysosomal vesicles and limit the accumulation of intraneuronally-produced Aβ. In this study, we determined the effect of ECE inhibition on intravesicular Aβ accumulation and aggregation in vitro and in vivo. In SH-SY5Y cells transfected with wild-type APP, primary neuronal cell cultures, and organotypic slice cultures from TgCRND8 mice overexpressing the amyloid precursor protein gene, we found that pharmacological inhibition of ECE activity with phosphoramidon increased intracellular and extracellular Aβ levels and promoted the formation of intraneuronal Aβ oligomers, a process that did not require internalization of secreted Aβ. In vivo, a single intracerebroventricular (ICV) injection of phosphoramidon into wild-type mice (n=6 per group) resulted in a 1313 ± 30% (mean ± se) increase in endogenous extracellular Aβ40 and a 237 ± 6% increase in intravesicular Aβ40, compared to vehicle-injected mice, after 16 hours ($P<0.0001$, unpaired t-test). ICV injection of phosphoramidon into 2-month-old TgCRND8 mice (n=6, pre-amyloid deposition) produced 561 ± 16% and 252 ± 14% increases in extracellular and intravesicular Aβ40 levels, respectively ($P<0.0001$). Intravesicular Aβ42 levels were elevated to a similar extent. Interestingly, while the number of intracellular Aβ oligomers was not significantly increased in phosphoramidon-treated mice, extracellular oligomers increased by 208 ± 34%. Since the contents of endosomal multi-vesicular bodies can be released through exosome secretion, we next measured Aβ in exosomes isolated from brains of phosphoramidon-injected TgCRND8 mice. Exosome-associated Aβ40 and Aβ42 were increased by 217 ± 12% and 167 ± 8.2%, respectively ($P<0.0001$). Our data supports that Aβ aggregation starts intraneuronally from a pool of Aβ produced within endosomal/lysosomal vesicles and suggests that exosome secretion is one of the pathways through which intracellularly-accumulated Aβ is released into the extracellular space. Alterations in endosomal/lysosomal function, and specifically ECE activity, may contribute to this process in Alzheimer's disease.

Disclosures: E.A. Eckman: None. **D. Clausen:** None. **R. Perez-gonzalez:** None. **E. Levy:** None. **J. Pacheco-Quinto:** None.

Nanosymposium

626. Alzheimer's Disease and Other Dementias: APP and Metabolites: Cleavage and Processing

Location: SDCC 33

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 626.04

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

Support: NINDS 5R01NS092497-08

Title: Conditional depletion of BACE1 in the adult mouse, characterization of behavioral and biochemical phenotypes

Authors: *S. LOMBARDO[1], A. TARR[2], T. ROSAHL[3], M. E. KENNEDY[4], G. TESCO[2]
[1]Neurosci., Tufts Univ., Boston, MA; [2]Neurosci., Tufts Univ. Sch. of Med., Boston, MA; [3]Dept. of Pharmacol., Merck & Co., Kenilworth, NJ; [4]Merck Res. Labs, Boston, MA

Abstract: Alzheimer's disease (AD) is a devastating neurodegenerative disorder that results in loss of memory and alteration of cognitive function. A key neuropathological event in AD etiology is the cerebral accumulation of the amyloid-β (Aβ) peptide. Aβ originates from serial proteolysis of the amyloid precursor protein (APP) and β-secretase is the first enzyme involved in APP cleavage. β-secretase has been identified as a membrane-tethered member of the aspartyl proteases, termed β-site APP cleaving enzyme 1 (BACE1). The generation of BACE1 null mice ($BACE1^{-/-}$) has clearly demonstrated that BACE1 is the limiting enzyme for Aβ generation. Thus, inhibiting BACE1 pharmacologically would be a straightforward strategy for AD treatment. Initial studies showed that genetic deletion of BACE1 did not produced any clear phenotype. However, following studies identified a multitude of phenotypes in $BACE1^{-/-}$ such as axon guidance defects, hypomyelination, increased astrogenesis, sensorimotor gating impairment and anxious phenotype. Some of these phenotypes have been linked to other specific BACE1 substrates (e.g., CHL1 and NRG1). While these findings shed some light on BACE1 function, they also raise concerns about the possible side effects of therapeutic BACE1 inhibition. Indeed, BACE1 inhibition impairing the cleavage of BACE1 substrates could possibly induce some of the phenotypes observed in $BACE1^{-/-}$ mice. However, due to the much higher expression level of BACE1 protein during postnatal development versus adulthood, it is possible that these phenotypes arise from its developmental role. To test this hypothesis, we are investigating the biology of BACE1 in conditional knock-out (cKO) mouse model (BACE1 flox). We crossed the BACE1 flox with the TR26-cre-ERT2 line that expresses the Cre recombinase under the control of a tamoxifen inducible system. BACE1 flox/ TR26-cre-ERT2 mice were treated with tamoxifen starting from 8 weeks of age to induce recombination in adult mice. Mice were tested 1 month after cessation of tamoxifen administration. The efficiency of recombination was validated with qPCR and Western blot for BACE1. BACE1 flox/ TR26-cre-ERT2 mice

displayed reduced BACE1 expression (30% residual expression in the cortex of mice injected with tamoxifen) with impairment of substrates cleavage. No behavioral deficit was detected in BACE1 flox/ TR26-cre-ERT2 after recombination. To conclude BACE1 depletion in adult mice appeared to be a safe approach and supports the use of BACE1 inhibitors as a therapeutic approach for AD. Potential deficits due to long term-inhibition of BACE1 are currently under investigation in aged mice.

Disclosures: S. Lombardo: None. **A. Tarr:** None. **T. Rosahl:** A. Employment/Salary (full or part-time):; Merck & Co. **M.E. Kennedy:** A. Employment/Salary (full or part-time):; Merck & Co.. **G. Tesco:** None.

Nanosymposium

626. Alzheimer's Disease and Other Dementias: APP and Metabolites: Cleavage and Processing

Location: SDCC 33

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 626.05

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

Support: NIH R21NS085711
NIH DP2 OD006662
SRA Merck

Title: Partial loss of BACE1's activity protects olfactory neuronal death after traumatic axonal injury

Authors: *M. W. ALBERS[1], L. CAO[1], S. HERRICK[1], I. COSTANTINO[2], S. REITZ[1], A. NEE[1], A. KEIM[1], A. D. ALBERS[3], M. E. KENNEDY[4]
[1]Massachusetts Gen. Hosp., Boston, MA; [2]Masschusetts Gen. Hosp., Boston, MA; [3]Endicott Col., Beverly, MA; [4]Merck Res. Labs, Boston, MA

Abstract: Traumatic brain injury (TBI) is frequently associated with a loss of olfactory function, which reduces the quality of life of patients and enhances their risk of environmental hazards. One mechanism of the olfactory loss is injury to the axons of primary olfactory sensory neurons (OSNs) just after they transverse the skull that results in degeneration of OSNs. After the initial injury, a secondary cascade of signaling networks are unleashed that cause neurodegeneration over the ensuing hours to months. One of the markers of diffuse axonal injury after TBI is an increase in the amyloid precursor protein (APP) and its cleavage product, the Aß peptides, which are also implicated in the neurodegenerative disease, Alzheimer’s disease (AD). Both AD and TBI are characterized by olfactory deficits, and we have previously shown that expression of human Aß causes olfactory deficits in a transgenic mouse model. To evaluate the role of Bace1-mediated cleavage products, we developed a reproducible paradigm of axonal injury of OSNs

within the skull after they pass the cribiform plate in vivo that resulted in loss of 39.1% of the olfactory epithelial thickness 3 days after injury in both male and female mice ($n = 5$, $p < 0.001$). We found that complete loss of Bace1 did not rescue OSN death following axotomy ($n = 5$). Additionally, knockout of APP did not mediate rescue of OSNs following axotomy ($n = 4$), and over expression of human APPsw did not exacerbate the loss of epithelial thickness (40.6%) $n = 4$). Surprisingly, we found that heterozygous knockout of Bace1 confers neuroprotection to OSNs with 39.6% vs. 18.4% loss of olfactory epithelial thickness ($n = 5$; $p < 0.01$). To determine whether partial loss of Bace1 is due to a reduction of protease activity, we treated mice with a specific, potent BACE protease inhibitor for five days before the axon injury. After subacute inhibition of the protease activity of Bace, we observed a similar rescue of olfactory neurons at intermediate doses ($n=4$; $p < 0.05$). Further, treatment of the Bace1 heterozygous mouse with subacute inhibition of the protease activity of Bace resulted in loss of the neuroprotective effect ($n =4$; $p < 0.01$). Moreover, knockout of APLP2, a validated BACE1 substrate and a homolog of APP, confers equivalent protection of olfactory neurons (18.6% loss of olfactory epithelial thickness) following axonal injury ($n = 4$, $p < 0.01$). These findings indicate that Bace1 mediates neuronal loss, perhaps through cleaving APLP2, following axonal injury, and they suggest that partial Bace1 inhibition may prevent neuronal loss following axonal injury, that is commonly observed in TBI.

Disclosures: **M.W. Albers:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Merck Research Laboratories. **L. Cao:** None. **S. Herrick:** None. **I. Costantino:** None. **S. Reitz:** None. **A. Nee:** None. **A. Keim:** None. **A.D. Albers:** None. **M.E. Kennedy:** A. Employment/Salary (full or part-time):; Merck Research Labs.

Nanosymposium

626. Alzheimer's Disease and Other Dementias: APP and Metabolites: Cleavage and Processing

Location: SDCC 33

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 626.06

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

Support: NS074256
AG046929

Title: BACE-1 regulate amyloid Beta (1-42)-induced neuroinflammation by modulating microglial function

Authors: ***N. SINGH**, X. HU, R. YAN
Dept. of Neurosci., UCONN Hlth., Farmington, CT

Abstract: Alzheimer's (AD) is a late-onset, progressive neurological disorder, characterized by the extracellular deposition of Amyloid beta (Aβ) / senile plaques and intracellular accumulation of neurofibrillary tangles (NFT) in the neuronal cells. Inefficient processing/clearance of amyloid plaques by the activated glial cells often leads to persistent oxidative stress and neuro-inflammation, causing irreversible loss of neurons in the hippocampus and cortex, often resulting in cognitive deficits. Identifying signaling molecules regulating Amyloid beta processing or clearance offers potential target in developing therapies for the treatment of AD. β-site amyloid precursor protein cleaving enzyme 1(BACE-1), an aspartyl proteases β-secretase enzyme, cleaves amyloid precursor protein (APP) at the β-site to release a soluble N-terminal fragment and a membrane-anchored C-terminal fragment. Previously, our lab had demonstrated that BACE-1 deficiency inhibits Amyloid plaque formation/deposition and reverse AD associated pathology in 5x FAD AD mice model. Intriguingly, BACE-1 deletion post Aβ plaque deposition also leads to significant clearance of Aβ in 5xFAD mice model. In the present study we hypothesize that besides regulating neuronal Amyloid processing, BACE-1 plays a major role in regulating microglial function. Using primary microglia culture derived from WT and BACE-1 deficient mice, we demonstrated that Bace-1 regulate microglial mediated clearance of Aβ (1-42) by modulating phagocytic activity. Our preliminary results demonstrate that BACE-1 activity suppression/inhibition significantly enhanced uptake of pH Rodo E. coli bioparticles as well as HiLyte™ Fluor labeled β-Amyloid (1-42) in both microglial and BV-2 cell line. Interestingly, our RNA-Seq data suggest that microglial BACE-1 regulate expression of numerous gene important for autophagy and phagocytosis 12 hr post Aβ (1-42) treatment. Furthermore, as compared to WT, Aβ treatment significantly increased the phosphorylation of signaling pathways associated with phagocytosis. Currently, our invitro results are further being validated in WT and Bace-1 KO 5xFAD mice models.

Disclosures: N. Singh: None. **X. Hu:** None. **R. Yan:** None.

Nanosymposium

626. Alzheimer's Disease and Other Dementias: APP and Metabolites: Cleavage and Processing

Location: SDCC 33

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 626.07

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

Support: NIH R01 AG022560

Title: Axonal organization defects in the hippocampus of adult conditional BACE1 knockout mice

Authors: *R. J. VASSAR
Dept. of Cell and Mol. Biol., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: BACE1 is the β-secretase enzyme that initiates production of the toxic Aβ peptide that accumulates in Alzheimer's disease brain. As such, BACE1 is a prime therapeutic target and several BACE1 inhibitor drugs are currently being tested in clinical trials. However, the safety of BACE1 inhibition is unclear. Germline BACE1 knockout mice have multiple neurological phenotypes, although these could arise from BACE1 deficiency during development. To address this question, we generated tamoxifen-inducible conditional BACE1 knockout mice in which the *Bace1* gene is ablated in the adult and found that they largely lack the phenotypes observed in germline BACE1 knockout mice. However, one BACE1-null phenotype, that of reduced length and disorganization of the hippocampal mossy fiber infrapyramidal bundle, an axonal pathway maintained by adult neurogenesis of dentate gyrus granule cells, is induced after BACE1 gene deletion in the adult brain. This defect of axonal organization correlated with reduced BACE1 cleavage of the neural cell adhesion molecule CHL1, which has previously been associated with an axon guidance mechanism. Although our results indicate that BACE1 inhibition in the adult may avoid phenotypes associated with BACE1 deficiency during development, they also suggest that BACE1 inhibitor drugs for Alzheimer's disease may disrupt the organization of an axonal pathway in the hippocampus, an important structure for learning and memory.

Disclosures: R.J. Vassar: None.

Nanosymposium

626. Alzheimer's Disease and Other Dementias: APP and Metabolites: Cleavage and Processing

Location: SDCC 33

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 626.08

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

Support: 2017 TGen Salt River Project Grant Program

Title: Germline ABCC1 mutation is associated with altered APP processing in a familial case of late-onset Alzheimer's disease

Authors: *W. M. JEPSEN[1], M. DE BOTH[1], A. L. SINIARD[1], A. HENDERSON-SMITH[1], K. RAMSEY[1], R. CASELLI[2], G. SERRANO[3], T. G. BEACH[3], M. HUENTELMAN[1]
[1]Neurogenomics, Translational Genomics Res. Inst., Phoenix, AZ; [2]Mayo Clin., Phoenix, AZ; [3]Banner Sun Hlth. Res. Inst., Sun City, AZ

Abstract: Alzheimer's disease (AD) is progressive neurodegenerative disorder that can be neither halted nor reversed by any current treatment. Because of this, further genetic understanding of the disease remains promising for the identification of novel therapeutic molecular targets. By identifying rare mutations in late-onset AD (LOAD) cases, it may be possible to identify a targetable pathway to alter disease progression. We analyzed a familial

case of late-onset AD - in which 6 of 10 siblings were diagnosed with AD - and have identified a rare, germline mutation in ABCC1(chr16:16216007 A>G, p.Y1189C) found in 3 affected females, but not in 2 unaffected siblings. Previous studies have shown ABCC1 double knock-out significantly decreases Abeta clearance across the BBB in an AD mouse model, and that an amino acid change at our position of interest (p.Y1189) alters substrate specificity. Here, we show that ABCC1(WT) overexpression significantly decreases Abeta1-40 and 1-42 levels in BE(2)-m17 cells in culture with a reduced effect in the Y1189C mutant line. Using small molecules, we also show that our ABCC1 cell lines are differentially affected by both thiethylperezine (TEP, an ABCC1-transport activator) and Reversan (an ABCC1 inhibitor). 25uM TEP decreases extracellular levels of Abeta1-40 in both ABCC1 cell lines, but Abeta1-42 only decreases in the WT line. 0.75uM Reversan resulted in cellular detachment of the ABCC1(WT) line with no effect on the empty vector or Y1189C line, suggesting that ABCC1 activity may influence extracellular matrix proteolysis, and that this effect is dramatically reduced in the Y1189C mutant. RNA-seq of the cell lines revealed that TIMP3, a membrane metalloprotease inhibitor capable of inhibiting the alpha-secretase pathway of APP cleavage, was significantly reduced in the ABCC1(WT) cell line versus the control line, with a smaller effect in the Y1189C line. Protein levels were consistent with mRNA. The mutation also resulted in a higher ratio of extracellular Abeta to soluble APPalpha. This suggests that the mutant skews APP processing towards the beta-secretase pathway, or specifically hinders Abeta transport. Taken together, our data show that the Y1189C mutation likely increases the amyloid burden in our AD family, and to our knowledge, this is the first germline mutation in ABCC1 to ever be associated with human disease, and only the second identification of a late-onset familial Alzheimer’s disease gene.

Disclosures: W.M. Jepsen: None. **M. De Both:** None. **A.L. Siniard:** None. **A. Henderson-Smith:** None. **K. Ramsey:** None. **R. Caselli:** None. **G. Serrano:** None. **T.G. Beach:** None. **M. Huentelman:** None.

Nanosymposium

626. Alzheimer's Disease and Other Dementias: APP and Metabolites: Cleavage and Processing

Location: SDCC 33

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 626.09

Topic: H.01. Animal Cognition and Behavior

Support: NHMRC Grant 1058672

Title: Sez6 protein family members are required for normal neuronal development and function: Implications for BACE inhibition

Authors: *A. NASH[1], B. HRUPKA[2], H. GIJSEN[2], M. PIGONI[3], S. F. LICHTENTHALER[3], H. TAKESHIMA[4], K. MUNRO[1], J. M. GUNNERSEN[1]
[1]Anat. and Neurosci., The Univ. of Melbourne, Melbourne, Australia; [2]Janssen Pharmaceutica, Beerse, Belgium; [3]DZNE - German Ctr. For Neurodegenerative Dis., Munich, Germany; [4]Grad. Sch. of Pharmaceut. Sci., Kyoto Univ., Kyoto, Japan

Abstract: Excitatory synapse maturation and maintenance are complex processes that begin early in development and continue throughout life. Seizure-related gene 6 (Sez6) knock-out (KO) mice revealed a role for Sez6 in dendritic arborisation and the development of excitatory synapses [1]. Sez6 and related family members, Sez6 Like and Sez6 Like 2, are expressed in neurons and are substrates of the Alzheimer's protease, β-APP cleaving enzyme 1 (BACE1; [2]). To elucidate the functions of Sez6 family proteins in the brain, we examined triple KO (TKO) mice in which all Sez6 family members are absent. Sez6 TKO mice performed poorly on the rotarod (as previously reported [3]) and longitudinal testing on the fixed and ledge beams revealed that Sez6 TKO motor performance deteriorates with age. Sez6 TKOs also showed behavioural deficits that indicate anxiety and impaired cognitive flexibility. TKO mice moved less in the elevated open field (EOF) test, failed to extinguish their fear response in the context fear extinction paradigm (48% freezing vs. 11% by wild-type (WT) on day 10, $p<0.0001$) and were slower to adapt to the goal location change in the reversal phase of the Morris water maze (MWM). Tracing of Golgi-Cox impregnated neurons (n=30 neurons, 6 mice/genotype) revealed that pyramidal neurons in the somatosensory cortex of TKO mice had altered dendritic spine morphology, with a shift away from mature mushroom spines (0.28 vs 0.42 spines/µm, $p<0.0001$) in favour of immature thin and stubby spines (0.4 vs 0.27 spines/µm, $p=0.0012$ and 0.17 vs 0.057 spines/µm, $p<0.0001$ respectively). To investigate how ectodomain shedding of Sez6 family proteins by BACE1 affects their function, mice were chronically treated with a BACE inhibitor (15 mg/kg/day for 8 weeks, n=12/group). BACE inhibition increased the movement of WT (15117 vs 10429 mm, $p=0.0157$), but not TKO (7678 vs 7897 mm, $p>0.99$), mice on the EOF. The response of WT and TKO mice to context fear conditioning was not significantly affected by BACE inhibition. However, in the MWM, there was a significant interaction between treatment and genotype ($p=0.018$) for pathlength in the reversal phase. Inhibitor treated WT mice travelled further to reach the goal than vehicle treated WT mice on the first day of reversal (7952 vs. 10860 mm, $p=0.047$) whilst the inhibitor did not affect the performance of the TKO mice ($p=0.197$). These results confirm that i) Sez6 family proteins are important for neuronal maturation, motor behaviours and cognitive flexibility; ii) shedding of the Sez6 protein ectodomains is involved in certain behaviours. [1] Gunnersen et al., 2007, Neuron [2] Kuhn et al., 2012, EMBO J [3] Miyazaki et al., 2006, FEBS Lett

Disclosures: B. Hrupka: A. Employment/Salary (full or part-time):; Employed by Janssen Pharmaceutica. **H. Gijsen:** A. Employment/Salary (full or part-time):; Employed by Janssen Pharmaceutica. **M. Pigoni:** None. **S.F. Lichtenthaler:** None. **H. Takeshima:** None. **K. Munro:** None. **J.M. Gunnersen:** None.

Nanosymposium

626. Alzheimer's Disease and Other Dementias: APP and Metabolites: Cleavage and Processing

Location: SDCC 33

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 626.10

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

Support: LISBOA-01-0145-FEDER-007391, project co-financed by FEDER, POR Lisboa 2020 - Programa Operacional Regional de Lisboa
FCT PTDC/BIM-MEC/47778/2014

Title: Early synaptic dysfunction in aging and Alzheimer's disease

Authors: *L. V. LOPES[1], M. TEMIDO FERREIRA[2], D. G. FERREIRA[1], J. E. COELHO[3], D. BLUM[4], H. MARIE[5], T. F. OUTEIRO[6], P. A. POUSINHA[7]
[1]Inst. de Medicina Molecular, Fac Med. Lisbon, Lisbon, Portugal; [2]Inst. de Medicina Mol., Lisboa, Portugal; [3]Faculdade de Medicina da Univ. de Lisboa, Inst. De Medicina Mol., Lisbon, Portugal; [4]Inserm UMR_S1172, Lille, France; [5]Inst. de Pharmacologie Moleculaire et Celluaire (IPMC), Valbonne, France; [6]Univ. Med. Ctr. Goettingen, Goettingen, Germany; [7]660 Route de Lucioles, CNRS IPMC UMR 7275, Valbonne, France

Abstract: Synaptic dysfunction plays a central role in Alzheimer's Disease (AD), since it drives the cognitive decline. Importantly, the adenosine A_{2A} receptor ($A_{2A}R$) encoding gene was recently associated to hippocampal volume in Alzheimer's disease patients (Horgusluoglu-Moloch *et al*, 2017, Neurobiol Aging). There is compelling evidence from animal models of a cortical and hippocampal upsurge of $A_{2A}R$ in glutamatergic synapses upon aging and AD. Such $A_{2A}R$ overactivation induces glutamate release via PKA/cAMP/CREB signalling, calcium influx and leads to hippocampus-dependent cognitive deficits. Conversely, the blockade of $A_{2A}R$, with either caffeine or more selective antagonists prevents hippocampus-dependent memory deficits and LTP impairments in aged animals and in several AD models. Accordingly, in humans, several epidemiological studies have shown that regular caffeine consumption decreases the risk of developing memory impairments in AD patients. Together, these data suggest that $A_{2A}R$ might be a good candidate as a trigger of synaptic dysfunction in aging and AD. In fact, we have recently shown that A2A blockers rescued mGluR5-evoked phosphorylation of NMDAR by alpha-synuclein oligomers in the hippocampus (Nat Neuroscience, 2017), hinting at a mGluR5-Fyn pathway controlled by $A_{2A}R$ in glutamatergic synapses. I will share recent data supporting a common underlying mechanism in early hippocampal deficits, which we are currently exploring across aging and neurodegeneration.
We showed a significant upsurge of $A_{2A}R$ in hippocampal neurons of aged humans, a phenotype aggravated in AD patients. Increased expression of $A_{2A}R$ driven by the CaMKII promoter

selectively in rat forebrain neurons was sufficient to mimic aging-like memory impairments and to uncover a shift in the threshold for plasticity in the hippocampus. This shift was due to an increased NMDA receptor gating and increased Ca^{2+} influx. We identified the mGluR5-NMDAR interplay as key player in the observed $A_{2A}R$-induced synaptic dysfunction. Importantly, we identified the same shift in memory-impaired aged rats and APP/PS1 mice modeling AD, a phenotype rescued upon $A_{2A}R$ blockade. Due to the aberrant $A_{2A}R$ signaling in pathological conditions, their blockade is particularly relevant for long-term therapies, since the alternative option of targeting directly either mGluR5 or NMDAR interferes with basal neuronal function, impairing memory, as these proteins are crucial components of the postsynaptic density.

Disclosures: L.V. Lopes: None. **M. Temido Ferreira:** None. **D.G. Ferreira:** None. **J.E. Coelho:** None. **D. Blum:** None. **H. Marie:** None. **T.F. Outeiro:** None. **P.A. Pousinha:** None.

Nanosymposium

626. Alzheimer's Disease and Other Dementias: APP and Metabolites: Cleavage and Processing

Location: SDCC 33

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 626.11

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

Support: ARC Grant DP150104321
NHMRC Grant 1143848

Title: LIMK1 depletion prevents deficits in an APP transgenic mouse model of Alzheimer’s disease

Authors: *L. M. ITTNER, A. VAN HUMMEL, A. A. ITTNER, Y. D. KE
Univ. of New South Wales, Sydney, Australia

Abstract: Alzheimer’s disease (AD) is characterized by progressive memory deficits with early damage of neuronal communication units, the synapses. LIM-domain kinase 1 (LIMK1) is a regulator of the actin cytoskeleton via phosphorylation (=inactivation) of ADF/cofilin and contributes to synaptic morphology. LIMK1 signaling has been implicated in cellular AD models. However, its role in disease remains mostly elusive. To investigate the role of LIMK1 in an AD mouse model in vivo, we crossed human mutant APP transgenic APP23 mice with *Limk1*-deficient $Limk1^{-/-}$ mice. The resulting APP23/$Limk1^{-/-}$ mice were subjected to behavioral testing, electroencephalography, histopathological analysis and excitotoxic challenges in comparison to APP23, $Limk1^{-/-}$ and non-transgenic littermates. These experiments were complemented by analysis of primary neurons and of human brain tissue from AD patients. Here, we show that depletion of Limk1 abolished memory deficits, network hypersynchronicity and ADF/cofilin pathology in mutant amyloid-β (Aβ) precursor protein (APP) transgenic AD

mice (APP23). Furthermore, Limk1 knockout mice (Limk1$^{-/-}$) were less susceptible to excitotoxic seizures and Limk1$^{-/-}$ neurons were resistant to Aβ-induced spine loss and cell death. Finally, LIMK1 levels were reduced in human AD brain samples, suggesting pathogenic relevance. In summary, our findings show that the LIMK1 signaling pathway contributes to functional deficits in AD mice, and depletion of Limk1 prevented their deficits.

Disclosures: L.M. Ittner: None. **A. van Hummel:** None. **A.A. Ittner:** None. **Y.D. Ke:** None.

Nanosymposium

627. Alzheimer's Disease and Other Dementias: Abeta and Tau Mechanisms and Therapeutics

Location: SDCC 7

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 627.01

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

Support: AMED under Grant Number 16dm0107056h0001
SENSHIN Medical Research Foundation
the Collaborative Research Project of the Brain Research Institute, Niigata University

Title: A new method to evaluate γ-secretase trimming activity in development of disease-modifying drugs targeting γ-secretase

Authors: *S. TAGAMI[1], K. YANAGIDA[1], T. IKEUCHI[2], M. IKEDA[1], M. OKOCHI[1]
[1]Osaka Univ. Grad. Sch. of Med., Suita Osaka, Japan; [2]Niigata University, Brain Res. Inst., Niigata, Japan

Abstract: Introduction: Aβ is generated by sequential intramembrane cleavages by γ-secretase. Following an initial ε-cleavage at the border between cytosol and transmembrane domain, γ-secretase cleaves the remaining membrane-bound long Aβ with stepwise trimming by mainly every 3 amino-acids. These small peptides such as ITL, VIV, and IAT were first identified using a cell-free γ-secretase cleavage assay. We found them inside cultured cells and also in brain of βAPP transgenic mice and named them as γ-byproducts. γ-Byproducts are not secreted and thus could serve as a more direct indicator of γ-secretase activity than secreted Aβ.
Objective: By quantification of γ-byproducts generated during sequential cleavages upon Aβ production, we aimed to address the effects of disease-modifying drugs targeting γ-secretase.
Methods: The γ-byproducts in samples were measured using LC/MS/MS (Quattro Premier XE tandem quadrupole mass spectrometer equipped with UPLC, Waters).
Results: Surprisingly, non-transition state analogue γ-secretase inhibitors did not decrease but increased the levels of γ-byproducts. This finding made us discard the belief that the inhibitors inhibit proteolytic function of γ-secretase and we looked into inside neurons. In addition to the increased level of γ-byproducts, we found accumulation of Aβ inside neurons derived from

human iPS cells, although non-transition state analogue γ-secretase inhibitors decreased secreted Aβ as previously reported.
Conclusions: From this seemingly paradoxical phenomenon, we propose that γ-secretase activity should also be evaluated in terms of the levels of γ-byproducts in development of disease-modifying drugs.

Disclosures: S. Tagami: None. **K. Yanagida:** None. **T. Ikeuchi:** None. **M. Ikeda:** None. **M. Okochi:** None.

Nanosymposium

627. Alzheimer's Disease and Other Dementias: Abeta and Tau Mechanisms and Therapeutics

Location: SDCC 7

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 627.02

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

Support: CIHR
Brain Canada
MSFHR

Title: The role of pannexin 1 in Alzheimer's disease

Authors: *Y. ZHANG, W. SIN, F. CAI, J. BECHBERGER, C. NAUS, W. SONG
Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disorder leading to progressive cognitive impairments and it accounts for 60-80% of dementia cases. However, the cause of the disease and underlying mechanisms remain unclear, and there is no effective prevention and disease-modifying treatment for AD. Pannexin 1 (Panx1) is a membrane channel and widely expressed in the central nervous system (CNS) including cortex and hippocampus, two most commonly affected domains in AD. Emerging evidence has shown that Panx1 is involved in long-term depression (LTD) and in a series of pathological processes including ischemic stroke and inflammation in the CNS. The role of Panx1 channel in the pathogenesis of AD is not well defined. Our study showed that Panx1 expression was unregulated in the brains of the transgenic AD model mice, including in neurons surrounding amyloid plaques. Pharmacological inhibition by probenecid from 5 weeks of age decreased Panx1 activity and significantly reduced Aβ plaque formation and tau phosphorylation in APP23/PS45 double transgenic mice. Furthermore, we found that blockade of Panx1 channels significantly increased neuronal survival and improved cognitive deficits in the AD mice. Taken together, our findings suggest that inhibition of Panx1 channel affects Alzheimer's pathogenesis and may be an effective therapeutic target for AD treatment.

Disclosures: Y. Zhang: None. **W. Sin:** None. **F. Cai:** None. **J. Bechberger:** None. **C. Naus:** None. **W. Song:** None.

Nanosymposium

627. Alzheimer's Disease and Other Dementias: Abeta and Tau Mechanisms and Therapeutics

Location: SDCC 7

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 627.03

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

Support: NIH Grant NS096730

Title: Vasoactivity as the driving force for paravascular clearance in the awake Alzheimer model mouse brain

Authors: *S. J. VAN VELUW[1], S. S. HOU[1], M. CALVO RODRIGUEZ[2], M. ARBEL-ORNATH[3], A. SNYDER[1], M. P. FROSCH[1], S. M. GREENBERG[1], B. J. BACSKAI[4]
[1]Massachusetts Gen. Hosp., Boston, MA; [2]Dept. of Neurol. Alzheimer Res. Unit, Mass. Gen. Hosp. and Harvard Med. Sch., Boston, MA; [3]Neurology/Alzheimer's Res. Unit, MGH, Charlestown, MA; [4]Dept Neurol., Mass Gen. Hosp., Charlestown, MA

Abstract: Cerebral arterioles have been observed to show rhythmic diameter oscillations at slow frequencies (~0.1 Hz), also known as ‘vasomotion’. These spontaneous arteriolar fluctuations may drive drainage of solutes including Aβ in interstitial fluid (*i.e.* paravascular clearance). We studied the relationship between vasoactivity and paravascular clearance in awake mice with and without vascular deposits of Aβ. Cranial windows were implanted in 8 months old transgenic (Tg) APP/PS1 and their wild-type (WT) littermates over visual cortex, and *in vivo* imaging was performed with 2-photon microscopy after i.v. injection of fluorescent dextran. Spontaneous diameter changes were recorded in arterioles. The vasodilation amplitude at 0.1 Hz was derived from the peak of the power distribution after Fourier transform. To physiologically increase the vasodilation amplitude, visual stimulation was performed by flashing a checkerboard (10 sec. on, 10 sec. off, repeatedly for 5 min.) in the mouse visual field. This evoked vascular reactivity resulted in an increase in power at 0.1 Hz. Paravascular clearance rates of extravasated dextran were measured continuously over 20 min. after laser irradiation of nearby venules. The rate of clearance along arterioles was expressed as area under the curve (AUC). To assess the effect of increased vasoactivity on clearance rates, visual stimulation was performed during clearing. Baseline clearance rates were recorded with the screen off. The amplitude of spontaneous vasodilations at 0.1 Hz correlated with clearance rates (r -0.56, p=0.12) (n=9 vessels) in WT mice. Visual stimulation resulted in a >2-fold increase in vasodilation amplitude (0.021 ± 0.010 with visual stimulation (n=10 vessels) vs. 0.007 ± 0.005 without (n=11 vessels), p=0.004), and faster clearance rates (615 ± 225 with visual stimulation (n=10 vessels) vs. 820 ± 370 without

(n=11 vessels), p=0.16). Interestingly, spontaneous ‘vasomotion’ was preserved in Tg mice with vascular Aβ (0.006 ± 0.006, n=7 vessels). Likewise, clearance rates in Tg mice (682 ± 294, n=7 vessels) were not different compared to WT. However, visual stimulation resulted in a smaller increase in vasodilation amplitude in Tg (0.015 ± 0.012, n=8 vessels) compared to WT (0.021 ± 0.010, n=10 vessels, p=0.23). Likewise, clearance rates were significantly slower during visual stimulation in Tg (936 ± 414, n=8 vessels) compared to WT (615 ± 225, n=10 vessels, p=0.052). Our findings suggest that rhythmic arteriolar fluctuations may be responsible for drainage of solutes. Targeting naturally occurring ‘vasomotion’ in Alzheimer patients may be a promising therapeutic option for the removal of Aβ from the brain.

Disclosures: S.J. Van Veluw: None. **S.S. Hou:** None. **M. Calvo Rodriguez:** None. **M. Arbel-Ornath:** None. **A. Snyder:** None. **M.P. Frosch:** None. **S.M. Greenberg:** None. **B.J. Bacskai:** None.

Nanosymposium

627. Alzheimer's Disease and Other Dementias: Abeta and Tau Mechanisms and Therapeutics

Location: SDCC 7

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 627.04

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

Title: An Isoaspartate-Abeta specific antibody attenuates Alzheimer’s disease-like pathology and behavioral deficits in 5xFAD transgenic mice

Authors: *S. SCHILLING, K. GNOTH, A. PIECHOTTA, S. BARENDRECHT, S. GEIßLER, E. JANSIG, R. EICHENTOPF, V. NYKIEL, H.-U. DEMUTH, H. CYNIS, J.-U. RAHFELD
Fraunhofer IZI-MWT, Halle/Saale, Germany

Abstract: A significant proportion of Aβ present brain of patients suffering from Alzheimer’s disease (AD) is posttranslationally modified as a result of peptide ageing and activation of modifying enzymes. Modification discerns these species from newly synthesized Aβ. Therefore, modified Aβ peptides represent interesting anchor points for immunotherapy. Recently, we presented the first monoclonal antibodies directed against isoaspartate (isoAsp)-modified Aβ and their successful application in 5xFAD transgenic mice. Here, our aim was to assess behavioral effects caused by isoAsp-Aβ antibody treatment by implementing a comprehensive phenotyoing battery.
5xFAD mice (n=9-12 per group) were treated by weekly intraperitoneal injection of isoAsp antibody (300 µg per week), isotype control antibody (IgG2a, 300 µg) or antibody 3D6 (IgG2a, 300 µg). The treatment was initiated at three months of age and pursued for nine months in total. The treatment outcome was evaluated using immunochemical methods and by assessing behavior (at 11months of age) in elevated plus maze (EPM), pole test, contextual fear

conditioning (CFC) and Morris water maze test paradigms (MWM). Wildtype and baseline animals were included as additional controls for behavioral and immunochemical analyses, respectively.
In contrast to 3D6, the treatment with isoAsp-Aβ antibody for 9 months led to a significant reduction of iso-Asp Aβ and general Aβ compared to isotype control. With regard to behavior, we observed a significantly lower time spent in open arms in EPM associated with isoAsp- and 3D6 treatments. In CFC, we detected a significant difference in context memory between WT and isotype control treated mice. The isoAsp- and 3D6 antibody treated groups did not significantly differ to WT and isotype control. In pole test, only isoAsp-Aβ antibody treated animals showed a trend towards improvement, isotype control and 3D6-treated animals performed significantly worse compared to WT. Finally, also in Morris water Maze only isoAsp-antibody treated animals were not significantly different to WT animals after 4 days of training. The results support the general concept that modified Aβ peptides are viable targets for immunotherapy. The attractiveness is due to a relatively low concentration of modified Aβ in brain and absence in the periphery. Thus, such tailored approaches might be favored to avoid common limitations of current Aβ antibodies in development.

Disclosures: S. Schilling: None. **K. Gnoth:** None. **A. Piechotta:** None. **S. Barendrecht:** None. **S. Geißler:** None. **E. Jansig:** None. **R. Eichentopf:** None. **V. Nykiel:** None. **H. Demuth:** None. **H. Cynis:** None. **J. Rahfeld:** None.

Nanosymposium

627. Alzheimer's Disease and Other Dementias: Abeta and Tau Mechanisms and Therapeutics

Location: SDCC 7

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 627.05

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

Support: NIH Grant R01-AG046275

Title: Identification of neurotoxic cross-linked Aβ heterodimers in Alzheimer's disease brain

Authors: *W. HONG[1], G. BRINKMALM[2], T. O'MALLEY[1], W. LIU[1], Z. WANG[1], X. SUN[1], M. FROSCH[3], E. PORTELIUS[2], H. ZETTERBERG[2], K. BLENNOW[2], D. WALSH[1]
[1]Dept. of Neurol., Brigham and Women'S Hosp. and Harvard Med. Sch., Boston, MA; [2]The Sahlgrenska Acad. at the Univ. of Gothenburg, Molndal, Sweden; [3]Massachusetts Gen. Hosp. and Harvard Med. Sch., Boston, MA

Abstract: Genetic, neuropathological, biochemical and biomarker studies indicate that accumulation of aggregated amyloid β-protein (Aβ) is an early event in the pathogenesis of Alzheimer's disease (AD) that may precede symptoms by 2-3 decades. Aβ can exist in multiple

forms, but the relative importance of these different forms is unknown. Aqueous extracts of AD brain which mediate disease-relevant toxicity in an Aβ-dependent manner contain ~4 kDa Aβ monomers, ~7 kDa Aβ species, and high molecular weight (HMW) Aβ species which range from ~30 to 700 kDa. HMW Aβ species are by far the most prevalent, but appear to be relatively inert unless dissociated to their component ~4 kDa and ~7 kDa Aβ species. Several lines of evidence suggest that both native ~7 kDa Aβ, and ~7 kDa Aβ released by denaturation of HMW Aβ, are neurotoxic. However, the molecular identity of these ~7 kDa Aβ species is controversial and their definitive identification has been hampered due to their low abundance. Here, we isolated microgram amounts of ~4 and ~7 kDa Aβ by solubilizing purified amyloid plaques in formic acid and then size separating the components. Thereafter, we used real-time imaging of living human neurons plus the sensitive functional assay of long-term potentiation (LTP) to assess the bioactivity of fractions rich in ~4 and ~7 kDa Aβ. The ~7 kDa species potently disrupted neuritic integrity of iPSC-derived neurons and blocked hippocampal LTP, whereas the ~4 kDa species had no effect. Subsequent mass spectrometry (MS) analysis of the same samples used for bioactivity assays revealed that the ~4 kDa fractions contained a rich diversity of Aβ alloforms encompassing a large number of N- and C-termini. For instance, using a combination of liquid chromatography (LC) and tandem MS (MS/MS) more than 35 different Aβ primary structures were detected in a sample from a single brain and yet greater heterogeneity was evident between brain samples. Applying an identical approach to ~7 kDa fractions we identified 11 mass matches consistent with covalently cross-linked Aβ heterodimers including: 1-37+1-38, 1-38+1-38, 1-38+1-39, 1-38+1-40, 1-39+1-40, 1-40+1-40, 2-38+1-40, 2-40+1-38, 2-40+1-40, 1-40+1-42, and 1-42+1-42. LC-MS/MS of undigested and trypsin digested ~7 kDa fractions confirmed the presence of Aβ heterodimers, the most abundant of which contained a cross-link between Asp1 and Glu22. These data demonstrate that covalently cross-linked Aβ heterodimers are present in AD brain and suggest that these dimers may play an important role in pathogenesis and are worthy of further investigation.

Disclosures: W. Hong: None. **G. Brinkmalm:** None. **T. O'Malley:** None. **W. Liu:** None. **Z. Wang:** None. **X. Sun:** None. **M. Frosch:** None. **E. Portelius:** None. **H. Zetterberg:** None. **K. Blennow:** None. **D. Walsh:** None.

Nanosymposium

627. Alzheimer's Disease and Other Dementias: Abeta and Tau Mechanisms and Therapeutics

Location: SDCC 7

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 627.06

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

Support: work partly supported by Merck Therapeutics

Title: Heterogeneity and predictability of tau seeding in the human brain, relevance for heterogeneity in clinical and neuropathological phenotypes and immunotherapy for Alzheimer's disease

Authors: *S. DUJARDIN[1], C. COMMINS[1], T. V. KAMATH[1], D. L. CORJUC[1], B. T. CORJUC[2], J. A. GONZALEZ[1], P. M. DOOLEY[1], S. L. DEVOS[1], B. D. MOORE[1], A. SERRANO-POZO[2], K. ATCHISON[3], M. P. FROSCH[2], F. ELWOOD[3], M. E. KENNEDY[3], B. T. HYMAN, MD,PhD[2]
[1]neurology, [2]Massachusetts Gen. Hospital, Harvard Med. Sc, Charlestown, MA; [3]Merck Res. Labs, Boston, MA

Abstract: Cognitive decline in Alzheimer's disease (AD) correlates with aggregation and spread of tau proteins. The precise mechanisms of tau aggregation are unknown but recent studies pinpoint tau seeding as a potential pathway. Indeed, small tau aggregates -so-called seeds- can induce focal fibrillization of intracellular non-aggregated tau via direct protein-protein contact. Tau aggregation can be triggered by "seeds" isolated from either tau-transgenic mice or tauopathy-positive human brains. This phenomenon is well described in vitro and in vivo but its relevance for human disease progression is yet to be proven. Here, we wondered if tau seeding can be correlated with the clinical progression of the pathology and if we can use it as a potential diagnostic or therapeutic target. The objectives were to 1-understand how tau seeding can be linked to clinical, anatomical and pathological characteristics and 2-try to reduce Tau seeding with the use of anti-tau antibodies recognizing diverse epitopes.
We selected a cohort of over 30 human AD patients from the Massachusetts ADRC brain bank based on clinical (AD diagnosed with at least 4 visits in the memory clinic) and neuropathological records (AD diagnosis confirmed, Braak stage VI, High burden using ABC scoring). We quantified tau seeding from these brains using a FRET-based cellular assay and systematically performed different histological, biochemical and cellular characterizations for each patient. Lastly, we tried to reduce seeding activity using diverse commercially available antibodies. We found a high degree of heterogeneity of tau seeding phenotypes among cases. Very interestingly, this variability closely correlates with the speed of clinical progression and the age of onset of the disease. As expected, histological tangle burden also correlates closely with seeding. In addition with biochemical characterizations (ELISA, Size exclusion chromatography, proteinase K digestion), these results suggest that only a small fraction of the total amount of tau present in the brain is capable to induce seeding in the FRET bioassay. Antibodies targeting total or post-translationally modified tau significantly reduced tau seeding but each brain sample displayed unique sensitivity to reduction arguing for the existence of various "bioactive" tau "strains". In conclusion, these results provide a novel characterization of the relevance of tau seeding in AD and add insights into the therapeutic potential of tau immunotherapy.

Disclosures: S. Dujardin: None. **C. Commins:** None. **T.V. Kamath:** None. **D.L. Corjuc:** None. **B.T. Corjuc:** None. **J.A. Gonzalez:** None. **P.M. Dooley:** None. **S.L. DeVos:** None. **B.D. Moore:** None. **A. Serrano-Pozo:** None. **K. Atchison:** A. Employment/Salary (full or part-

time):; Merck. **M.P. Frosch:** None. **F. Elwood:** A. Employment/Salary (full or part-time):; Merck. **M.E. Kennedy:** A. Employment/Salary (full or part-time):; Merck. **B.T. Hyman:** None.

Nanosymposium

627. Alzheimer's Disease and Other Dementias: Abeta and Tau Mechanisms and Therapeutics

Location: SDCC 7

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 627.07

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

Title: Physiological role of dendritic tau protein on AMPA receptor dynamics

Authors: *M. KANATANI[1], H. BANNAI[3], Y. SOEDA[2], S. MAEDA[4], A. TAKASHIMA[2]
[1]Gakushuin Univ., Kamifukuoka-Shi, Japan; [2]Gakushuin Univ., Toshima,Tokyo, Japan; [3]Lab. Developmental Neurobio., JST PRESTO, RIKEN CBS, Wako-shi,Saitama, Japan; [4]Physiol., Keio Univ. Sch. of Med., Shinjuku, Japan

Abstract: The neurofibrillary tangle (NFT), which is a hyperphosphorylated and aggregated form of a microtubule-associated protein Tau, is a pathological characteristic of tauopathies including Alzheimer's disease. Under physiological conditions, Tau is soluble and is generally localized in axons. Recently, there are several lines of evidence suggesting the involvement of Tau in physiological postsynaptic functions. Previous studies have confirmed that glutamate stimulation leads to increased expression of Tau in cultured neuronal dendrites and postsynaptic compartments in dendritic spines. It has also been found that long-term depression (LTD) in excitatory synapse of hippocampal CA1 is impaired in Tau knockout (TauKO) mice, while long-term potentiation (LTP) remains intact. However, physiological role of dendritic Tau has not been fully clarified yet. LTD process requires the dispersion of the AMPA receptor (AMPAR) from the postsynaptic membrane by lateral diffusion and the removal of AMPARs from the plasma membrane by means of endocytosis. Therefore, the impairment of LTD in tau deficient neurons suggests the possibility that Tau could be involved in the regulation of dendritic AMPAR dynamics: i.e. surface mobility or the endocytosis. In order to investigate the physiological role of Tau in AMPAR dynamics, here we compared the lateral mobility of AMPARs on the plasma membrane in cultured hippocampal neurons from TauKO mice to those form wild type. Using a super resolution imaging "quantum dot-single particle tracking (QD-SPT)" that enables analyzing the behavior of one molecule, we examined the effect of Tau knockout on AMPAR dynamics at single molecule resolution. The diffusion coefficient of the AMPAR GluA1 subunit tagged with a quantum dot was measured in the presence or absence of glutamate-induced neuronal excitation. Here we report that the surface AMPARs on neurons from TauKO mice showed impaired diffusion dynamics compared with WT neurons. This result indicates that the presence of tau may be involved in the control of AMPAR dynamics on the

plasma membrane in the physiological state. We also established novel experimental system to visualize endocytosis of endogenous AMPAR using pH sensitive fluorescent dye. Here we will discuss the effect of Tau on endocytosis examined by this method.

Disclosures: H. Bannai: None. **Y. Soeda:** None. **S. Maeda:** None. **A. Takashima:** None.

Nanosymposium

627. Alzheimer's Disease and Other Dementias: Abeta and Tau Mechanisms and Therapeutics

Location: SDCC 7

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 627.08

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

Support: R01NS073899
MCDN-15-370051

Title: Peptidyl-prolyl isomerase, CyP40, disrupts tau fibrils

Authors: *L. J. BLAIR[1,2], J. D. BAKER[2], L. B. SHELTON[2], D. ZHENG[2], C. A. DICKEY[2]
[1]Mol. Med., USF Byrd Inst., Tampa, FL; [2]Mol. Med., Univ. of South Florida, Tampa, FL

Abstract: The microtubule associated protein, tau, forms neurotoxic oligomers and fibrils in Alzheimer’s disease (AD) and other tauopathies. Previous work, from our lab and others’, demonstrated that proteins containing peptidyl prolyl-isomerase activity (PPIase), alter the aggregation and toxicity of tau. We have now found that one of these PPIases, Cyclophilin 40 (CyP40), not only regulates the aggregation of tau, but also breaks apart tau fibrils in a PPIase dependent manner. Overexpression of CyP40 by AAV9 transduction in aged rTg4510 tau transgenic mice reduced insoluble and oligomeric tau levels while preserving neurons and cognitive function. This work identifies CyP40 as a novel human tau disaggregase. Further work is necessary to characterize this interaction and determine if this novel mechanism of controlling tau aggregates can be therapeutically beneficial for the treatment of AD and other tauopathies.

Disclosures: L.J. Blair: None. **J.D. Baker:** None. **L.B. Shelton:** None. **D. Zheng:** None. **C.A. Dickey:** None.

Nanosymposium

627. Alzheimer's Disease and Other Dementias: Abeta and Tau Mechanisms and Therapeutics

Location: SDCC 7

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 627.09

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

Support: Alzheimer Society
NSERC

Title: Tau phosphorylation undergoes circadian oscillations controlled by body temperature and disrupted by sleep deprivation

Authors: *I. GUISLE[1,2], M. GRATUZE[1], F. MORIN[1], V. MONGRAIN[3], S. HÉBERT[1], E. PLANEL, Jr[1]
[1]CHUL, Quebec, QC, Canada; [2]Univ. Laval, Quebec, QC, Canada; [3]Ctr. for Advanced Res. in Sleep Med., Montreal, QC, Canada

Abstract: Tau protein is an important pathological marker of Alzheimer’s disease (AD) since its level of phosphorylation and aggregation correlates with the progression of the disease. Sleep disturbances are common in Alzheimer's disease, and previous studies have demonstrated that tauopathy can disrupt normal circadian clock function both at the behavioral and molecular levels. Another emerging theory relates to insufficient sleep as an underlying cause or risk of AD. However, how normal sleep and sleep disturbances can affect tau phosphorylation is not well understood. As we had previously demonstrated that core temperature can affect tau phosphorylation and since body temperature follows circadian oscillations, we hypothesized that tau phosphorylation might be subject to circadian oscillations due to temperature. In a first set of experiments in mice (n=20, females, 6months, C57BL6), we showed that the phosphorylation of tau follows a circadian rhythm inversely correlated with body temperature; i.e. when the animals sleep, their temperature is lower and tau is more phosphorylated compared to awake mice. When mice were exposed to higher ambient temperatures (34°C, n=10, females, 6months, C57BL6), circadian variations in body temperature were abolished so were the circadian variations in tau phosphorylation, suggesting that body temperature *per se* is involved in the circadian rhythm of phosphorylation of tau. In a second set of experiments, we explored the consequences of sleep disruption of tau phosphorylation. While sleep restriction (due for instance to medical conditions or lifestyle) mimics better the clinical pathology and human experience, sleep deprivation represents a standard method to assess the molecular mechanisms affected by sleep loss. When we exposed mice to sleep deprivation (n=17, males and females, 6months, C57BL6), sleep-induced hypothermia and tau hyperphosphorylation were abolished. Altogether, our results

suggest that tau phosphorylation follows a circadian rhythm driven at least in part by body temperature and that forced awakening prevents sleep-induced hyperphosphorylation of tau.

Disclosures: I. Guisle: None. **M. Gratuze:** None. **F. Morin:** None. **V. Mongrain:** None. **S. Hébert:** None. **E. Planel:** None.

Nanosymposium

627. Alzheimer's Disease and Other Dementias: Abeta and Tau Mechanisms and Therapeutics

Location: SDCC 7

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 627.10

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

Support: This work is supported by the US Department of Veterans Affairs

Title: Characterization of Alzheimer’s disease risk factors in a *C. elegans* model of tauopathy

Authors: *S. J. BENBOW[1,2], B. C. KRAEMER[1,2,3,4]
[1]Geriatric Res. Educ. and Clin. Ctr., Veterans Affairs Puget Sound Hlth. Care Syst., Seattle, WA; [2]Gerontology and Geriatric Med., Univ. of Washington Sch. of Med., Seattle, WA; [3]Dept. of Psychiatry and Behavioral Sci., [4]Dept. of Pathology, Univ. of Washington, Seattle, WA

Abstract: Aberrant aggregation, misfolding, and mislocalization of the microtubule-associated protein tau characterize several neurodegenerative diseases, termed tauopathies. Alzheimer’s disease (AD) is the most common tauopathy and most prevalent form of dementia within the global aging population. AD is distinguished from related dementias by the presence of two aggregant protein pathologies: intracellular neurofibrillary tangles (NFTs) composed of aggregated tau protein and extracellular amyloid-ß (Aß) plaques.
While heritable mutations in amyloid precursor protein (APP) and presenilins 1 and 2 (PSEN1, PSEN2) have considerably advanced our understanding of AD pathogenesis, they account for only a small portion of total AD cases. The majority of cases are classified as sporadic late-onset Alzheimer’s disease and present without known causative mutations. However, human genomic studies have revealed a number of genetic variants contributing significant risk for AD. Genetic analysis by genome wide association studies (GWAS) has led to the identification of several novel genetic risk factors for AD (e.g. ABCA7, PICALM, DSG2, INPP5D, MEF2C, PTK2B, SLC24H4-RIN3, and ABI3).
We have observed that a subset of these gene variants modulate the severity of tau pathology in our *C. elegans* model of tauopathy. In this model, pan-neuronal expression of human tau recapitulates several features of human disease including accumulation of detergent-insoluble phosphorylated tau aggregates, abnormal behavior, neurodegeneration, and shortened lifespan. Loss of function mutations in homologous genes corresponding to the human AD risk factors

abt-2 (ABCA7), and *hmr-1* (DSG2) enhance motility defects in human tau expressing worms. Candidate genes that affect tau-induced motility phenotypes will be further tested for the ability to modulate pathological tau and neurodegeneration. Identification of the molecular mechanisms underpinning genetic risk for AD remains a key unaddressed area and may provide novel therapeutic targets.

Disclosures: S.J. Benbow: None. **B.C. Kraemer:** None.

Nanosymposium

627. Alzheimer's Disease and Other Dementias: Abeta and Tau Mechanisms and Therapeutics

Location: SDCC 7

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 627.11

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

Support: NIH AG051086
NIH AG010133

Title: Role of MicroRNAs regulating expression of proteins involved in Alzheimer's disease

Authors: *D. K. LAHIRI[1], R. WANG[1], N. CHOPRA[1], B. MALONEY[1], N. H. GREIG[2], K. SAMBAMURTI[3]
[1]Dept. of Psychiatry, Indiana Univ. Sch. of Med., Indianapolis, IN; [2]Drug Design & Develop. Section, LNS, Intramural Res. Program, Natl. Inst. On Aging, NIH, Baltimore, MD; [3]Neurosciences, MUSC, Charleston, SC

Abstract: Genetic, epigenetic, and environmental factors play significant roles in Alzheimer's disease (AD) etiology. We hypothesize that AD results from misregulation of key biochemical pathways and their regulatory molecules, including transcription and translation factors and non-coding RNAs. This could culminate in classic AD pathology brain extra-neuritic plaques from aggregates of amyloid-β peptide (Aβ), cleaved from the Aβ precursor protein (APP). Expression studies suggest that dysregulation of proteins involved in Aβ production, such as APP and β-secretase, or BACE1, and/or Aβ degradation, such as membrane metallo-endopeptidase (MME/neprilysin), contribute to excess Aβ deposition. Repressor element 1 silencing transcription factor (REST) has also emerged in relationship to AD. MicroRNAs (miRNAs) are non-coding small RNAs that typically downregulate mRNA translation via mRNA 3'-UTR sequences, and, consequently, many cellular processes. But their expression is often dysregulated in human diseases, including AD. Recently discovered miRNAs in body fluids (serum, plasma) and brain tissues with altered levels in AD patients include miR-9, -101, -153, -181d, and -339-5p. We study how specific miRNA species regulate genes involved in AD, using neuronal cultures and human brain tissue specimens from control and AD subjects. Our results revealed

novel regulatory interactions. Specifically, we observed the downregulation of APP by miR-101 and miR-153; BACE1 by miR-339-5p; MME by miR-181d and REST by miR-9. In addition, we determined that miR-346 uniquely *upregulates* APP levels via the APP *5'UTR* in human cultures. Altogether, these multiple unique regulatory interactions may serve as novel therapeutic targets and enable the development of treatment strategies beneficial against AD. Thanks to grant supports from the National Institute on Aging (NIH)

Disclosures: D.K. Lahiri: None. **R. Wang:** None. **N. Chopra:** None. **B. Maloney:** None. **N.H. Greig:** None. **K. Sambamurti:** None.

Nanosymposium

628. Parkinson's Disease: Mechanisms and Genetics

Location: SDCC 25

Time: Wednesday, November 7, 2018, 8:00 AM - 9:45 AM

Presentation Number: 628.01

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS083498
NIH Grant AG049479

Title: DJ-1 is critical for the integrity and function of endoplasmic reticulum-mitochondria tethering

Authors: *X. ZHU, Y. LIU
Case Western Reserve Univ., Cleveland, OH

Abstract: The loss-of-function mutations of DJ-1 are associated with autosomal recessive early-onset Parkinson's disease yet the underlying pathogenic mechanism remains elusive. Prior studies suggest perturbation in endoplasmic reticulum (ER)-mitochondria tethering is involved in mitochondrial dysfunction and neurodegeneration in various neurodegenerative diseases including Parkinson disease. Indeed, we found that DJ-1 is an ER-mitochondria contacts resident protein using both imaging and biochemical methods. DJ-1 is part of the Grp75-IP3R complexes and directly interacts with Grp75. Interestingly, in M17 neuroblastoma cells, loss of DJ-1 led to significant loss of ER-mitochondria tethering proteins in the mitochondria-associated membrane (MAM) and reduced Grp75-IP3R interaction. Proximity ligation assay and ultrastructural study clearly demonstrated significantly reduced ER-mitochondria contacts in the DJ-1 knockout M17 cells. These disruptions were accompanied by disturbed mitochondrial calcium uptake following ER release and reduced ATP production in these cells. Overall, these data suggest that DJ-1 plays a critical role in the maintenance of the integrity and function of ER-mitochondria tethering and impaired ER-mitochondria tethering could contribute to the pathogenic effects of DJ-1 mutations.

Disclosures: X. Zhu: None. **Y. Liu:** None.

Nanosymposium

628. Parkinson's Disease: Mechanisms and Genetics

Location: SDCC 25

Time: Wednesday, November 7, 2018, 8:00 AM - 9:45 AM

Presentation Number: 628.02

Topic: C.03. Parkinson's Disease

Support: PSC-CUNY Research Award (ENHC-48-45 to M.E.F.-P.)
NIH MD007599 to Hunter College infrastructure from NIMHD
The Graduate Center, City University of New York

Title: Phoshorylation at Ser 65 diminishes calcium-dependent calpain cleavage of Parkin: Relevance to Parkinson's disease

Authors: *M. E. FIGUEIREDO-PEREIRA[1], F. CHEUNG[2], H. WANG[1], P. ROCKWELL[1]
[2]Biol. Sci., [1]Hunter Col., New York, NY

Abstract: Mitochondrial impairment and calcium (Ca^{++}) dyshomeostasis are linked to the pathogenesis of Parkinson's disease (PD). When intracellular ATP levels are lowered, Ca^{++}-ATPase pumps are impaired causing cytoplasmic Ca^{++} to be elevated leading to calpain activation. As far as we know, the effect of calpain activation on Parkin integrity has not been previously investigated. To address this gap, we examined the effects of mitochondrial inhibitors [oligomycin (Oligo), antimycin or rotenone] on endogenous Parkin integrity in rat midbrain and cerebral cortical cultures. The three drugs induced calpain-cleavage of Parkin to ~36.9/43.6 kDa fragments. In contrast, neuronal treatments with the proinflammatory prostaglandin J2 (PGJ2) and the proteasome inhibitor epoxomicin induced caspase-cleavage of Parkin to fragments of a different size, as shown previously by others to occur under apoptotic conditions. We also determined that calpain-cleaved Parkin was enriched in neuronal mitochondrial fractions**.** Pre-treatment with the phosphatase inhibitor okadaic acid prior to Oligo-treatment, stabilized full-length Parkin, as detected by phosphorylation of Ser^{65} on its UbL domain, and reduced Parkin cleavage by calpain. Similarly, stabilizing intracellular ATP levels with cyclocreatine moderately mitigated Parkin cleavage by calpain. Nevertheless, raising intracellular cAMP with PACAP27 (pituitary adenylate cyclase activating peptide) prevented caspase but not calpain-cleavage of Parkin. Computational analysis predicted that calpain cleavage of Parkin liberates its UbL domain. In summary, our data support a cleavage mechanism that could prevent long-lasting Parkin activation. This mechanism reflects the critical and disease-relevant impact of mitochondrial impairment on Parkin integrity and could influence the pathogenesis of PD.

Disclosures: M.E. Figueiredo-Pereira: None. **F. Cheung:** None. **H. Wang:** None. **P. Rockwell:** None.

Nanosymposium

628. Parkinson's Disease: Mechanisms and Genetics

Location: SDCC 25

Time: Wednesday, November 7, 2018, 8:00 AM - 9:45 AM

Presentation Number: 628.03

Topic: C.03. Parkinson’s Disease

Support: Helmholtz Association VH-NG- 1123
Marie Curie Career Integration Grant CIG304108
German Research Council DFG, DE 2157/2-1

Title: Enhancing mitochondrial biogenesis and function in Parkinson's disease

Authors: *M. DELEIDI[1], D. C. SCHÖNDORF[2], D. IVANYUK[3], P. BADEN[3], A. SANCHEZ-MARTINEZ[4], S. DE CICCO[3], C. YU[1], L. SCHWARZ[5], G. DI NAPOLI[1], V. PANAGIOTAKOPOULOU[1], S. NESTEL[6], B. HEIMRICH[6], T. GASSER[1], A. WHITWORTH[4]
[1]German Ctr. for Neurodegenerative Diseases/Dzne, Tübingen, Germany; [2]Neurodegeneration, DZNE Tübingen, Tuebingen, Germany; [3]DZNE, Tuebingen, Germany; [4]MRC-MBU Cambridge, Cambridge, United Kingdom; [5]Lukas Schwarz, Tübingen, Germany; [6]Dept. of Neuroanatomy, Univ. of Freiburg, Freiburg, Germany

Abstract: While mitochondrial dysfunction is emerging as key in Parkinson's disease (PD), a central question remains whether mitochondria are actual disease drivers and boosting mitochondrial biogenesis and function ameliorates pathology. Here, we address these questions using patient-derived induced pluripotent stem cells (iPSCs) and Drosophila models of GBA-related PD (GBA-PD), the most common PD genetic risk. Patient-derived neurons as well as neurons from GBA knockout iPSCs, generated by CRISPR-Cas9 technology, show defects in mitochondrial morphology and function. In addition, patient-derived neurons display a significant increase of endoplasmic reticulum stress responses and changes in NAD+ metabolism. In this respect, recent studies have shown that the activation of pathways related to mitochondrial biogenesis and energy metabolism, such as the NAD+/Sirtuin 1 pathway, provides protection against ageing-related disease. Here, we show that human neurons rely on nicotinamide phosphoribosyltransferase (NAMPT) for maintenance of the basal NAD+ pool, they are responsive to NAD+ precursors and utilize NRK1 as the main metabolic pathway to synthetize NAD+ from NAD+ precursors in a NAMPT independent manner. Increasing intracellular NAD+ concentrations via the NAD+ precursor nicotinamide riboside (NR) significantly ameliorates mitochondrial function in patient neurons. Importantly, NR prevents the age-related dopaminergic neuronal loss and motor decline in fly models of GBA-PD. Our study reveals mitochondrial dysfunction as a key driver of disease and suggests NR as a viable clinical avenue for neuroprotection in PD and other neurodegenerative diseases.

Disclosures: M. Deleidi: None. **D.C. Schöndorf:** None. **D. Ivanyuk:** None. **P. Baden:** None. **A. Sanchez-Martinez:** None. **S. De Cicco:** None. **C. Yu:** None. **L. Schwarz:** None. **G. Di Napoli:** None. **V. Panagiotakopoulou:** None. **S. Nestel:** None. **B. Heimrich:** None. **T. Gasser:** None. **A. Whitworth:** None.

Nanosymposium

628. Parkinson's Disease: Mechanisms and Genetics

Location: SDCC 25

Time: Wednesday, November 7, 2018, 8:00 AM - 9:45 AM

Presentation Number: 628.04

Topic: C.03. Parkinson’s Disease

Title: In silico simulation of parkin cellular pathways: Elucidating mechanisms of Parkinson’s disease

Authors: *J. C. HALL, B. HARDAGE, J. W. RYAN, A. D. LEE, B. BEHROUZ
NeuroInitiative, Jacksonville, FL

Abstract: Mutations in the parkin gene are the greatest genetic risk factors for early onset Parkinson’s disease (PD). Though sporadic, late onset, cases of PD have unknown etiologies, understanding the cellular mechanisms of established genetic contributors, such as parkin, can help investigators find novel converging pathways likely to play a part in sporadic PD. Parkin, an E3 ubiquitin ligase, is recruited to the mitochondria when neurons are stressed, and the enzyme directs protein degradation and mitophagy by “tagging” (ubiquitinating) substrates found in the outer mitochondrial membrane. In addition to regulating mitophagy and ubiquitination, parkin has also been implicated in many other factors involved in mitochondrial homeostasis such as fission and fusion, transport, biogenesis, and overall quality control. Computational and bioinformatic approaches can help us fully understand the numerous pathways involved in parkin signaling. We used computer simulation software (SEED) driven by biological data sources to analyze parkin protein interactions and the downstream effects of altering parkin expression or activity. Our simulation software creates a virtual 3-dimensional cell, where various biochemical entities (proteins, lipids, neurotransmitters, etc.) can move according to Newtonian laws of physics and interact according to biological rules. The data fed into SEED included biochemical entity information extracted from UniProt and ChEBI, expression level data for substantia nigra pars compacta from Allen Brain Institute and Glaab et al. 2015, and biochemical interaction data from the IntAct database and BioGRID. All interaction data was curated by our internal team and supplemented with PubMed literature searches. Specific biological systems examined include mitophagy, intracellular trafficking (such as the endolysosomal pathway), and cellular stress response pathways such as MAPK and mTOR. Our simulation and network analysis mapped out several pathways involved in parkin signaling, highlighting proteins which could hold potential as therapeutic targets for PD.

Disclosures: **B. Hardage:** A. Employment/Salary (full or part-time):; NeuroInitiative. **J.W. Ryan:** A. Employment/Salary (full or part-time):; NeuroInitiative. **A.D. Lee:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroInitiative. **B. Behrouz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroInitiative.

Nanosymposium

628. Parkinson's Disease: Mechanisms and Genetics

Location: SDCC 25

Time: Wednesday, November 7, 2018, 8:00 AM - 9:45 AM

Presentation Number: 628.05

Topic: C.03. Parkinson’s Disease

Support: Ministry of Health and Department of Educational Assistance, University and Research of the Autonomous Province of Bolzano

Title: The small GTPase Rin modulates alpha-synuclein inclusions: Implications for familial and idiopathic Parkinson's disease

Authors: *J. OBERGASTEIGER[1], G. FRAPPORTI[1], C. ÜBERBACHER[1], C. ASCIONE[1], C. CORTI[1], A.-M. CASTONGUAY[2], M. LÉVESQUE[2], M. MORARI[3], A. A. HICKS[1], P. P. PRAMSTALLER[1], M. VOLTA[1]
[1]Inst. For Biomedicine, Eurac Res., Bolzano, Italy; [2]Dept. of psychiatry and neurosciences, Univ. Laval, Canada, Quebec, QC, Canada; [3]Univ. of Ferrara, Ferrara, Italy

Abstract: The etiology of Parkinson´s disease (PD) is still undefined and familial cases provided hints for mechanisms involved in the disease. In particular, alpha-synuclein (aSyn) and leucine-rich repeat kinase 2 (LRRK2) gene alterations lead to autosomal dominant PD with many commonalities to the idiopathic disorder, such as aSyn containing inclusions, which are the neuropathological hallmark of the disease. The mechanisms underlying formation and clearance of aggregates are still unclear, but hypothesized to involve different cellular processes, like autophagy. In addition to the genetic causes, several risk factors have been associated to increased susceptibility to disease by genome-wide association studies. RIT2 is a novel PD risk factor and codes for the protein Rin, which has been scarcely investigated, but plays interesting cellular functions. It is a small GTPase mediating neurite outgrowth through p38 and ERK1/2 MAPK signaling pathways and influencing several cellular processes, including the ones above. Moreover, Rin is enriched in neurons of the rat substantia nigra pars compacta and is reduced in human PD brains. However, investigation of the relevance of Rin-dependent signaling cascades and interactions with PD-causing gene products is currently lacking. We observed that RIT2 mRNA and Rin protein levels are reduced in neuroblastoma cell lines overexpressing WT or mutant LRRK2. 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 pSer129-aSyn positive inclusions. Consistent with previous reports, we found that inclusion-bearing cells also display alterations in the autophagy-lysosomal pathway (ALP), with an accumulation of the autophagosome marker LC3, a reduction in the number of lysosomes and an increase in their size. Importantly, acute overexpression of Rin strongly reduces the burden of aSyn inclusions in these cells, while reducing the number of LC3 puncta, augmenting the number of lysosomes per cell and limiting the increase in diameter. To extend these findings, we turned to mouse primary cortical neuron cultures and induced aSyn aggregation by treatment with synthetic aSyn fibrils. We are currently assessing the consequences of Rin overexpression in this model. Our data suggest that Rin, aSyn and LRRK2 share common cellular mechanisms ultimately impacting aSyn aggregation and indicate a prominent contribution of the ALP. Modulating Rin signaling might constitute an experimental strategy to combat synucleinopathy in both familial and idiopathic neuropathology models.

Disclosures: J. Obergasteiger: None. **G. Frapporti:** None. **C. Überbacher:** None. **C. Ascione:** None. **C. Corti:** None. **A. Castonguay:** None. **M. Lévesque:** None. **M. Morari:** None. **A.A. Hicks:** None. **P.P. Pramstaller:** None. **M. Volta:** None.

Nanosymposium

628. Parkinson's Disease: Mechanisms and Genetics

Location: SDCC 25

Time: Wednesday, November 7, 2018, 8:00 AM - 9:45 AM

Presentation Number: 628.06

Topic: C.03. Parkinson’s Disease

Support: FNR/P13/ 6682797
Horizon2020 692320 CENTRE-PD

Title: Exploration of the modifier role of GBA in patient-derived cellular models of familial Parkinson's disease

Authors: *Z. HANSS[1], I. BOUSSAAD[1], F. MASSART[1], N. CASADEI[2], S. GOLDWURM[3,4], R. KRÜGER[1,5]
[1]Luxembourg Ctr. for Systems Biomedicine, Univ. of Luxembourg, Belvaux, Luxembourg; [2]Inst. of Med. Genet. and Applied Genomics, Univ. of Tübingen, Tübingen, Germany; [3]Dept. of Neurosci., Univ. of Turin, Turin, Italy; [4]Parkinson Institute, IstitutiClinici di Perfezionamento, Milan, Italy; [5]Ctr. Hospitalier de Luxembourg, Luxembourg, Luxembourg

Abstract: Objective: We present here the first phenotyping of patient-derived double-mutant *GBA1-PARK2* cellular models and aim to understand the specific contribution of *GBA* mutation to Parkinson’s disease (PD) relevant phenotypes.
Background: 23 genes have now been identified as being causative for PD. Nevertheless,

patients harbouring the same mutation can present a heterogeneity in penetrance, phenotype and age of onset which could be due to modifying factors influencing disease onset and progression. Mutations in the *GBA1* gene, encoding the glucocerebrosidase (GCase), are an important and common risk factor for familial and sporadic PD. Interestingly, patients carrying *GBA1* mutations are more likely to progress to dementia, develop earlier axial motor symptoms and have a slightly earlier age of onset compared to non-carrier PD patients. Consequently, mutations in *GBA1* may have a modifier effect on PD causal genes and influence the pathophysiology.
Methods: To study the role of GBA on a familial PD background, fibroblasts from a PD patient harbouring a homozygous mutation in the *PARK2* gene and a point mutation in the *GBA1* gene have been reprogrammed into induced pluripotent stem cells (iPSC) and differentiated into small neuronal precursor cells to finally generate midbrain-specific dopaminergic neurons. To explore the specific contribution of *GBA* mutation to different cellular phenotypes, the GCase activity was either rescued pharmacologically or by gene correction using CRISPR Cas9 technology.
Results: Characterisation of the cellular models revealed an impairment in GCase protein level and activity and a loss of Parkin. The patient-derived cells present mitochondrial dysfunction and increased apoptosis under oxidative stress conditions compared to controls. Also an impairment of alpha-synuclein metabolism has been observed in patient's lines.
Conclusion: The strategies used to restore GCase activity in the double-mutant lines rescued the observed phenotypes and therefore give directions to novel neuroprotective treatment approaches acting on modifiers.

Disclosures: Z. Hanss: A. Employment/Salary (full or part-time):; University of Luxembourg. **I. Boussaad:** None. **F. Massart:** None. **N. Casadei:** None. **S. Goldwurm:** None. **R. Krüger:** None.

Nanosymposium

628. Parkinson's Disease: Mechanisms and Genetics

Location: SDCC 25

Time: Wednesday, November 7, 2018, 8:00 AM - 9:45 AM

Presentation Number: 628.07

Topic: C.03. Parkinson's Disease

Support: FNR/P13/6682797
NCER13/BM/11264123
Horizon2020 CENTRE PD/692320

Title: Impaired autophagic clearance in patient-derived dopaminergic neurons carrying a Parkinson's disease-linked mutation in VPS35

Authors: *S. LARSEN[1], P. A. BARBUTI[1], I. BOUSSAAD[1], P. ANTONY[1], G. D. MELLICK[2], R. KRÜGER[1,3]

[1]Luxembourg Ctr. for Systems Biomedicine, Belvaux, Luxembourg; [2]Griffith Inst. for Drug Discovery, Nathan, Australia; [3]Ctr. Hospitalier de Luxembourg, Luxembourg, Luxembourg

Abstract: Objective: To study the molecular mechanisms underlying neurodeneration in Parkinson's disease (PD) related to a mutation in *VPS35* and its relation to relevant neuronal phenotypes.
Background: *VPS35* gene has been linked to PD, as point mutations in this gene cause an autosomal-dominant form of PD, clinically resembling the sporadic disease. Vps35 is part of the retromer complex and is responsible for the trafficking and sorting of various proteins in the endosomal pathway, including proteins implicated in autophagy and lysosomal processes. Consequently, we hypothesise that a mutation in *VPS35* will lead to an autophagic clearance impairment.
Methods: Fibroblasts from a patient carrying a heterozygous PD-linked point mutation in *VPS35* and from unaffected age- and gender-matched controls were reprogrammed into induced pluripotent stem cells (iPSC). These iPSCs were differentiated into neuronal precursor cells (NPC) and further differentiated into midbrain-specific dopaminergic neurons (mDAN). To define the specific contribution of the point mutation in *VPS35* to the pathophysiology, isogenic lines will be generated using CrispR-Cas9 technology.
Results: Three cellular models (iPSCs, NPCs and mDAN) have successfully been generated from patient's fibroblasts. Their characterization confirmed the suitability and specificity of these models for studying PD-relevant cellular phenotypes *in vitro*. Functional characterization revealed a decrease of the autophagic flux in the patient line compared to the control lines. Furthermore, the heterozygous PD-linked point mutation in *VPS35* leads to an accumulation of alpha-synuclein and an impairment of the mitochondria.
Conclusion: Functional characterization of the PD-causing mutation in VPS35 indicate impaired cellular clearance mechanisms as a potential converging point of different PD-related mutations. Future studies will focus on complementation and rescue of these cellular phenotypes by genetic and pharmacological modification.

Disclosures: S. Larsen: None. **P.A. Barbuti:** None. **I. Boussaad:** None. **P. Antony:** None. **G.D. Mellick:** None. **R. Krüger:** None.

Nanosymposium

629. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Neurodegeneration

Location: SDCC 24

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 629.01

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: RO1NS079637

RO1NS097722
F31NS092202

Title: Time-course of neuropathological events in hyperhomocysteinemic amyloid depositing mice

Authors: D. HAWTHORNE[1], *E. M. WEEKMAN[2,1], T. L. SUDDUTH[1], B. R. PRICE[1], A. WOOLUMS[1], D. M. WILCOCK[1]
[1]Physiol., Univ. of Kentucky, Lexington, KY; [2]Lexington, KY

Abstract: Vascular contributions to cognitive impairment and dementia (VCID) are increasingly recognized as a significant cause of dementia, behind only Alzheimer's disease (AD). Furthermore, VCID co-morbid with AD is extremely common, estimated to occur in at least 60% of AD cases. While the contribution of VCID to clinical dementia is increasingly recognized, the mechanistic underpinnings of VCID has been lacking, in part due to a lack of relevant animal models.
We have previously shown that induction of hyperhomocysteinemia (HHcy) via a diet deficient in folate, vitamins B6 and B12, and enriched in methionine produces a mouse model of VCID and a co-morbidity model when induced in APP/PS1 mice. While the pathological characteristics of HHcy have been identified, the time course for these changes and the corresponding cognitive decline is unclear. In this study, we examined neuroinflammation, microhemorrhages, amyloid deposition, and cognition along a time course of 2, 4, 6, 10, 14 and 18 weeks on diet in our co-morbidity model.
Immunohistochemistry for CD11b, which stains both resting and activated microglia, showed an increase in staining starting at 6 weeks on the HHcy diet. Further characterization of the neuroinflammatory response revealed an increase in the pro-inflammatory markers IL-1β, TNFα, IL-6 and IL-12a starting at 6 weeks in the APP/PS1 mice on the HHcy diet. Cognition was tested using the two-day radial arm water maze. Significant cognitive decline began at 10 weeks on the HHcy diet. Prussian blue staining and magnetic resonance imaging revealed a significant increase in microhemorrhages starting at 14 weeks on the HHcy diet. Finally, induction of HHcy in the APP/PS1 mice resulted in redistribution of amyloid from the parenchyma to the vasculature starting at 14 weeks on diet.
Overall, induction of HHcy in APP/PS1 mice leads to first neuroinflammation, followed by cognitive decline, and finally, microhemorrhages and redistribution of amyloid to the vasculature. Taken together, this data suggests that neuroinflammation is an initiator in HHcy mediated VCID and provides a possible target for therapeutics.

Disclosures: D. Hawthorne: None. **E.M. Weekman:** None. **T.L. Sudduth:** None. **B.R. Price:** None. **A. Woolums:** None. **D.M. Wilcock:** None.

Nanosymposium

629. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Neurodegeneration

Location: SDCC 24

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 629.02

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Joseph Drown Foundation

Title: Aberrant resident memory CD8 T cells mediate pathological neurodegeneration and age-related cognitive decline

Authors: *C. J. WHEELER[1], A. PANWAR[1], A. RENTSENDORJ[1], M. JHUN[1], R. CORDNER[1,2], N. YEAGER[2], R. PECHNICK[3], G. DUVALL[1], A. MARDIROS[1,4], D. GOLCHIAN[1], H. SCHUBLOOM[1], L.-W. JIN[5], Y. KORONYO[1], M. KORONYO-HAMAOUI[1,2], K. L. BLACK[1], R. COHEN[6]
[1]Dept. of Neurosurg., [2]Dept. of Biomed. Sci., Cedars-Sinai Med. Ctr., Los Angeles, CA; [3]Dept. of Psychopharmacology & Behavioral Sci., Western Univ. Med. Sch., Pomona, CA; [4]Dept. of Hematology, City of Hope Med. Ctr., Duarte, CA; [5]Dept. of Med. Pathology and Lab. Med., M.I.N.D. Institute, Univ. of California Davis, Davis, CA; [6]Dept. of Psychiatry & Behavioral Sci. and Neurosci. Program, GDBBS, Emory Univ., Atlanta, GA

Abstract: Aging contributes to multiple disorders, but specific age-related factors responsible for discrete pathologies remain unclear. This is particularly true of sporadic neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's (PD), whose causes apart from aging itself remain mysterious. T cell dysfunction could contribute to inflammation and degeneration in many age-related tissue disorders. Indeed, homeostatic CD8 T cell expansion is among the earliest properties of human aging, inducing phenotypic and functional changes by middle age, and altering tissue resident memory T (T_{RM}) subpopulations. The impact of this process has been difficult to assess, however, because in experimental rodents its incidence and impact is low. To bypass these limitations, we injected CD8 T cells into thymus-deficient (nude) mice, which promoted rapid homeostatic expansion of aberrant $CD103^+$ resident memory CD8 T cells ($^{hi}T_{RM}$) indistinguishable from CD8 T cells expanded in affected aged animals. A subset of antigen-reactive $^{hi}T_{RM}$ were selectively increased in brain, and their presence surprisingly conferred neurodegenerative pathology on recipients. This neuropathology, which was dependent on both lytic (Perforin1) and pro-inflammatory (IFNγ) activity in donor T cells, included induction of Amyloid Precursor Protein (APP) cleavage products and diffuse amyloid plaque accumulation in brain, fibrillary inclusions in neurons, neuroinflammation, and cognitive impairment with age, with loss of neurons, synaptic markers and brain mass. CD103 deficiency also reduced CD8 in brain, and inhibited age-related cognitive decline in immunosufficient mice. Conversely,

injection of $^{hi}T_{RM}$ into wild-type mice induced neuronal loss, and synergized with brain injury to cause amyloidosis and increase tauopathy. Finally, antigen-specific aberrant CD8 T cells were altered both in blood of cognitively impaired patients, and within AD brain, suggesting unique relevance to human neurodegeneration. Our findings have important implications for the involvement of CD8 T cell dysfunction in age-related tissue pathology, and for the initiation and treatment of sporadic neurodegenerative disorders.

Disclosures: C.J. Wheeler: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intellectual property rights/patent holder. **A. Panwar:** None. **A. Rentsendorj:** None. **M. Jhun:** None. **R. Cordner:** None. **N. Yeager:** None. **R. Pechnick:** None. **G. Duvall:** None. **A. Mardiros:** None. **D. Golchian:** None. **H. Schubloom:** None. **L. Jin:** None. **Y. Koronyo:** None. **M. Koronyo-Hamaoui:** None. **K.L. Black:** None. **R. Cohen:** None.

Nanosymposium

629. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Neurodegeneration

Location: SDCC 24

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 629.03

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NIA R01 AG056478
NIH/NIA R01 AG055865
The BrightFocus Foundation Award
The National Center for Advancing Translational Sciences through CTSI Grant UL1TR000124
The Coins for Alzheimer's Research Trust (C.A.R.T) Fund
The Saban Family Foundation
The Maurice Marciano Family Foundation

Title: The bright side of osteopontin/SPP1 in Alzheimer's disease: Immunomodulation, Aβ clearance, and synaptic preservation

Authors: *M. KORONYO-HAMAOUI[1,2], Y. KORONYO[1], J. SHEYN[1], D.-T. FUCHS[1], S. LI[3], K. L. BLACK[1], A. RENTSENDORJ[1]
[1]Dept. of Neurosurgery, Maxine Dunitz Neurosurgical Res. Inst., [2]Dept. of Biomed. Sci., Cedars-Sinai Med. Ctr., Los Angeles, CA; [3]The Inst. of Life Sci., Wenzhou Uinversity, Zhejiang, China

Abstract: Background: Osteopontin (OPN, SPP1) is a secreted glycosylated phosphoprotein involved in cell migration, immune response, cell survival, and homeostasis after brain damage. Previously, we demonstrated that immunomodulation approaches in animal models of

Alzheimer's disease (AD) increased cerebral SPP1/OPN expression in myelomonocytes surrounding Aβ plaques along with substantial attenuation of neuropathology and cognitive deficit. However, other studies suggested that SPP1/OPN is a biomarker of disease-associated or plaque-associated microglial phenotype. **Methods:** To determine the role of SPP1/OPN in disease progression and possible protection, we investigated its expression pattern in brains and retinae from MCI and AD patients. We further analyzed OPN in brains of glatiramer acetate (GA)-immunized versus PBS-control $APP_{SWE}/PS1_{dE9}$ transgenic (ADtg) mice and its relationship with biomarkers of disease severity, immune response, and synaptic integrity. We then explored possible mechanisms of action in primary macrophage cultures, including effects of SPP1/OPN inhibition, knockout, and gain-of-function on macrophage phenotype. **Results**: We found that reduced amyloid Aβ-plaque, soluble $Aβ_{40}$ and $Aβ_{42}$ levels, and vascular Aβ burden in the entorhinal cortex, cingulate cortex, and hippocampus following immunomodulation in ADtg mice was associated with a substantial upregulation of cerebral SPP1/OPN surrounding plaques. Treatment combining GA and peripheral blood enrichment of $CD115^+$ monocytes further increased OPN levels in innate immune cells at plaque sites. SPP1/OPN-expressing infiltrating macrophages were directly involved in phagocytosis of Aβ plaques. Strong linear correlations between osteopontin and macrophage infiltration as well as tight inverse relations between osteopontin and Aβ-plaque burden were revealed. Correlations were also discovered between SPP1/OPN and astrogliosis, synaptic density, and cognitive status. In vitro studies demonstrated that GA directly upregulates osteopontin expression in bone marrow-derived macrophages and promotes a highly phagocytic, anti-inflammatory, and pro-healing phenotype. This was reversed upon OPN siRNA inhibition and genetic KO while restored with supplementation of OPN. Finally, OPN was identified in myelomonocytes surrounding Aβ plaques and tightly predicted Aβ burden in human AD brains and retinae. **Conclusions**: We identified SPP1/OPN expression in innate immune cells at amyloid plaque lesion sites in brains and retinae of AD patients and demonstrated its novel protective role in animal AD models. Hence, SPP1/OPN may be a promising therapeutic target for AD.

Disclosures: M. Koronyo-Hamaoui: None. **Y. Koronyo:** None. **J. Sheyn:** None. **D. Fuchs:** None. **S. Li:** None. **K.L. Black:** None. **A. Rentsendorj:** None.

Nanosymposium

629. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Neurodegeneration

Location: SDCC 24

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 629.04

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Truchard Donation
Mary Easton Alzheimer Center

BX003485

Title: A novel mixed model of dementia using an Alzheimer rat transgenic model with hypertension

Authors: *S. A. FRAUTSCHY[1], C. ZHU[1], M. R. JONES[1], S. HU[1], X. ZUO[1], C. OKUMA[1], P. DENVER[1], P. KIM[1], E. KO[1], D. CASTRO[1], H. V. VINTERS[1], R. M. COHEN[2], G. M. COLE[1]
[1]Neurol., UCLA and VA, Los Angeles, CA; [2]Psychiatry, Emory, Atlanta, GA, CA

Abstract: Late onset dementia cases with Alzheimer (AD) pathology commonly include some vascular pathology or small vessel disease (SVD). Since other pathologies may lower efficacy of therapeutics directly targeting AD pathology, models that recapitulate mixed dementia are needed. Because stroke prone spontaneously hypertensive rats (SHR-SP) have polygenic risk for SVD, we crossed the TgF344-AD rats, that develop age-dependent cognitive deficits and Abeta and tau pathology, onto the SHR-SP line. Preliminary analysis of F2 Tg rats from the resultant cross (75% SHR-SP background) aged to 18-20 months displayed high (160 mm Hg) systolic BP similar to SHR-SP, compared with other groups (120-30 mm Hg). In the hippocampus, relative to the SHR-SP and WKY groups, the cross showed robustly elevated GFAP, soluble and insoluble ptau and Aquaporin 4 relative, compared to moderate elevations in the TgF344-AD rats (by Western and ICC). Myelin basic protein was reduced in F344-AD and AD+ SHR-SP hippocampus. ICC revealed evidence of SVD and limited BBB breakdown along with significantly elevated hippocampal microgliosis (Iba-1), Aquaporin-4 (AQP4). Compared to TgF344-AD rats, the cross showed more Ptau (ps422 and CP13) accumulation. The plaques in the cross were more diffuse as compared to the more neuritic and coarse plaques in the TgF344-AD. OxPhos blots showed complex I deficits in the FAD+ groups and additional mitochondrial deficits in the cross. Westerns of entorhinal cortex revealed also revealed that the cross showed the highest levels of GFAP and caspase-cleaved actin. Finally the cross showed albumin and rat IgG leakage in the neuropil indicative of some small vessel damage. Overall, these results support amplification synergism between hypertension and FAD leading to increases in neuroinflammation, tau, vascular and metabolic pathology. The development of this mixed dementia model will permit testing pleiotropic treatments directed at both the AD and hypertension present in at least 30% of late onset dementia cases.

Disclosures: S.A. Frautschy: None. **C. Zhu:** None. **M.R. Jones:** None. **S. Hu:** None. **X. Zuo:** None. **C. Okuma:** None. **P. Denver:** None. **P. Kim:** None. **E. Ko:** None. **D. Castro:** None. **H.V. Vinters:** None. **R.M. Cohen:** None. **G.M. Cole:** None.

Nanosymposium

629. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Neurodegeneration

Location: SDCC 24

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 629.05

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)
International Union of Biochemistry and Molecular Biology (IUBMB)
International Society for Neurochemistry (ISN)
Promoting Research Opportunities for Latin American Biochemists (PROLAB) grant
Diabetes Canada
Canadian Institutes for Health Research (CIHR)

Title: Tau pathology-induced insulin resistance in animal models of Alzheimer`s disease

Authors: *R. A. GONÇALVES[1,3,4], N. WIJESEKARA[4], S. E. BOEHNKE[3], N. M. LYRA E SILVA[2,3], S. T. FERREIRA[2], D. P. MUNOZ[3], P. E. FRASER[4], F. G. DE FELICE[2,3]
[1]Federal Univ. of Rio De Janeiro, Rio De Janeiro, Brazil; [2]Federal Univ. of Rio De Janeiro, Rio DE Janeiro, Brazil; [3]Ctr. for Neurosci. Studies, Queens Univ., Kingston, ON, Canada; [4]Tanz Ctr. for Res. in Neurodegenerative Diseases, Univ. of Toronto, Krembil Discovery Tower, Toronto, ON, Canada

Abstract: Alzheimer's disease (AD) is historically recognized as a disorder of memory but the neuropathological spectrum of AD is complex and patients present other alterations such as impaired peripheral glucose homeostasis. Microtubule associated protein tau assists in polymerizing and stabilizing microtubules and tau pathophysiology has been implicated in AD. Tau protein is expressed in the central nervous system and abnormally phosphorylated tau, a prominent hallmark of Alzheimer's pathology in the brain, is also found in pancreatic tissues of type 2 diabetes (T2D) patients. These findings raise the possibility that tau pathology is related to metabolic dysfunction in T2D and AD. However, the effects of tau pathophysiology on peripheral metabolic regulation have been poorly investigated. In the present study, we evaluate metabolic parameters of a global tau knockout mouse model generated by the insertion of a neomycin cassette on exon 1 of the tau gene. Glucose and insulin tolerance tests were performed, and fasting plasma insulin and leptin levels were measured using ELISA. Our findings demonstrate that at early ages (4-5 months), systemic tau deletion leads to glucose intolerance, hiperleptinemia and increased body weight. We also observed elevated proinsulin levels and impaired glucose-stimulated insulin secretion, which indicates beta cell dysfunction. At later age (1 year) TauKO mice becomes insulin resistant. These results suggest tau protein may play a role in whole body glucose homeostasis and also suggest that previously unrecognized functions of

tau may be a complicating factor when using animal models of TauKO background. Moreover, we detected increased and decreased ThioS and insulin staining, respectively, in pancreatic tissues from a Non-human primate model of AD that presents glucose intolerance in the GTT and markers of inflammation in the hypothalamus. Our results suggest tau pathophysiology might mediate metabolic alterations observed in AD and that hypothalamic inflammation may have a role in these events. Understanding the link between tau pathophysiology and metabolic alterations is of great importance to establishing the complete contribution of tau protein to AD pathogenesis.

Disclosures: R.A. Gonçalves: None. **N. Wijesekara:** None. **S.E. Boehnke:** None. **N.M. Lyra e Silva:** None. **S.T. Ferreira:** None. **D.P. Munoz:** None. **P.E. Fraser:** None. **F.G. De Felice:** None.

Nanosymposium

629. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Neurodegeneration

Location: SDCC 24

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 629.06

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: State of California Department of Public Health Alzheimer's Disease Program (RFA #16-10054, QLM)
VA MERIT (BX000542, GMC)
NIH RO1 (AT008916, GMC)
NIH RO1 (AG13471, GMC)
NIH R21 (AG050269, SAF)
R01 AG040770 (LGA)
K02 AG048240 (LGA)

Title: Neuronal pentraxins: Synaptic-derived plasma biomarkers in Alzheimer's disease

Authors: *Q.-L. MA[1], E. TENG[1], X. ZUO[1], M. JONES[1], B. TETER[1], E. Y. ZHAO[1], C. ZHU[1], F. RELAMPAGOS[1], T. BILOUSOVAD[1], K. H. GYLYS[1], L. G. APOSTOLOVAE[1,2], M. J. LADU[3], M. A. HOSSAING[4], S. A. FRAUTSCHY[1], G. COLE[1]
[1]UCLA, Los Angeles, CA; [2]Indiana Univ. Sch. of Med., Indianapolis, IN; [3]Univ. of Illinois at Chicago, Chicago, IL, USA, Chicago, IL; [4]The Johns Hopkins Univ. Sch. of Medicine,, Baltimore, MD

Abstract: Synaptic deficits are central to Alzheimer disease (AD) pathogenesis and driven by soluble beta-amyloid (Abeta) oligomers, tauopathy and metabolic deficits that correlate closely with cognitive decline. Apolipoprotein ε4 (APOE4), the most common genetic risk factor for

sporadic AD, accelerates both Abeta and tau pathology contributing to dysregulation of glutamate receptor function and synaptic plasticity as well as inflammation. Despite progress in identifying CSF biomarkers, synaptic-related plasma biomarkers are poorly explored, particularly surrogate biomarkers that could be use to monitor drug efficacy. Therefore, we evaluated the neuronal pentraxin family of potential CNS-derived plasma biomarkers (NPTX1, NPTX2 and their receptor NPTXR), all related to synaptic pathology. It has been reported that NPTX2 (NP2) knockout mice display an exaggerated microglia/macrophage activation following nerve injury compared with wild type mice, suggesting NP2, and perhaps other neuronal pentraxins, might also participate in regulating CNS innate immunity. NPTX1 (NP1) is preferentially expressed in brain and involved in glutamate receptor internalization. NP1 is secreted pre-synaptically, reported induced by Abeta oligomers via GSK3beta activation, and implicated in excitatory synaptic and mitochondrial deficits. Relative to normal elderly, plasma NP1 by ELISA was elevated in patients with mild cognitive impairment (MCI) and elevated further in the subset who progressed to early stage AD. In those patients, there was a trend towards increased NP1 levels in APOE4 carriers relative to non-carriers. In AD model E3- and E4FAD mice, NP1 and its fragments and NPTXR fragments were increased in brain and plasma of 7-8 month-old E4FAD mice relative to E3FAD mice, and within mouse, blood and brain levels were correlated. Plasma NP1 was higher in E4FAD+ (APOE4+/+/FAD+/−) relative to E4FAD- (non-carrier; APOE4+/+/FAD−/−) mice, consistent with NP1 response to Abeta. Brain and plasma NP1 and NPTXR fragments were reduced by dietary n-3 fatty acid DHA supplementation in E4FAD mice accompanied by improved cognitive (MWM) deficits. NP2 is reduced in AD and E4FAD mice, but is less specifically CNS-derived. These findings indicate that plasma neuronal pentraxins may identify and track early synaptic deficits in MCI and early-stage AD. This suggests that these pentraxins may provide surrogate biomarker potential for blood biomarkers relevant to synaptic deficits, the closest pathological correlate of cognitive decline.

Disclosures: Q. Ma: None. **E. Teng:** None. **X. Zuo:** None. **M. Jones:** None. **B. Teter:** None. **E.Y. Zhao:** None. **C. Zhu:** None. **F. Relampagos:** None. **T. Bilousovad:** None. **K.H. Gylys:** None. **L.G. Apostolovae:** None. **M.J. LaDu:** None. **M.A. Hossaing:** None. **S.A. Frautschy:** None. **G. Cole:** None.

Nanosymposium

629. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Neurodegeneration

Location: SDCC 24

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 629.07

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIA P01AG012411

NCRR P20RR020146
Roy and Christine Sturgis Charitable and Educational Trust

Title: The Alzheimer amyloid-β protein impairs peripheral glucose tolerance via corticosteroid perturbation

Authors: R. D. HENDRIX[1], A. K. ODLE[2], G. V. CHILDS[3], *S. W. BARGER[4,5]
[1]Dept. of Neurobio. & Developmental Sci., [2]Neurobio. & Developmental Sci., [3]Neurobio. and Developmental Sci., [4]Dept Geriatrics, Univ. of Arkansas for Med. Sci., Little Rock, AR; [5]Geriatric Research, Educ. and Clin. Ctr., Central Arkansas Veterans Healthcare Syst., Little Rock, AR

Abstract: Alzheimer's disease (AD) and type-2 diabetes mellitus (T2DM) show significant links in comorbidity and some functional deficits, such as impaired glucose tolerance, dementia, and reduced cerebral metabolic rate of glucose (CMRglc). It is not clear if insulin resistance associated with T2DM promotes AD pathogenesis or instead that amyloid β-peptide (Aβ) or other pathogens in AD impair glucose utilization. We have previously documented impacts of the Aβ precursor (APP) on peripheral metabolism. To test the hypothesis that Aβ itself can lead to glucose intolerance, we employed the BRI-Aβ42 mouse; this line expresses human $A\beta_{1\text{-}42}$ in the CNS without overexpressing APP. Because the hypothalamus is a key metabolic control center, we analyzed gene expression for peptides in the melanocortin system that control feeding and energy expenditure, parameters which were directly measured in whole-animal calorimetry cages. The role of glucocorticoids in altered blood glucose was also assessed by targeting the hypothalamic-pituitary-adrenal (HPA) axis through adrenalectomy. Finally, we assessed BRI-Aβ42 mice ablated of APP. Our data are consistent with the hypothesis that human $A\beta_{1\text{-}42}$ impairs glycemic control. However, it does so independently of APP, differences in peripheral insulin production or resistance, obesity, altered melanocortin outputs, or fasting hyperglycemia. Aβ-transgenic mice had elevated corticosterone levels, and adrenalectomy ameliorated the glycemic phenotype, suggesting that the HPA axis contributes to this peripheral pathology. Aβ expression was associated with lower CMRglc and lower brain levels of insulin receptor substrate-1, suggesting the possibility of CNS-specific insulin resistance. These findings indicate that Aβ accumulation in the CNS is sufficient, even in the absence of APP, to perturb peripheral endocrinology and blood glucose levels in a manner that at least partially depends upon corticosteroid elevation. The extent to which this depends upon altered function of insulin or insulin-like growth factors in the Aβ-affected brain is being explored.

Disclosures: R.D. Hendrix: None. **A.K. Odle:** None. **G.V. Childs:** None. **S.W. Barger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Royalties from Millipore-Sigma.

Nanosymposium

629. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Neurodegeneration

Location: SDCC 24

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 629.08

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: TDP43promotesneurodegenerationby impairing theneurovascular unit

Authors: *M.-L. B. SELENICA
Col. of Pharmacy, Byrd Alzheimer Institute, USF, Tampa, FL

Abstract: Aging is also accompanied by low-grade systemic inflammation, termed "inflammaging." To determine the role of low-grade systemic inflammation in the progression of neuronal TDP43 pathology, mice were given intracranial AAV injections in the frontal cortex to overexpress TDP43 in corticospinal neurons and groups were subjected to an intraperitoneal LPS administration challenge to simulate low-grade systemic inflammation. Our study reveals a novel role of elevated corticospinal neuronal TDP43 in neurovascular unit impairment, an effect that during systemic inflammation, may precipitate neuronal loss and synaptic dysfunction through peripheral blood cell infiltration. These results, along with other reports, shed light on the significance of neurovascular unit function during neurodegenerative disease and highlight its importance as a therapeutic target.

Disclosures: M.B. Selenica: None.

Nanosymposium

629. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Neurodegeneration

Location: SDCC 24

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 629.09

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01AG055770
R01AG054434

Title: ApoE4 aggregation and hypolipidation is implicated in Alzheimer's disease pathology in cellular, animal and human studies

Authors: V. RAWAT[1], O. LIRAZ[2], J. JOHANSSON[3], H. CHUI[1], M. G. HARRINGTON[4], D. M. MICHAELSON[5], *H. N. YASSINE[1]
[1]USC, Los Angeles, CA; [2]Tel Aviv Univ., Tel Aviv, Israel; [3]Resverlogix Corp, San Ramon, CA; [4]Huntington Med. Res. Inst., Pasadena, CA; [5]Tel-Aviv Univ., Tel-Aviv, Israel

Abstract: Aim: ApoE4 is the strongest genetic risk factor for late-onset Alzheimer's disease (AD) risk, but the critical mechanisms of how ApoE4 increases AD risk are not clear. In the brain, ApoE is lipidated by ABCA1 to form ApoE HDL particles. In AD animal models, ApoE4 is hypolipidated. Overexpressing ABCA1 or removing poorly lipidated ApoE4 from the brain prevents brain amyloid accumulation. The goal of this study is to understand the mechanisms of hypolipidated brain ApoE4 particles.
Methods: We used cell cultures, human apoE4 (hApoE4) targeted replacement mice, and cerebrospinal fluid from humans grouped by APOE genotype to study ABCA1 - ApoE4 interactions. Results: Treatment of ABCA1 expressing cells with recombinant ApoE4 increased the percentage of ApoE4 and ABCA1 in aggregates and decreased ABCA1 expression and activity in vitro by favoring ABCA1 trafficking into late endosomes destined for lysosomal degradation. In vivo, hippocampal homogenates from 4 months-old male and female hApoE4 mice had significantly more aggregated ApoE and ABCA1 proteins compared with hippocampal homogenates from hApoE3 mice. ApoE - ABCA1 aggregation was associated with hypolipidated ApoE4. Treatment with the ABCA1 agonist CS6253 in vivo and in vitro decreased ApoE4 hypolipidation and the percentage of aggregated ABCA-1 and ApoE4 particles. Concomitantly, treatment with CS6253 reversed AD phenotype in hApoE4 mice with lowering of intraneuronal Aβ and P-tau, glutaminergic, presynaptic-vesicle proteins VGlut1 and VGAT and cognitive decline as assessed by Morris-water-test and novel-object-recognition (all $p<0.05$). In humans, CSF ApoE was resolved in four distinct bands by electrophoresis α0 (>669 KDa), α1 (600 KDa), α2 (440 KDa) and α3 (232-140 KDa, hypolipidated). Amount of total ApoE present in α0 size was reduced in ε4/ε4 vs ε3/ε3 individuals (3.208 % (SD 0.6156; n=3) vs 8.904 (SD 0.6156 %; n=29), $p<0.05$), whereas total ApoE in α2 size (hypolipidated) was increased in ε4/ε4 vs ε3/ε3 individuals (60.68 % (SD 8.207; n=3) vs 37.34 % (SD 16.80; n=31), $p<0.05$). This shift to smaller apoE particles was associated with decreased ABCA-1 activity of CSF of ε4/ε4 carriers.Conclusions: Increased aggregation of ApoE4 particles associate with ABCA1 aggregation and lysosomal degradation. Enhancing brain ABCA1 activity decreases ApoE4 hypolipidation and aggregation and reverses AD phenotype. Strategies to enhance brain ABCA1 activity hold promise in the prevention of ApoE4-driven AD.

Disclosures: V. Rawat: None. **O. Liraz:** None. **J. Johansson:** A. Employment/Salary (full or part-time):; Artery Therapeutics. **H. Chui:** None. **M.G. Harrington:** None. **D.M. Michaelson:** None. **H.N. Yassine:** None.

Nanosymposium

629. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Neurodegeneration

Location: SDCC 24

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 629.10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NIA R21AG055024 (BT)
NCCIH RO1 AT006816 (GMC, SAF)
Easton Drug Discovery Foundation (GMC, SAF)
VA Merit BX000542 (GMC)
NIH/NIA P01AG030128 (MJL)
NIH/NIA R21AG048498 (MJL)

Title: ApolipoproteinE isotype-dependent modulation of microRNA-146a transcription

Authors: *B. TETER[1], A. VERDUZCO[3], M. LADU[4], P. M. SULLIVAN[5], S. A. FRAUTSCHY[2], G. M. COLE[2]
[1]Dept. Neurol. (UCLA) and GRECC (VA), [2]Dept. Neurology, Med. (UCLA) and GRECC (VA), Univ. Calif. Los Angeles, Veterans Admin. GLAHS, Los Angeles, CA; [3]UCLA, Scripps Res. Inst., Los Angeles, CA; [4]Anat. and Cell Biol., Univ. of Illinois, Chicago, Chicago, IL; [5]Med. (Geriatrics)(Duke), GRECC (VA),, Duke University, Durham Veterans Affairs Med. Ctr., Durham, NC

Abstract: The apolipoprotein E (apoE) isotype apoE4 is a prevalent genetic risk factor for Alzheimer's disease (AD) that can modulate systemic and central inflammation, independent of amyloid accumulation. Although disruption of innate immune toll-like receptor (TLR) signaling is modulated by apoE isotype and observed in AD, these ApoE isotype specific effects remain poorly understood. Therefore, we examined the effect of apoE isotype on brain levels of major regulators of TLR signaling including miR146a, a microRNA enriched in the brain. We used 6 month old apoE3 or apoE4 targeted replacement mice with and without mutant familial AD (FAD) transgenes. ApoE4 reduced levels of miR146a compared to apoE3, both in the brain (29%; $p < 0.0001$) and plasma (47%; $p < 0.05$), which correlated with each other ($r2=0.74$; $p < 0.05$). The presence of 5xFAD transgenes increased brain miR146a in both apoE3 (E3FAD) and apoE4 (E4FAD) mice; however, miR146a levels in E4FAD mice remained lower than in E3FAD mice (62%; $p < 0.05$), despite increased amyloid and inflammation. Supporting these observations, apoE4 brains showed increased expression of interleukin receptor associated kinase-1, IRAK1 (160%; $p < 0.05$) (normally downregulated by miR146) that inversely correlated with miR146a levels ($r2=0.637$; $p < 0.0001$). Reduced negative feedback of TLR signaling (by miRNA146a) can explain early-life hypersensitivity to innate immune stimuli

(including Aβ) in apoE4 carriers. Thus, apoE4 causes early dysregulation of a central controller of the innate immune system both centrally and systemically. This defect persists with FAD pathology and may be relevant to ApoE4 AD risk. The mechanism of the apoE4 effect on miR146a was examined at the level of miR146a gene promoter regulation. The PU.1 transcription factor is known to regulate the miR146a gene, but its mRNA was not significantly changed by apoE genotype. Further studies examine the association with acetylated histone H3 at the miR146a gene promoter as a potential apoE-modulated regulator of promoter activity and activation, and the effect of exercise. ApoE isotype effects on immune function involving miR146a control of TLR signaling is a candidate nexus of interaction with factors including exercise, age and Aß pathology.

Disclosures: B. Teter: None. **A. Verduzco:** None. **M. LaDu:** None. **P.M. Sullivan:** None. **S.A. Frautschy:** None. **G.M. Cole:** None.

Nanosymposium

629. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Neurodegeneration

Location: SDCC 24

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 629.11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Identification and functional significance of tau citrullination in models of tauopathies

Authors: D. LEE[1], Z. QUADRI[1], A. KOVALENKO[1], C. MA[1], M. WATLER[1], J. CALAHATIAN[1], L. SANDUSKY-BELTRAN[3], J. B. HUNT[1], *L. B. SHELTON[2], M.-L. B. SELENICA[1]
[1]Pharmaceut. Sci., [2]Mol. Med., Univ. of South Florida, Tampa, FL; [3]Neurosci., New York Univ., New York, NY

Abstract: Key words: tau, citrullination, inflammation, Alzheimer's disease
The number of tauopathies continues to increase and impact neuronal health. Despite worldwide efforts, ***no*** disease modifying agents exist on the market for ***any*** of the tauopathies. Strategies aimed at reducing disordered or aggregation-prone proteins include increasing degradation/ clearance, decreasing kinases that modify tau metabolism, inhibiting aggregation, modulating inflammation, altering post-translational modification, among others. Tau deposition elicits numerous clinical, phenotypic, and pathological outcomes, which likely stems from post-translational modifications that alter structure and function. Our groups recently uncovered a novel posttranslational modification of tau, named *citrullination*, caused by the enzyme peptidylarginine deiminase (PADs). PAD induce citrullination irreversibly converts arginine residues within proteins/ peptides to citrulline. Structurally, this conversion permanently alters the target by producing loss of positive charges, changes in protein stability and adding a 0.98

Dalton increase in mass. We identified several findings that suggest that: 1) Tau can become citrullinated at 13 out 14 arginine residues; 2) tau citrullination prevents fibrillization but may increases oligomers; 3) novel tau-cit antibodies show various tau deposition profiles in mice with tauopathies. Our central hypothesis states that PAD4 expression/ activity impacts tau aggregation, oligomerization, and metabolism. We will determine the extent of tau neuropathology and behavior following manipulations that alter tau citrullination. We will measure various components of the tau phenotype in transgenic mice. These studies are designed to provide new evidence for tau citrullination and the role of PAD4 during tauopathies. It will establish a new area of investigation regarding the function of citrullination that may potentially lead to new therapeutic targets against tauopathies.

Disclosures: D. Lee: None. **Z. Quadri:** None. **A. Kovalenko:** None. **C. Ma:** None. **M. Watler:** None. **J. Calahatian:** None. **L. Sandusky-Beltran:** None. **J.B. Hunt:** None. **L.B. Shelton:** None. **M.B. Selenica:** None.

Nanosymposium

630. The Chemical Senses : Dynamics and Plasticity of Olfactory and Gustatory Coding

Location: SDCC 23

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 630.01

Topic: D.05. Olfaction and Taste

Support: NIH grant R56DC015584
ISF grant 816/14
Marie Curie Career Integration grant 334341

Title: Active sampling optimizes processing of changes in odor concentration

Authors: *R. SHUSTERMAN[1,2]
[1]Univ. of Oregon, Eugene, OR; [2]Univ. of Haifa, Haifa, Israel

Abstract: We actively shape our sensory input by our sampling behavior. Further, we adjust our sampling behavior to *optimally* sample an area or object of interest. However, the benefit of this flexibility in sampling behavior is unknown - does it facilitate sensory processing? In olfaction animals control sniff rate: in rodents, sniffing varies between 2 to 10 Hz. However, how modulating sniff rate benefits neural processing is not known. Increases in sniff rate are especially prominent during odor tracking tasks. Odor tracking entails sampling and comparing odor concentrations across various points in space and time. Consequently, to track odors animals should have an ability compare odor concentrations across sequential sniffs (hereafter referred to as ΔC_t). Our recent work has revealed that ΔC_t representation begins in the OB. A subset of mitral/tufted cells (MTCs), the projection neurons of the OB, respond to odor concentrations in a history dependent manner (Parabucki et al., 2017). Here we show that fast

sniffing improves ΔC_t processing in the olfactory system. Sniff rate strongly affects the processing of time-varying input, enhancing the contrast between concentrations. When we present identical concentration on two consecutive cycles, the odor information acquired during the second sniff cycle is redundant and therefore it is filtered out during fast sampling. Further, we predict that faster sniffing will improve the behavioral perception of ΔC_t.

Disclosures: R. Shusterman: None.

Nanosymposium

630. The Chemical Senses : Dynamics and Plasticity of Olfactory and Gustatory Coding

Location: SDCC 23

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 630.02

Topic: D.05. Olfaction and Taste

Support: ISF China 2545/16
Marie Curie

Title: A mirror symmetric excitatory link coordinates odor maps across olfactory bulbs

Authors: M. GROBMAN[1], T. DALAL, 52900[2], H. LAVIAN, 52900[2], R. SHMUEL, 52900[2], K. BELELOVSKY, 52900[2], A. KORNGREEN, 52900[2], *R. HADDAD[2]
[1]Bar ilan university, ramat gan, Israel; [2]Bar Ilan Univ., Ramat Gan, Israel

Abstract: Sensory input from vision, audition and olfaction arrives at the brain from bilateral and offset channels, but still perceived as a unified percept. Such unity could be explained either by simultaneous projections to both hemispheres, or by rapid information transfer between hemispheres. Sharing information across hemispheres is conceptually simple when sensory information is topographically organized because contralateral inputs can converge onto callosal recipient neurons that match the ipsilateral receptive fields. Odor information, however, is not topographically organized in odor space and projects unilaterally, which raises the question of whether odors are encoded separately in each hemisphere and if so, how odor perceptual unity is achieved. Here we report a novel circuit that interconnects mirror-symmetric isofunctional output neurons between the two mouse olfactory bulbs, which enables the sharing of odor information across hemispheres. Using optogenetics, we show that at least 38% of mitral and tufted (M/T) cells are inter-connected such that activating M/T cells in one bulb excites mirror-symmetric M/T cells located in the contralateral bulb. This connectivity is likely to be mediated through a one-to-one mapping from M/T cells to neurons in the ipsilateral anterior olfactory nucleus pars externa (AONpE) which project to the contralateral bulb and form glutamatergic synapses on mirror M/T cells. The M/T cell responses to a panel of odors delivered to the ipsi- or contralateral nostrils revealed that mirror-symmetrically connected neurons respond to similar odors whereas unconnected neurons do not respond to odors from the contralateral nostril,

indicating that these inter-hemispherically connected neurons are iso-functional. Furthermore, odors delivered through the contra-nostril elicited a response in the ipsi-bulb that facilitated their identification. Thus, this circuit enables the sharing of odor information across hemispheres despite the lack of known topographical organization in the olfactory cortex and suggests that the glomerular maps in the olfactory bulbs are the equivalent of cortical sensory maps in other sensory systems.

Disclosures: M. Grobman: None. **T. Dalal:** None. **H. Lavian:** None. **R. Shmuel:** None. **K. Belelovsky:** None. **A. Korngreen:** None. **R. Haddad:** None.

Nanosymposium

630. The Chemical Senses : Dynamics and Plasticity of Olfactory and Gustatory Coding

Location: SDCC 23

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 630.03

Topic: D.05. Olfaction and Taste

Support: Sir Henry Wellcome fellowship (103044) to EG
Wellcome Trust Career Development Fellowship (088301) to MSG
BBSRC grant (BB/N014650/1) to MSG
ERC Consolidator Grant (725729; FUNCOPLAN) to MSG

Title: Brief sensory deprivation triggers cell type-specific structural and functional plasticity in olfactory bulb neurons

Authors: *E. GALLIANO[1,2], C. HAHN[1], D. J. BYRNE[1], M. S. GRUBB[1]
[1]King's Col. London, London, United Kingdom; [2]Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Can alterations in experience trigger different plastic modifications in neuronal structure and function, and if so, how do they integrate at the cellular level? To address this question, we interrogated the circuitry in the mouse olfactory bulb (OB) responsible for the earliest steps in odour processing. At just one synapse away from the sensory periphery, activity in the OB can be readily and reliably altered by alterations in sensory experience, in our case achieved by 24 h unilateral naris occlusion. Immunohistochemical labelling for the immediate early gene c-fos confirmed that this manipulation decreased overall activity levels in specific OB neuronal populations. We found that such brief sensory deprivation produced structural and functional plasticity in just one highly specialised OB cell type: axon-bearing dopaminergic neurons in the glomerular layer. After 24 h naris occlusion, the AIS in OB dopaminergic neurons became significantly shorter in length, a structural modification that was also associated with a decrease in intrinsic excitability. These effects were specific to the AIS-positive OB dopaminergic sub-population, because no experience-dependent alterations in intrinsic

excitability were observed in AIS-negative OB DA cells. Moreover, 24 h naris occlusion produced no structural changes at the AIS of the other major axon-bearing cell types in the glomerular layer- external tufted cells - nor did it alter their intrinsic excitability. By specifically acting on excitability in one specialised dopaminergic subpopulation, experience-dependent plasticity in early olfactory networks might act to fine-tune sensory processing in the face of continually fluctuating input.

Disclosures: E. Galliano: None. **C. Hahn:** None. **D.J. Byrne:** None. **M.S. Grubb:** None.

Nanosymposium

630. The Chemical Senses : Dynamics and Plasticity of Olfactory and Gustatory Coding

Location: SDCC 23

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 630.04

Topic: D.05. Olfaction and Taste

Support: Duke University
NIH Grant DC-015525

Title: Distinct dynamics for representations of odor and choice in piriform cortex

Authors: A. E. MUNSCH, *K. M. FRANKS, K. A. BOLDING
Neurobio., Duke Univ., Durham, NC

Abstract: Mice can rapidly form long-lasting attractive or aversive associations to a previously neutral odor. Information about both odor identity and odor value are represented in piriform cortex (Gire et al, 2013). We wished to examine how these different odor features are encoded. We trained head-fixed mice to perform a two-odor discrimination task in a go/no-go operant conditioning task while recording spiking activity from populations of neurons in anterior piriform cortex. Trained mice rapidly learned to lick for a water droplet in response to the rewarded odor (Hit trial) but not the unrewarded odor (Correct Reject trial), achieving criterion (80% correct) within 26 ± 20 trials **(**mean ± st. dev., n = 10 sessions with 6 mice**)**. The odor-reward contingency was reversed multiple times over the course of a single session. Performance was poor immediately after reversal, resulting in a number of Miss trials and False Alarm trials, but mice soon learned the new reward contingency (40 ± 22 trials after 1st reversal). This experimental paradigm allowed us to dissociate features of the neural response selective for odor and choice. A linear decoder could correctly classify responses to odor and choice from single-trial population activity using spike counts in a sliding 50-ms window. Odor-decoding accuracy peaked 118 ± 99 ms after inhalation and remained elevated over the 2-s odor stimulus. Choice information evolved more slowly, peaking 2.32 ± 1.27 s after inhalation. During the first sniff after odor delivery, many more cells selectively encoded odor than choice (odor, 40.7 ± 8.1%; choice, 13.9 ± 7.8%; odor-choice interactions, 10.9 ± 4.9%; 2-way ANOVA). However, over the

full trial, including the choice and reward periods, the number of choice-responsive neurons rose to include the majority of cells, substantially overlapping with the odor-selective population (mean ± st. dev.: odor, 53.3 ± 12.4%; choice, 65.3 ± 16.6%; odor-choice interactions, 30.7 ± 14.8%). Different odors transiently activated distinct ensembles of neurons, consistent with an ensemble code for odor identity. By contrast, the choice-selective signal consisted of broad, long-lasting suppression during Go trials, consistent with a rate code for choice. The timing of this suppression closely corresponded to the licking rate, preceding the choice window and lasting throughout the choice and reward periods. Thus, odor and choice are encoded by partially overlapping neural populations during distinct temporal windows. Choice-related signals may reflect top-down inputs conveying either ongoing motor activity or anticipation of reward, that could modulate odor sensitivity and learning in piriform cortex.

Disclosures: A.E. Munsch: None. **K.M. Franks:** None. **K.A. Bolding:** None.

Nanosymposium

630. The Chemical Senses : Dynamics and Plasticity of Olfactory and Gustatory Coding

Location: SDCC 23

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 630.05

Topic: D.05. Olfaction and Taste

Support: Howard Hughes Medical Inistitute
Helen Hay Whitney Fellowship

Title: Imposing structure on odor representations during learning in OFC and mPFC

Authors: *C. BOBOILA[1], P. WANG[2], N. STEIN[2], R. AXEL[2]
[1]Neurosci., [2]Columbia Univ., New York, NY

Abstract: Neurons in the piriform cortex receive convergent input from random collections of olfactory glomeruli. As a consequence, odors elicit an unstructured and distributive representation of neural activity in the piriform that encodes odor identity. A restoration of order must therefore be implemented downstream to elicit an appropriate behavioral output. We performed 2-photon endoscopic imaging during learning in piriform and a downstream associative area, the orbitofrontal cortex (OFC). Piriform odor responses are unaffected by learning. In contrast, before learning, neurons responsive to odor in the OFC are sparse and non-specific, but after learning, over 30% of OFC neurons exhibit strong responses to the rewarded CS+ odors but not to the CS- odors. Moreover, the same population of OFC neurons respond to all CS+ stimuli, and these responses are dependent upon context and internal state. Therefore, information about odor identity in the piriform is transformed by the convergence of sensory and cognitive inputs to create representations of predictive value in OFC.
We have also examined the role of OFC in associative learning. We divided our task into two

epochs: pre-training, during which mice learn that a single odor predicts water, and discrimination, in which mice learn to distinguish between novel CS+ and CS- odors. Optogenetic silencing of OFC during pre-training results in a significant impairment in the learning. However, if mice have learned a prior association with an intact OFC, OFC silencing during discrimination does not affect the learning of new associations. Through imaging, we also observe that OFC's value representation is only robust when mice are learning their first association. Therefore, both imaging and inhibition results suggest that OFC is necessary for initial task acquisition.
We next examined the roles of other association areas in our task. We found that silencing the medial prefrontal cortex (mPFC) impaired learning during discrimination but not during pre-training, opposite to OFC silencing. The importance of the mPFC during discrimination is also reflected by our imaging results. First, in contrast to the OFC, a significant percentage (25%) of mPFC neurons acquire CS+ responses during discrimination training. Moreover, a non-overlapping set (30%) of mPFC neurons acquire responses to CS- odors during discrimination training. Therefore, both imaging and inhibition results suggest that the mPFC is necessary for discrimination learning after initial task acquisition. While distributed representations of learning emerge in the OFC and mPFC, each may possess unique and specialized roles in learning.

Disclosures: C. Boboila: None. **P. Wang:** None. **N. Stein:** None. **R. Axel:** None.

Nanosymposium

630. The Chemical Senses : Dynamics and Plasticity of Olfactory and Gustatory Coding

Location: SDCC 23

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 630.06

Topic: D.05. Olfaction and Taste

Support: NIH Grant R01DC015426

Title: Sleep deprivation enhances encoding of odors in piriform cortex and food intake through piriform-insula connectivity

Authors: *T. KAHNT[1], S. BHUTANI[2], J. D. HOWARD[2], R. REYNOLDS[2], P. C. ZEE[2], J. A. GOTTFRIED[3]
[1]Dept. of Neurol., [2]Northwestern Univ., Chicago, IL; [3]Dept. of Neurol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Sleep deprivation has marked effects on ingestive behavior. In a sleep-deprived state, dietary choices shift toward consumption of high-energy foods. This effect may be driven by alterations in the levels of appetite-regulating compounds, including endocannabinoids. Here we test the role of central olfactory processing in mediating the association between sleep loss, endocannabinoids, and food intake. Healthy-weight human subjects (N=25, 10 male) participated

in a crossover olfactory functional magnetic resonance imaging (fMRI) experiment. After one week of sleep stabilization, participants were randomly assigned to one night of deprived sleep (DS, 4h) or one night of non-deprived sleep (NDS, 8h). 4 weeks later, subjects participated in the other condition. On the next evening, subjects underwent fMRI scanning while smelling calorie-dense food and non-food control odors. Blood samples were also collected during the fMRI session. After fMRI scanning, subjects had ad libitum access to high-calorie snack items in the form of an all-you-can-eat buffet. We used a searchlight-based multi-voxel pattern analysis to identify brain regions encoding food vs non-food odors in the two sleep states. Subjects in the DS state consumed food items with a significantly higher energy density and had increased serum levels of the endocannabinoid-like compound 2-oleoylglycerol (2-OG). Importantly, both measures were correlated across subjects, suggesting that sleep-dependent food intake is driven by changes in the endocannabinoid system (ECS). We also tested whether this relationship was accounted for by changes in central olfactory responses to food odors. In a DS state, fMRI-based encoding of odors in the piriform cortex was increased, but this effect was not related to food intake or 2-OG. However, sleep-dependent food intake was predicted by changes in functional connectivity between piriform and insular cortex. Importantly, the relationship between 2-OG and sleep-dependent food intake was formally mediated by piriform-insula connectivity. These findings demonstrate that DS modulates odor-evoked piriform responses and highlight a ECS-related olfactory mechanism through which DS may alter dietary behavior.

Disclosures: T. Kahnt: None. **S. Bhutani:** None. **J.D. Howard:** None. **R. Reynolds:** None. **P.C. Zee:** None. **J.A. Gottfried:** None.

Nanosymposium

630. The Chemical Senses : Dynamics and Plasticity of Olfactory and Gustatory Coding

Location: SDCC 23

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 630.07

Topic: D.05. Olfaction and Taste

Support: Samuel Freeman Fellowship

Title: DeepNose: An artificial neural network that represents the space of odorants

Authors: *N. TRAN[1], D. R. KEPPLE[1], S. SHUVAEV[2], A. KOULAKOV[2]
[1]Cold Spring Harbor Lab. Watson Sch. of Bio, Cold Spring Harbor, NY; [2]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Representations of odorants by olfactory receptors (ORs) are combinatorial: one molecule activates many receptors, and one receptor is activated by many molecules. In human, about 350 ORs have to encode a large space of odor molecules. We used artificial neural networks to determine the factors influencing the composition of ORs ensembles and their

responses. We hypothesize that ORs are 3D spatial filters whose responses serve to identify molecular features. As a result, these ORs can be "trained" similarly to 2D visual filters using conventional machine learning methods, such as back-propagation. We trained DeepNose, a multilayer neural network whose architecture explicitly reflects the 3D geometry of ligand-receptor interaction. First, we tested a deep autoencoder consisting of an encoder, which converts each molecule into a feature vector, and a decoder, which recovers the molecule structure from the feature vector. This unsupervised learning approach allows inferring features of the chemical space based of 3D structure of millions of available molecules. We used 10^5 molecules obtained from the PubChem3D database to train the autoencoder to high level of accuracy (R=0.98). Since autoencoder attempts to find a low-dimensional representation of the chemical space created from a large number of odorants, resulting ensemble of 3D filters is functionally analogous to the OR ensemble. Second, we trained the classifier based on annotated datasets. DeepNose features, when paired with a neural network classifier, can predict physical properties such as water solubility (R = 0.98). We further tested DeepNose's ability to predict odor perceptual descriptors included in the Flavornet dataset. Previous work used ISOMAP to approximate human olfactory perceptual space and found that this perceptual space to be low dimensional: 10 "perceptual coordinates" can capture the majority of information from 197 odorant descriptors. DeepNose could predict location in this low-dimensional space with R = 0.66. We argue that DeepNose network can extract chemical features predictive of various bioactivities including human odor percepts.

Disclosures: N. Tran: None. **D.R. Kepple:** None. **S. Shuvaev:** None. **A. Koulakov:** None.

Nanosymposium

630. The Chemical Senses : Dynamics and Plasticity of Olfactory and Gustatory Coding

Location: SDCC 23

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 630.08

Topic: I.06. Computation, Modeling, and Simulation

Support: Aileen Andrew Foundation Grant IIS-1254123
NSF Grant IOS-1556388
NSF Grant IOS-1556337

Title: Hyperbolic geometry of the olfactory space

Authors: *F. ZHOU[1], B. H. SMITH[2], T. O. SHARPEE[3]
[1]Biol., UCSD, San Diego, CA; [2]Schl Life Sci., Arizona State Univ., Tempe, AZ; [3]Salk Inst., San Diego, CA

Abstract: The reason that the sense of smell can be used to avoid poisons or estimate a food's nutrition content is because biochemical reactions create many by-products. Thus, the production

of a specific poison by a plant or bacteria will be accompanied by the emission of certain sets of volatile compounds. An animal can therefore judge the presence of poisons in the food by how the food smells. This perspective suggests that the nervous system can classify odors based on statistics of their co-occurrence within natural mixtures rather than from the chemical structures of the ligands themselves. We show that this statistical perspective makes it possible to map odors to points in a hyperbolic space. Hyperbolic coordinates have a long but often underappreciated history of relevance to biology. For example, these coordinates approximate distance between species computed along dendrograms, and more generally between points within hierarchical tree-like networks. We find that both natural odors and human perceptual descriptions of smells can be described using a three-dimensional hyperbolic space. This match in geometries can avoid distortions that would otherwise arise when mapping odors to perception. We identify three axes in the perceptual space that are aligned with odor pleasantness, its molecular boiling point and acidity. Because the perceptual space is curved, one can predict odor pleasantness by knowing the coordinates along the molecular boiling point and acidity axes.

Disclosures: B.H. Smith: None. **T.O. Sharpee:** None.

Nanosymposium

630. The Chemical Senses : Dynamics and Plasticity of Olfactory and Gustatory Coding

Location: SDCC 23

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 630.09

Topic: D.05. Olfaction and Taste

Support: NIH Grant R01DA035025

Title: The coding of valence and identity in the mammalian taste system

Authors: *L. WANG[1,2], S. GILLIS-SMITH[1,2], Y. PENG[1,2], J. ZHANG[1,2], X. CHEN[1,2], C. D. SALZMAN[3,4], N. J. P. RYBA[5], C. S. ZUKER[1,2]
[1]HHMI and Departments of Biochem. and Mol. Biophysics, [2]Dept. of Neurosci., [3]Neurosci., [4]Dept. of Psychiatry and New York State Psychiatric Inst., Columbia Univ., New York, NY; [5]5National Inst. of Dent. and Craniofacial Res., NIH, Bethesda, MD

Abstract: The ability of the taste system to identify a tastant (what does it taste like?) enables animals to recognize and discriminate between the different basic taste qualities. The valence of a tastant (is it appetitive or aversive?) specifies its hedonic value, and the execution of selective behaviors. Here we examine how sweet and bitter are afforded valence versus identity. We show that sweet and bitter cortex project to topographically distinct areas of the amygdala, with strong segregation of neural projections conveying appetitive versus aversive taste signals. By manipulating selective taste inputs to the amygdala, we show that it is possible to impose

positive or negative valence to a neutral water stimulus, and even to reverse the hedonic value of a sweet or bitter tastant. Remarkably, animals with silenced amygdala no longer exhibit behavior that reflects the valence associated with direct stimulation of taste cortex, or with delivery of sweet and bitter chemicals. Nonetheless, these animals can still identify and discriminate between tastants, just as wildtype controls do. These results help explain how the taste system generates stereotypic and predetermined attractive and aversive taste behaviors, and substantiate distinct neural substrates for the discrimination of taste identity and the assignment of valence.

Disclosures: L. Wang: None. **S. Gillis-Smith:** None. **Y. Peng:** None. **J. Zhang:** None. **X. Chen:** None. **C.D. Salzman:** None. **N.J.P. Ryba:** None. **C.S. Zuker:** None.

Nanosymposium

630. The Chemical Senses : Dynamics and Plasticity of Olfactory and Gustatory Coding

Location: SDCC 23

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 630.10

Topic: B.04. Ion Channels

Support: NIH Grant R01DC013741

Title: Otop1 defines a new family of proton channels in the taste and vestibular systems

Authors: Y.-H. TU[1], B. TENG[1], H. TURNER[1], R. CHANG[2], W. YE[3], D. ARTIGA[1], E. MULHALL[4], *E. R. LIMAN[1]
[1]Section of Neurobio., Univ. of Southern California (USC), Los Angeles, CA; [2]Dept. of Neurosci. and Dept. of Cell. and Mol. Physiol., Yale Univ. Sch. of Med., New Haven, CT; [3]Dept. of Physiol., UCSF, San Francisco, CA; [4]Harvard Med. Sch., Boston, MA

Abstract: Of the five basic tastes, sour, which allows animals to detect acids prior to ingestion, is perhaps the least well understood. Sour tastes are detected by a subset of taste receptor cells that express the molecule Pkd2l1, although Pkd2l1 is not required for sour responses. We previously showed that Pkd2L1-expresssing taste cells respond to acids with action potentials, and that an inward proton current, presumably carried by proton-selective ion channels, contributes to this response. To identify the molecular basis for the proton current, we performed RNAseq on genetically identified sour and non-sour taste cells. Genes whose expression was enriched in sour taste cells and that encoded novel membrane proteins were tested for proton channel activity following expression in heterologous cell types. Of 41 candidates tested, one, Otopetrin1 (Otop1) generated large currents in response to lowering extracellular pH. Otop1 encodes a protein with 12 predicted transmembrane domains and no homology to known ion channels. Otop1 was first identified as the gene that is mutated in the tlt strain of mice, which have severely compromised vestibular function due to loss of calcium carbonate containing otoconia. We show that the tlt mutation of Otop1 causes a reduction in the proton current, thus

providing an explanation for the vestibular defect. Otopetrins form a family of genes with two other vertebrate homologs, Otop2 and Otop3 and orthologs in invertebrate species. We find that Otop2 and Otop3 and a drosophila ortholog also generate proton currents, with distinct pH sensitivity. Otop proteins are widely distributed throughout the body, where their functions are completely unknown. This work establishes the Otopetrin channels as a new family of proton channels with widespread distribution and functions in vertebrates and invertebrates.

Disclosures: Y. Tu: None. **B. Teng:** None. **H. Turner:** None. **R. Chang:** None. **W. Ye:** None. **D. Artiga:** None. **E. Mulhall:** None. **E.R. Liman:** None.

Nanosymposium

630. The Chemical Senses : Dynamics and Plasticity of Olfactory and Gustatory Coding

Location: SDCC 23

Time: Wednesday, November 7, 2018, 8:00 AM - 10:45 AM

Presentation Number: 630.11

Topic: D.05. Olfaction and Taste

Support: 5K01-DK103832-04
1R03-DK114500-01
The Dana Foundation
The Hartwell Foundation
1OT2OD023849-01

Title: The taste of calories in the gut

Authors: K. BUCHANAN, M. M. KAELBERER, M. KLEIN, M. M. MONTOYA, *D. V. BOHORQUEZ
Med., Duke Univ., Durham, NC

Abstract: The rewarding feeling of sugars begins in the gut. Here, glucose is sensed by specialized epithelial cells, referred to as enteroendocrine cells. As reflected in their name, they were thought to communicate with nerves only through hormones. But, these cells have several features observed in epithelial transducers like voltage-gated ion channels, synaptic vesicles, and synaptic adhesion proteins. Using a monosynaptic rabies virus, we discovered that enteroendocrine cells of the small intestine synapse with vagal nodose neurons. Thus, we hypothesized that enteroendocrine cells synapse with vagal neurons to transduce sensory signals from sugars and sugar-substitutes devoid of caloric value. Sorting such signals at the gut epithelium could modulate how the brain perceives the caloric value of ingested nutrients. By combining molecular tools with whole nerve recordings and optogenetics, we found the following:Enteroendocrine cells, but not vagal neurons, sense sugars. In vitro, sucrose, D-glucose, and sucralose stimulate calcium transients in enteroendocrine cells but not vagal nodose neurons. And, unlike vagal nodose neurons, purified enteroendocrine cells express significant

amounts of sugar sensing receptors, including the taste receptors T1r2 and T1r3, and the electrogenic transporterSlc5a1 (SGLT1). Enteroendocrine cells sense sucrose and non-caloric sucralose through separate molecular receptors. When delivered in the lumen of the intestine, both sucrose and calorie free sucralose significantly stimulate vagal firing rate as indicated by whole nerve recordings. Vagal response to sucrose, but not sucralose, is abolished when SGLT1 is blocked with phloridzin. The opposite occurs when murine sweet taste receptors are blocked with gurmarin. Enteroendocrine cells are necessary to transduce sensory stimuli onto vagal neurons. In a mouse in which enteroendocrine cells expressthe excitatory channelrhodopsin2, a 473nm intraluminal laser stimulus rapidly increases vagal firing rate. Whereas in a mouse in which enteroendocrine cells express the inhibitory halorhodopsin, a 532nm laser stimulus during nutrient perfusion attenuates the sucrose and sucralose responses. And, they do so using glutamate as a neurotransmitter. A finding we confirmed, in part, by using the glutamate sensor iGluSnFR.These findings introduce the concept of neurotransmission in gut-brain sensory transduction. A concept in which enteroendocrine cells serve as sensors for the caloric value of nutrients.

Disclosures: K. Buchanan: None. **M.M. Kaelberer:** None. **M. Klein:** None. **M.M. Montoya:** None. **D.V. Bohorquez:** None.

Nanosymposium

631. Depression and Bipolar Disorders: Neural Mechanisms

Location: SDCC 5

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 631.01

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: JPB Foundation
the Leon Black Family Foundation
United States Army Medical Research Acquisition Activity grant

Title: Targeting cholinergic interneurons of thenucleus accumbens rescues depressive behaviors

Authors: *J. CHENG, G. UMSCHWEIF, Y. SAGI, P. GREENGARD
Rockefeller Univ., New York, NY

Abstract: Major Depressive Disorder (MDD) affects about twenty percent of the population worldwide. Due to its clinical and etiological heterogeneity, the pathophysiology of this disease has been difficult to elucidate despite intense research over several decades. Cholinergic interneurons (ChIs) in the nucleus accumbens (NAc) have been implicated in drug addiction, reward and mood disorders, but the physiological role of ChIs in depression and the underlying molecular mechanisms have not been addressed. Here, we show that ChI activity is reduced in p11 conditional knockout mice, an established animal model of depression. Chemogenetic

inhibition of NAc ChIs in wild-type mice induces anhedonia-like behaviors, whereas enhancement of ChI activity reverses depressive phenotypes. Furthermore, we identify the key molecules underlying the disrupted activity of ChIs in depressed mice. Targeting the key molecules successfully rescues depressive mice. In summary, the present study broadens our understanding of the pathophysiology of MDD and provides insights for the development of a new class of antidepressants.

Disclosures: J. Cheng: None. **G. Umschweif:** None. **Y. Sagi:** None. **P. Greengard:** None.

Nanosymposium

631. Depression and Bipolar Disorders: Neural Mechanisms

Location: SDCC 5

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 631.02

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Comparison of RNAseq in medium spiny neuron subpopulations isolated using nuclear-FACS, whole cell-FACS or RiboTag affinity purification

Authors: *H. KRONMAN[1], F. RICHTER[1], R. CHANDRA[2], B. LABONTÉ[3], M. LOBO[4], E. J. NESTLER[1]
[1]Dept of Neurosci. and Friedman Brain Institute,, Icahn Sch. of Med. at Mount Sinai, Brooklyn, NY; [2]Anat. and Neurobio., Univ. of Maryland Baltimore, Baltimore, MD; [3]Neurosci. and Psychiatry, Laval Univ., Quebec, QC, Canada; [4]Anat. and Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Isolation of cell populations is beginning to allow the untangling of complex biological interactions that exist in the niche of a single tissue. Several studies have compared whole cell and nuclear isolation, but this work is typically performed in cell culture, which lacks the complexity of in vivo tissues, or focused on a subset of total RNA, and limited conclusions are drawn about the types of transcripts identified by each technique. Furthermore, few studies compare these FACS-based techniques to ribosomal affinity purification, and none do so genome-wide. The absence of a methodical comparison of whole cell-FACS, nuclear-FACS, and RiboTag is becoming problematic as these techniques are used increasingly by the field.
We addressed this gap by systematically comparing these three approaches in the context of D1 and D2 dopamine receptor-expressing medium spiny neuron (MSN) subtypes of the nucleus accumbens (NAc). We find that nuclear-FACS-seq generates a substantially longer list of differentially expressed genes between the two cell types, capturing numerous shorter-length and non-coding transcripts. Non-coding transcripts are absent in the RiboTag-seq dataset, and lowly represented in the whole cell-FACS-seq dataset. RiboTag-seq has much lower coverage of the transcriptome than the other methods, capturing only protein-coding genes and presumably only those that require ongoing translation. Despite this low coverage, RiboTag-seq data very

efficiently distinguishes D1- and D2-MSNs, perhaps due to the low-complexity, low-noise nature of the dataset. The more complex nuclear- and whole cell-FACS-seq data demonstrate that D2-MSNs express a larger number of transcripts in the nucleus, while D1-MSNs exhibit a larger number of transcripts in the whole cell, suggesting fundamental cell-type differences in mechanisms of transcriptional regulation and subcellular transport of RNAs. We are also utilizing these datasets to characterize method- and cell type-enriched biological networks through the use of WGCNA. We generated modules both within and across methods to produce comprehensive transcriptional maps of D1- and D2-MSN biology.
Together, our results demonstrate the relative strengths of cell-type specific RNA-seq with these distinct approaches and provide insight into the mechanisms of transcriptional control at play in D1- and D2-MSNs.
Supported by NIDA, NIMH, and HDRF

Disclosures: H. Kronman: None. **F. Richter:** None. **R. Chandra:** None. **B. Labonté:** None. **M. Lobo:** None. **E.J. Nestler:** None.

Nanosymposium

631. Depression and Bipolar Disorders: Neural Mechanisms

Location: SDCC 5

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 631.03

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: F32-MH110128 (MRC)
R01-MH101180 (AAG)

Title: Enhanced affective dysregulation and dopamine hypofunction in female rodents during the early postpartum period

Authors: *M. RINCÓN-CORTÉS, A. A. GRACE
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The period after childbirth (i.e. postpartum period) is a time of elevated risk for the development of affective disorders (Stowe and Nemeroff, 1995; Pawluski et al., 2017). The highest rates of anxiety and depression in women occur following childbirth, with most (50-85%) new mothers experiencing a transient affective disturbance (i.e. postpartum blues) 1-2 weeks postpartum, and 10-15% developing postpartum depression (PPD) (Thurgood et al., 2009; O'Hara and McCabe, 2013). Yet, there is little data regarding the neural adaptations in response to parity and during the postpartum period, and neurobiological underpinnings of increased affective dysregulation during the postpartum remain poorly understood. In both humans and rodents, alterations in maternal affect have been partially attributed to the rapid and robust changes in ovarian and stress hormones associated with the onset of motherhood (Brummelte

and Galea, 2016), which can alter the activity of the mesolimbic dopamine (DA) system. The mesolimbic DA system originates in the ventral tegmental area (VTA) and plays a pivotal role in both affective processes and the pathophysiology of depression (Tye et al. 2013; Grace, 2016; Rincón-Cortés and Grace, 2017). However, little is known about postpartum DA function. To this end, we used the elevated plus maze (EPM) and the three-chambered social approach test (SAT) to compare anxiety-like and social behavior in virgin and postpartum female rats across different timepoints (i.e. early, mid, late), followed by single-unit extracellular recordings to measure 3 parameters of VTA DA neuron activity: i) number of spontaneously active DA neurons (i.e. population activity or cells/track), ii) basal firing rate and iii) firing pattern (i.e. percentage of spikes firing in bursts). Our results show time-dependent changes in affect and VTA DA neuron activity in postpartum females compared with virgins (n=7-10 per group; $p<0.05$), with early/mid postpartum females showing greater effects (i.e. high anxiety, low social motivation, reduced number of DA cells/track). At 1-week postpartum, a split was observed in which approximately half the dams exhibited high neurobehavioral dysregulation (i.e. negative affect, DA hypofunction). These findings suggest a link between affective dysregulation and attenuated DA function in early postpartum females and a persistence of effects in a subset of rats.

Disclosures: M. Rincón-Cortés: None. **A.A. Grace:** F. Consulting Fees (e.g., advisory boards); Dr. Grace received consultant fees from Lundbeck, Pfizer, Otsuka, Asubio, Autofony, and Janssen, and is on the advisory board for Alkermes, Newron and Takeda..

Nanosymposium

631. Depression and Bipolar Disorders: Neural Mechanisms

Location: SDCC 5

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 631.04

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CIHR MOP 111049

Title: Effects of depression and childhood adversity on the volumes of the amygdala subnuclei and hippocampal subfields

Authors: *A. AGHAMOHAMMADI SERESHKI[1], N. J. COUPLAND[2], P. SILVERSTONE[2], K. HEGADOREN[3], R. CARTER[2], P. SERES[4], N. V. MALYKHIN[4]
[1]Neurosci. and Mental Hlth. Inst., [2]Dept. of Psychiatry, [3]Fac. of Nursing, [4]Biomed. Engin., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Effects of depression and childhood adversity on the volumes of the amygdala subnuclei and hippocampal subfields. Introduction: The hippocampus (HC) and the amygdala (AG) are amongst structures affected by major depressive disorder (MDD). Although a

volumetric reduction in the HC has been reported in most studies, previous studies of the AG changes in MDD have been inconsistent. Childhood adversity has been recognized as an important risk factor for developing depression in adulthood. Both the HC and the AG show a protracted postnatal development with a high density of glucocorticoid receptors which both make them vulnerable to childhood adversity. The main goal of the present study was to investigate the effects of MDD and history of childhood adversity on different AG subnuclei (lateral, basal and accessory basal nuclei as well as cortical and centromedial groups) and HC subfield [cornu ammonis (CA1-3), subiculum and dentate gyrus] volumes. Methods: 35 healthy participants and 35 patients meeting DSM-IV criteria for MDD were recruited. Symptom severity was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D). Magnetic Resonance Imaging (MRI) datasets were acquired on a 4.7T Varian Inova scanner. The program DISPLAY (MNI, Montreal, QC) was used to manually trace AG subnuclei and HC subfields using reliable volumetric methods. Childhood adversity was assessed on the Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998), which assesses physical (PA), sexual (SA) and emotional (EA) abuse as well as emotional (EN) and physical (PN) neglect. Results: MDD-patients did not differ from controls in age, sex and education (all $p>0.05$). The volumes of the amygdala subnuclei did not significantly differ between MDD-patients and controls. The volumes of the AG and its subnuclei did not correlate with HAM-D or MDD-duration (*p*s > .2). We found negative relationships between the volumes of the basal (r: -0.387, $p < .027$) and accessory basal (r: -0.322, $p < 0.068$) nuclei of the AG and EA. Also, total CA1-3 volume negatively correlated with total CTQ score (r: -0.591, $p < .0003$), EA (r: -0.502, $p < .003$), PA (r: -0.635, $p < .0001$), EN (r: -0.469, $p < .006$) and PN (r: -0.442, $p < .001$). Conclusion: These results provide the first in-vivo evidence of the negative associations between childhood adversity and the volumes of the CA1-3 subfield of the HC as well as basal and accessory basal nuclei of the AG.

Disclosures: A. Aghamohammadi Sereshki: None. **N.J. Coupland:** None. **P. Silverstone:** None. **K. Hegadoren:** None. **R. Carter:** None. **P. Seres:** None. **N.V. Malykhin:** None.

Nanosymposium

631. Depression and Bipolar Disorders: Neural Mechanisms

Location: SDCC 5

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 631.05

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH R01-MH0104344
VA VISN 22 MIRECC
NIH T32 MH018339

Title: Acetylcholinergic mechanisms of depressive-like behaviors induced by seasonally-relevant short active photoperiod

Authors: *Z. A. COPE[1], C. VAN DE CHAPPELLE[3], M. A. KWIATKOWSKI[2], L. LAVADIA[2], D. DULCIS[2], J. W. YOUNG[2,4]
[2]Dept. of Psychiatry, [1]Univ. of California San Diego, La Jolla, CA; [3]Div. of Pharmacol., Univ. of Utrecht, Utrecht, Netherlands; [4]Res. Service, VA, San Diego, CA

Abstract: Environmental factors, such as seasonal variations in day length, can influence switching between mood states in bipolar disorder (BD) in a direction-specific manner. Consistent with sufferers of Seasonal Affective Disorder, BD patients exhibit depressive episodes as photoperiod availability decreases in Fall and Winter (short active; SA). Similar effects are also seen in mice (Young et al, 2018) and rats (Dulcis et al, 2013) exposed to SA photoperiods. Pharmacological-induced increases of acetylcholine by the acetylcholinesterase (AChE) inhibitor physostigmine (PHYSO) induces depression in BD sufferers (Janowsky et al. 1972), and induces depressive-relevant behavior in mice, e.g. increased immobility of mice in the Forced Swim Test (FST, Mineur et al., 2013). Here, we tested the hypothesis that acetylcholine signaling is necessary for the expression of depressive-like behaviors following exposure to SA photoperiod (SAP). In C57BL/6 mice, PHYSO dose dependently increased sensitivity to punishment (non-target responding on trials following a low-frequency punishment) resulting from a target response (Target Lose-Shift, $F_{(3,54)}=6.23$, $p<0.01$). Such punish-sensitivity is consistent with humans with MD or BD. Mice pretreated with PHYSO (0.03 mg/kg) or saline 30 minutes before FST followed by the muscarinic acetylcholine receptor antagonist scopolamine (SCOP, 0.03, 0.05 mg/kg) or the nicotinic acetylcholine receptor antagonist mecamylamine (MEC, 0.56, 0.75 mg/kg). SCOP ($F_{(2,49)}=5.3$, $p<0.01$) and MEC ($F_{(2,52)}=4.6$, $p<0.05$) selectively decreased FST immobility in mice pretreated with PHYSO. Next, mice were housed in SAP (19H light : 5H dark) for 2 weeks before FST. SAP increased immobility in two separate cohorts ($F_{(1,70)}=6.5$, $p<0.05$, $F_{(1,143)}=4.3$, $p<0.05$). In cohort 1, SCOP treatment (0.03 mg/kg) reduced immobility irrespective of photoperiod ($F_{(1,70)}=6.9$, $p<0.05$). As per our *a priori* hypotheses, this main effect was driven by significantly reduced immobility in the SAP, not in the NAP mice. In cohort 2, MEC treatment (0.56 mg/kg) slightly reduced immobility irrespective of photoperiod, but not significantly ($F_{(1,143)}=2.0$, $p=0.15$). In combination, two ineffective doses (0.3 mg/kg MEC, 0.01 mg/kg SCOP) additively decreased FST immobility ($F_{(3,142)}=3.0$, $p<0.05$). These results indicate a pivotal role for ACh neurotransmission in the expression of depressive-like behaviors resulting from exposure to SAP. Ongoing experiments will attempt to verify increased ACh levels in hippocampus following SAP exposure using *in-vivo* microdialysis as well as whether virally-delivered exogenous human AChE can block expression of this effect.

Disclosures: Z.A. Cope: None. **C. van de Chappelle:** None. **M.A. Kwiatkowski:** None. **L. Lavadia:** None. **D. Dulcis:** None. **J.W. Young:** None.

Nanosymposium

631. Depression and Bipolar Disorders: Neural Mechanisms

Location: SDCC 5

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 631.06

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Laurate Institute for Brain Research

Title: A novel approach to investigate targeted hypercortisolemia in discrete brain regions modulating major depression disorder

Authors: *A. C. JOHNSON[1], W. K. SIMMONS[2], M. P. PAULUS[2], B. GREENWOOD-VAN MEERVELD[1,3,4]
[1]Res. 151, VA Med. Ctr., Oklahoma City, OK; [2]Laureate Inst. For Brain Res., Tulsa, OK; [3]Oklahoma Ctr. for Neurosci., [4]Dept. of Physiol., Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK

Abstract: INTRODUCTION: Major depressive disorder (MDD) is a significant healthcare burden due to inadequate symptom management. While the causes of MDD are unknown, approximately 50% of MDD patients hypersecrete cortisol (CORT), suggesting a relationship between hypothalamic-pituitary-adrenal axis dysregulation and depression. In a pilot study of MDD patients with hypercortisolemia, functional imaging demonstrated insula and amygdala activity was positively correlated with diurnal peak plasma CORT, suggesting a relationship between MDD symptoms, stress hormones, and brain regions that contribute to interoception and emotion. Since direct, invasive modulation of discrete subcortical brain regions in MDD patients is not possible, our overall objective was to determine if a model of targeted hypercortisolemia induced by stereotaxic placement of CORT micropellets at either the insula or the central nucleus of the amygdala (CeA) would induce depression-like behaviors in rodents. **METHODS:** Studies were conducted in male Fischer 344 rats (200-275 g) that randomly received bilateral micropellets (30 μg) of cholesterol (CHOL) or CORT implanted onto the insula or CeA, n=10/group. All rats underwent assays for depression-like/anhedonia behavior using standard methods: sucrose preference on days 5-8 post-surgery, novelty suppressed feeding on day 7 post-surgery, forced swim training on day 8 and testing on day 9 post-surgery. Data (mean ± SEM) were analyzed using two-factor analysis of variance with Tukey's post-hoc comparisons. **RESULTS:** Rats with CORT implanted on the insula exhibited depression-like behavior in the forced swim assay measured as an increase in immobility compared to the CHOL-implanted control (130.0 ± 21.7 s vs. 48.0 ± 10.8 s, p=0.005). In contrast, CORT implanted at the CeA did not affect depression-like behavior compared to the CHOL-implanted control (112.0 ± 16.3 s vs. 70.0 ± 12.8 s, p=0.26). There were no clear depression-like or anhedonia behaviors demonstrated by the sucrose preference or novelty suppressed feeding assays due to heterogeneous responses

within each group. **CONCLUSIONS:** We were able to reverse-translate the findings from the pilot imaging studies in MDD patients with hypercortisolemia by demonstrating that CORT at the insula, but not the CeA, could induce depression-like behavior in the forced swim assay. This study validates the reverse-translational approach of using clinical imaging to guide targeted investigations of brain function in rodent models and provides a new model for mechanistic studies of the etiology of MDD, with the opportunity for forward translational studies of new therapeutics.

Disclosures: A.C. Johnson: None. **W.K. Simmons:** A. Employment/Salary (full or part-time):; Janssen Research & Development, LLC., Johnson & Johnson. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on a patent regarding appetite change in depression. **M.P. Paulus:** None. **B. Greenwood-Van Meerveld:** None.

Nanosymposium

631. Depression and Bipolar Disorders: Neural Mechanisms

Location: SDCC 5

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 631.07

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: MH101146
DA035217
F30MH115536
Research and Education Initiative Fund, Advancing a Healthier Wisconsin (AHW)

Title: HCN2 channels in the ventral tegmental area regulate behavioral responses to chronic stress

Authors: *C. R. VICKSTROM[1], P. ZHONG[3], X. LIU[2], Y. HU[2], L. YU[2], H.-G. YU[4], Q.-S. LIU[2]
[1]Dept. Pharmacol. and Toxicology, [2]Dept. of Pharmacol. and Toxicology, Med. Col. of Wisconsin, Milwaukee, WI; [3]Mol. and Cell. Biol., Univ. of California, Berkeley, Berkeley, CA; [4]Dept. of Physiology, Pharmacol. & Neurosci., West Virginia Univ., Morgantown, WV

Abstract: Dopamine neurons in the ventral tegmental area (VTA) are powerful regulators of depression-related behavior. Dopamine neuron activity is altered in chronic stress-based models of depression, but the underlying mechanisms remain incompletely understood. In this study, we sought to investigate the mechanisms whereby chronic mild unpredictable stress (CMS), a commonly-used rodent model of depression, leads to alterations in VTA dopamine neuron activity and behavioral deficits. We found that adult mice subjected to CMS exhibited depressive and anxiety-like behavior, which was associated with decreased VTA dopamine neuron firing in

vivo and ex vivo. Dopamine neuron firing is governed by voltage-gated ion channels, in particular hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. Following CMS, HCN-mediated currents were decreased in nucleus accumbens-projecting VTA dopamine neurons. Furthermore, shRNA-mediated HCN2 knockdown in the VTA was sufficient to recapitulate CMS-induced depressive- and anxiety-like behavior in stress-naïve mice, whereas VTA HCN2 overexpression largely prevented CMS-induced behavioral deficits. Together, these results reveal a critical role for HCN2 in regulating VTA dopamine neuronal activity and depressive-related behaviors, and highlight interesting mechanistic differences between CMS and other chronic stress-based models of depression.

Disclosures: C.R. Vickstrom: None. **P. Zhong:** None. **X. Liu:** None. **Y. Hu:** None. **L. Yu:** None. **H. Yu:** None. **Q. Liu:** None.

Nanosymposium

631. Depression and Bipolar Disorders: Neural Mechanisms

Location: SDCC 5

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 631.08

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH R01 MH108562
Silvio O. Conte Center for Neuroscience Research Vanderbilt University
1P50MH096972

Title: Investigating photoperiod effects during sensitive developmental periods for serotonergic circuit function and behavior

Authors: *J. K. SIEMANN[1], N. REDDY[1], C. A. GRUETER[2], B. A. GRUETER[2], D. G. MCMAHON[1]
[1]Dept of Biol. Sci., Vanderbilt Univ., Nashville, TN; [2]Anesthesiol., Vanderbilt Univ. Sch. of Med., Nashville, TN

Abstract: Early life experiences during critical developmental time frames have been linked to increased risk for neurodevelopmental disorders later in life. The serotonergic system is implicated in mood disorders and is impacted by the duration of daylight or photoperiod. Previously our lab has shown that mice raised under Long summer-like photoperiods of 16 hours of light and 8 hours of darkness each day (LD 16:8) demonstrate an increased firing rate in dorsal raphe serotonin neurons, increased serotonin and norepinephrine concentrations and anti-anxiety and anti-depressive like behaviors compared to animals developed under either Short winter-like (LD 8:16) or Equinox (LD 12:12) photoperiods. Here we examined whether prenatal photoperiod, the photoperiod experienced during gestation (E0-P0), can have lasting effects on this system. Mice were exposed prenatally to either Long or Short photoperiods and then

switched to the opposing photoperiod at birth (P0). We observed that Long photoperiod exposure *in utero* can program DRN firing rate in adolescence (P30) and early adulthood (P50) in the mouse. Interestingly, animals that developed only prenatally under Short photoperiods and were switched to Long photoperiods (S-L) at birth, demonstrated increased serotonin ($p = 0.0082$; $F(2, 69) = 5.157$), 5-hydroxyindoleacetic acid ($p = 0.0053$; $F(2, 69) = 5.661$) and norepinephrine ($p = 0.0347$; $F(2, 69) = 3.53$) midbrain content compared to animals raised under Equinox photoperiods or switched from Long to Short photoperiods (L-S) at birth. In addition, S-L animals demonstrated anti-anxiety and anti-depressive like behaviors, driven by age and sex dependent differences. When utilizing the open field test (OFT), we observed significant main effects of photoperiod ($p = 0.0114$; $F(2, 94) = 4.696$) and of age ($p < 0.0001$; $F(1, 94) = 16.73$) for total thigmotaxis. While using the tail suspension test, we observed significant main effects of photoperiod ($p = 0.0287$; $F(2, 94) = 3.688$) of age ($p < 0.0001$; $F(1, 94) = 42.47$) and of sex ($p < 0.0001$; $F(1, 94) = 23.1$) for total time spent immobile. Thus, it appears that exposure to Long photoperiods can program DRN serotonin neuronal firing rate *prenatally* and can modulate midbrain monoamine content resulting in protective effects for anxiety and depressive-like behaviors during *perinatal* development. Based on these findings we are further investigating the role of photoperiod throughout adolescence along with assessing circuit level questions by investigating photoperiodic effects in brain regions connected to the dorsal raphe including the nucleus accumbens and prefrontal cortex, which are consistently implicated in mood-related disorders.

Disclosures: J.K. Siemann: None. **N. Reddy:** None. **C.A. Grueter:** None. **B.A. Grueter:** None. **D.G. McMahon:** None.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.01

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA025646
NIH Grant F31 DA045430

Title: CB1 receptor-mediated regulation of limbic plasticity and HPA activity during memory reconsolidation shapes cocaine memory strength

Authors: *J. A. HIGGINBOTHAM[1], N. JONES[1], R. WANG[1], S. TAN[1], M. A. PRESKER, JR[2], R. FUCHS[1]
[1]Washington State Univ., Pullman, WA; [2]Brain Hlth. Inst., Rutgers - The State Univ. of New Jersey, Piscataway, NJ

Abstract: Context-cocaine memory reconsolidation, the process by which previously consolidated memories are re-stabilized following retrieval-induced destabilization, is critical for drug context-induced cocaine-seeking behavior. Therefore, it has been theorized that interference with memory reconsolidation can weaken context-drug associative memories and thereby mitigate the propensity for relapse. Here, we examined whether cannabinoid type 1 receptor (CB1R) stimulation during memory reconsolidation regulates (a) plasticity-related protein (PRP) expression/activation in the basolateral amygdala (BLA) or dorsal hippocampus (DH), (b) hypothalamic-pituitary-adrenal (HPA) axis activity, and (c) subsequent context-induced cocaine-seeking behavior. Sprague-Dawley rats were trained to lever press for cocaine infusions in a distinct environmental context (≥10 days) followed by extinction training in a different context (7 days) during daily 2-hour sessions. On post-cocaine day 8, the groups received CB1R antagonist (AM251; 3 mg/kg, IP or 0.3µg/0.5µL/hemisphere, intra-BLA) or vehicle (VEH) treatment immediately after brief re-exposure to the drug-paired context (to prompt memory retrieval, destabilization, and reconsolidation), six hours after re-exposure to the drug-paired context (i.e., treatment outside of the time window of reconsolidation), or after no re-exposure (i.e., home cage control). Exposure to the drug-paired context increased BLA and DH PRP expression/activation in the BLA and DH as well as serum corticosterone concentrations during the putative time of memory reconsolidation. Systemic AM251 treatment inhibited these effects on PRP expression/activation and attenuated subsequent cocaine-seeking behavior, relative to VEH. Conversely, intra-BLA AM251 treatment augmented serum corticosterone concentrations during the putative time of memory reconsolidation and potentiated subsequent cocaine-seeking behavior, relative to VEH. Together, these findings suggest that CB1R populations are functionally heterogeneous. CB1R populations bidirectionally control drug context-induced motivation for cocaine by regulating BLA and DH cellular plasticity, HPA axis activation, and cocaine memory strength during memory reconsolidation.

Disclosures: J.A. Higginbotham: None. **N. Jones:** None. **R. Wang:** None. **S. Tan:** None. **M.A. Presker:** None. **R. Fuchs:** None.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.02

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA035958
NIH Grant AA020919

Title: Methamphetamine triggers dopamine release through calcium dependent processes

Authors: *J. T. YORGASON[1], D. M. HEDGES[4], M. C. WOODBURY[2], B. WILLIAMS[3], S. STAPLEY[3], N. LEWIS[3], J. J. NELSON[3], F. P. BELLINGER[5], M. ANDRES[6], S. C. STEFFENSEN[1]
[1]Brigham Young Univ., Provo, UT; [2]Neurosci., Brigham Young Univ., South Jordan, UT; [3]Neurosci., Brigham Young Univ., Provo, UT; [4]SCI Inst., Univ. of Utah, Salt Lake City, UT; [5]Cell & Mol. Biol., Univ. of Hawai'i at Manoa Dept. of Cell and Mol. Biol., Honolulu, HI; [6]PBRC, Univ. of Hawai‘i, Ph.D., Honolulu, HI

Abstract: Methamphetamine (METH) enhances exocytotic dopamine (DA) release, and induces dopamine transporter (DAT) mediated efflux in terminal regions such as the nucleus accumbens (NAc). We previously demonstrated that the sigma receptor is involved in METH effects on these two different types of dopamine release. The sigma receptor is a chaperone protein located on the interface between the mitochondria and endoplasmic reticulum, and upon activation triggers calcium release which may be involved in METH effects on dopamine transmission. The present study investigated the role of intracellular and extracellular calcium in METH effects on dopamine release. METH caused increases in intracellular calcium levels that were reduced by intracellular calcium depletion. Depletion of intracellular Ca2+ stores also attenuated METH effects on dopamine release. Similarly, blocking the IP3 receptor reduced METH effects on dopamine. The intracellular calcium chelator BAPTA-AM also inhibited METH effects. Next, the role of extracellular calcium was examined. Zero extracellular calcium conditions prevented electrically stimulated dopamine release. However, under these conditions METH still initiated DA efflux, albeit at reduced amounts. Similarly, blocking voltage gated Ca2+ channels with Cd2+ resulted in reduced electrically evoked dopamine release and METH effects on dopamine release. Taken together, these results show that METH induces DA release in the NAc through a cascade involving both intracellular and extracellular calcium activity.

Disclosures: J.T. Yorgason: None. **D.M. Hedges:** None. **M.C. Woodbury:** None. **B. Williams:** None. **S. Stapley:** None. **N. Lewis:** None. **J.J. Nelson:** None. **F.P. Bellinger:** None. **M. Andres:** None. **S.C. Steffensen:** None.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.03

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA031767

Title: Hypocretin/orexin in rostromedial tegmental nucleus: Anatomy and function on cocaine self-administration in rats

Authors: *S. J. SIMMONS, R. M. MARTORANA, E. M. CLARK, F. H. TRAN, J. L. BARR, J. M. MUSCHAMP
Ctr. for Substance Abuse Res., Temple University, Lewis Katz Sch. of Med., Philadelphia, PA

Abstract: Addictions to psychostimulants continue to present a public health crisis facing communities on an international scale. Psychostimulants augment extracellular catecholamines—notably, dopamine (DA) arising from ventral tegmental area (VTA)—in structures associated with processing rewards and emotions. Transmitters and peptides that regulate the ability of psychostimulants to perturb central neurochemical transmission present attractive targets in effort to normalize pathological motivation associated with their abuse. Hypothalamic hypocretin/orexin (hcrt/ox) innervates VTA with evidence supporting functional roles in regulating motivated behaviors including for drug-seeking. In the past decade, the caudal division of VTA (rostromedial tegmental nucleus [RMTg]) was highlighted for its ability to negatively regulate VTA DA and participate in encoding aversive stimuli. Available evidence depicts the hypothalamus as a principal input to RMTg, although the cellular phenotypes and functions of this connection have not been resolved. The present study was conducted to map hcrt/ox afferents across the ventral midbrain (i.e., to VTA and RMTg) and assess how hcrt/ox transmission perturbation in VTA and RMTg impacts motivation and affect in a model of psychostimulant addiction. In Experiment 1, rats received fluorescent retrograde tracer injections within VTA or RMTg, and tissue was harvested to measure tracer-containing hcrt/ox cells across hypothalamus. Results show that hcrt/ox projects to VTA and RMTg at comparable densities. In Experiment 2, rats were bilaterally cannulated above VTA or RMTg and underwent jugular vein catheterization for intravenous cocaine self-administration (0.75 mg/kg/inf). After training, rats received either the clinically-available hcrt/ox receptor antagonist suvorexant within VTA or the hcrt/ox peptide within RMTg. Ultrasonic vocalizations (USVs) were measured as an index of shifts in affective state based on emission frequency (i.e., 22- vs 50-kHz). Whereas intra-VTA suvorexant had negligible effects on motivated cocaine-taking, intra-RMTg hcrt/ox produced significant suppression of cocaine-taking without appreciably altering USV emissions. Future studies will address which neurochemically-defined cell populations hcrt/ox transmits to and determine physiological effects of hcrt/ox on RMTg cells—these circuits may participate in processing stimuli as “rewarding” and “aversive” which are critical contributors in the development of substance use disorders and other psychiatric conditions characterized by dysregulated reward processing.

Disclosures: S.J. Simmons: None. **R.M. Martorana:** None. **E.M. Clark:** None. **F.H. Tran:** None. **J.L. Barr:** None. **J.M. Muschamp:** None.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.04

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Intramural Research Program

Title: Optogenetic dissection of cell type-specific neural circuits underlying nicotine reward versus aversion in mice

Authors: *C. J. JORDAN, G.-H. BI, E. L. GARDNER, Z.-X. XI
Mol. Targets and Medications Discovery Br., Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Nicotine, the primary addictive component in tobacco, can produce paradoxical effects that are either rewarding or aversive. However, the neural mechanisms underlying nicotine reward *versus* aversion remain poorly understood. Recent studies suggest that nicotinic acetylcholine receptors (nAchR), particularly α4β2 subunits, are expressed in both dopaminergic (DA) and GABAergic neurons in the ventral tegmental area (VTA). Accordingly, activation of nAchRs in VTA DA or GABA neurons may produce rewarding or aversive effects, respectively. The net effect of nicotine may thus depend upon individual differences in the balance of α4β2 expression or activity on VTA DA vs. GABA neurons. In the present study, we combined mouse drug self-administration in mice, RNAscope in situ hybridization, Cre-LoxP and optogenetic approaches to understand the neural mechanisms mediating nicotine reward or aversion. First, using intravenous nicotine self-administration and classical conditioned place preference models, we found that nicotine is neither rewarding nor aversive in mice. Next, using RNAscope, we found that α4β2 nAchRs mRNA is expressed in tyrosine hydroxylase (TH)-positive DA neurons as well as non-DA (e.g., GABA) neurons in the VTA. Then, we selectively expressed light-sensitive channelrhodopsin in VTA DA or GABAergic neurons of transgenic DAT-Cre or Vgat-Cre mice. Optogenetic activation of VTA DA neurons produced robust, frequency-dependent optogenetic intracranial self-stimulation (oICSS) and strong place preferences for the laser-paired side of a two-chamber apparatus. In contrast, activation of VTA GABA did not sustain oICSS responding and produced place aversions to the laser-paired chamber. Whereas cocaine or oxycodone administration enhanced oICSS responding, indicated by left- and upward shifts in response-frequency curves, nicotine (0.25 and 0.5 mg/kg, s.c.) dose-dependently suppressed oICSS curves, suggesting aversive effects due to reduced DA-dependent brain-stimulation reward. Pretreatment with mecamylamine (a non-selective nAchR antagonist), dihydro-β-erythroidine (a selective α4β2 antagonist), and methyllycaconitine (a selective α7 antagonist) dose-dependently blocked nicotine attenuation of oICSS. These findings suggest nicotine produces aversive effects via α4β2- and α7 nAchR-mediated reductions in DA-dependent brain reward. Given that optogenetic stimulation maximally activates VTA DA neurons, nAchRs on DA neurons seem unlikely to drive these effects. Therefore, future studies will elucidate whether α4β2 nAchRs on VTA GABAergic neurons contribute to nicotine-induced aversion to DA neuron stimulation.

Disclosures: C.J. Jordan: None. **G. Bi:** None. **E.L. Gardner:** None. **Z. Xi:** None.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.05

Topic: G.08. Drugs of Abuse and Addiction

Support: DA015369
DA012513
DA003906
DA037722
DA016511

Title: Cell type specific neuroadaptations and metaplasticity in the nucleus accumbens core in a novel model of THC self administration in rats

Authors: *D. NEUHOFER[1], L. N. BELOATE[2], V. CHIOMA[3], S. M. SPENCER[4], P. W. KALIVAS[5]
[1]Neurosci., MUSC, Charleston, SC; [2]Neurosci. Dept., [3]Neurosciences, [4]Neurosci., Med. Univ. of South Carolina, Charleston, SC; [5]Neurosci. Res., Med. Univ. S Carolina, Charleston, SC

Abstract: Our understanding of the neural mechanisms underpinning addiction and relapse to marijuana has been hampered by the lack of a self-administration and relapse rodent model. We employ a novel protocol using intravenous self-administration of two constituents of marijuana, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) to examine how contingent marijuana exposure changes glutamatergic neurotransmission in the nucleus accumbens (NAc), thereby affecting synaptic plasticity and drug seeking behavior. Glutamatergic plasticity in the NAc is a key neuronal substrate of appetitive learning that allows adaptive behavioral responding to changing environmental contingencies. Consequently, dysfunction in the expression of synaptic plasticity parallels behavioral deficits in many murine models of neuropsychiatric diseases, including addiction. One form of impaired plasticity associated with chronic drug use is loss of a postsynaptically expressed NMDA-dependent LTD induced by a low frequency pairing protocol (i.e. 1-5 Hz stimulation + depolarization of the postsynaptic cell to -50 mV) in NAc medium spiny neurons (MNSs). In vivo and in vitro LTD is abolished after withdrawal or extinction from cocaine self-administration, and in vivo after extinction from heroin self-administration. These studies indicate that, despite the different neuroadaptations caused by chronic heroin or cocaine, both drugs induce similar impairments in synaptic plasticity. Our data indicate that THC+CBD use can be added to the list of addictive drugs that produce a loss of NMDAR-LTD in NAc MSNs. This metaplasticity accompanies with strong desensitization of CB1 receptors. Since CB1R regulate glutamate release, their desensitization could be a possible explanation for THC+CBD induced metaplasticity. Furthermore, we discovered that LTD is

restored in animals undergoing cue-induced reinstatement of THC+CBD seeking. MSNs can express either D1 or D2 receptors and it has been demonstrated that these two distinct populations differently regulate reward behaviors. Preliminary data using two newly developed D1- and D2-Cre transgenic rats transfected with AAV2-EF1a-DIO-eYFP to specifically label D1 and D2 MSNs, we demonstrated that THC+CBD induces cell type specific neuroadaptations and metaplasticity.

Disclosures: D. Neuhofer: None. **L.N. Beloate:** None. **V. Chioma:** None. **S.M. Spencer:** None. **P.W. Kalivas:** None.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.06

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH R01 MH065974
CIHR Post-Doctoral Fellowship

Title: Cocaine alters projection-specific synaptic connectivity in the nucleus accumbens

Authors: *C. BAIMEL, L. M. MCGARRY, A. G. CARTER
New York Univ., New York, NY

Abstract: Repeated exposure to drugs of abuse alters neural circuits within the nucleus accumbens (NAc). Medium spiny neurons (MSNs) are the principle cells of the NAc and are often divided into two broad subpopulations based on expression of dopamine 1 or 2 receptors. The activity of $D1^+$ and $D2^+$ MSNs is regulated by multiple long-range excitatory inputs to the NAc, including from the ventral hippocampus (vHPC) and the basolateral amygdala (BLA), and drug exposure strongly alters these synaptic connections onto $D1^+$ MSNs in an input-specific manner. However, $D1^+$ MSNs are not a homogenous cell population, and can be further subdivided by their downstream projection targets, including the ventral pallidum and the ventral tegmental area. Yet the basal synaptic connectivity and the impact of repeated drug exposure on these output-specific circuits remains unknown. Here we use anatomical tools, whole-cell electrophysiology, two-photon microscopy and optogenetics to examine how repeated cocaine exposure alters the connectivity of excitatory inputs onto projection-target defined neurons in the mouse NAc medial shell. We find that in drug-naïve mice, there are projection-target specific differences in response to activation of long-range excitatory inputs.
We also demonstrate how exposure to repeated cocaine alters these connections in a projection-target dependent manner. Together, our work reveals how repeated cocaine reorganizes both cell-type and projection-target specific connectivity in the NAc.

Disclosures: C. Baimel: None. **L.M. McGarry:** None. **A.G. Carter:** None.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.07

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R00DA032681
PhRMA Foundation Research Starter Grant

Title: Microglial activation in the nucleus accumbens during nicotine withdrawal

Authors: A. ADELUYI[1], M. FISHER[2], L. R. FREEMAN[4], S. CHAN[5], S. DAVIS[3], M. WYATT[1], *J. R. TURNER[1]
[1]DDBS, Univ. of South Carolina Col. of Pharm., Columbia, SC; [2]Col. of Pharm., [3]Univ. of South Carolina, Columbia, SC; [4]Biol. and Neurosciences, Furman Univ., Greenville, SC; [5]DDBS, Med. Univ. of South Carolina Col. of Pharm., Charleston, SC

Abstract: Tobacco smoking is the leading cause of preventable morbidity and mortality globally. Yet, about 80% of smokers attempting to quit, fail. Smoking cessation interventions developed to improve quit success rate among smokers have been ineffective in reducing nicotine withdrawal phenotypes underlying smoking relapse. Recent studies show that nicotine withdrawal during smoking cessation may lead to increased inflammatory responses and consequential oxidative load. While the role of oxidative stress in the pathogenesis of many neurodegenerative disorders is established, its contribution to the nicotine withdrawal phenotypes is unknown. To evaluate excessive production of reactive oxygen species (ROS) and its contribution to the development of anxiety-like behavior during nicotine withdrawal, mice were subjected to 48h withdrawal following chronic treatment (15days) with either saline or nicotine (18 mg/kg/day) via osmotic minipump implantation. A day prior to withdrawal, and each morning for the next 3 days, both saline and nicotine-treated mice received either vehicle or N-acetylcysteine (NAC - 150 mg/kg per day) intraperitoneally, and behavioral tests were conducted 30 minutes post-injection at the 24h (Open field test - OF) and 48h (Marble-burying test - MB) time points. In this experiment, we used NAC as an antioxidant tool and found that increased expression of pro-inflammatory cytokines (TNFα and IL1β mRNA) and associated ROS in the nucleus accumbens during withdrawal were attenuated by NAC treatment. A similar profile was seen in NADPH oxidase 2 (NOX2) mRNA and protein expression analysis, suggesting this molecule as the key producer of ROS during nicotine withdrawal. Further studies in the nucleus accumbens showed microglial activation during nicotine withdrawal. Interestingly, amongst the cell types in the brain, NOX2 is mainly expressed in microglia, suggesting that ROS induction during nicotine withdrawal is microglia-related. Finally, our behavioral studies showed

that NAC-treated withdrawal mice displayed anxiolytic effects in both OF and MB task in contrast to the vehicle-treated counterparts. Altogether, our evidence suggests that microglial activation and associated Nox2-induced ROS in the nucleus accumbens drive anxiogenic behavior during nicotine withdrawal in mice. Our findings demonstrate that nicotine withdrawal induces oxidative stress via activation of microglial-Nox2 pathway, which drive the development of anxiety-like behavior during smoking cessation. Therefore, antioxidants targeting ROS production via this pathway may be promising compounds for smoking cessation therapeutics.

Disclosures: A. Adeluyi: None. **M. Fisher:** None. **L.R. Freeman:** None. **S. Chan:** None. **S. Davis:** None. **M. Wyatt:** None. **J.R. Turner:** None.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.08

Topic: G.08. Drugs of Abuse and Addiction

Title: Neuron subtype-specific role of ten-eleven translocation protein 1 (TET1) in cocaine addiction

Authors: *J. FENG, H. XU, G. KAPLAN, A. BROWN, R. HEDINGER, V. JOSEPH
Dept. of Biol. Sci., Florida State Univ., Tallahassee, FL

Abstract: DNA methylation is considered a key epigenetic mechanism underlying drug addiction. Recently, additional DNA epigenetic modifications have been identified through the oxidation of methylated DNA cytosine to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5-fC), 5-carboxylcytosine (5-caC) by ten-eleven translocation proteins (TET), which may lead to DNA demethylation. Genes of the three members of the TET family are expressed in the adult brain; however, their potential role in drug addiction is still largely unknown. Our previous study found that TET1 in the nucleus accumbens (NAc) is implicated in cocaine action, suggesting a functional role of DNA modifications in cocaine-induced behavioral responses. In the present study, we investigated the impact of *Tet1* deletion in either dopamine D1 receptor-expressing medium spiny neurons (D1-MSN) or dopamine D2 receptor-expressing MSNs (D2-MSN) in mouse NAc on behavioral responses to cocaine in reward- and addiction-related behavioral paradigms. The rewarding effect of cocaine on mice with TET1 deficiency in D1- or D2-MSNs was evaluated using the conditioned place preference (CPP) paradigm. Operant intra-venous self-administrations (SFA) of cocaine was also evaluated. Our research found that D1-MSN specific knockout of *Tet1* in male mice enhances the rewarding value of cocaine, potentiates the vulnerability to cocaine binge, and amplifies the incentive motivation for taking cocaine. Collectively, these data suggest neuron subtype-specific roles of TET1 in cocaine reward and reinforcement.

Disclosures: J. Feng: None. **H. Xu:** None. **G. Kaplan:** None. **A. Brown:** None. **R. Hedinger:** None. **V. Joseph:** None.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.09

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH F32 DA044691
NIH R01 DA038138

Title: Local inhibitory circuitry in the nucleus accumbens

Authors: *S. L. SCUDDER, E. E. MACDONALD, A. G. CARTER
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: The nucleus accumbens (NAc) is largely composed of medium spiny neurons (MSNs), which integrate excitatory inputs from diverse brain regions and project to multiple downstream areas. MSNs rely on long-range glutamatergic input to fire, making the exact details of their activation a critical focus of study. However, while the importance of feed-forward inhibition in regulating projection neuron activity has been long appreciated in cortical areas, little is known about whether such a circuit mechanism exists in the ventral striatum, including which cell types are responsible. A small population of local inhibitory interneurons is known to exist in the NAc, but it is unclear what drives the activity of these cells and how they regulate the firing of nearby MSNs. We first demonstrate that activation of fibers from the ventral hippocampus (vHPC) elicits robust feed-forward inhibition in both D1+ and D1- MSNs. We show that GABAergic neurons expressing parvalbumin (PV+) and somatostatin (SOM+) are comingled with MSNs in the medial shell of the NAc and exhibit distinct morphological and physiological properties. We find that both classes of interneurons receive direct glutamatergic input from the vHPC, with distinct synaptic properties compared to MSNs. Additionally, we determine how different classes of interneurons are capable of inhibiting D1+ and D1- MSNs, indicating which cell types participate in feed-forward inhibitory circuits. Finally, we demonstrate that repeated cocaine exposure has different effects on the excitation and inhibition of MSNs. Together, our results highlight a previously under-appreciated role for local interneurons in controlling MSN activation in response to glutamatergic input, and may provide additional mechanisms for altering the output of the NAc during reward learning or exposure to drugs of abuse.

Disclosures: S.L. Scudder: None. **E.E. Macdonald:** None. **A.G. Carter:** None.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.10

Topic: G.08. Drugs of Abuse and Addiction

Support: DA033404
DA040965
P30GM103398

Title: Time course of changes in parvalbumin and perineuronal nets in the rat medial prefrontal cortex after activation of a cocaine-associated memory

Authors: B. A. SORG[1], A. E. GONZALEZ[2], *J. H. HARKNESS[3], J. M. BLACKTOP[4], E. T. JORGENSEN[5], T. E. BROWN[6]
[1]Integrative Physiol. and Neurosci., [2]Washington State Univ., Vancouver, WA; [3]Neurosci., Washington State University, Vancouver, Vancouver, WA; [4]Dept. of Integrative Physiol. and Neurosci., Washington State Univ. Vancouver, Vancouver, WA; [5]Neurosci., [6]Sch. of Pharm., Univ. of Wyoming, Laramie, WY

Abstract: Perineuronal nets (PNNs) are specialized extracellular matrix structures that wrap primarily around parvalbumin-containing, fast-spiking interneurons (PV-FSIs) in the medial prefrontal cortex (mPFC). We previously found that PNNs in the mPFC were necessary for the consolidation and reconsolidation of cocaine-associated memories and more recently that cocaine exposure alters the intensity of PNNs and PV in the mPFC. Here we examined the time course of changes in PV and PNN intensity after reactivation of a cocaine-associated memory. Rats were initially trained for cocaine-induced conditioned place preference (CPP) with three injections of saline (1 mL/kg, intraperitoneal, ip) alternating with three injections of cocaine (12 mg/kg, ip). Re-exposure occurred 1 day later in a drug-free state, and rats were killed at either 30-45 min, 2 hr, 6 hr, or 24 hr later. A separate cohort of rats was killed prior to any re-exposure as a baseline control (t = 0). Brain slices were stained and quantified for PNNs using *Wisteria floribunda* agglutinin (WFA) or PV. Changes in the intensity of WFA were small in magnitude, but significantly increased at 6 hr, and then decreased 24 hr later. The changes in PV intensity were greater, with a 35% decrease in PV intensity just 30-45 min after re-exposure to the CPP chamber. While this initial decrease gradually diminished over time, there was still a small but sustained decrease of PV intensity up to 24 hr later. Slice electrophysiology studies in FSIs in the mPFC surrounded by PNNs (likely containing PV) showed that re-exposure to the CPP chamber reduced the number of action potentials at the 30 min and 2 hr time points, but that normal levels were resumed 24 hr later. These findings indicate that reactivating a cocaine-associated CPP

memory produces rapid decreases in PV content, which may reflect the decrease in firing, while early PNN intensity changes mirrored those of PV but were smaller in magnitude.

Disclosures: B.A. Sorg: None. **A.E. Gonzalez:** None. **J.H. Harkness:** None. **J.M. Blacktop:** None. **E.T. Jorgensen:** None. **T.E. Brown:** None.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.11

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA033404 to Barbara A. Sorg
NIH Grant DA040965 to Barbara A. Sorg
WSU Alcohol & Drug Abuse Research Program Grant 124777 to Jordan M. Blacktop

Title: Role of anterior dorsal lateral hypothalamic area perineuronal nets in cue-induced reinstatement of cocaine-seeking behavior

Authors: *J. M. BLACKTOP[1], B. A. SORG[2]
[1]Dept. of Integrative Physiol. and Neurosci., Washington State Univ. Vancouver, Vancouver, WA; [2]Integrative Physiol. and Neurosci., Washington State Univ., Vancouver, WA

Abstract: Addiction involves drug-induced neuroplasticity of the circuitry of motivated behavior, which includes the medial forebrain bundle and the lateral hypothalamic area (LHA). Emerging at the forefront of neuroplasticity regulation are specialized extracellular matrix structures that form perineuronal nets (PNNs) around parvalbumin positive (PV^+) fast-spiking interneurons (FSINs), making them a promising target for the regulation of drug-induced neuroplasticity. Brain regions within the circuitry of motivated behavior with comparatively high PNN expression may provide neurobiological insight into maladaptive drug-induced neuroplasticity and subsequent drug seeking. Very little is known about how PNN-expressing neurons in the LHA control drug-seeking behavior. We previously reported that the dorsal and intermediate zones of the anterior lateral hypothalamic area (LHAad) exhibited robust PNN expression using the PNN marker *Wisteria floribunda* agglutinin (WFA), and that approximately two-thirds of WFA positive neurons co-expressed PV. Removal of PNNs with the enzyme chondroitinase ABC (Ch-ABC) blocked the acquisition of cocaine- but not sucrose-induced CPP and self-administration. Here we focused on the rodent model of relapse (reinstatement). The goals of this set of experiments were to: 1) determine whether PNN expression within the LHAad is necessary for cue-induced reinstatement 2) characterize the phenotype of LHAad PNN-surrounded neurons, and 3) determine mesocorticolimbic inputs to and projections from the LHAad. Here we report that LHAad PNNs are necessary for the expression of cue-induced

reinstatement of cocaine- but not sucrose-seeking behavior. The phenotype of LHAad PNN-surrounded neurons was determined using the excitatory markers VGLUT2 and glutamate and the inhibitory markers GAD65/67 and GABA. Predominant co-localization of WFA with VGLUT2 and GABA over GAD65/67 and glutamate suggests that the PNN-rich LHAad receives dense glutamatergic input and is predominantly GABAergic. The LHAad does not express significant amounts of galanin, orexin, or melanin-concentrating hormone (MCH). Retrobead injections demonstrates that the LHAad provides minimal input into the PL PFC and NAc, receives robust PL PFC input, and provides moderate input into the VTA. In summary, these data indicate that PNN expression in the LHAad: 1) is necessary for expression of cue-induced reinstatement of cocaine-seeking behavior 2) is predominantly co-localized with PV+ GABAergic neurons that receives robust glutamatergic inputs, and 3) receives input from layer V of the prefrontal cortex and provides input into the VTA.

Disclosures: J.M. Blacktop: None. **B.A. Sorg:** None.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.12

Topic: G.08. Drugs of Abuse and Addiction

Support: DA033404
DA040965
Washington State University Alcohol and Drug Abuse Research Program

Title: Perineuronal net removal decreases cue-induced reinstatement in cocaine self-administering rats

Authors: *J. WINGERT[1], J. H. HARKNESS[2], R. TODD[3], B. A. SORG[4]
[1]Neurosci., Washington State Univ. Vancouver, Vancouver, WA; [2]Neurosci., Washington State University, Vancouver, Vancouver, WA; [3]Dept. of Vet. and Comparative Anatomy, Pharmacology, and Physiol., [4]Integrative Physiol. and Neurosci., Washington State Univ., Vancouver, WA

Abstract: Repeated exposure to cocaine can lead to the formation of persistent drug memories. Activation of these drug memories are a motivating force behind drug seeking behavior. One of the important brain structures for cocaine-induced drug seeking behavior and memory is the medial prefrontal cortex (mPFC). Here we investigated the effects of chondroitinase-ABC (Ch-ABC) on the reconsolidation of a cocaine-associated memory. Ch-ABC is an enzyme that degrades perineuronal nets (PNNs), a dense extracellular matrix structure surrounding a subset of GABAergic interneurons within the mPFC. We hypothesized that a novel reactivation session is

necessary to induce updating of habituated self-administration drug memories and in turn make the memory susceptible to weakening in the absence of PNNs. Male rats were trained to lever press for cocaine on a fixed ratio 1 (FR1) schedule of reinforcement for 10 days followed by injection of Ch-ABC in the mPFC. Three days following Ch-ABC, rats were given a 30 min memory reactivation session on either an FR1 or a novel variable ratio 5 (VR5) schedule of reinforcement. The next day, rats were tested for memory reconsolidation by measuring lever-pressing behavior for 30 min under extinction and then 30 min during cue-reinstatement. Ch-ABC did not affect the extinction; however, rats Ch-ABC reduced cue reinstatement when memory was reactivated by the VR5 session, indicating that memory is reconsolidated only when a novel reactivation session is used. Our results suggest that PNNs in the mPFC may be a target for novel therapies in cocaine addiction.

Disclosures: J. Wingert: None. **J.H. Harkness:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Washington State University. **R. Todd:** None. **B.A. Sorg:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Washington State University.

Nanosymposium

632. Circuitry and Cell-Type Specific Neurophysiology of Addiction

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 632.13

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA033404
NIH Grant DA040965
Washington State University Commercialization Gap fund FY 2017
Washington State University Postdoctoral Alcohol and Drug Abuse Research Program
NSF ICORPS Award# 1547873

Title: Oxidative stress and sleep: The role of perineuronal nets

Authors: J. H. HARKNESS[1], P. N. BUSHANA[2], R. TODD[3], W. C. CLEGERN[4], *B. A. SORG[5], J. P. WISOR[4]
[1]Neurosci., Washington State University, Vancouver, Vancouver, WA; [2]Integrative Physiol. and Neurosci., Washington State Univ., Spokane, WA; [3]Dept. of Vet. and Comparative Anatomy, Pharmacology, and Physiol., Washington State Univ., Vancouver, WA; [4]Washington State Univ., Spokane, WA; [5]Integrative Physiol. and Neurosci., Washington State Univ., Vancouver, WA

Abstract: Extracellular matrix aggregations called perineuronal nets (PNNs) surround the synapses of fast-spiking, parvalbumin (PV)-containing GABAergic interneurons. PNNs are important for stabilization of synapses following learning and for limiting plasticity after the critical period. Additionally, PNNs protect PV+ cells from oxidative stress at the cost of their own integrity. As they encounter reactive oxygen species, the major components of PNNs, chondroitin sulfates, are consumed as a substrate in oxidative buffering reactions. Oxidative stress increases in the brain during periods of wakefulness, and is alleviated by sleep. PNN intensity fluctuates with age, memory, experience, and drug exposure. To assess the role of PNNs during sleep/wake cycles, we investigated diurnal variation in PNN intensity in the prelimbic prefrontal cortex (PFC). The intensity of PNNs, the oxidative stress marker 8-oxo-dG, and PV were quantified in the rat PFC using PIPSQUEAK image analysis software at four time points (ZT0, ZT6, ZT12, ZT18) during the diurnal cycle. In the prelimbic PFC, PNNs displayed a diurnal rhythm, with significantly less intensity at ZT6 and significantly more intensity at ZT12 and ZT18 compared with ZT0. PV intensity was also increased at ZT18 compared to ZT0. To assess the impact of sleep deprivation on the intensity of PNNs, 8-oxo-dG, and PV, a separate group of rats was sleep deprived for 6 hours starting at ZT0. The intensity of PNNs, PV, and 8-oxo-dG were elevated in the prelimbic PFC of sleep-deprived rats compared with those allowed to spontaneously sleep. Smaller and fewer changes were found in the orbitofrontal PFC. We determined that PNNs fluctuate throughout the sleep/wake cycle, and this pattern is slightly altered by disrupting sleep. Understanding the relationship between PNN deposition and degradation during sleep/wake cycles may offer insights for therapeutic interventions related to sleep-related problems, including cognitive impairment during sleep loss.

Disclosures: J.H. Harkness: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Washington State University. **P.N. Bushana:** None. **R. Todd:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Washington State University. **W.C. Clegern:** None. **B.A. Sorg:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Washington State University. **J.P. Wisor:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.01

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust 101208/z/13/z

Title: Navigation using grid-like representations in artificial agents

Authors: *A. BANINO[1], C. BARRY[2], D. KUMARAN[3]
[1]Deepmind, London, United Kingdom; [2]UCL, London, United Kingdom; [3]DeepMind, London, United Kingdom

Abstract: Deep neural networks have achieved impressive successes in fields ranging from object recognition to complex games such as Go. Navigation, however, remains a substantial challenge for artificial agents, with deep neural networks trained by reinforcement learning failing to rival the proficiency of mammalian spatial behaviour, which is underpinned by grid cells in the entorhinal cortex. Grid cells are thought to provide a multi-scale periodic representation that functions as a metric for coding space and is critical for integrating self-motion (path integration) and planning direct trajectories to goals (vector-based navigation). Here we set out to leverage the computational functions of grid cells to develop a deep reinforcement learning agent with mammal-like navigational abilities. Specifically we trained a recurrent network to perform path integration, leading to the emergence of representations resembling grid cells, as well as other entorhinal cell types. Our findings show that emergent grid-like representations furnish agents with a Euclidean spatial metric providing a foundation for proficient navigation.

Disclosures: A. Banino: None. **C. Barry:** None. **D. Kumaran:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.02

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH100121
NIH Grant F32 NS098808

Title: Hippocampal cognitive maps formed through spatial navigation generalize to non-spatial contexts

Authors: *K. R. SHERRILL[1], R. J. MOLITOR[1], M. L. MACK[2], A. R. PRESTON[1]
[1]Univ. of Texas At Austin, Austin, TX; [2]Univ. of Toronto, Toronto, ON, Canada

Abstract: Prominent memory theories posit that cognitive maps are formed by integrating knowledge across distinct experiences. Neuroimaging studies indicate that the hippocampus (HPC) works in concert with medial prefrontal cortex (mPFC) to support formation of integrated cognitive maps. An important advantage of cognitive maps is their flexibility; information

learned in one context can be generalized to new situations. Our goal is to provide a representational account of this flexibility by characterizing how spatial cognitive map formation impacts processing in non-spatial contexts. Here, participants learned the locations of novel objects in distinct virtual environments during active navigation. Before and after learning, participants viewed the novel objects in isolation during fMRI scanning. If a distinct cognitive map is formed for each environment, objects experienced within the same environment should: (1) come to be represented similarly and (2) be neurally separable from objects experienced in different environments. Using representational similarity analysis, we calculated changes in pattern similarity for the novel objects from pre- to post-learning. We found that neural patterns in HPC and mPFC became: (1) more similar for same-environment objects and (2) more separable for different-environment objects, providing a direct measurement of cognitive map formation. Twenty-four hours later, participants were scanned while performing an incidental sequence task using the same objects from the spatial learning task. Participants made preference judgements for the objects. Unbeknownst to participants, objects were presented in sequential triplets comprising three objects from either the same or different environments. We predicted that cognitive maps formed during navigation would modulate behavior (response times) and neural responses (repetition suppression) for same- relative to different-environment triplets. Participants were slower to respond to an object at triplet boundaries, a behavioral marker of sequence segmentation. At the neural level, HPC showed increased repetition suppression for same- relative to different-environment triplets, indicating HPC representations of cognitive maps are brought to bear in new contexts. Furthermore, using pattern classification, we found increasing environment reactivation across same-environment triplets that directly related to HPC suppression. Collectively, these findings provide representational evidence of cognitive map flexibility showing how spatial experience shapes processing in new non-spatial contexts.

Disclosures: K.R. Sherrill: None. **R.J. Molitor:** None. **M.L. Mack:** None. **A.R. Preston:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.03

Topic: H.01. Animal Cognition and Behavior

Support: NSF STC award CCF-1231216

Title: Assessing the role of hippocampal replay in retrospective revaluation

Authors: *H. L. PENAGOS[1], S. J. GERSHMAN[3], M. A. WILSON[2]
[1]Picower Inst. for Learning and Memory, [2]Picower Inst. Learn/Memory, MIT, Cambridge, MA; [3]Harvard Univ., Cambridge, MA

Abstract: Computational accounts of decision-making portray action selection as the result of a competition between model-free and model-based systems. The former relies on repeatedly selecting previously rewarded actions while the latter uses an internal model of the environment to plan goal-directed behavior. The model-based system thus reflects the cognitive map hypothesis. Recent human data suggest that in the case of retrospective revaluation tasks, where subjects are allowed to change their preference between two choices after new independent evidence has been presented, a cooperative interaction between the two systems better accounts for the observed decision-making behavior. A key prediction of this cooperative architecture is that the model-based system replays and simulates experiences offline, linking all available evidence, to train the model-free system for future online action selection. Given the strong resemblance between hippocampal replay and the predicted role of the model-based system in retrospective revaluation, we designed a navigational version of the human task and recorded spiking activity in the hippocampus of four rats. We show that, like humans, rats are able to change prior preferences in light of new evidence with a stronger effect at the beginning of the testing sessions. Inspection of hippocampal activity during periods of quiet wakefulness, reveals that the hippocampus progressively incorporates new independent information, and represents it alongside previously acquired experiences. The joint representation of accumulated evidence is consistent with an offline mechanism that evaluates all potential options subjects could consider for action selection. Together with previous findings showing that pharmacological inactivation of the hippocampus prevents behavior consistent with model-based planning in rats, these results suggest that hippocampal replay is a suitable mechanism for the extraction and evaluation of the reward structure of the environment that allows model-based planning, in line with the cognitive map hypothesis.

Disclosures: H.L. Penagos: None. **S.J. Gershman:** None. **M.A. Wilson:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.04

Topic: H.01. Animal Cognition and Behavior

Support: NSF STC award CCF-1231216

Title: Hippocampal remapping as learned clustering of experience

Authors: *H. SANDERS[1], M. A. WILSON[2], S. GERSHMAN[3]
[2]Picower Inst. Learn/Memory, [1]MIT, Cambridge, MA; [3]Harvard Univ., Cambridge, MA

Abstract: A cognitive map describes the rules by which one expects the world to work. However, different rules apply under different circumstances, so we might expect that one would have many distinct cognitive maps. Hippocampal place cells have been identified as a potential substrate for the neural instantiation of cognitive maps. Indeed, it has been found that the hippocampus uses different maps for different environments. This phenomenon is known as hippocampal remapping. Past work has asked which environmental features lead to remapping, but no consistent answer has been reached. Any particular manipulation of the environment can have variable effects across training paradigms, across time, and across animals. However, this approach has ignored the place of context identification as part of a larger learning process.
In order to address this question, we must explicitly raise some of the complexities that make the context learning problem an intrinsically difficult problem. The animal does not know a priori what features of the environment will be relevant, nor does it have direct access to context identity labels. Fundamentally, this corresponds to an unsupervised clustering problem, where the animal receives a stream of experiences and must cluster them in a data-driven manner.
We model context learning as Bayesian nonparametric clustering. Our model recapitulates disparate phenomena associated with remapping. One is that the amount of experience with an environmental manipulation can diametrically change remapping behavior. Another is the difference in processing of familiar and novel environments. Another is that it can capture the seemingly contradictory responses to morphing environments found in different laboratories.
Our results emphasize that learning plays a large role in hippocampal remapping. Formalizing context learning as a clustering problems allows us to capture a range of experimental results that have not yet been explained by a single theoretical framework. This model also provides novel predictions including the effect of variability in training as well as providing novel analyses including characterizing animal-to-animal variability.

Disclosures: H. Sanders: None. **M.A. Wilson:** None. **S. Gershman:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.05

Topic: H.01. Animal Cognition and Behavior

Support: Alzheimer Society Canada Doctoral Award
CIHR Grant 49566

Title: Global and local hippocampal representations during virtual reality spatial navigation

Authors: *I. BRUNEC[1,2], B. BELLANA[1,2], J. OZUBKO[3], J. ROBIN[2], M. BARENSE[1,2], M. MOSCOVITCH[1,2]
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Rotman Res. Institute, Baycrest, Toronto, ON, Canada; [3]SUNY Geneseo, Geneseo, NY

Abstract: The ability to navigate in familiar environments requires reliance on a cognitive map, created from repeated experiences within those environments. At the same time, efficient navigation requires local representations embedded within the global map context. The hippocampus supports a gradient of representational granularity along its anteroposterior axis. It is hypothesized that the anterior hippocampus (aHPC) supports global contexts, and the posterior hippocampus (pHPC) supports local, detailed representations. In the present studies, we examined aHPC and pHPC representations while participants navigated in a virtualized version of a familiar environment (Toronto) using images from Google Street View. We found that when participants freely navigated familiar routes, signal across voxels in aHPC showed a lower degree of change over time and greater signal redundancy, relative to pHPC. Consistent with our hypothesis, this finding suggests that information is represented on a more local scale in pHPC, relative to aHPC. In a follow-up study, we examined goal coding in the hippocampus and were able to reconstruct the map of the goals in the environment from hippocampal activity patterns. Further, we examined participants' tendency for map-based navigation, relative to scene-based navigation, and found that greater map-based navigation tendency correlated with more distinctive location coding in the hippocampus. Together, these results point to a fundamental role of the hippocampus in maintaining cognitive maps of the environment at multiple scales.

Disclosures: I. Brunec: None. **B. Bellana:** None. **J. Ozubko:** None. **J. Robin:** None. **M. Barense:** None. **M. Moscovitch:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.06

Topic: H.01. Animal Cognition and Behavior

Support: Google Employment
NSF CRCNS IIS-120 7833
The John Templeton Foundation

Title: Compression by grid cells to support hierarchical reinforcement learning in the cognitive map

Authors: *M. M. BOTVINICK[1], K. L. STACHENFELD[3,1], D. MCNAMEE[4], S. GERSHMAN[2]
[1]Princeton Univ., Princeton, NJ; [2]Princeton Univ., Brooklyn, NY; [3]DeepMind, London, United Kingdom; [4]Computat. and Biol. Learning Lab., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Our goal is to understand the cognitive map from the perspective of how spatial representations might support reinforcement learning (RL). Toward that end, we characterize grid cells as a compact representation of the transition dynamics across all temporal scales of a task by modeling grid cells as encoding eigenvectors of the transition matrix. These eigenvectors yield a compact representational basis that can be used to dimensionally reduce the place cell code in hippocampus. We review a number of reasons why this is useful from a reinforcement learning perspective. First, the eigenvectors can be used to denoise the hippocampal place code by applying topologically sensitive smoothing to the spatial representations. This enables RL mechanisms to smoothly generalize reward representations to topologically neighboring states. Second, these eigenvectors provide multi-scale support to place maps by encoding distinct topological structure across spatial scales. This allows the same eigenvectors to scale planning to long spatial scales thus allowing large maps to be learned faster. Furthermore, the same eigenvector code also can be used to support different place maps with the same underlying adjacency structure, suggesting a substrate for transfer across contexts.
Importantly, this putative entorhinal representation also comprises a useful basis for planning hierarchically. The eigenvectors can be used to factor the transition dynamics into position- and time- dependent terms. This means that space and time can be represented in separate population codes and flexibly recombined to estimate location at different times in the future and at arbitrary temporal resolutions. These eigenvectors can also be used to extract subgoals at environmental bottlenecks.
Since this model of grid cells depends on temporal adjacency rather than physical distance in space, it predicts that environmental geometry should have specific effects on grid fields. We apply this model to tasks from recent experiments with grid cells that manipulate the geometry of spatial tasks and show that we capture many observed phenomena. We can also apply our model to non-spatial tasks thus interfacing with recent data suggesting that abstract conceptual spaces may also be represented with a gridlike code.

Disclosures: M.M. Botvinick: A. Employment/Salary (full or part-time):; DeepMind, Google. **K.L. Stachenfeld:** A. Employment/Salary (full or part-time):; DeepMind, Google. **D. McNamee:** None. **S. Gershman:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.07

Topic: H.01. Animal Cognition and Behavior

Support: NSERC RGPIN-2014-04947
Google Faculty Award
CIFAR

Title: Mice adapt differently to changes in the reward and transition structure of the environment

Authors: *S. SATHIYAKUMAR[1], A. CARSON[2], B. A. RICHARDS[3]
[1]Univ. of Toronto, Scarborough, ON, Canada; [3]Biol. Sci., [2]Univ. of Toronto Scarborough, Scarborough, ON, Canada

Abstract: The ability to rapidly adapt to changes in the environment is vital to our survival. One possible mechanism for promoting adaptability is the flexible representations of the hippocampus. Traditionally, the hippocampus has been thought of as a cognitive map representing the current state of the environment. But, an emerging theory of hippocampal function suggests that this might not be the case. The hippocampus may actually be representing a predictive map, by computing the successor representation. This theory makes explicit predictions about the ability to adapt to two different types of change. First, mice should be able to easily adapt to changes to the reward structure of the environment. Second, it will be more challenging for mice to adapt to changes to the transition structure of the environment. We have developed a novel behavioural paradigm using a Y-maze to test the performance of mice on these changes. Their performance on these complex tasks and the neural substrates that are employed to complete them have never been investigated. Furthermore, the time dependent role of neural substrates in these tasks also remains unknown. We report that mice are able to adapt to reward changes in the environment but find it challenging to adapt to changes in transition structure. Furthermore, mice are able to adapt better to changes after a shorter delay when the hippocampus is still likely engaged compared to mice that underwent a longer delay. This work provides preliminary insights about the possible predictive nature of the hippocampus.

Disclosures: S. Sathiyakumar: None. **A. Carson:** None. **B.A. Richards:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.08

Topic: H.01. Animal Cognition and Behavior

Support: Simons Collaboration on the Global Brain

Title: Probing variability in a cognitive map using manifold inference from neural dynamics

Authors: *R. J. LOW, S. J. LEWALLEN, D. ARONOV, R. NEVERS, D. W. TANK
Princeton Univ., Princeton, NJ

Abstract: Hippocampal neurons fire selectively in local behavioral contexts such as the position in an environment or phase of a task. These behavioral firing fields may reflect an underlying cognitive map of task-relevant variables. However, behavioral firing fields correspond to the average activity of single neurons over repeated behavioral conditions, and do not account for relationships between neurons or for moment-to-moment activity, which varies across trials. This variability is not well understood, and could reflect noise or structure, such as the encoding of additional cognitive information.
Here, we investigated whether single-trial hippocampal activity reflects a deeper organization at the population level. We developed a novel manifold learning algorithm incorporating temporal dynamics, in order to characterize population activity as a trajectory on a nonlinear space of possible network states. The manifold's structure captures correlations between neurons and temporal relationships between states---constraints that arise from underlying network architecture and inputs. Using measurements of activity over time but no information about exogenous behavioral variables, we recovered hippocampal activity manifolds during spatial navigation and non-spatial tasks in rats.
Manifolds were low dimensional and smoothly encoded task-related variables, but contained an extra dimension beyond the measured behavioral variables. Many neurons formed compact firing fields on the manifold by firing selectively in local neighborhoods of network states. The network followed a different trajectory through these fields on each trial, which accounted for trial-to-trial variability in the amplitude and relative timing of individual neuronal responses. The network trajectory could also diverge from encoding current behavior, and briefly traverse neighboring manifold points corresponding to past, future, or nearby behavioral states.
Our results suggest that hippocampal activity is constrained to low dimensional, nonlinear manifolds, and is strongly modulated but not completely determined by measured behavioral variables. Trial-to-trial variability is structured, and reflects variation in the network's trajectory through fields on manifold, which span an extra ‘hidden’ dimension.

Disclosures: R.J. Low: None. **S.J. Lewallen:** None. **D. Aronov:** None. **R. Nevers:** None. **D.W. Tank:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.09

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant T32MH112507-01
National Security Science and Engineering Faculty Fellowship (Office of Naval Research Grant N00014-15-1-0033)

Title: Hippocampal representation of contexts and journeys during goal-directed navigation

Authors: *J. CRIVELLI-DECKER[1], A. CLARKE[1,2], C. RANGANATH[1]
[1]Ctr. for Neurosci., UC Davis, Davis, CA; [2]Univ. of Cambridge, Cambridge, United Kingdom

Abstract: The hippocampus is involved in both episodic and spatial memory. Theories of hippocampal function attempt to bridge these two seemingly separate research lines by proposing either that hippocampus anchors memories to a cognitive map of space (O'Keefe & Nadel, 1978), or that it encodes a multidimensional "memory space", that systematically links related episodes in the same context (Eichenbaum et al., 1999). To test these theories, we created a novel paradigm in which participants use buttons to actively navigate through a series of different animals in two distinct "zoo" contexts, each structured to be analogous to the plus maze used in studies of the rodent hippocampus (e.g., Behar & Shapiro, 2012). Animal images and pairwise sequential associations between the animals were identical across both contexts, but the global configurations were shifted such that the route to navigate from the same start and endpoints varied across the two contexts. During the exploration phase, subjects were oriented to the plus maze layouts and then allowed to explore each zoo by making button presses (Up, Down, Left, or Right) to move to another animal. After participants learned the zoo layout, they were scanned during a task that required them to use button presses to actively "navigate" from a starting animal to a goal animal. We expected that, if the hippocampus represented two-dimensional maps of the contexts, then hippocampal voxel patterns would reflect the current animal participants were viewing during navigation, whereas if the hippocampus represented points along a journey, voxel patterns would differentially represent each animal in a manner specific to the sequence of animals between the start and the goal. Consistent with the latter idea, hippocampal activity patterns were sensitive to the specific zoo context and the context-specific animal sequence participants were traversing on the current trial. Together, these findings suggest that during goal-directed navigation, the hippocampus represents the spatio-temporal

relationships between current and future events, rather than the current location in an environment.

Disclosures: J. Crivelli-Decker: None. **A. Clarke:** None. **C. Ranganath:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.10

Topic: H.01. Animal Cognition and Behavior

Support: ONR MURI N00014-16-1-2832

Title: Constructing neural cognitive maps of time, space and concepts

Authors: *Z. TIGANJ, N. A. CRUZADO, A. LUZARDO, M. W. HOWARD
Ctr. for Memory and Brain, Dept. of Psychological and Brain Sci., Boston Univ., Boston, MA

Abstract: Constrained by results from classic behavioral experiments we provide a neural-level cognitive architecture for navigating memory and decision making space as a cognitive map. We propose a canonical microcircuit that can be used as a building block for working memory, spatial navigation, decision making and cognitive control. The controller controls gates to route the flow of information between the working memory and the evidence accumulator and sets parameters on the circuits. We show that this type of cognitive architecture can account for results in behavioral experiments such as item recognition and judgment of recency. We compare predictions of the formal model to recent neurophysiological data. The neural dynamics generated by the cognitive architecture provides a good match with neurophysiological data from rodents and monkeys. For instance, it generates cells tuned to a particular amount of elapsed time (time cells), to a particular position in space (place cells) and to a particular amount of accumulated evidence.

Disclosures: Z. Tiganj: None. **N.A. Cruzado:** None. **A. Luzardo:** None. **M.W. Howard:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.11

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust Senior Research Fellowship WT104765MA
Wellcome Trust New Investigator Award 096689/Z/11/Z

Title: Navigation of abstract discrete worlds by rhesus macaques

Authors: *J. BUTLER[1], S. MARK[1], T. E. J. BEHRENS[3,2], S. KENNERLEY[1]
[1]Inst. of Neurology, Sobell Dept., [2]Inst. of Neurology, Wellcome Ctr. for Human Neuroimaging, Univ. Col. London, London, United Kingdom; [3]Wellcome Ctr. for Integrative Neuroimaging, Univ. of Oxford, Oxford, United Kingdom

Abstract: To navigate spatial environments it is thought the brain builds a 'cognitive map' representing the different features of the environment (Tolman, 1948). Cells in the hippocampal and entorhinal system encode different features of spatial environments, making it likely they form the building blocks of a cognitive map (O'Keefe & Dostrovsky, 1971; Hafting et al., 2005). Recently these systems have also been found to encode features of non-spatial environments, such as the head and neck lengths of birds (Constantinescu et al., 2016) or the different frequencies of audible sound (Aronov et al., 2017). The ability to navigate non-continuous domains, however, has not yet been investigated. We therefore developed a novel behavioural task to test the navigation of non-spatial discrete environments composed of graphs of interconnected stimuli. A custom-made tablet system was used to train two rhesus macaques (Macaca mulatta) in their home cage. Several different environments were taught to the subjects, ranging from a linear track of 10 stimuli to a large 6x12 environment with 4 edges per node. Both subjects learnt all environments to a high ability, being able to navigate to targets many positions away with few errors. There was no correlation between direction and performance (e.g. A:C vs C:A), suggesting that subjects learnt the map in a direction-dependent manner. Later parts of each map were learnt quicker than earlier parts, demonstrating that subjects extracted global statistics of each environment to facilitate their navigation. For most trials there were multiple routes of equal length that led to the target location. When navigating, a tree search-based strategy would favour all of these routes equally, whereas a successor representation (SR)-based strategy would prefer particular routes over others depending on the different features and assigned values of each route. Both subjects consistently showed strong biases for certain routes over others on all maps tested, suggesting they used an SR-based strategy of navigating. We have therefore shown that non-human primates can navigate complex abstract environments and

employ sophisticated strategies to facilitate this process. We are preparing to perform simultaneous electrophysiological recordings in the hippocampus, entorhinal cortex, and multiple subregions of the prefrontal cortex to elucidate the cellular representations that underlie these behaviours.

Disclosures: J. Butler: None. **S. Mark:** None. **T.E.J. Behrens:** None. **S. Kennerley:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.12

Topic: H.01. Animal Cognition and Behavior

Support: The Templeton Foundation

Title: Sculpting cognitive maps: Multi-scale predictive representations shape memory and planning

Authors: *I. MOMENNEJAD[1], I. BRUNEC[2], N. D. DAW[1]
[1]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]Univ. of Toronto, Toronto, ON, Canada

Abstract: We extract structures from dynamically unfolding streams of experience. As we navigate the world, what kinds of representations does the brain build and store in memory, or retrieve in order to make decisions? How does the brain update these representations? Previously we have shown behavioral evidence that the human brain builds and stores predictive maps (i.e. the successor representation) in memory that cache multi-step dependencies and uses them for fast and flexible planning (Momennejad et al. 2017, Nat Hum Beh). We have also shown that predictive representations and planning policies are updated via offline replay that prioritizes replay of trajectories marked with uncertainty through striatal, frontal cortex, and hippocampal interactions (Momennejad et al. 2017, bioRxiv). Drawing on this work, we propose that the brain simultaneously learns and stores multiple predictive maps at different scales of abstraction. A candidate neural structure for learning multi-scale predictive maps is the long axis of the hippocampus. The anterior hippocampus (ventral hippocampus in rodents) has been associated with larger place fields, integration of states further apart, and longer time horizons, while the posterior (rodent: dorsal) hippocampus is more myopic. We hypothesized to observe predictive maps with information about states further away in the anterior hippocampus, and predictive maps with myopic horizons in the posterior hippocampus. We test this hypothesis using representational similarity and machine learning to analyze neuroimaging data during virtual navigation of familiar and novel routes. We examine the structure of correlations between steps

along each trajectory to uncover multi-scale predictive representations along the long axis of the hippocampus. We predict that in the familiar compared to novel paths, the anterior hippocampus caches predictive maps with larger scales (i.e. mapping relations to goals or successor states that are distal), while the posterior hippocampus caches predictive maps with smaller scales (i.e. maps information about more proximal states). At decision time, selecting the optimal representation scale depends on the statistical structures of the world and downstream input from task representations. Such task-dependent learning and selection of predictive representations with optimal scales enable goal-directed clustering, segmenting, and chunking of ongoing experience. Computationally, these multi-scale predictive maps can be used to estimate temporal and cognitive distance between events (e.g. distance to goal or duration judgments) during decision making.

Disclosures: I. Momennejad: None. **I. Brunec:** None. **N.D. Daw:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.13

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 1P01HD080679
Leverhulme Trust grant RPG-2014-075
Wellcome Trust Senior Investigator Award WT106931MA

Title: A non-spatial account of place and grid cells based on clustering models of concept learning and memory

Authors: *R. M. MOK, B. C. LOVE
Univ. Col. London, London, United Kingdom

Abstract: There is increasing interest in how the brain might use non-spatial cognitive maps to represent conceptual relations, which raises the question of what type of algorithm the brain would use to support these computations. Place and grid cells are thought to support a map-like representation for space, but recent work suggests grid cells might also map conceptual spaces. The hippocampal-entorhinal (HPC-EC) circuit appears to play a role across multiple cognitive domains including navigation, memory and category learning - does this brain circuit perform a common computation across these tasks? If so, what is the relationship between representations in conceptual and spatial tasks? We propose that the brain uses a clustering algorithm to build representations in both conceptual and spatial navigation tasks. In this account, spatial tasks are a subset of a more general class of concept learning tasks, rather than a distinct subclass or a basis

for concept learning. Clustering models have successfully modeled concept learning behaviour and representations in HPC. We present a clustering model that produces place and grid cell-like activity when applied to spatial tasks. We simulated an agent who explored a square or circular environment uniformly across 2D space. The model starts with clusters at random points, and on each trial, the closest cluster moves its position slightly toward the agent's location. After exploration, clusters spread out and often formed a hexagonal pattern. Our model replicated empirical findings, producing maps like grid and irregular spatially-selective (ISS) cells in a square and circular box. We propose that place cells are clusters in feature space representing specific concepts (c.f. 'concept' cells), and grid and ISS cells monitor a subset of place cells, in terms of error or uncertainty of category membership, enabling category knowledge. Communication between grid and place cells provides a link between concepts and can be structured in various ways from simple associations to feature-based categories to hierarchical structures. As such, grid and ISS cells in the EC may work with subsets of place cells in the HPC for the organization of conceptual knowledge.

Disclosures: R.M. Mok: None. **B.C. Love:** None.

Nanosymposium

633. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC 1

Time: Wednesday, November 7, 2018, 8:00 AM - 11:30 AM

Presentation Number: 633.14

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH100121
NIH Grant MH114869

Title: Events with common structure become organized within a hierarchical cognitive map in hippocampus and frontoparietal cortex

Authors: *N. W. MORTON[1], M. L. SCHLICHTING[2], A. R. PRESTON[1]
[1]The Ctr. for Learning & Memory, The Univ. of Texas at Austin, Austin, TX; [2]Dept. of Psychology, Univ. of Toronto, Toronto, ON, Canada

Abstract: Recent research suggests that the episodic memory system links individual events according to their shared features, allowing for inference about unobserved relationships among event elements. However, a true cognitive map also allows one to generalize information learned in one setting to another, distinct setting. For example, learning your way around a city may involve learning about the downtown area of that city, compared to midtown and uptown areas. Such a cognitive map goes beyond individual relationships among events to represent a general structure of how the city is organized, which may promote adaptive behavior in a new city. For

example, based on your cognitive map, you might infer that upscale restaurants are likely to be located downtown. Here, our goal was to dissociate brain regions that link information from different events from those that extract higher-order structure across different settings. Participants learned pairs of novel objects (AB, BC) that were drawn from distinct triads (ABC), each with three unique objects. After learning, each object was presented in isolation during fMRI scanning, allowing us to measure the neural representations of individual objects. First, we isolated regions for which lower-order cognitive map representations linked indirectly related items within a given triad (A and C), allowing us to predict the relationship between item patterns in a left-out presentation of that triad. We then searched for regions where the representational structure was common across all triads, reflecting a higher-order cognitive map. We found that anterior hippocampus representations linked event elements within a triad. Specifically, activation patterns showed a consistent geometric relation between indirectly related items within a given triad, allowing us to predict the relation between item patterns in a left-out presentation of that triad. In contrast, frontoparietal representations showed evidence of a common structure of neural activity across different triads. This common structure allowed us to predict the relationships between item activity patterns across triads, suggesting that different triads had come to be represented with parallel neural codes. Our results suggest that together, anterior hippocampus and frontoparietal regions represent a cognitive map consisting of a hierarchical structure that supports inference about specific relationships and generalization across settings.

Disclosures: N.W. Morton: None. **M.L. Schlichting:** None. **A.R. Preston:** None.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.01

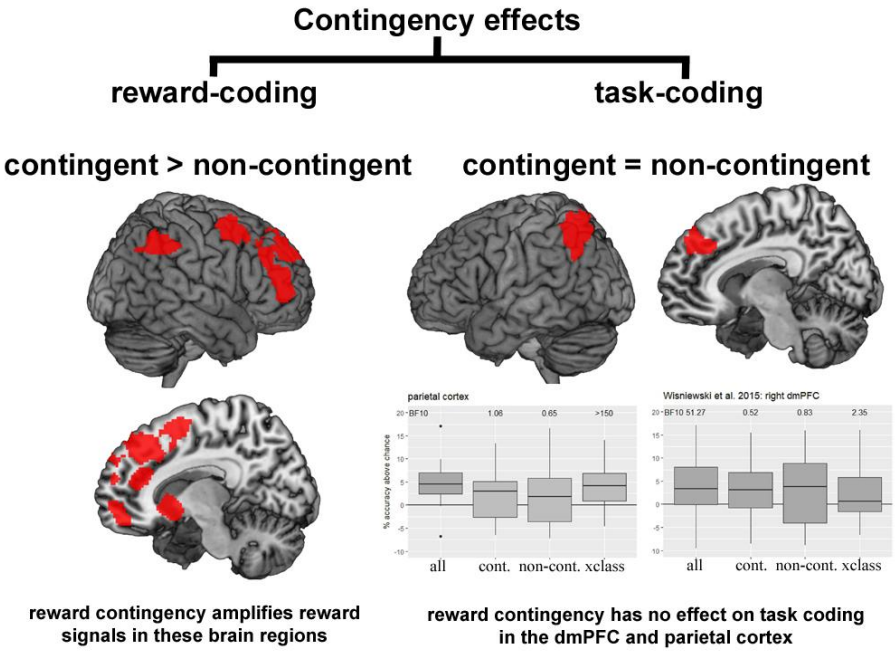
Topic: H.02. Human Cognition and Behavior

Support: FWO grant FWO.OPR.2013.0136.01
FWO and MSCA grant agreement 665501
NWO Vidi Grant
ERC Starting Grant

Title: Outcome contingency modulates reward coding but not task coding in the brain

Authors: *D. WISNIEWSKI[1], B. U. FORSTMANN[2], M. BRASS[1]
[1]Dept. of Exptl. Psychology, Ghent Univ., Gent, Belgium; [2]Univ. of Amsterdam, Amsterdam, Netherlands
Abstract:

We make choices every day of our life, and we expect them to lead to favorable outcomes. While our choices are often directly linked to specific outcomes, sometimes the relationship between a choice and its outcome is less clear. Much previous research investigated the effects of outcomes (e.g. monetary rewards) on decision-making and other cognitive processes. However, this research mostly conflated the effects of the presence of reward outcomes (rewards present vs absent), with their contingency on behavior (rewards dependent on choices vs independent of choices). Here, we isolate effects of reward contingency both on the neural coding of chosen tasks and reward outcomes in a value-based choice paradigm, using fMRI, state-of-the-art multivariate pattern analysis (MVPA) and computational modelling methods. In each trial, subjects chose to perform one of two different tasks, receiving varying rewards after successful performance. In some trials these rewards were contingent on subjects' choices, while in others they were not. We found reward outcomes to be encoded in a wide-spread brain network including the ventral striatum, dorso-medial prefrontal cortex (dmPFC) and parietal cortex. MVPA revealed that reward signals were amplified when rewards were contingent on subjects' behavior, as compared to when they were not. We further found chosen tasks to be encoded in the dmPFC and parietal cortex as well. Interestingly, these task representations were not modulated by reward contingency. We thus show that contingency effects on reward coding do not propagate to task (or choice) coding in this value-based choice paradigm. Our findings inform current debates on the neural basis of motivational and cognitive control, with both processes increasingly being seen as two aspects of one underlying neural mechanism. We highlight the role of the dmPFC and parietal cortex in linking motivational and cognitive control in the brain, but also show that reward-related and choice-related information processing can be partially dissociated.



Disclosures: D. Wisniewski: None. **B.U. Forstmann:** None. **M. Brass:** None.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.02

Topic: H.02. Human Cognition and Behavior

Support: FWO.OPR.2015.0024.01

Title: Proactive control enhances sustained and transient effort in rewarded tasks: Combined EEG and pupillometry studies

Authors: *M. KOSTANDYAN[1], K. BOMBEKE[2,1], T. CARSTEN[1], R. M. KREBS[1], W. NOTEBAERT[1], N. C. BOEHLER[1]
[1]Ghent Univ., Gent, Belgium; [2]Imec-Mict-UGent, Ghent Univ., Ghent, Belgium

Abstract: Introducing incentive manipulations, such as rewarding fast and accurate performance, usually triggers increased effort, which is reflected in enhanced electrophysiological and physiological effort markers (e.g., effort-related electroencephalography (EEG) components and pupil size accordingly). However, it is not fully clear under which circumstances monetary reward promotes performance, and which role effortful proactive control plays therein. In the present study, we compared two reward schemes using combined pupillometry and EEG measures in a Flanker task to investigate how reward influences effortful proactive control. In Experiment 1, we used a pure block-based reward manipulation with correct and fast responses being always rewarded in reward blocks as compared to no-reward blocks. Increased sustained effort in the reward blocks was observed, which was reflected in increased sustained pupil size. Yet, this sustained effort was not accompanied by a behavioral reward benefit, suggesting a failure of translating increased effort into a behavioral pay-off. In Experiment 2, we introduced a mixed block- and trial-based reward manipulation (i.e., rewarded blocks with potentially rewarded and non-rewarded trials intermixed with pure no-reward blocks), which resulted in a behavioral benefit for the reward-related trials. Consistently, we observed both reward-related sustained and transient pupil-size increases accompanied by increased markers of transient preparatory effort preceding target onset and reward modulations of target processing in the EEG data. Taken together, both experiments featured increased sustained pupil size in the reward-related blocks, with an additional transient reward-related increase in pupil size only in Experiment 2. Furthermore, an EEG-related fronto-central reward-related modulation during target processing, likely reflecting reward modulations of target selection, arose earlier in Experiment 2 compared to Experiment 1. Thus, our data are in accordance with previous research suggesting that monetary reward triggers proactive effort-

related control state, and indicate that in the present task context a transient form of preparatory effort is more relevant for behavior than a sustained form.

Disclosures: M. Kostandyan: None. **K. Bombeke:** None. **T. Carsten:** None. **R.M. Krebs:** None. **W. Notebaert:** None. **N.C. Boehler:** None.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.03

Topic: H.02. Human Cognition and Behavior

Support: NIH T32 NS047987
Office of Naval Research

Title: Reward-related brain activity during successful memory encoding

Authors: *M. S. COHEN, L. Y. CHENG, K. A. PALLER, P. J. REBER
Dept. of Psychology, Northwestern Univ., Evanston, IL

Abstract: Memory encoding can be enhanced by offering rewards for subsequent successful test performance, increasing motivation to remember. We hypothesize that this process is supported by two distinct mechanisms: improved strategic effort during study, and direct enhancement of memory storage via connections from neural reward systems to the medial temporal lobe (MTL). We used fMRI to measure brain activity in young adult humans during learning of novel abstract kaleidoscope images. On each trial, two images were presented in different screen quadrants: one arbitrarily designated as high-value (in points), and one as low-value. Neuroimaging data was collected across 16 trials per list in which each of the 16 stimuli were presented twice. These study trials were immediately followed by a test of item recognition (yes/no) and spatial location memory. Feedback about the total number of points earned was provided, to motivate attention to item value. Six study/test cycles were completed in the scanner. Increased activity was observed during successful memory encoding in a dorsal frontoparietal network, in ventral lateral occipitotemporal cortex, and in a semantic network that includes ventrolateral prefrontal cortex. A network of regions associated with reward, including ventral tegmental area (VTA) and nucleus accumbens (NAcc), was defined using Neurosynth. Activity in these regions was higher during any successful memory encoding, whether the items subsequently remembered had been marked as high or low value. A psychophysiological interaction analysis showed that functional connectivity between a right hemisphere MTL seed region and a cluster in right VTA was greater during encoding trials that led to successful memory for any item, compared with unsuccessful encoding trials. These results suggest that when motivated to gain rewards,

dopaminergic areas of the brain potentiate memory storage within the MTL and effectively become part of the successful memory network. Activity associated with strategic control of memory was observed in dorsal posterior parietal cortex (dPPC), where increased activity was observed during encoding selective for high-value vs. low-value items. This region also exhibited increased connectivity with right lateral temporal cortex during particularly successful memory trials (both high and low value items remembered) and the strength of this connectivity correlated across participants with memory selectivity. Thus, while reward system activity was observed to contribute to enhanced memory encoding, a separate mechanism supports the metacognitive strategic control of memory encoding processes.

Disclosures: M.S. Cohen: None. **L.Y. Cheng:** None. **K.A. Paller:** None. **P.J. Reber:** None.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.04

Topic: H.02. Human Cognition and Behavior

Support: NCRG Seed Grant 20R75517

Title: The effects of sensory reward cues during cost-benefit decision making

Authors: *M. V. CHERKASOVA[1], L. CLARK[2], J. BARTON[2], A. STOESSL[2], C. A. WINSTANLEY[2]
[1]Neurol., [2]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Reward cues can potently influence behavior. In addicted individuals, they can trigger drug seeking and relapse. While much theoretical and empirical work has focused on how reward cues acquire incentive salience and come to signal behavioral goals, these accounts do not explain how this translates into the series of actions required to achieve these goals, especially in the face of other potentially conflicting goals, such as abstinence. Here we consider the influence of cues on decision making as one candidate mechanism: when decisions are made to pursue the addiction, the benefits may be judged to outweigh the costs. Indeed, rodent data suggest that reward-paired cues can bias cost-benefit decision making in a dopamine (DA) dependent manner: pairing food rewards with audio-visual cues increased risky choice on a rodent gambling task, and this effect was dependent on D3 receptor signaling (Barrus et al, 2016). We have observed similar behavioral effects in healthy human volunteers: casino-inspired sensory cues accompanying monetary rewards promoted riskier choice. Individuals were differentially susceptible to these risk-promoting effects. Volunteers identified as cue-sensitive "sign-trackers", using a measure of eye gaze fixations on reward-predictive cues during

Pavlovian conditioning, were preferentially susceptible to risk-promoting effects of cues on decision making, but only when cues appeared in a reward-predictive temporal position, rather than simply accompanying rewards. Because sign-tracking behavior is DA-dependent in animal models, these findings indirectly implicate DA signaling in risk-promoting effects of cues in human subjects. Our data in Parkinson's disease patients on and off DA therapy implicate DA signaling more directly, as risk-promoting effects of cues in Parkinson's patients were modulated by anti-Parkinsonian medications. Finally, in addition to their risk-promoting effects, sensory reward cues can modulate arousal as reflected in patterns of pupil dilation; this points to additional noradrenergic influences. Together, our data support the hypothesis that biasing effects of cues on decision making represent one mechanism whereby cue exposure translates into action. By biasing cost-benefit decision making - particularly in cue-sensitive individuals - reward cues could enable actions necessary to pursue the addiction, while also helping maintain states of heightened arousal during these risky pursuits.

Disclosures: M.V. Cherkasova: None. **L. Clark:** A. Employment/Salary (full or part-time):; Province of British Columbia and the British Columbia Lottery Corporation. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Svenska Spel. F. Consulting Fees (e.g., advisory boards); Cambridge Cognition Ltd.. **J. Barton:** None. **A. Stoessl:** None. **C.A. Winstanley:** F. Consulting Fees (e.g., advisory boards); Shire, Hogan Lovells LLP.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.05

Topic: H.02. Human Cognition and Behavior

Support: the Honda Basic Science Research Institute
NRF grant 2016R1C1B2015901 by the Korea government
NSF BCS 1539717
NIH 2R01EY019466-07

Title: Differences in the value of feedback in perceptual learning are revealed in the attention and the visual sensory processing areas, but not in the reinforcement processing

Authors: *D. KIM[1,2], D.-W. KANG[1], S. NISHINA[3], Y. SASAKI[2], T. WATANABE[2]
[1]Asan Med. Ctr., Seoul, Korea, Republic of; [2]Brown Univ., Providence, RI; [3]Honda Res. Inst. Japan, Saitama, Japan

Abstract: While mechanisms underlying perceptual learning (PL) are poorly understood, it is suggested that both attention and reward signals gate PL. A trial feedback informs the correctness of subjects' responses and enhances PL. However, how trial feedbacks influence on PL is unclear, as trial feedback signals serve as a reward, or increase attention on visual processing. Here, we addressed whether feedback signals on PL act on reinforcement processing or selective attention, by measuring neural activations in brain regions involved in reinforcement, attention and visual areas. Especially, we changed the reward value of the feedback signals, and examined which brain regions were associated with the differential value. If higher rewards act on reinforcement processing, whose activation should be higher in one condition than the other. We used a texture discrimination task. Training lasted about for two weeks, with 14 daily training. There were 3 sessions, before and one day after the first training (early phase) and after the last training (late phase). In the test sessions, we measured subjects' performance of the task, and brain activations by functional MRI. There were 2 conditions: Subjects were asked to fast for five hours before each of training and test sessions in the high condition (n=13), but not in the low condition (n=12). Subjects in the both conditions received water drops from a water feeder for a correct response in the task as a feedback signal. First, the both conditions show significant performance improvements. The degree of performance improvement in the test sessions was higher for the high condition, indicating the value of feedback signals modulates the degree of PL. Second, while a significant activation was observed in the reinforcement processing such as the putamen in the both conditions in the early phase, there was no significant difference between the conditions, indicating that the degree of reward processing is equivalent for both conditions. Third, higher fMRI activation was found in the high than low conditions in the visual and attention areas in the early phase. In later phase, these differences in fMRI activation decreased, indicating the difference in reward value emerged in the visual and attention areas only in the early phase of training. Such interaction between the value and training phase was statistically significant by a 2-way ANOVA (condition x session) in these areas. Together, the results demonstrate that the value of feedback signal of PL acts on the attentional processing, in the early phase of training, rather than on the reinforcement processing.

Disclosures: D. Kim: None. **D. Kang:** None. **S. Nishina:** None. **Y. Sasaki:** None. **T. Watanabe:** None.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.06

Topic: H.02. Human Cognition and Behavior

Support: NSF CRCNS grant (BCS-1309346)

Title: Humans underestimate reward probability and overestimate environmental volatility in a multi-armed bandit task - insights from a Bayesian analysis of human learning and decision-making

Authors: *D. GUO[1], A. J. YU[2]
[1]Electrical and Computer Engin., UCSD, La Jolla, CA; [2]Cognitive Sci., Univ. of California San Diego, La Jolla, CA

Abstract: Humans and animals frequently have to make choices among options with imperfectly known reward outcomes. In psychology and neuroscience, this is often studied using the multi-armed bandit task, in which subjects repeatedly choose among bandit arms with fixed but unknown reward probabilities. Here, we manipulate the mean and variance of reward rates of the arms (2 x 2 design: high and low mean and variance of reward rate), to identify the statistical learning and decision strategies used by humans. Using a Bayesian ideal learner modeling framework, which naturally captures inferential uncertainty and incorporates prior knowledge, in combination with a Softmax decision policy, we find that human learning is best captured by the Dynamic Belief Model (DBM), which assumes that subjects believe the reward rate of each arm to undergoes discrete, unsignaled jumps, known as change points. Our result is consistent with previous studies showing that DBM accounts for human choice behavior better than FBM, which assumes the reward rates to be fixed (consistent with the experimental design), in a variety of tasks. We also find that DBM accounts for human choice behavior better than a standard reinforcement learning model. Additionally, using DBM, we find that human subjects have prior reward expectations that consistently underestimate true reward rates, especially in high-reward environments (the underestimation effect disappears if we use FBM instead). This surprising underestimation finding is corroborated by subjects' self-report: when asked to estimate reward probabilities of arms never chosen during a game, subjects consistently report estimates similar to those recovered using DBM, thus also underestimating true and experienced reward rates. Using simulations that combine DBM with Softmax, we find that cumulative reward is maximized by assuming a lower prior mean reward than the true reward rate. In other words, one can compensate for the incorrect nonstationarity assumption of DBM by using a lower prior mean, so as to achieve a higher cumulative reward outcome. Intriguingly, we find that human prior reward expectations are a compromise between experienced reward rates and those that maximize cumulative reward.

Disclosures: D. Guo: None. **A.J. Yu:** None.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.07

Topic: H.02. Human Cognition and Behavior

Support: National Institutes of Health Blueprint Initiative for Neuroscience Research Grant (U01 MH93765)
Harvard University Mind, Brain, and Behavior Interfaculty Initiative Grant
National Institute for Drug Abuse Grant (R03 DA037405)

Title: Development of prefrontal cortical connectivity and the enduring effect of learned value on cognitive control

Authors: *J. Y. DAVIDOW[1], M. A. SHERIDAN[2,3,4], K. R. VAN DIJK[5], R. M. SANTILLANA[3], J. SNYDER[2,3], C. M. VIDAL BUSTAMANTE[1], B. R. ROSEN[6], L. H. SOMERVILLE[1]
[1]Dept. of Psychology and Ctr. for Brain Sci., Harvard Univ., Cambridge, MA; [2]Dept. of Psychology and Neurosci., Univ. of North Carolina, Chapel Hill, NC; [3]Dept. of Developmental Med., Children's Hosp. Boston, Boston, MA; [4]Dept. of Pediatrics, Harvard Med. Sch., Boston, MA; [6]Radiology, [5]Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Inhibitory control, the capacity to suppress an inappropriate response, is a process employed for guiding action selection in the service of goal-directed behavior. Under neutral circumstances, inhibitory control success improves from childhood to adulthood, and has been associated with developmental gains in functional activation and connectivity of the prefrontal cortex. However, the ability to exercise inhibitory control is challenged in certain contexts including by appetitive cues, a phenomenon that may be particularly pronounced in youths. Here, we examine the magnitude and temporal persistence of learned value's influence on inhibitory control in a cross-sectional sample of 8-25 year olds (N=127). Participants first underwent conditioning of a motor approach response to two initially neutral cues, with one cue reinforced with monetary reward and the other with no monetary outcome. Subsequently, during fMRI participants re-encountered these cues as No-Go targets in a nonreinforced Go-No-Go paradigm. While the influence of learned value increasingly disrupted inhibitory control with increasing age, in young adults this pattern remitted over the course of the task, whereas during adolescence the impairing effect of reward history persisted. Successful No-Go performance to the previously rewarded target was related to greater recruitment of the right inferior frontal gyrus and age-related increase in functional connectivity between the inferior frontal gyrus and the ventromedial prefrontal cortex for the previously rewarded No-Go target over the control target. Together, results indicate the complex influence of value on goals over development relies upon the increased coordination of distinct higher-order regions in the prefrontal cortex.

Disclosures: J.Y. Davidow: None. **M.A. Sheridan:** None. **K.R. Van Dijk:** Other; currently employed by Pfizer Inc.. **R.M. Santillana:** None. **J. Snyder:** None. **C.M. Vidal Bustamante:** None. **B.R. Rosen:** None. **L.H. Somerville:** None.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.08

Topic: H.02. Human Cognition and Behavior

Support: NSF GRFP
NSF IGERT
Stanford Innovation Grants

Title: Hippocampal pattern separation supports reinforcement learning

Authors: *I. C. BALLARD[1], A. D. WAGNER[2], S. M. MCCLURE[3]
[1]Helen Wills Neurosci. Inst., Univ. of California, Berkeley, Berkeley, CA; [2]Dept. of Psychology, Stanford Univ., Stanford, CA; [3]Psychology, Arizona State Univ., Tempe, AZ

Abstract: Animals rely on learned associations to make decisions. Associations can be based on relationships between object features (e.g., the three-leaflets of poison ivy leaves) and outcomes (e.g., rash). More often, outcomes are linked to multidimensional states (e.g., poison ivy is green in summer but red in spring). Feature-based reinforcement learning fails when the values of individual features depend on the other features present. One solution is to assign value to multifeatural conjunctive representations. We tested if the hippocampus formed separable conjunctive representations that enabled learning of response contingencies for stimuli of the form: AB+, B-, AC-, C+. Pattern analyses on functional MRI data showed the hippocampus formed conjunctive representations that were dissociable from feature components and that these representations influenced striatal PEs. Our results establish a novel role for hippocampal pattern separation and conjunctive representation in reinforcement learning.

Disclosures: I.C. Ballard: None. **A.D. Wagner:** None. **S.M. McClure:** None.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.09

Topic: H.02. Human Cognition and Behavior

Support: Social Science Matrix, UC Berkeley

Title: Neuroeconomic mechanisms for heterogeneous traders with real stock-trading platforms and a transition from nonbubble-related deliberation to bubble-related reinforcement learning underlying herding or overextrapolation

Authors: *J. L. HARACZ[1], H. L. TOHID[2]
[1]Dept. of Psychological and Brain Sci., Indiana Univ., Bloomington, IN; [2]Ctr. for Mind and Brain, UC Davis, Davis, CA

Abstract: Objective: A proposed asset-price bubble biomarker, low trade-related lateral neocortical activity (Haracz, 2017), may develop as investors increasingly discard nonbubble-related deliberation to use trading strategies based on less cognitively demanding processes (e.g., herding, extrapolation, and reinforcement learning [RL]). This review aims to: 1) find evidence for the proposed biomarker in traders; 2) identify brain mechanisms hypothetically mediating the transition away from deliberation.
Methods: A systematic literature review focused on studies of traders and nondeliberative brain mechanisms potentially involved in trading that drives asset-price bubbles.
Results: In a fMRI study of professional traders, deliberative traders showed more lateral neocortical activation compared to confident, impulsive traders (Raggetti et al., 2017). Studies of brain mechanisms underlying herding, or social conformity, are consistent with a RL account of social conformity. In this view, sharing a consensus with others may be experienced as a rewarding outcome (Stallen & Sanfey, 2015; Wu et al., 2016). Accordingly, enhanced activity in the ventral striatum, a key reward-processing area, was associated with exposure to stimuli liked by others (Stallen & Sanfey, 2015; Wu et al., 2016). Experiencing better outcomes than other subjects was associated with increased ventral striatal (VS) activity (Luo et al., 2018). Another experience that may be linked to bubble-related asset purchases may be anticipatory affect, or sentiment (Shefrin, 2015), due to the opportunity for realizing gains. Anticipatory affect and realizing gains are both associated with increased VS activity (Knutson & Greer, 2008; Frydman et al., 2014). Along with overextrapolation (Cassella & Gulen, in press), the above sources of reinforcement may drive bubble-building purchases that are overreactions by behavioral feedback traders to stock purchases of rational investors responding to good news about particular stocks (De Long et al., 1990).
Conclusions: Stock traders' fMRI results support the proposal that low trade-related lateral neocortical activity may be a bubble biomarker. Nonbubble-related deliberation may give way to bubble-related RL associated with the biomarker. Over time (e.g., 15 years [Shefrin, 2015]), transitions between these mechanisms may account for findings that investors' collective judgments about risk and expected returns show features of both the rational pricing view emphasized by standard theory (Fama & French, 2004) and the sentiment-based view of behavioral finance (Baker & Wurgler, 2007; Huang et al., 2015; Shefrin, 2015; Balcilar et al., 2018).

Disclosures: J.L. Haracz: None. **H.L. Tohid:** None.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.10

Topic: H.02. Human Cognition and Behavior

Support: DFG PE1627/5-1

Title: Reduced exploration during reward-based learning in gambling addiction

Authors: *J. PETERS[1], A. WIEHLER[2], K. CHAKROUN[3]
[1]Univ. of Cologne, Dept. of Psychology, Biol. Psychology, Cologne, Germany; [2]Motivation Brain Behavior, ICM - Hop. Pitie Salpetriere, Paris, France; [3]Univ. Med. Ctr. Hamburg-Eppendorf, Dept. of Systems Neurosci., Hamburg, Germany

Abstract: Gambling disorder, as recognized by the DSM-5, has been liked to perturbations in the brain valuation system with both hypo and hyper activations depending on the context (Balodis et al., 2012; Miedl, Peters, & Büchel, 2012; Van Holst, Veltman, Van Den Brink, & Goudriaan, 2012). Behaviorally, gambling disorder is associated with increased impulsivity (Wiehler & Peters, 2015) as well as impairments in cognitive control, behavioral flexibility and learning (Leeman & Potenza, 2012; van Timmeren, Daams, van Holst, & Goudriaan, 2018). During learning in volatile environments, agents need to continuously balance exploitation (selection of options with known values) and exploration (selection of options with uncertain values). Here we hypothesized that impaired behavioral flexibility in gambling disorder would specifically reduce exploration during reinforcement learning.
We tested this hypothesis in a human sample of n=23 problem and pathological gamblers and n=19 matched controls. During fMRI, all participants performed a four-armed bandit task (Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006). The task requires a continuous tracking of reward contingencies to maximize gains. Cognitive modeling revealed a superior fit of a reinforcement learning model with first order perseveration and an uncertainty-dependent "exploration bonus" parameter in both groups. However, uncertainty-driven exploration was significantly reduced in the gamblers compared to healthy controls, and significantly associated with gambling-related cognitive distortions. Neural representations of option values in the ventro-medial prefrontal cortex and reward prediction error representations in the ventral striatum were similar in the two groups.
In line with previous findings regarding impaired behavioral flexibility, our results reveal a specific impairment in uncertainty-based exploration in gambling addiction that might contribute to the clinical manifestation of compulsive gambling behavior in the face of negative consequences.

Disclosures: J. Peters: None. **A. Wiehler:** None. **K. Chakroun:** None.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.11

Topic: H.02. Human Cognition and Behavior

Title: Neural correlates of cue reactivity induced by smoking-related videos in adult daily smokers

Authors: *S. HUANG, A. S. WEIGARD, S. L. HENRY, S. J. WILSON, C. HUANG-POLLOCK
Psychology, The Pennsylvania State Univ., University Park, PA

Abstract: Cigarette smoking is the leading cause of premature death from disease. The neural response to smoking cue pictures in daily smokers has been extensively investigated. However, some scholars argue that the use of videotaped stimuli better resembles the real-world cue exposures in that they provide richer contextual and realistic information. Tong et al. (2007) developed a promising set of standardized smoking and neutral videos depicting real-world scenarios. Recent evidence has validated the effectiveness of the use of these videos in behavioral studies; however, to our knowledge, these videos have not yet been tested with functional magnetic resonance imaging (fMRI).
To address this gap, the current study adopted fMRI to examine the brain responses to these smoking videos in adult daily smokers. Nineteen healthy daily smokers (age range: 18-42, age = 27.3 ± 7.4 yrs, 10 females) who smoked >= 5 cigarettes per day (11.9 ± 4.7 cig/day) were asked to refrain from smoking for 12 hrs prior to the experiment. In a block design, subjects were shown twelve 20-s videos with cigarette smoking behaviors and twelve with neutral behaviors in the MRI scanner. Ten regions of interest (ROIs) with a radius of 8 mm were created based on past reward-related literature including dorsal anterior cingulate cortex (dACC), bilateral amygdala, bilateral striatum, etc. Repeated-measure *t* tests indicated that the bilateral amygdala showed stronger reactivity to smoking vs. neutral video cues. To evaluate how the cross-talk between the amygdala and other brain regions was moderated by video cue type, functional connectivity analyses were conducted using the generalized form of psychophysiological interaction (gPPI). The repeated-measure ANOVA with within-subject factors of Hemisphere (left vs. right amygdala) and Cue Type suggested that bilateral amygdala had enhanced positive connectivity with bilateral inferior frontal cortex (IFC) and greater negative connectivity with right caudate and dACC during smoking vs. neutral videos.
In conclusion, our findings evince that the cue-induced activation in the bilateral amygdala may

reflect the strengthened negative salience of the smoking video cues when the cigarette rewards are not available. The results also suggest that, during the presentation of smoking videos, the bilateral amygdala may show increased positive interactions with brain regions involved in cognitive inhibition and increased negative associations with brain regions mediating reward-related processing. In sum, our study provides support for the application of these novel smoking videos to detect the neural cue reactivity in neuroimaging paradigms.

Disclosures: S. Huang: None. **A.S. Weigard:** None. **S.L. Henry:** None. **S.J. Wilson:** None. **C. Huang-Pollock:** None.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.12

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01DA041264
Margaret Q. Landenberger Research Foundation

Title: Neural correlates of value-driven attentional capture in addiction

Authors: *O. MORGAN[1], J. A. CREIGHTON[1], M. B. SLAPIK[1], B. A. ANDERSON[2], C. L. MARVEL[1]
[1]Dept. of Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Dept. of Psychological and Brain Sci., Texas A&M, College Park, TX

Abstract: Value-driven attentional capture is the phenomenon in which stimuli that have been associated with reward draw attention, even when viewed out of context. In previous studies, we have shown that individuals with drug dependence (DD) exhibit more pronounced attentional capture by task-irrelevant non-drug reward cues than do controls, and that impulsivity is a predictor of attentional capture as late as 6 months after training. Here, we use fMRI to identify the neural correlates of attentional capture in individuals with a history of DD and in healthy controls. We hypothesized that brain regions linked to reward-based attention, including dorsal striatum (DS), ventral striatum (VS), and anterior insula (AI), would reflect group differences in attentional capture. Participants currently consist of five individuals with prior history of DD with at least 60-days abstinence, and eight demographically-matched controls. A brief reward training phase and a test phase were conducted during fMRI scanning. In the training phase, each of two color stimuli differentially predicted a monetary reward. In the test phase, the same color stimuli served as distractors in an unrewarded visual search for a shape singleton target. Attentional capture was measured as the increase in response time on trials in which the

previously high value-associated distractor was present, versus trials in which it was absent. Trait impulsivity was measured using the Barratt Impulsiveness Scale. Preliminary analyses revealed behavioral findings consistent with prior results: the DD group exhibited higher attentional capture and trait impulsivity than did controls, and DD trait impulsivity trended towards predicting attentional capture. In the DD group, trait impulsivity predicted differences in VS response on trials when the distractor was present vs. absent. This VS response correlated with attentional capture in controls, and trended for the DD group. DS response also trended towards correlating with attentional capture in the DD group. Contrast analyses within the test phase revealed hyperactivity in bilateral AI in the DD group relative to controls. Preliminary results support the hypothesis that value-driven attentional capture reflects mechanisms of reward processing that underly addiction, and suggest DS, VS, and AI as neural substrates of hypersensitive attentional capture.

Disclosures: O. Morgan: None. **J.A. Creighton:** None. **M.B. Slapik:** None. **B.A. Anderson:** None. **C.L. Marvel:** None.

Nanosymposium

634. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC 4

Time: Wednesday, November 7, 2018, 8:00 AM - 11:15 AM

Presentation Number: 634.13

Topic: H.02. Human Cognition and Behavior

Support: NHRI-EX103-10113EC
MOST106-2314-B-182-001
NSC-106-2811-B
CMRPG5H0051
CMRPGF0092

Title: Tactile motion is used to guide hand movement

Authors: *P.-C. HSU[1], J.-J. HUANG[1,3,4], Y.-C. PEI[1,3,4,2]
[1]Sch. of Med., [2]Healthy Aging Res. Ctr., Chang Gung Univ., Taoyuan, Taiwan; [3]Dept. of Physical Med. and Rehabil., [4]Ctr. of Vascularized Tissue Allograft, Chang Gung Mem. Hosp. at Linkou, Taoyuan, Taiwan

Abstract: In daily life, haptic approaches rely on cutaneous, proprioceptive afferents, and functional hand movements. However, it remains unclear whether information obtained from cutaneous input can guide hand movement. To study this issue, we developed a novel touch scanning system that the touchpad can move with arbitrary direction and speed on the XY plane while the human subject drew the movement trajectory on the moving touchpad. During the

experiment, the subject first placed his right index finger on the touchpad, the touchpad then moved at a speed of 0, 20, 40 or 60 mm/s on a proximal-to-distal or distal-to-proximal directions that are orthogonal to the lower edge of the touchpad, and the subject drew a left-to-right straight line on the touchpad according to the instruction. In the object centered experiment, the subject was asked to draw a straight line parallel to the lower edge of the moving touchpad. In the body centered experiment, the subject was asked to draw a straight line parallel to the axis from left shoulder to right shoulder. In the object centered experiment, the subjects can mostly use tactile motion perceived through the finger pad to adjust the motion trajectory by drawing a line almost parallel to the lower edge of the touchpad, indicating that tactile motion can fruitfully guide hand movement. Surprisingly, in the body centered experiment, the subjects were still trying to draw a line parallel to the lower edge of the touchpad even though the instruction was to draw body-centered line, indicating that the subjects could not neglect the cutaneous input and still followed an object centered movement pattern. Control experiments were also performed when the touchpad was moving at the direction parallel to the lower edge of the touchpad while the subject drew a proximal-to-distal line following an object centered or body centered movement, and the results yielded similar conclusions. In summary, even though joint position sense provides precise information of hand position, the central nervous system still relies on tactile motion to guide hand movement. These findings are reminiscent of visual tracking in that the sensory-motor organ will intuitively keep track of the attended object, such as using saccade or hand movement.

Disclosures: P. Hsu: None. **J. Huang:** None. **Y. Pei:** None.

Nanosymposium

635. Advances in Molecular, Genetic, and Imaging Techniques

Location: SDCC 2

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 635.01

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant RF1MH114126

Title: Towards a viral reporter toolbox for prospective marking of human and mouse neocortical cell classes and types

Authors: *B. P. LEVI[1], J. K. MICH[2], J. T. TING[2], L. T. GRAYBUCK[3], A. H. CETIN[3], B. E. KALMBACH[2], S. YAO[3], E. E. HESS[3], S. SOMASUNDARAM[2], Z. YAO[4], J. A. MILLER[2], M. MORTRUD[3], R. P. GWINN[5], C. COBBS[6], A. KO[7,8], C. D. KEENE[9], B. TASIC[3], H. ZENG[3], E. LEIN[2]
[2]Human Cell Types, [3]Structured Sci., [4]MAT, [1]Allen Inst. for Brain Sci., Seattle, WA; [5]Epilepsy Surgery and Functional Neurosurg., [6]The Ben and Catherine Ivy Ctr. for Advanced Brain Tumor Treatment, Swedish Neurosci. Inst., Seattle, WA; [7]Univ. of Washington Sch. of Med., Dept. of

Neurolog. Surgery, Seattle, WA; [8]Regional Epilepsy Ctr., Harborview Med. Ctr., Seattle, WA; [9]Dept. of Pathology, Univ. of Washington Sch. of Med., Seattle, WA

Abstract: Despite differences in gross morphology of the human and mouse neocortex, it is not yet clear how the cell types and their functional circuitry differ across species. Large-scale single cell transcriptomics efforts have begun to chart a molecular taxonomy of neocortical cell types in both mouse and human, and are poised to reveal molecular differences between cell types. However, to uncover the key functional differences between the human and mouse neocortex, it is critical to understand how these cell types are similar and different from each other on both phenotypic and functional levels. Transgenic tools are widely employed to dissect the functional role of mouse cell classes/types, but these tools are usually species-specific and are not applicable for human brain research. As a result, the most comprehensive modern toolbox for genetic labeling, the collection of Cre and reporter mice, does not allow for systematic phenotypic and functional comparison of orthologous mouse and human cell types.
Here we present our progress on producing and validating a new generation of viral vectors for prospective, rapid-onset labeling of human and mouse cell classes/types. To build cross-species cell class/type-specific viral-based reporters, we are analyzing neocortical single cell RNA-seq and chromatin accessibility data sets to identifying regulatory elements proximal to conserved cell class/type-specific genes. After screening, we will validate reporter vectors in adult mouse and human neocortical slice cultures by testing phenotype and function of labeled neuronal populations. This validated set of viral reporter vectors will facilitate direct comparison of the phenotype and function of orthologous mouse and human neuronal cell classes/types, and eventually will lead to a better understanding of how the human neocortex differs from the mouse.
This research was supported by the NIMH and NIA of the NIH under Award Number RF1MH114126, and by Paul G. Allen. The content is solely the responsibility of the authors and does not necessarily represent the views of the funders.

Disclosures: B.P. Levi: None. **J.K. Mich:** None. **J.T. Ting:** None. **L.T. Graybuck:** None. **A.H. Cetin:** None. **B.E. Kalmbach:** None. **S. Yao:** None. **E.E. Hess:** None. **S. Somasundaram:** None. **Z. Yao:** None. **J.A. Miller:** None. **M. Mortrud:** None. **R.P. Gwinn:** None. **C. Cobbs:** None. **A. Ko:** None. **C.D. Keene:** None. **B. Tasic:** None. **H. Zeng:** None. **E. Lein:** None.

Nanosymposium

635. Advances in Molecular, Genetic, and Imaging Techniques

Location: SDCC 2

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 635.02

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIDA Grant 1R01DA036909-01 REVISED

NIH Grant RF1MH114126

Title: Cell type-specific enhancer discovery through scRNA-seq and scATAC-seq for a new generation of viral tools

Authors: *L. T. GRAYBUCK[1], A. SEDENO-CORTES[4], T.-N. NGUYEN[4], T. K. KIM[4], M. WALKER[4], G. LENZ[4], B. E. KALMBACH[2], E. J. GARREN[3], J. K. MICH[3], S. YAO[3], M. MORTRUD[5], B. P. LEVI[3], J. T. TING[2], E. LEIN[6], A. H. CETIN[5], T. L. DAIGLE[1], H. ZENG[7], B. TASIC[1]
[1]Mol. Genet., [2]Human Cell Types, [3]Allen Inst. For Brain Sci., Seattle, WA; [4]Mol. Genet., [5]Viral Technol., [6]Human Cell Types, [7]Structured Sci., Allen Inst. for Brain Sci., Seattle, WA

Abstract: The functional interplay of diverse neural cell types gives rise to the complex functions of neural tissues. To fully understand the biology of the brain, we need to be able to distinguish and describe these cell types, and identify markers to selectively label and perturb cell types for further study. In mouse, recombinase driver lines have been used to great effect to label cell populations that share gene expression. However, use of recombinant drivers requires vivarium resources, and husbandry and management of mouse breeding. To get cell type-specific labeling near the resolution revealed by single-cell RNA-seq (scRNA-seq) experiments, one often needs to utilize timed tamoxifen treatment or triple crosses with low frequency of usable animals for experiments. These problems could be significantly ameliorated through the development of strategies and viral tools to allow brain-wide cell type-specific somatic labeling. Here we report novel transcriptomic and epigenetic data sets, and a new strategy to employ them to create cell type-specific somatic labeling in the mouse neocortex. We have identified cell type-specific enhancer elements through a combination of single-cell ATAC-seq and scRNA-seq. In conjunction with new, efficient AAV viral capsids, we have generated cell type-specific viral labeling tools for several cortical cell types. These tools can be delivered using simple, minimally invasive retro-orbital injection methods to reliably label specific neural cell populations without the need for complicated breeding or induction. These new tools enable a simplified method for prospective marking of cell types, and have enabled rapid and comprehensive cell type-specific assessment of transcriptomics, electrophysiology, morphology, and connectivity. Furthermore, we anticipate these datasets and our new viral labeling strategy will allow efficient development of cell type-specific marking tools essential for the functional assessment of the taxonomy of cell types in the mouse brain.
The project described was supported by award number 1R01DA036909-01 REVISED from the National Institute on Drug Abuse and by the NIMH and NIA of the NIH under Award Number RF1MH114126. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health and the National Institute on Drug Abuse.
We wish to thank the Allen Institute founders, Paul G. Allen and Jody Allen, for their vision, encouragement, and support.

Disclosures: L.T. Graybuck: None. **A. Sedeno-Cortes:** None. **T. Nguyen:** None. **T.K. Kim:** None. **M. Walker:** None. **G. Lenz:** None. **B.E. Kalmbach:** None. **E.J. Garren:** None. **J.K.**

Mich: None. **S. Yao:** None. **M. Mortrud:** None. **B.P. Levi:** None. **J.T. Ting:** None. **E. Lein:** None. **A.H. Cetin:** None. **T.L. Daigle:** None. **H. Zeng:** None. **B. Tasic:** None.

Nanosymposium

635. Advances in Molecular, Genetic, and Imaging Techniques

Location: SDCC 2

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 635.03

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NFSC Grant 31630039

Title: Dissection of the protocadherin enhancer by crispr DNA-fragment editing

Authors: J. SHOU, J. LI, *Q. WU
Shanghai Jiao Tong Univ., Shanghai City, China

Abstract: The mammalian clustered protocadherins (Pcdh) are central for neuronal development and connectivity. By a combination of CRISPR DNA-fragment editing and chromosome-conformation capture methods, we recently demonstrated that the relative orientation of enhancer and its specific long-distance chromatin interactions with target promoters determine cell-specific expression patterns in individual neurons in the brain. To further develop the CRISPR DNA-fragment editing method, we find that disrupting CtIP, which is thought to function in NHEJ, enhances precise DNA-fragment deletion. In addition, by analyzing the inserted nucleotides at the junctions of DNA-fragment editing and characterizing the cleaved products, we find that Cas9 endonucleolytically cleaves the noncomplementary strand with a flexible scissile profile upstream of -3 position of the PAM site *in vivo* and *in vitro*, generating overhanged DSB ends. Moreover, we find that engineered Cas9 nucleases have distinct cleavage profiles. Finally, Cas9-mediated nucleotide insertions are nonrandom and are equal to the combined sequences upstream of both PAM sites with predicted frequencies. Thus, precise and predictable DNA-fragment editing could be achieved by perturbing DNA repair genes and using appropriate PAM configurations. Using this method, we designed a series of paired sgRNAs to dissect the HS5-1 enhancer. We screened single cell CRISPR inversion clones for precise inversion of single CBSs as well as their combinations with the middle region of the HS5-1 enhancer. Remarkably, inversion of CBSb alone or its combination with the middle region leads to a significant decrease in DNA-looping interactions between HS5-1 and protocadherin alpha promoters and a corresponding increase of DNA-looping interactions with the protocadherin beta and gamma promoters; Whereas inversion of CBSa alone or its combination with the middle region causes no significant alteration of directional DNA-looping interactions. RNA-seq experiments demonstrated the functional consequences of alteration of higher-order chromatin domain architecture. Thus, the relative orientation of the single boundary CBS determines the

directions of long-distance chromatin-looping interactions between the distal enhancer and target promoters.

Disclosures: J. Shou: None. **J. Li:** None. **Q. Wu:** None.

Nanosymposium

635. Advances in Molecular, Genetic, and Imaging Techniques

Location: SDCC 2

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 635.04

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: F31-DA042514
DP1-DA039650
R00-DA034681
F32-DA041778
T32-NS061788
T32-GM008361

Title: A neuron-optimized CRISPR/dCas9 toolbox for robust and specific gene regulation across neuronal subpopulations

Authors: *K. E. SAVELL, J. S. REVANNA, N. A. GOSKA, M. E. ZIPPERLY, J. J. TUSCHER, C. G. DUKE, F. A. SULTAN, J. J. DAY
Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Gene expression patterns define neuronal phenotypes and are dynamic regulators of neuronal function in the developing and adult brain. Furthermore, specific gene programs are altered by neuronal activity and behavioral experience, and dysregulation of these programs is implicated in numerous neuropsychiatric diseases. The study of gene expression has traditionally relied on the use of overexpression vectors, transgenic animals, and knockdown approaches such as RNA interference. While valuable, these techniques do not manipulate the endogenous gene locus, require costly and time-consuming animal models, and generally target one gene at a time. Recent advances in CRISPR/Cas9 genome editing has enabled previously unparalleled control of genetic sequence, transcriptional states, and epigenetic modifications. However, these advances have not been readily adapted in the central nervous system due to limitations in transgene expression in post-mitotic neurons. Here, we optimized a dual lentivirus CRISPR system for targeted gene modulation via fusion of either a synergistic transactivator (VPR) or transcriptional repressor (KRAB) to a catalytically dead Cas9 (dCas9). A neuron-specific promoter enabled target specific control of gene expression in several neuronal subpopulations, including primary cortical, hippocampal, and striatal rat cultures. This modular virus approach enabled both CRISPR activation (CRISPRa) and CRISPR interference (CRISPRi) with the same guide RNAs,

with dCas9-VPR targeting to diverse gene promoters inducing robust increases in gene expression and dCas9-KRAB targeting suppressing gene expression. To mimic more complex gene expression programs that resemble changes found *in vitro* and *in vivo,* we multiplexed guide RNAs targeting the immediate early genes *Fos, Fosb,* and *Egr1*, which resulted in coordinated control of gene expression of all three genes. To examine the efficiency of the CRISPRa system in the adult central nervous system, we co-infused dCas9-VPR and guide RNA expressing lentiviruses directed to a non-targeting control or *Fosb* into the ventral striatum of adult rats. Immunohistochemistry revealed a robust increase in Fosb protein in hemispheres receiving the *Fosb* guide RNA, demonstrating that selective induction of gene expression resulted in increased protein translation. Future directions involve generation of inducible CRISPRa and CRISPRi constructs that allow temporally specific modulation of expression. Taken together, our results suggest that CRISPR/dCas9 transcriptional alteration may provide a way to manipulate gene expression patterns that contribute to neuronal function and behavior.

Disclosures: K.E. Savell: None. **J.S. Revanna:** None. **N.A. Goska:** None. **M.E. Zipperly:** None. **J.J. Tuscher:** None. **C.G. Duke:** None. **F.A. Sultan:** None. **J.J. Day:** None.

Nanosymposium

635. Advances in Molecular, Genetic, and Imaging Techniques

Location: SDCC 2

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 635.05

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: K99/R00 HD084759
P50 HD012303
R01 HD072754
R01 HD082567
F31 HD098652
ONR grant N00014-13-1-0285
NIH/NEI R01EY027011

Title: The importance of characterizing Cre-alleles: A comparative study of the impact of neuronal development and behavior in mice with conditional deletion of the homeodomain transcription factors Six6 and Vax1 using two different Gnrh-promoter driven Cre-alleles

Authors: *H. M. HOFFMANN[1], E. PANDOLFI[2], J. S. LEE[2], R. J. HU[2], C. TRANG[2], V. A. NGUYEN[2], D. SKOWRONSKA-KRAWCZYK[2], M. R. GORMN[2], P. L. MELLON[2]
[1]Animal Sci., Michigan State Univ., East Lansing, MI; [2]UCSD, La Jolla, CA

Abstract: Increasingly, studies utilize cell-specific deletion of genes *in vivo* by taking advantage of conditional gene deletion by CRE recombination. Despite numerous advantages, this strategy

also has limitations such as ectopic CRE-expression and germline recombination, creating mosaic and gene knock-out offspring. Two commonly used gonadotropin-releasing hormone (*Gnrh*)-driven CRE-expressing mice both target GnRH neurons, a hypothalamic neuronal population required for fertility. To determine where recombination occurs, we used lineage-tracing and found that the two *Gnrh*-driven CRE mouse lines target very different numbers of neurons in the $Lhrh^{cre}$ and $Gnrh^{cre}$ mice from embryonic day 12 onward. To determine if the difference in targeting between these two *Cre*-expressing mouse lines would impact GnRH neuron development, we deleted the homeodomain transcription factors *Vax1* and *Six6* using both the $Lhrh^{cre}$ and $Gnrhr^{cre}$. The development of GnRH neurons and the number of GnRH neurons was comparable in all the studied mice. However, fertility was differently impacted in $Six6^{flox}$:$Gnrh^{cre}$ versus the $Six6^{flox}$:$Lhrh^{cre}$. A detailed comparison of the adult brain structures targeted by the two *Cre*-expressing mouse lines, revealed extensive expression of CRE in the olfactory bulb, septum and parts of the hypothalamus, including the suprachiasmatic nucleus (SCN), using $Gnrh^{cre}$, but not $Lhrh^{cre}$. Both *Six6* and *Vax1* are required for development of the SCN, the master pacemaker of the body and important in female fertility. To determine if the $Gnrh^{cre}$ targeting to the SCN impacted circadian behavior in $Six6^{flox}$:$Gnrh^{cre}$ and $Vax1^{flox}$:$Gnrh^{cre}$, we evaluated running wheel activity in these mice. Both $Six6^{flox}$:$Gnrh^{cre}$ and $Vax1^{flox}$:$Gnrh^{cre}$ mice had disrupted wheel running activity in constant darkness, reflecting impaired SCN function, whereas this was not the case using the $Lhrh^{cre}$. Further, some $Six6^{flox}$:$Gnrh^{cre}$ mice were unable to entrain to light, due to absence of visual evoked potentials. In conclusion, the differences in expression pattern between the two *Cre*-mouse lines impacted fertility and circadian behavior to different degrees when deleting the homeodomain transcription factors *Six6* or *Vax1*. Thus, both *Cre*-strains are useful to understand GnRH neuron development; however, in most cases the $Lhrh^{cre}$ would be preferred for gene deletion if reproductive behavior or the LH surge are to be studied.

Disclosures: H.M. Hoffmann: None. **E. Pandolfi:** None. **J.S. Lee:** None. **R.J. Hu:** None. **C. Trang:** None. **V.A. Nguyen:** None. **D. Skowronska-Krawczyk:** None. **M.R. GormN:** None. **P.L. Mellon:** None.

Nanosymposium

635. Advances in Molecular, Genetic, and Imaging Techniques

Location: SDCC 2

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 635.06

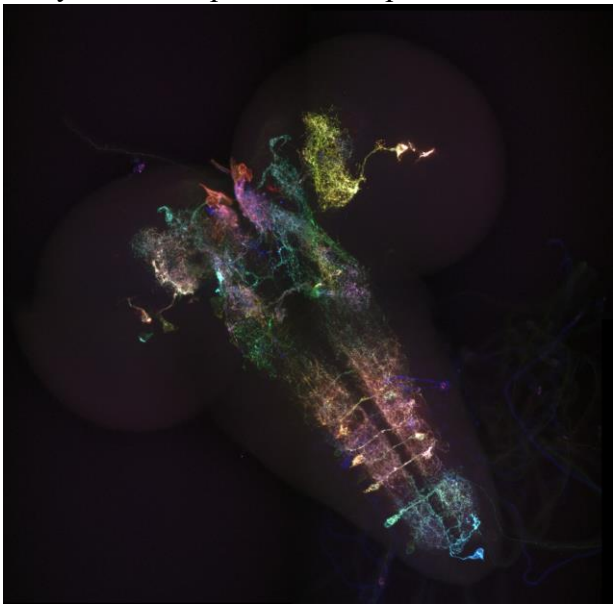
Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH R01MH110932
NIH R01AI130303
NIH U01MH109147

Title: Multispectral transsynaptic labeling reveals *Drosophila* neural circuits at the single neuron resolution

Authors: *Y. LI[1], E. EDWARDS[1], T.-H. HUANG[2], Y. ZHAO[1], M. GHAZZI[1], C. LOIS[2], D. CAI[1]
[1]Cell and Developmental Biol., Univ. of Michigan, Ann Arbor, MI; [2]Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: Obtaining accurate neuronal wiring diagrams is key to the understanding of the cellular basis of brain functions. It is a challenging task, because even in a Drosophila brain, there are >100,000 neurons being highly interconnected. Recent advances in transsynaptic tracing permit highlighting only those neurons being directly connected. Labeling the presynaptic neurons by one color and the postsynaptic cells by another, connections can be identified by light microscopy. However, critical details of the connectome, such as arbors of individual neurons are missing because even the simplest neural networks compose over tens to hundreds of neurons that their intermingled processes are indistinguishable in monochromatic labeling.
We developed Bitbow, a digital form of the multispectral labeling tool, Brainbow, to suit the needs for transsynaptic labeling at the single neuron resolution. Unlike any other Brainbow-like flies that rely on heat-shock induced Flp recombination, Bitbow fly undergoes automatic transient recombination in all neurons and generates >200 easily distinguishable colors (attached fig showing larva Serotonergic neurons labeled by Bitbow, as an example). This makes Bitbow a direct replacement for many UAS-reporters. Importantly, we successfully combined Bitbow with TRACT (Huang et al. eLife 2017) to transsynaptically label postsynaptic neurons in many distinct colors. This pioneers a way to allow us using light microscope to reveal direct neural circuits at the single neuron resolution. The mapped arbors of each postsynaptic neuron further enabled us to identify neuronal subtypes and novel connection patterns. In summary, Bitbow, as a powerful and easy-to-use tool will enable high-throughput morphology and connectivity analysis with unprecedented speed and resolutions.



Disclosures: E. Edwards: None. **T. Huang:** None. **Y. Zhao:** None. **M. Ghazzi:** None. **C. Lois:** None. **D. Cai:** None.

Nanosymposium

635. Advances in Molecular, Genetic, and Imaging Techniques

Location: SDCC 2

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 635.07

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: U01MH106018

Title: Second-generation monosynaptic tracing

Authors: *I. R. WICKERSHAM, L. JIN, M. MATSUYAMA, H. A. SULLIVAN, Y. HOU, T. K. LAVIN, N. E. LEA, K. R. BABCOCK, M. PRUNER
McGovern Inst. for Brain Res., MIT, Cambridge, MA

Abstract: Monosynaptic tracing using G-deleted rabies virus remains the state of the art for determining the direct inputs to a targeted cell type or single neuron, but the cytotoxicity of the first-generation system restricts its usefulness. We have recently introduced second-generation, double-deletion-mutant rabies viral vectors that cause no detectable perturbation of transduced neurons on any timescale examined[1]. We previously showed that the new vectors are well suited for direct retrograde targeting with broad tropism and no toxicity, for expression of recombinases in projection neurons. Here we show that second-generation rabies viral vectors can also be used for monosynaptic tracing, permanently labeling direct inputs to defined groups of postsynaptic neurons targeted on the basis of Cre expression, with no toxicity to the transsynaptically labeled neurons.
1. Chatterjee, S. *et al.* Nontoxic, double-deletion-mutant rabies viral vectors for retrograde targeting of projection neurons. *Nat Neurosci* **21**, 638-646 (2018).

Disclosures: I.R. Wickersham: None. **L. Jin:** None. **M. Matsuyama:** None. **H.A. Sullivan:** None. **Y. Hou:** None. **T.K. Lavin:** None. **N.E. Lea:** None. **K.R. Babcock:** None. **M. Pruner:** None.

Nanosymposium

635. Advances in Molecular, Genetic, and Imaging Techniques

Location: SDCC 2

Time: Wednesday, November 7, 2018, 8:00 AM - 10:00 AM

Presentation Number: 635.08

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: JST CREST Grant Number JPMJCR1652
JSPS Grants-in-Aid for Young Scientists (B) 16K21636
JSPS Grant-in-Aid for Scientific Research (C) 18K07777

Title: Genetically encoded reporter for bimodal optical and PET imaging in the mammalian brain

Authors: *M. SHIMOJO[1], M. ONO[1], H. TAKUWA[1], M. FUJINAGA[2], T. KIKUCHI[2], C. SEKI[1], M. TOKUNAGA[1], J. MAEDA[1], Y. TAKADO[1], M. TAKAHASHI[1], T. MINAMIHISAMATSU[1], N. SUZUKI[3], Y. TOMITA[3], M.-R. ZHANG[2], A. MAXIMOV[4], T. SUHARA[1], N. SAHARA[1], M. HIGUCHI[1]
[1]Dept. of Functional Brain Imaging Res., [2]Dept. of Radiopharmaceuticals Develop., Natl. Inst. of Radiological Sci., Chiba, Japan; [3]Dept. of Neurol., Keio Univ. Sch. of Med., Tokyo, Japan; [4]Dept. of Neurosci., The Scripps Res. Inst., La Jolla, CA

Abstract: In vivo neuroimaging with a gene reporter is a fundamental technology for real-time and longitudinal tracking of molecular dynamics in the mammalian brain. Among various imaging modalities, positron emission tomography (PET) offer superior advantage to monitor disposition of a biosynthesized molecule in living animal and human. However, visualization of a genetically targeted reporter protein in the nervous system by PET has been hampered due to the lack of radioactive ligand capable of penetrating blood-brain barrier. In the present study, we demonstrate that E.coli dihydrofolate reductase (ecDHFR) and its small chemical antagonist trimethoprim (TMP) serve a technical platform for in vivo fluorescence and PET reporter imaging in living mouse brain. Individual neurons expressing ecDHFR can be visualized by two-photon laser microscopy after intravenous administration of TMP conjugated to a fluorophore, whereas the macroscopic distribution of ecDHFR in these animal brain was successfully imaged by PET following administration of radioactive ^{11}C-labeled TMP ([^{11}C]TMP) or new ^{18}F-labeled TMP analogue ([^{18}F]FE-TMP). We also demonstrate the utility of TMP for manipulating turnover of a destabilized ecDHFR mutant fused to a catalytic domain of phosphodiesterase 10A (PDE10A), which could be monitored in vivo with a highly specific PET ligand [^{18}F]MNI-659. Finally, a protein-fragment complementation assay with ecDHFR N-terminal and C-terminal domains was applied to PET detection of tau protein self-assemblies in the brain. Our findings indicate the crucial advantage of bimodal optical and PET reporter imaging for the micro to macro visualization of the expression, turnover, and complex formation of genetically targeted proteins in the living animal brain.

Disclosures: M. Shimojo: None. **M. Ono:** None. **H. Takuwa:** None. **M. Fujinaga:** None. **T. Kikuchi:** None. **C. Seki:** None. **M. Tokunaga:** None. **J. Maeda:** None. **Y. Takado:** None. **M. Takahashi:** None. **T. Minamihisamatsu:** None. **N. Suzuki:** None. **Y. Tomita:** None. **M. Zhang:** None. **A. Maximov:** None. **T. Suhara:** None. **N. Sahara:** None. **M. Higuchi:** None.

Nanosymposium

711. Astrocytes: Disease Mechanisms

Location: SDCC 32

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 711.01

Topic: B.11. Glial Mechanisms

Support: NIMH Grant R00 MH093458
Johns Hopkins Medicine Discovery Fund
NIH Grant S10OD016374
NIH R01MH113645

Title: Behavioral changes and their molecular basis in mice lacking interleukin-33

Authors: *E. DOHI, E. Y. CHOI, I. V. L. ROSE, A. MURATA, S. CHOW, M. NIWA, S.-I. KANO
Dept. of Psychiatry and Behavioral Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Interleukin (IL)-33 is a member of the IL-1 family of cytokines. IL-33 is expressed in nuclei and secreted as alarmin upon cellular damage to deliver a danger signal to the surrounding cells. Previous studies showed that IL-33 is expressed in the brain and that it is involved in neuroinflammatory and neurodegenerative processes in both humans and rodents. Nevertheless, the role of IL-33 in physiological brain function and behavior remains poorly understood. In this study, we have investigated the behaviors of mice lacking IL-33 (*Il33*$^{-/-}$ mice). IL-33 is constitutively expressed throughout the adult mouse brain, mainly in oligodendrocyte-lineage cells and astrocytes. Notably, *Il33*$^{-/-}$ mice exhibited reduced anxiety-like behaviors in the elevated plus maze (EPM) and the open field test (OFT), as well as deficits in social novelty recognition, despite their intact sociability, in the three-chamber social interaction test. The immunoreactivity of c-Fos proteins, an indicator of neuronal activity, was altered in several brain regions implicated in anxiety-related behaviors, such as the medial prefrontal cortex (mPFC), amygdala, and piriform cortex (PCX), in *Il33*$^{-/-}$ mice after the EPM. Altered c-Fos immunoreactivity in *Il33*$^{-/-}$ mice was not correlated with IL-33 expression in wild-type (WT) mice nor was IL-33 expression affected by the EPM in WT mice. Thus, our study has revealed that *Il33*$^{-/-}$ mice exhibit multiple behavioral deficits, such as reduced anxiety and impaired social recognition. Our findings also indicate that IL-33 may regulate the development and/or maturation of neuronal circuits, rather than control neuronal activities in adult brains. Further experiments to determine cell-type specific roles of IL-33 and the effects of sex on *Il33*$^{-/-}$ mice are in progress.

Disclosures: E. Dohi: None. **E.Y. Choi:** None. **I.V.L. Rose:** None. **A. Murata:** None. **S. Chow:** None. **M. Niwa:** None. **S. Kano:** None.

Nanosymposium

711. Astrocytes: Disease Mechanisms

Location: SDCC 32

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 711.02

Topic: B.11. Glial Mechanisms

Support: R01EY017427
R01EY024997
P30EY008126
T32EY007135
Glaucoma Research Foundation
Research to Prevent Blindness Inc.

Title: Chronic neurodegenerative stress siphons energetic resources from nearby healthy tissue

Authors: *M. L. COOPER[1], W. S. LAMBERT[2], D. J. CALKINS[3]
[1]Vanderbilt Univ., Nashville, TN; [2]Vanderbilt Eye Inst., Nashville, TN; [3]Dept Ophthal & Visual Sci., Vanderbilt Univ. Med. Ctr., Nashville, TN

Abstract: Neurons rely upon astrocyte glycogen stores, the brain's largest energy reserve. Metabolic collaboration between neurons and astrocytes is critical in neurodegenerative disease, which commonly involves metabolic stress. This is especially true of the optic projection, because retinal ganglion cells (RGCs) must fire without saltatory conduction for much of their initial length. The most prevalent optic neuropathy is glaucoma, which challenges RGC axons through sensitivity to intraocular pressure (IOP). This sensitivity causes deficits within the optic nerve even as the retinal cell body persists. Here, we aim to examine the metabolic components of astrocyte endogenous protection during early phases of neurodegeneration. IOP was unilaterally elevated in 86/122 mice via microbead occlusion of aqueous flow (MO). 55 mice received a contralateral saline injection as internal control. IOP was monitored for up to 4 weeks. Glycogen content was determined in 93 mice using Abcam assay ab65620. 1 week after IOP elevation, 29 mice received an intravitreal (IV) injection of ^{18}F-FDG in the contralateral naïve eye. After 1 hour, the % injected dose transferred to the stressed optic projection was determined with positron emission tomography (PET) and CT scans. 6 of the scanned mice underwent optic nerve transection or a sham procedure. MO significantly elevated IOP in all conditions ($p<0.001$). 4 days of IOP elevation reduce glycogen stores in the microbead nerve compared to saline ($p=0.058$). However, 1 and 2 weeks after MO, saline nerves contain less glycogen than contralateral microbead nerves ($p=0.014$; $p=0.083$). Further, 1-4 weeks of MO cause glycogen stores to diminish in both the microbead and saline nerve compared to naïve levels ($p<0.001$; $p<0.001$; $p<0.001$). PET scans after IV ^{18}F-FDG injection in the naïve eye show that glucose moves from the healthy to the stressed optic projection after 1 week of IOP elevation compared

to naïve control animals ($p<0.001$). After unilateral optic nerve transection, but not sham, contralateral elevations in IOP no longer cause glucose to move between projections ($p<0.001$). Chronic unilateral IOP elevation, causes deficits in astrocytic energy reserves in both optic projections. Concurrently, glucose moves from the healthy projection to the stressed tissue. Optic nerve transection eliminates glucose transport but ^{18}F-FDG is still visible in the bladder, meaning this energetic siphoning does not occur through blood or CSF. This evidence suggests a novel protective function of astrocytes during chronic neurodegenerative stress wherein they redistribute resources from healthy areas of the brain to actively degenerating regions.

Disclosures: M.L. Cooper: None. **W.S. Lambert:** None. **D.J. Calkins:** None.

Nanosymposium

711. Astrocytes: Disease Mechanisms

Location: SDCC 32

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 711.03

Topic: B.11. Glial Mechanisms

Support: Inst. for Clinical and Translational Sciences (UCI-ICTS) KL2 award KL2TR001416
ICTS pilot award UL1-TR0001414
UC Cancer Research Coordination Committee award CRN-17-426143
American Cancer Society Research Scholar Grant RSG-17-146-01

Title: Astrocytic dysfunction: Insights and role in the irradiated brain

Authors: *M. M. ACHARYA[1], A. D. BADDOUR[1], B. D. ALLEN[1], T. H. NGUYEN[1], D. T. LE[1], N. RU[1], J. D. BADDOUR[1], M. MARKARIAN[1], R. A. ARANDA[1], J. REEMMER[2], D. BOISON[2], J. E. BAULCH[1]
[1]Dept of Radiation Oncology, Univ. of California Irvine, Irvine, CA; [2]R.S. Dow Neurobio. Labs., Legacy Res. Inst., Portland, OR

Abstract: Radiation therapy (RT)-induced cognitive dysfunction (RICD) causes significant distress and reduces quality of life for cancer survivors. With >16 million survivors in the US, one third of patients treated with cranial RT experience clinically significant cognitive decline that persists long-term post-RT. However, many of the molecular mechanisms underlying RICD remain to be defined. Our data show that cranial RT impairs hippocampus and cortex-dependent behavior in rodents that was concomitant with reduced neurogenesis and persistent neuroinflammation (astrogliosis & microgliosis). Astrocytes form complex glial networks and modulates synaptic plasticity. Using adult mice exposed to 9Gy cranial-RT, we found that cognitively impaired mice brains had astrocytic hypertrophy with elevated expression of astrogliosis genes and microglial activation 6wk post-RT. Astrogliosis was linked with elevated complement (C1q and C3a) activation in the irradiated brain. Therefore, we hypothesize that

detrimental changes in astrocyte function significantly contribute to cognitive impairments. Astrocytes also regulate the function of gliotransmitters including, adenosine (ADO) via cytosolic adenosine kinase (ADK). RT significantly elevates astrocytic ADK. In this study, we show that pharmacologic inhibition of ADK after RT prevented cognitive decline and astrogliosis. To better understand the mechanistic regulation of astrocytic ADK in the neuropathology of RT, and restoration of cognitive function via synaptic ADO augmentation, we utilized miRNA-mediated gene silencing (>90% in vivo) of astrocytic ADK. Cranially irradiated (9Gy) adult mice underwent cognitive testing 6wk post-RT exhibited significant decline in performance on all behavior tasks (*e.g.* novel object recognition, object in place, temporal order). Two weeks later (8wk post-RT), those mice received stereotaxic injection of either scrambled or ADK knockdown (KD) vector. The same mice were then re-tested for behavior 4wk later (12wk post-RT). RT-treated mice receiving astrocytic ADK KD showed significant restoration of cognitive function compared to RT-treated mice receiving the scrambled vector. Molecular analyses of RT-treated mice brains showed significantly elevated hippocampal ADK and inflammation that was linked with astrogliosis. Conversely, ADK KD in the irradiated mice showed relatively less ADK expression and reduced astrogliosis. These pharmacologic and gene silencing approach provides direct evidence that cranial RT disrupts astrocyte function and that interventions targeted to reduce ADK and astrogliosis may ameliorate RT-induced cognitive impairments.

Disclosures: A.D. Baddour: None. **B.D. Allen:** None. **T.H. Nguyen:** None. **D.T. Le:** None. **N. Ru:** None. **J.D. Baddour:** None. **M. Markarian:** None. **R.A. Aranda:** None. **J. Reemmer:** None. **D. Boison:** None. **J.E. Baulch:** None.

Nanosymposium

711. Astrocytes: Disease Mechanisms

Location: SDCC 32

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 711.04

Topic: B.11. Glial Mechanisms

Support: MEXT KAKENHI Grant #14522993
AMED #17dm017088h0002
Takeda Science foundation

Title: Susceptibility to carbonyl stress in schizophrenia derived neural cellsderived neural cells

Authors: *Y. HORIUCHI[1,2], M. ISHIKAWA[2], S. KOIKE[3], A. MORI[1], K. TORIUMI[1], N. OBATA[1], M. MIYASHITA[1], M. ISHIKAWA[1], Y. OGASAWARA[3], H. OKANO[2], M. ARAI[1]
[1]Tokyo Metropolitan Inst. of Med. Sci., Tokyo, Japan; [2]Dept. of Physiol., Keio Univ. Sch. of Med., Tokyo, Japan; [3]Meiji Pharmaceut. Univ., Department of Analytical Biochemistry, Japan

Abstract: Schizophrenia (SZ) is a debilitating brain disorder with a worldwide prevalence of about 1 %. Genetic predisposition in SZ is clear, but multiple factors contribute to its susceptibility. Accumulating evidence has suggested that metabolic disturbance such as oxidative stress (OS) and carbonyl stress (CS) may be impaired in SZ. Our group reported that enhanced carbonyl stress (higher levels of plasma pentosidine, a well-known biomarker for advanced glycation end products; AGEs, and decreased serum vitamin B6 levels) were found in a subpopulation of schizophrenic patients. Furthermore, we found the correlation between carbonyl stress and clinical features such as high ratio of inpatients, long duration of hospitalization and higher daily doses of antipsychotics, suggesting that those patients might be treatment-registrant cases. Of interest, a frameshift mutation in the glyoxalase I (GLO1) gene, a key enzyme for removal of reactive carbonyl compound was found in SZ. However, the biological mechanism of SZ is still unclear. Astrocytes facilitate neuronal maturation by regulating exogenous stress. Antioxidant defense is one example of this type of astrocyte function. We hypothesize that astrocytes may have a deficit in energy metabolism resulting in neuronal damage in SZ, which might be involved in SZ pathology in carbonyl stress context. As a first step of the study, we examined how pentosidine accumulation affects to neuron and astrocyte using iPS cells. We generated TUJ1 positive neurons and GFAP positive astrocyte from SZ patient and normal control subjects. And then we measured the AGE level of the cells and the energy metabolism such as glycolysis and mitochondrial respiration in the cells. We found that pentosidine was accumulated in SZ patient derived astrocyte. Our strategy will provide important clues for understanding of SZ.

Disclosures: Y. Horiuchi: None. **M. Ishikawa:** None. **S. Koike:** None. **A. Mori:** None. **K. Toriumi:** None. **N. Obata:** None. **M. Miyashita:** None. **M. Ishikawa:** None. **Y. Ogasawara:** None. **H. Okano:** None. **M. Arai:** None.

Nanosymposium

711. Astrocytes: Disease Mechanisms

Location: SDCC 32

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 711.05

Topic: B.11. Glial Mechanisms

Support: ML4 Foundation Grant
Georgia W. Woodruff School Startups Funds
NIH T32-GM008433

Title: Fingolimod phosphate inhibits astrocyte inflammatory activity in mucolipidosis IV

Authors: *L. WOOD[1], L. WEINSTOCK[2], A. FURNESS[4], S. HERRON[4], S. SMITH[4], S. SANKAR[3], S. DEROSA[4], D. GAO[4], M. MEPYANS[4], A. ROSATO[5], D. MEDINA[5], A. VARDI[6], N. FERREIRA[7], S. CHO[6], A. FUTERMAN[6], S. SLAUGENHAUPT[8], Y.

GRISHCHUK[8]
[1]Mechanical Engin. and Inst. for Bioengineering and Biosci., [2]Dept. of Biomed. Engin. and Inst. for Bioengineering and Biosci, [3]Dept. of Biomed. Engin., Georgia Inst. of Technol., Atlanta, GA; [4]Massachusetts Gen. Hosp., Boston, MA; [5]Telethon Inst. of Genet. and Med. (TIGEM), Pozzuoli, Italy; [6]Dept. of Biomolecular Sci., Weizmann Inst. of Sci., Rehovot, Israel; [7]Inst. of Pharmacol. and Toxicology, Univ. of Zurich-Vetsuisse, Zurich, Switzerland; [8]Ctr. for Human Genet. Res., Massachusetts Gen. Hospital/Harvard Med. Sch., Boston, MA

Abstract: Problem Statement: Mucolipidosis IV (MLIV) is an orphan neurodevelopmental disease that causes severe neurologic dysfunction and loss of vision. Currently there is no therapy for MLIV. It is caused by loss of function of the lysosomal channel mucolipin-1, also known as TRPML1. Knockout of the *Mcoln1* gene in a mouse model mirrors clinical and neuropathological signs in humans and shows robust activation of microglia and astrocytes in early symptomatic stages of disease, without overt signs of neuronal injury. Since the majority of MLIV patients do not express any MCOLN1 transcripts, treatment options are limited in MLIV. We believe that identifying and modulating the cellular pathways affected by loss of TRPML1 is a tractable way to address the MLIV treatment challenge. **Objectives:** Since astrocytes are activated by postnatal day 10 in an MLIV mouse model, the goal of this study was to identify dysfunctional pathways in astrocytes that may be targeted to promote astrocyte homeostasis in MLIV. **Methods:** We used astrocyte cultures derived from *Mcoln1*$^{-/-}$ mice to identify dysregulated inflammatory signaling pathways that may be targeted to promote astrocyte homeostasis. We identified these pathways by coupling multivariate analysis of cytokines, kinase signaling, and gene expression data. Cytokine protein expression and intracellular kinase signaling was quantified using Luminex multiplexed immunoassays (Millipore) and gene expression was quantified using RNAseq. Protein data were analyzed using discriminant partial least square regression analysis and RNAseq data were analyzed using Gene Set Enrichment Analysis (GSEA). **Results:** We found that *Mcoln1*$^{-/-}$ mice over-express numerous pro-inflammatory cytokines, some of which were also over-expressed in astrocyte cultures. Changes in the cytokine profile in *Mcoln1*$^{-/-}$ astrocytes are concomitant with changes in phospho-protein signaling, including activation of PI3K/Akt and MAPK pathways. Moreover, GSEA identified enrichment of the sphingosine-1-phosphate pathway, which is up-stream of both PI3K/Akt and MAPK pathways. We found that the pan-S1P functional inhibitor Fingolimod promotes cytokine homeostasis, down-regulates signaling within the PI3K/Akt and MAPK pathways, and restores the lysosomal compartment in *Mcoln1*$^{-/-}$ astrocytes. **Conclusion:** Our data suggest that fingolimod is a promising candidate for preclinical evaluation in the MLIV mouse model. Given its success for treatment of re-lapsing multiple sclerosis, it may be rapidly translatable into the first clinical trial for treatment of MLIV.

Disclosures: L. Wood: None. **L. Weinstock:** None. **A. Furness:** None. **S. Herron:** None. **S. Smith:** None. **S. Sankar:** None. **S. DeRosa:** None. **D. Gao:** None. **M. Mepyans:** None. **A. Rosato:** None. **D. Medina:** None. **A. Vardi:** None. **N. Ferreira:** None. **S. Cho:** None. **A. Futerman:** None. **S. Slaugenhaupt:** None. **Y. Grishchuk:** None.

Nanosymposium

711. Astrocytes: Disease Mechanisms

Location: SDCC 32

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 711.06

Topic: B.11. Glial Mechanisms

Support: The National Natural Science Foundation of China(NSFC-RGC: 31761163005)
The NSFC (31671116）
The National Basic Research Program of China (973 Program: 2015CB856402）
The External Cooperation Program of the Chinese Academy of Sciences (172644KYSB20160057 and GJHZ1508)
Shenzhen Government Basic Research Grants (JCYJ20160429190927063, JSGG20160429190521240, and JCYJ20150529143500959)

Title: Astrocytes modulate excitatory neurons within BLA-NAc circuit to rescue deficiency in risk avoidance of DISC1 mice

Authors: *X. ZHOU, Q. XIAO, L. XIE, F. YANG, J. TU
The Brain Cognition and Brain Dis. Inst., Shenzhen Inst. of Advanced Technology, CAS, GuangDong, China

Abstract: Astrocytes are now emerging as key participants in many aspects of brain development, function and disease. Recent studies in rodents have suggested that astrocytes use both secreted and contacted signals to change the niche of the neurons and regulate neural circuits by refining the neuronal connections within the circuit. Here we demonstrated the effects of astrocytes on the modulation of neuron's function for treatment of anxiety disorders.
We choose disrupted-schizophrenia-1 (DISC1) truncated mouse model since *Disc1* is a general risk factor in psychiatric disorders. These mice exhibited the deficiency phenotype in risk avoidance and innate anxiety expression through behavioral tests. The ability of excitability in BLA neurons were also reduced via whole cell patch recordings.
Then we found that light stimulation of expressing engineered channelrhodopsin 2 (ChR2) - astrocytes in BLA significantly compensated the deficiency of innate anxiety expression in DISC1 mice. With whole cell patch recordings, we further found that there were some type of neurons showing response to the optogenetic activated astrocytes. We herein hypothesize there are different cell subtypes in BLA excitatory cells which exist different responses to activated astrocytes.
In order to exclude the effects of gliosis induced by virus injection, we selectively controlled astrocytes by using *DISC1*$^{+}$*/GFAP*$^{+}$*/ChR2*$^{+}$ triple transgenic mice further confirmed the contribution of astrocytes to modulating neural circuits responsible for the abnormal anxiety expression in DISC1 mice. After behaviour tests, c-Fos mapping implicated that nucleus

accumbens (NAc) might be the downstream target for the BLA astrocyte's stimulation.
In conclusions, a better understanding of how astrocytes modulate neural circuits in the healthy and disease brain might lead to the development of new therapeutic strategies to treat brain diseases like anxiety disorder.

Disclosures: X. Zhou: None. **Q. Xiao:** None. **L. Xie:** None. **F. Yang:** None. **J. Tu:** None.

Nanosymposium

711. Astrocytes: Disease Mechanisms

Location: SDCC 32

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 711.07

Topic: B.11. Glial Mechanisms

Support: the University of Copenhagen R40-A3311
the Lundbeck Foundation R126-A12462
the NORDEA Foundation Grant to the Center for Healthy Aging 315600
the NOVO-Nordisk Foundation NNF15OC0017366
Russian Science Foundation 17-74-20089
the Danish Medical Research Council 0602-01965B FSS

Title: Spontaneous astrocytic Ca^{2+} activity abounds in electrically suppressed ischemic penumbra of aged mice

Authors: *J. C. FORDSMANN[1,1], R. P. MURMU[1], C. CAI[1], A. BRAZHE[2], K. J. THOMSEN[1], S. A. ZAMBACH[1], M. LØNSTRUP[1], B. L. LIND[1], M. J. LAURITZEN[1,3]
[1]Dept. of Neurosci., Univ. of Copenhagen, Copenhagen, Denmark; [2]Fac. of Biol., Moscow State Univ., Moscow, Russian Federation; [3]Dept. of Clin. Neurophysiol., Glostrup Hosp., Glostrup, Denmark

Abstract: Experimental focal cortical ischemic lesions consist of an ischemic core and a potentially salvageable peri-ischemic region, the ischemic penumbra. The activity of neurons and astrocytes is assumed to be suppressed in the penumbra because the electrical function is interrupted, but this is incompletely elucidated. Most experimental stroke studies used young adult animals whereas stroke is prevalent in the elderly population. Using two-photon imaging *in vivo*, we here demonstrate extensive but electrically silent, spontaneous Ca^{2+} activity in neurons and astrocytes in the ischemic penumbra of 18-24 month old mice 2-4 hours after middle cerebral occlusion. In comparison, stroke reduced spontaneous Ca^{2+} activity in neurons and astrocytes in adult mice (3-4 month of age). In aged mice, stroke increased astrocytic spontaneous Ca^{2+} activity considerably while neuronal spontaneous Ca^{2+} activity was unchanged. Blockade of action potentials and of purinergic receptors strongly reduced spontaneous Ca^{2+} activity in both neurons and astrocytes in the penumbra of old stroke mice. This indicates that

stroke had a direct influence on mechanisms in presynaptic terminals and on purinergic signaling. Thus, highly dynamic variations in spontaneous Ca^{2+} activity characterize the electrically compromised penumbra, with remarkable differences between adult and old mice. The data are consistent with the notion that aged neurons and astrocytes take on a different phenotype than young mice. The increased activity of the aged astrocyte phenotype may be harmful to neurons. We suggest that the abundant spontaneous Ca^{2+} activity in astrocytes in the ischemic penumbra of old mice may be a novel target for neuroprotection strategies.

Disclosures: J.C. Fordsmann: None. **R.P. Murmu:** None. **C. Cai:** None. **A. Brazhe:** None. **K.J. Thomsen:** None. **S.A. Zambach:** None. **M. Lønstrup:** None. **B.L. Lind:** None. **M.J. Lauritzen:** None.

Nanosymposium

712. Imaging Studies and Biomarkers in Alzheimer's Disease

Location: SDCC 31C

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 712.01

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

Support: BrightFocus A2017081S
Cure Alzheimer's Fund

Title: *In vivo* stable isotope labeling & quantitative mass spectrometry imaging of Aβ plaque deposition and neuronal metabolism in human AD brain

Authors: *N. C. WILDBURGER[1], G. S. DAY[1], W. SIGURDSON[1], M. SULLIVAN[1], A. PETERS[1], L. WATKINS[1], R. E. SCHMIDT[2], R. J. BATEMAN[1]
[1]Neurol., [2]Pathology and Immunol., Washington Univ. in St. Louis Sch. of Med., Saint Louis, MO

Abstract: Background: Alzheimer's disease (**AD**) is a neurodegenerative disorder with clinical manifestations of progressive memory decline and is the most common form of age-related dementia. AD is characterized by two distinct pathologies – the extracellular deposition of **amyloid-beta** leading to amyloid plaques and the intracellular accumulation of **tau** in neurons leading to neurofibrillary tangles and labeled neurites in plaques. Despite recent advances in our understanding of AD there is a critical gap in our knowledge of '*What is the turnover of plaques at different stages of AD*?' and '*Does tau neurofibrillary formation in neurons ultimately lead to neuronal hypometabolism and death*?' We provide the first, direct measurements of AD in a cross-sectional cohort including individuals with symptomatic AD and age-similar cognitively normal controls.
Methods: Our approach utilizes *in vivo* incorporation universally labeled ^{15}N-Spirulina (*i.e.,* **SILK**) into Aβ plaque and neurons with and without tauopathy in human AD participants via

oral labeling of participants in hospice with very mild-to-mild AD dementia (Clinical Dementia Rating [CDR] 0.5-1), moderate-to-severe AD dementia (CDR 2-3), and age-similar cognitively normal controls (CDR 0). Dementia was staged using standard clinical measures, including a telephone interview with a reliable informant (used to derive the CDR), and Montreal Cognitive Assessment (MoCA) and AD8. Neuropathological diagnoses were established via brain-only autopsy in accordance with by National Institute on Aging–Alzheimer's Association criteria. Additional a brain regions were prepared using established SEM protocols and isotopically imaged by nanoscale secondary ion mass spectrometry (**NanoSIMS**) in a combined approach we term **SILK-SIMS**.
Results: 1) The incorporation of tracer into plaques in participants with symptomatic AD suggests that plaques formation is a dynamic process, with evolution occurring over days, even in later stages of disease. **2**) Higher levels of tracer incorporation were associated with increased disease severity (by CDR). **3**) With increasing CDR, neurons incorporated more tracer (a proxy for function or activity) compared to age-similar cognitively normal controls.
Conclusions: Increased tracer incorporation may reflect increased deposition into plaques and neuronal over-compensation in disease.SILK-SIMS studies provide invaluable information on plaque dynamics and neuronal health in the normal and diseased brain. These studies offer new avenues for investigation into pathological mechanisms of the disease, with implications for therapeutic development.

Disclosures: N.C. Wildburger: None. **G.S. Day:** None. **W. Sigurdson:** None. **M. Sullivan:** None. **A. Peters:** None. **L. Watkins:** None. **R.E. Schmidt:** None. **R.J. Bateman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); C2N Diagnostics.

Nanosymposium

712. Imaging Studies and Biomarkers in Alzheimer's Disease

Location: SDCC 31C

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 712.02

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

Support: NIH R01 AG033106

Title: Global brain oxygen metabolism is reduced but vascular function is intact in amnestic mild cognitive impairment

Authors: *B. P. THOMAS[1,4], M. SHENG[1], B. Y. TSENG[5], T. TARUMI[5], K. MARTIN-COOK[2], K. B. W. WOMACK[2], M. C. CULLUM[3], B. D. LEVINE[5], B. RYPMA[4], R. ZHANG[5], H. LU[1,6]
[1]Advanced Imaging Res. Ctr., [2]Neurol., [3]Neuropsychology, Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [4]Ctr. for Brain Health, Univ. of Texas at Dallas, Dallas, TX; [5]Inst. of Exercise

and Envrn. Medicine, Presbyterian Hosp., Dallas, TX; [6]Radiology, Johns Hopkins Univ., Baltimore, DC

Abstract: Current research in Alzheimer disease (AD) treatment emphasizes the need for early detection. Amnestic Mild Cognitive Impairment (MCI) is a clinically definable early stage of AD. Clear MCI diagnosis is challenging, and it is not known which biomarkers might be most diagnostic. In this study, we used several MRI modalities to characterize MCI neurobiology. 44 MCI patients (age 64.0±6.6) were diagnosed based on standard Petersen criteria, and 28 elderly controls (EC) (age 65.6±6.8) were scanned on a Philips 3T MRI. The following MRI biomarkers were measured from all subjects: global resting $CMRO_2$, oxygen extraction fraction (OEF), cerebral blood flow (CBF), and cerebrovascular reactivity (CVR) to CO_2 inhalation. MCI patients had a CDR of 0.5 and EC had a CDR of 0. Mini-Mental-State-Exam scores did not differ between groups (EC 29.0±1.0; MCI 28.9±1.4; p=0.71), confirming the early stage of MCI. Global $CMRO_2$ was 12.9% lower (p=0.005) in MCI patients compared to EC. This metabolic deficit could not be attributed to brain atrophy, as the $CMRO_2$ calculation accounts for brain volume. In fact, brain volume was not different between groups (p=0.64). We further assessed whether this $CMRO_2$ reduction was due to insufficient oxygen availability or less neural oxygen extraction from blood. Specifically, oxygen availability can be assessed by examining CBF and arterial oxygen saturation (Ya). CBF indicates the amount of blood available to the brain, and Ya indicates the percentage of oxygen carried by blood. Neither global CBF (p=0.80) nor Ya (p=0.57) was different between groups. In contrast, when comparing the OEF between groups, OEF was lower by 10% (p=0.016) in MCI patients. Global $CMRO_2$ was found to be correlated (r=0.256, p=0.03) with LM-delayed recall scores across all subjects (including both MCI and EC). Within the MCI group, global $CMRO_2$ showed a similar association with LM-delayed recall scores (r=0.259), although not statistically significant due to a smaller sample size (p=0.047, single tailed test). CVR data provide additional insights on vascular function in MCI, as CVR is presumably not strongly dependent on metabolism and is thought to be more vascular-specific. Neither voxel-by-voxel CVR comparison nor global CVR quantification revealed a significant difference between the MCI and EC, suggesting minimal vascular deficit in MCI patients. In conclusion, the present work suggests that global brain oxygen metabolism is diminished in MCI, which is primarily attributed to a reduced extraction fraction of oxygen by the tissue. Global blood flow and CVR in MCI patients showed no difference from EC. Imaging markers reported here may prove useful in clear MCI diagnosis.

Disclosures: B.P. Thomas: None. **M. Sheng:** None. **B.Y. Tseng:** None. **T. Tarumi:** None. **K. Martin-Cook:** None. **K.B.W. Womack:** None. **M.C. Cullum:** None. **B.D. Levine:** None. **B. Rypma:** None. **R. Zhang:** None. **H. Lu:** None.

Nanosymposium

712. Imaging Studies and Biomarkers in Alzheimer's Disease

Location: SDCC 31C

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 712.03

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

Support: R03 RAG060263A

Title: Endogenous compensation for Alzheimer's neuropathology is genotype dependent

Authors: *T. W. SCHMITZ[1], H. SOREQ[3], J. POIRIER[4], R. N. SPRENG[2]
[1]Dept. of Neurol. & Neurosurg., [2]Montreal Neurolog. Inst., McGill Univ., Montreal, QC, Canada; [3]Hebrew Univ. Jerusalem, Jerusalem, Israel; [4]Douglas Mental Hlth. Univ. Inst., Montreal, QC, Canada

Abstract: In order to prevent the devastating effects of Alzheimer's disease (AD), identification and remediation of the earliest pathologies is of central importance. The vast majority of human research on AD focuses on individuals who are experiencing signs and symptoms of mild cognitive impairment (MCI). Unfortunately however, MCI only emerges after a long preclinical period of disease progression, characterized by pronounced neuropathology in subcortical and cortical regions of the brain.
We capitalized on the rich multimodal datasets available through the Alzheimer's Disease Neuroimaging Initiative to identify cognitively normal (CN) humans in preclinical stages of disease. This was accomplished using highly sensitive cerebrospinal fluid (CSF) biomarkers of AD neuropathology. We then isolated carriers of the APOE ε4 allele (ε4+), a genetic AD risk factor closely linked to neuronal dysfunction and degeneration, to assess its interaction with CSF biomarkers of preclinical disease progression. Using these biologically informed grouping strategies (N=420, mean Age=72.1, 209 Females), we leveraged gene expression and longitudinal structural MRI data to examine whether the early pathological cascade of preclinical AD can be traced to the cholinergic neurons of the basal forebrain (BF). Post-mortem histology work identifies the cholinergic BF neurons as among the cell types most vulnerable to AD neuropathology, and the earliest to exhibit abnormal degeneration.
We provide novel evidence that central cholinergic metabolism—the genetic regulation of ACh biosynthesis and breakdown by CHAT and ACHE, respectively—is differentially altered in preclinical CN adults depending on APOE genotype. As CSF biomarkers of neuropathology increase in CN adults, cholinergic metabolism was up-regulated among those without the APOE ε4 allele, but not among e4 carriers. Crucially, these genotype-dependent patterns covaried with longitudinal degeneration of the BF: up-regulation of CHAT tracked with decreased BF degeneration in ε4- CN individuals. By contrast, in ε4+ CN individuals, CHAT expression declined in tandem with increased NbM degeneration. These interrelationships were not

attributable to ACHEI drugs, indicating that the cholinergic BF compensates for neuropathology via endogenous transcriptional control of ACh metabolism. Our findings indicate that central cholinergic metabolism can flexibly adapt to neuropathology. Moreover, this flexibility is strongly affected by genotype, which dissociates neurobiological trajectories of brain ageing before clinically detectable memory impairments emerge.

Disclosures: T.W. Schmitz: 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.; Pfizer Scientific Services Evaluation Agreement. **H. Soreq:** None. **J. Poirier:** None. **R.N. Spreng:** 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.; Pfizer Scientific Services Evaluation Agreement.

Nanosymposium

712. Imaging Studies and Biomarkers in Alzheimer's Disease

Location: SDCC 31C

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 712.04

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

Support: NIH: AG-054048

Title: Blood-based protein variants distinguish different proteinopathies in Alzheimer’s patients: Relationship with cognitive decline and disease progression

Authors: *S. M. WILLIAMS, P. SCHULZ, M. R. SIERKS
Sch. for Engin. of Matter, Transport and Energy, Arizona State Univ., Tempe, AZ

Abstract: Biomarkers that can predict and diagnose the onset of Alzheimer’s disease (AD) are essential for selecting effective therapeutic treatments. We previously isolated single chain-variable fragments (scFvs) that recognize blood-based biomarkers of neurodegenerative diseases and here utilize a panel of 10 to characterize a set of 50 blinded longitudinal human plasma cases where 25 converted to AD during the course of the study. Three scFvs bound oligomeric variants of amyloid-beta (Aß), two bound oligomeric variants of tau, three bound TDP-43 variants and two bound oligomeric variants of α-synuclein. Each scFv alone distinguished between AD plasma samples and controls. Based on the biomarker profiles, the AD cases were classified as either Aß (72%) or tau dominant (28%). At least one Aß or tau variant was detected in 96% or 84% of all AD cases, respectively, indicating their importance as AD biomarkers. In addition, around 48% of the AD patients had oligomeric α-synuclein variants, which is consistent with the number of reported AD cases with Lewy body pathology. The protein variants showed

significant negative correlations with MMSE scores, though the specific variants depended on disease stage (pre-MCI, MCI and AD). Some of the non-converting control cases also showed the presence of different protein variant biomarkers, potentially indicating pre-symptomatic onset of different neurodegenerative diseases. These results indicate that a panel of scFvs targeting neurodegenerative disease related protein variants can be used to detect blood-based biomarkers of AD, even many years before symptoms show up, and may discriminate between which patients would best benefit from Aß or tau based therapeutic treatments.

Disclosures: P. Schulz: None. **M.R. Sierks:** None.

Nanosymposium

712. Imaging Studies and Biomarkers in Alzheimer's Disease

Location: SDCC 31C

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 712.05

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

Support: VA San Diego Grant BX003040
NIH Grant AG047484
NIH Grant BX003040
NIH Grant AG0051839

Title: Quantitative proteomics of plasma-derived neuronal exosomes during the progression of Alzheimer's disease

Authors: *S. CANCHI[1,2], C. N. WINSTON[1], J. J. MORESCO[3], J. R. YATES, III[3], R. A. RISSMAN[1,2]
[1]Neurosciences, UCSD Sch. Med., La Jolla, CA; [2]Veteran's Affairs San Diego Healthcare Syst., San Diego, CA; [3]Dept. of Chem. Physiol., The Scripps Res. Inst., La Jolla, CA

Abstract: Effective preclinical diagnosis of Alzheimer's Disease (AD) is critica for clinical trials design and development of disease-modifying therapeutics. Concurrent to structural changes identified using neuroimaging, clinically validated cerebrospinal fluid (CSF) biomarkers including amyloid beta and tau proteins offer the ability to predict rates of cognitive decline across different stages of clinical Alzheimer's Disease (AD). However, CSF collection for AD diagnosis has complicated clinical trials enrollment due to its perceived intrusive and invasive nature. While, blood-based biomarkers offer an attractive alternative, small changes in concentrations, lack of validated choices for assay platforms coupled with challenges in confirming whether observed changes are truly brain-specific changes have complicated progress in this area. In this study, we performed a protein analysis contained within human plasma derived neuronal exosomes, which provide a snapshot of cellular functional state and may help to address some of these limitations. Exosomes were isolated from plasma of subjects enrolled in

a randomized clinical trial, with clinical progression of mild cognitive impairment (MCI) to dementia. Exosomes originating from neurons i.e. NDE's were enriched by absorption with anti-L1CAM antibody. Protein identification and quantification were done using the Integrated Proteomics Pipeline (IP2). Tandem MS/MS spectra were extracted and searched against Uni-Prot human database with reversed sequences using ProLuCID. DTA Select was used to filter peptide candidates and assemble into proteins and protein groups with at least two unique peptide hits per protein with a false positive rate of 0.05 at the protein level. Total of 143 proteins were identified, of which 98 were unique to MCI-stable and 6 were unique to MCI converted to AD (ADC) subjects. Of the 39 shared proteins, 20 had higher concentration in MCI-stable compared to ADC including amyloid precursor protein (APP). Functional enrichment for the unique proteins revealed distinct pathways and ontology with known association to AD in ADC. These results highlight the predictive utility of plasma derived exosomes as biomarkers for preclinical diagnosis of AD.

Disclosures: S. Canchi: None. **C.N. Winston:** None. **J.J. Moresco:** None. **J.R. Yates:** None. **R.A. Rissman:** None.

Nanosymposium

712. Imaging Studies and Biomarkers in Alzheimer's Disease

Location: SDCC 31C

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 712.06

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

Support: NIH 1RF1AG054199-01
1R01AG054672-01
1R56AG057469-01
AARF-16-442664

Title: Proteomic and biophysical characterization of Extracellular Vesicles isolated from Alzheimer's disease brain tissues

Authors: A. M. DELEO[1], M. SETHI[2], S. MURAOKA[3], M. MEDALLA[4], Y. WANG[3], S. GOLANTLA[6], H. E. GENDELMAN[6], S. IKEZU[3], J. ZAIA[2], *T. IKEZU[5]
[1]Pharmacol. and Exptl. Therapeut., Boston Univ. Schol of Med., Boston, MA; [2]Biochem., [3]Pharmacol. and Exptl. Therapeut., [4]Anat. and Neurobio., [5]Pharmacol. and Neurol., Boston Univ. Sch. of Med., Boston, MA; [6]Dept. of Pharmacol. and Exptl. Neurosci., Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Background: Studies have found tau-containing extracellular vesicles (EVs) isolated from multiple biospecimens from Alzheimer's disease (AD) patients, even in prodromal cases. We have recently shown that EVs derived from microglia were able to spread tau to neurons in a

model of AD, suggesting their role in AD progression. Here we generated proteomic profiles of EVs isolated from cortical grey matter of control (CTRL) and AD cohorts for bioinformatic analysis. **Methods:** EV-enriched fractions were isolated from AD and CTRL brains from two independent brain banks. Their biophysical and molecular properties were characterized by nanoparticle tracking analysis (NTA) and liquid chromatography tandem mass-spectrometry. The data were subjected to bioinformatic analysis of functional properties and disease associations. **Results:** NTA analysis revealed that brain-derived exosomes have a mode diameter of 118.2±3.3 and 134.7±5.9 nm for AD and CTRL ($p=0.0176$), although the average values were significantly smaller by electron microscopic analysis. Proteomic analysis showed that EVs from each bank commonly expressed 387 or 412 proteins for the CTRL or AD condition, respectively. Unsupervised hierarchical clustering of each cohort of proteins showed that the majority of samples segregate by disease status. Each sample had at least a 55% overlap with commonly observed exosomal proteins as defined by the Exocarta database, and were significantly enriched in this category by Gene Ontology analysis. Both CTRL and AD EVs contain tau, which had more phosphorylated sites in the AD cohort. AD-derived EVs also contained a wider variety of proteins (88 AD brain-unique proteins vs 64 for CTRL brains) and were enriched in a group of molecules found on cell surfaces. Ingenuity Pathway Analyses of the entire set of proteins expressed in each condition revealed enhanced expression of APP metabolism, prion diseases ontology, and stress-activated p38 MAPK cascade in AD EVs. In contrast, the CTRL EVs showed enhanced expression of neurogenic proteins and those associated with microtubules and their organization. **Conclusions:** There are significant differences in the protein signatures in EVs derived from AD as compared to CTRL brains, despite their biophysical similarities. AD samples are enriched in APP metabolism and prion disease proteins over CTRL, and express unique cell surface molecules.

Disclosures: A.M. DeLeo: None. **M. Sethi:** None. **S. Muraoka:** None. **M. Medalla:** None. **Y. Wang:** None. **S. Golantla:** None. **H.E. Gendelman:** None. **S. Ikezu:** None. **J. Zaia:** None. **T. Ikezu:** 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.; Abbvie, Eisai, Ono Pharma. F. Consulting Fees (e.g., advisory boards); Takeda.

Nanosymposium

712. Imaging Studies and Biomarkers in Alzheimer's Disease

Location: SDCC 31C

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 712.07

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

Support: U24NS100591
UH2NS100608

UH2NS100588
UH2NS100598
UH2NS100599
UH2NS100605
UH2NS100614

Title: MarkVCID: Vascular contributions to cognitive impairment and dementia biomarkers development and validation

Authors: *R. A. CORRIVEAU[1], J. T. GLADMAN[1], L. MCGAVERN[1], M. S. ALBERT[2], K. ARFANAKIS[3], A. CAPRIHAN[4], C. DECARLI[5], M. FORNAGE[6], K. G. HELMER[7], G. JICHA[8], A. H. KASHANI[9], J. KRAMER[10], H. LU[2], J. RINGMAN[9], G. A. ROSENBERG[4], J. A. SCHNEIDER[11], K. SCHWAB[7], S. SESHADRI[12], R. TRACY[13], D. J. J. WANG[9], D. M. WILCOCK[8], S. M. GREENBERG[7]
[1]NINDS/NIH, Rockville, MD; [2]Johns Hopkins Univ., Baltimore, MD; [3]Illinois Inst. of Technol., Chicago, IL; [4]Univ. of New Mexico, Albuquerque, NM; [5]Univ. of California Davis, Davis, CA; [6]Univ. of Texas Hlth. Sci. Ctr., Houston, TX; [7]Massachusetts Gen. Hosp., Boston, MA; [8]Univ. of Kentucky, Lexington, KY; [9]USC, Los Angeles, CA; [10]Univ. of California, San Francisco, CA; [11]Rush Univ., Chicago, IL; [12]Boston Univ., Boston, MA; [13]Univ. of Vermont, Burlington, VT

Abstract: The World Health Organization reports that 47.5 million people are affected by dementia worldwide. The burden of illness due to dementia approaches crisis proportions. Evidence from epidemiology and pathology studies indicates that damage to the vascular system is associated with an increased risk of many types of dementia and neurodegeneration. The science of vascular contributions to cognitive impairment and dementia (VCID) integrates diverse aspects of biology and incorporates the roles of multiple cell types that support the function of neural tissue including lipoprotein metabolism. The MarkVCID consortium, established by the NINDS/NIH in 2016 via 2 RFAs, develops and rigorously validates candidate biomarkers for small vessel VCID. The goal of the consortium is to deliver high-quality VCID biomarkers ready for use in large scale clinical trials. During phase I (years 1-2; year 2 is in presently in progress), biomarker development projects (sites), with support from the Coordinating Center, have established the consortium, including consortium agreements, best practices and standardized protocols, and have further developed candidate biomarkers. During phase II (years 3-5) the consortium sites will independently perform cross-site validation studies to further evaluate and develop biomarker candidates to readiness for large scale multi-site clinical validation studies and, if successful, for use in interventional clinical trials. To facilitate the transition from phase I to phase II, the seven sites recently nominated more than a dozen biomarker paradigms, including both fluid biomarkers and imaging biomarkers, designed to diagnose, determine risk for, monitor, and prognose small vessel VCID. After a selection process including input from the Coordinating Center on behalf of the MarkVCID consortium, an External Advisory Committee, and NINDS leadership, independent cross-site testing and validation of the most promising small vessel VCID biomarkers is scheduled to start in July of 2018. Here we will report the outcome of the selection process and progress on multi- site validation of selected candidate small vessel VCID biomarker paradigms.

Disclosures: R.A. Corriveau: None. **J.T. Gladman:** None. **L. McGavern:** None. **M.S. Albert:** None. **K. Arfanakis:** None. **A. Caprihan:** None. **C. DeCarli:** None. **M. Fornage:** None. **K.G. Helmer:** None. **G. Jicha:** None. **A.H. Kashani:** None. **J. Kramer:** None. **H. Lu:** None. **J. Ringman:** None. **G.A. Rosenberg:** None. **J.A. Schneider:** None. **K. Schwab:** None. **S. Seshadri:** None. **R. Tracy:** None. **D.J.J. Wang:** None. **D.M. Wilcock:** None. **S.M. Greenberg:** None.

Nanosymposium

713. Alzheimer's Disease and Other Dementias: Abeta: Pathologic Mechanisms

Location: SDCC 33

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 713.01

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

Support: NIA Grant AG047779-01
US Army Medical Research Contract W81XWH-14-1-0046
NIH R01 GM071966
Fisher Center for Alzheimer's Disease Research

Title: Selective neuronal vulnerability in Alzheimer’s disease: A network-based analysis

Authors: *J.-P. ROUSSARIE[1], V. YAO[4], Z. PLAUTZ[2], S. KASTURIA[2], C. ALBORNOZ[2], E. F. SCHMIDT[3], L. BRICHTA[2], A. BARNEA[2], N. HEINTZ[3], P. R. HOF[5], M. HEIMAN[6], M. FLAJOLET[2], O. TROYANSKAYA[4], P. GREENGARD[2]
[1]Greengard Lab., [2]Mol. & Cell. Neurosci., [3]Lab. of Mol. Biol., Rockefeller Univ., New York, NY; [4]Princeton Univ., Princeton, NJ; [5]Icahn Sch. of Med. at Mount Sinai, New York, NY; [6]Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: Alzheimer’s Disease (AD) is a striking example of the selective cell tropism displayed in most neurodegenerative diseases. Early clinical symptoms (such as memory loss) are caused by the selective build-up of tau pathology and degeneration of principal neurons of the entorhinal cortex layer II (ECII), followed by CA1 pyramidal cells in the hippocampus. In contrast, other brain regions, such as the primary sensory cortices, are relatively resistant to pathology until later stages of the disease. An important step towards understanding this selective neuronal vulnerability, and towards uncovering therapeutic targets for disease-modifying drugs, is elucidating the molecular signature that differentiates vulnerable neurons from others, and the pathological mechanisms that preferentially takes place within these neurons. We present here a novel approach using a tightly integrated computer-directed experimental approach, with both mouse models and human publicly available data, to understand pathways leading to tau pathology in vulnerable neurons. Using high quality neuron-type specific molecular profiles of ECII, CA1, and five other types of neurons much more resistant to AD, which we generate using the bacTRAP technology, and a large compendium of human functional genomics data, we

construct *in silico* network models of neuron-type specific function for AD vulnerable and resistant neurons. Integrating these with AD quantitative genetic data using a machine-learning approach, we then uncover genes most functionally associated with tau pathology in vulnerable neurons. Analyzing these results together with cell-type specific gene expression changes associated with aging and with Aβ accumulation, we then provide the first molecular framework to understand the complex interplay between age, Aβ, and tau within vulnerable neurons. In particular we highlight a functional cluster of genes involved in synaptic vesicle release and axonogenesis, which is modulated by aging and Aβ accumulation that might be responsible for selective neuronal vulnerability. With a completely unbiased data-driven approach, we also find that tau and α-Synuclein are very central genes in ECII neurons, and we reveal functional partners for the two genes, which could be relevant for ECII vulnerability.

Disclosures: J. Roussarie: None. **V. Yao:** None. **Z. Plautz:** None. **S. Kasturia:** None. **C. Albornoz:** None. **E.F. Schmidt:** None. **L. Brichta:** None. **A. Barnea:** None. **N. Heintz:** None. **P.R. Hof:** None. **M. Heiman:** None. **M. Flajolet:** None. **O. Troyanskaya:** None. **P. Greengard:** None.

Nanosymposium

713. Alzheimer's Disease and Other Dementias: Abeta: Pathologic Mechanisms

Location: SDCC 33

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 713.02

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

Support: 5R21AG047505-02
2T32AG000222-26

Title: A recipe for neurotoxicity: The prion protein, promiscuous binding, and soluble protein aggregates?

Authors: *G. T. CORBETT[1], A. ASFAW[1], T. C. HALL[1], Z. WANG[1], W. LIU[1], J. COLLINGE[2], M. PERKINTON[3], A. BILLINTON[3], D. M. WALSH[1]
[1]Neurol., Brigham & Women's Hospital/Harvard Med. Sch., Boston, MA; [2]MRC Prion Unit at UCL, Univ. Col. London Inst. of Prion Dis., London, United Kingdom; [3]MedImmune, Ltd., AstraZeneca Neurosci. Innovative Medicines, Cambridge, United Kingdom

Abstract: A feature of many neurodegenerative disorders is the presence of macroscopic aggregates formed from neuronal proteins of unrelated sequences. Alzheimer’s disease (AD) is characterized by extracellular plaques containing amyloid β-protein (Aβ) and intracellular neurofibrillary tau tangles. In Parkinson’s disease and dementia with Lewy bodies, α-synuclein (αS) accumulates within neurons as Lewy bodies and Lewy neurites, and multi-chain assemblies of misfolded cellular prion protein (PrP^C) are found in transmissible spongiform

encephalopathies. While soluble aggregates of these proteins are believed to drive pathogenesis, the processes by which these species interact with cells to induce toxicity is unclear. Soluble aggregates of Aβ (sβAs) are known to bind to PrP^C and PrP is necessary for certain aspects of Aβ neurotoxicity. Aβ binding is mediated by 2 distinct sites on PrP, one centered around residues 23-27 (*site I*) and the other around residues 95-110 (*site II*). The finding that PrP^C can serve as a receptor for soluble aggregates of Aβ is consistent with the hypothesis that the unstructured N-terminus of PrP^C acts as a molecular sensor which can interact with a broad range of ligands, including β-sheet-rich proteins. Here, we sought to determine if soluble aggregates of αS (sαAs) and tau (sτAs) bound to PrP^C and whether PrP^C was required for the toxicity mediated by these proteins.

Recombinant PrP was immobilized on microtiter plates, then various concentrations of monomeric or aggregated protein was added and bound proteins detected using specific antibodies. Importantly, sαAs and sτAs bound to PrP with high affinity, and as with Aβ, monomers and end-stage fibrils displayed little or no binding. Moreover, anti-PrP antibodies to *sites I* and *II* effectively displaced sαAs and sτAs and deletion of these sites substantially attenuated binding. Additionally, the interaction with tau required the microtubule binding region, and the binding of αS involved the non-amyloid component domain. High-content imaging and bioactivity assays utilizing primary mouse and iPSC-derived human neurons revealed that soluble aggregates of all three proteins interact with PrP on neuronal surfaces and exert dose- and time-dependent neurotoxicity, and that binding and toxicity can be prevented by anti-PrP antibodies. These results suggest that PrP may play an important role in a variety of late-life neurodegenerative diseases and that therapeutic targeting of PrP may offer a plausible means to treat conditions which often involve a mixture of proteinopathies.

Disclosures: G.T. Corbett: None. **A. Asfaw:** None. **T.C. Hall:** None. **Z. Wang:** None. **W. Liu:** None. **J. Collinge:** None. **M. Perkinton:** None. **A. Billinton:** None. **D.M. Walsh:** None.

Nanosymposium

713. Alzheimer's Disease and Other Dementias: Abeta: Pathologic Mechanisms

Location: SDCC 33

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 713.03

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

Support: NIH P30 NS045776
NIH AG048080
NIH AG15379
NIH AG014713
Cure Alzheimer’s Fund
BrightFocus Foundation

Title: Aβ42/40 ratio regulates tau pathology in 3D human neural cell culture models of AD

Authors: *D. KIM, S. KWAK, E. BRAND, K. J. WASHICOSKY, J. PARK, D. VON MAYDELL, K. BRENNER, J. L. ARONSON, E. BYLYKBASHI, S. CHOI, R. E. TANZI
Genet. and Aging Res. Unit, MIND, Massachusetts Gen. Hospital/ Harvard Med. Sch., Charlestown, MA

Abstract: Aβ42 is thought to be a key mediator of Alzheimer's disease (AD) pathogenesis, which is strongly supported by the fact that most familial AD mutations increase the Aβ42/40 ratio. However, the impact of Aβ42, Aβ42/40 ratio, and other Aβspecies on AD pathogenic cascade has not been fully studied in human neuronal cells. Previously, we showed that 3D-differentiated human neural progenitor cells (hNPCs) harboring familial mutations in amyloid βprecursor protein (APP,*Swedish/London*) and presenilin 1 (PS1,ΔE9) display robust Aβ accumulation (Aβplaque-like)and Aβ-driven tau hyperphosphorylation/aggregation (neurofibrillary tangle (NFT)- like). Here we generated multiple clonal AD hNPCs that express differentAβ42/40 ratios and total Aβlevels and analyzed phospho-tau (p-tau) accumulation and aggregation using immunofluorescence, ELISA, and Western blot of 1% sarkosyl-soluble and -insoluble fractions.We found that insoluble p- and total-tau accumulations correlate with Aβ42/40 ratio, not total Aβ levels. To exclude the potential contribution of PS1ΔE9 on other γ-secretase substrates, we also generated new clonal AD hNPCs harboring APP transmembrane domain (TMD) mutations that can modulate Aβ48-45-42 or Aβ49-46-43-40 sequential cleavages without overexpressing PS1ΔE9. hNPCs with the APP TMD mutation that elevates Aβ42/40 ratio robustly increased p-tau pathology while the APP TMD cells with decreased Aβ42/40 ratio did not show p-tau pathology in the same 3D differentiation conditions. Finally, we established a non-cell-autonomous 3D culture system sharing soluble Aβ species through a 0.4 μM pore membrane. Again, we found only soluble Aβ species from hNPCs with high Aβ42/40 ratio, not ones from low Aβ42/40 ratio, induced insoluble p-tau accumulations in control hNPCs without familial AD mutations. Our results demonstrate that Aβ42/40 ratio, not total Aβlevels regulate tau pathology in 3D human neural cell culture models of AD. We are currently analyzing Aβ42-specific pathogenic cascades using unbiased RNA-seq analysis.

Disclosures: D. Kim: None. **S. Kwak:** None. **E. Brand:** None. **K.J. Washicosky:** None. **J. Park:** None. **D. von Maydell:** None. **K. Brenner:** None. **J.L. Aronson:** None. **E. Bylykbashi:** None. **S. Choi:** None. **R.E. Tanzi:** None.

Nanosymposium

713. Alzheimer's Disease and Other Dementias: Abeta: Pathologic Mechanisms

Location: SDCC 33

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 713.04

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

Support: NIH grant AG027544 (FML)
NIH grant AG00538 (FML)
NIH grant U54 AG054349 (DBV, AM, MAW, KGN, GRM, AJT, FML)
The BrightFocus Foundation A2015535S (FML)
The Alzheimer's Association #NIRG-15-363477 (DBV)
The Alzheimer's Association #AARF-16-440760 (SF)
LLHF grant 2013-A-016-FEL (DBV)

Title: hAb-KI mice: A novel tool for investigating risk factors in sporadic Alzheimer's cases

Authors: *D. BAGLIETTO-VARGAS[1], S. FORNER[2], A. C. MARTINI[2], L. TRUJILLO-ESTRADA[2], C. NUÑEZ-DIAZ[3], E. A. KRAMÁR[2], S. JIANG[2], D. P. MATHEOS[2], C. DA CUNHA[2], A. GUTIERREZ[3], K. N. GREEN[2], M. A. WOOD[2], A. MORTAZAVI[2], G. R. MACGREGOR[2], A. J. TENNER[2], F. M. LAFERLA[2]
[1]Neurobio. and Behavior, Univ. of California, Irvine|910005640|0, Irvine, CA; [2]Univ. of California, Irvine, CA; [3]Univ. of Malaga /CIBERNED, Malaga, Spain

Abstract: Over the past two-decade researchers have focused their efforts on developing animal models to dissect the molecular mechanisms underlying AD, and to assist with the identification and development of potential therapies. Although these models have provided useful insights into the mechanisms of disease, the initial optimism for hastening drug development was perhaps premature, as successes in treating AD in mouse models have not been translated into the clinic. The discordance between preclinical efficacy in animal models and the lack of success during transition into clinical testing could be due to some of the inherent limitations that arise when modeling the disease in rodents, for instance, the significant overexpression of familial AD (FAD)-associated mutated proteins and the dependence of artificial transcriptional regulatory elements, among several other limitations. Therefore, new models are urgently needed to circumvent the persistent limitations found in current animal models. Here, we used an innovative animal model to better understand pathophysiological events that occur in the sporadic form of the disease. Our model, termed hAβ-KI, expresses wild-type human Aβ under the control of the endogenous mouse APP gene. Using the natural mouse promoter gives the opportunity to more accurately mimic the natural progression of the disease, particularly sporadic forms of AD that are not attributable to dominant genetic mutations and to determine the impact of many AD risk factors in Aβ pathogenesis.The hAβ-KI mouse line develops age dependent increase in diffuse Aβ aggregates which were associated with behavior and long-term potentiation deficits at 18 months of age. Moreover,we used this novel model to better understand how human Aβ seeds spread and facilitate Aβ pathology in our newly developed hAβ-KI mice compared to a traditional FAD model, the 3xTg-AD mouse model. Our findings demonstrated that Aβ aggregates occur earlier in the 3xTg-AD vs hAβ-KI and that a longer term of treatment is necessary to accelerate diffusible Aβ pathology in the hAβ-KI mice. This knockin model represents an important first step towards the development of next-generation animal models that hopefully will provide better predictive outcomes for human patients, which can turn into safe and effective clinical applications.

Disclosures: D. Baglietto-Vargas: None. **S. Forner:** None. **A.C. Martini:** None. **L. Trujillo-Estrada:** None. **C. Nuñez-Diaz:** None. **E.A. Kramár:** None. **S. Jiang:** None. **D.P. Matheos:** None. **C. Da Cunha:** None. **A. Gutierrez:** None. **K.N. Green:** None. **M.A. Wood:** None. **A. Mortazavi:** None. **G.R. MacGregor:** None. **A.J. Tenner:** None. **F.M. LaFerla:** None.

Nanosymposium

713. Alzheimer's Disease and Other Dementias: Abeta: Pathologic Mechanisms

Location: SDCC 33

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 713.05

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

Support: International graduate school molecular medicine/ funding 4th PhD year

Title: The role of PICALM and associated APP adaptor proteins in APP endocytosis

Authors: *L. MERTHAN, B. VON EINEM, C. VON ARNIM
Ulm University/Neurology, Ulm, Germany

Abstract: One hallmark of Alzheimer’s disease (AD) are the amyloid plaques, which are generated by the aggregation of mainly amyloid β (Aβ), a proteolytic cleavage product of the amyloid precursor protein (APP). To initiate this cleavage, APP has to be endocytosed to endosomal compartments. The phosphatidylinositol binding and clathrin assembly protein (PICALM) is involved in clathrin-mediated endocytosis and was previously identified as a genetic risk factor for AD. Furthermore, Aβ level are increased upon overexpression of PICALM. The detailed mechanism of how PICALM enhances APP endocytosis and Aβ production is still unknown. Therefore, we here tested a hypothesized PICALM-APP interaction. Using co-immunoprecipitation (CoIP), we showed an interaction between PICALM and APP which was abrogated by mutation of the APP YENPTY motif. This motif is known as an interacting partner of the PTB domain of APP adaptor proteins that are known to regulate APP traffic and endocytosis. Hence, we hypothesized that these proteins can mediate or influence the interaction of PICALM and APP. To test this, we performed CoIP which showed binding of PICALM and APP adaptor proteins. We confirmed these findings in living cells by using a bimolecular fluorescence complementation assay. We further tested, if the interaction of APP adaptor proteins with PICALM has functional impact on and APP endocytosis and processing. To do so, we applied FACS analysis and a biotinylation based internalization assay. As shown before, we found that PICALM alone enhances the internalization of APP. This was further modulated by the presence of APP adaptor proteins.
The results of this study indicate that PICALM interacts with and influences the endocytosis and processing of APP. Furthermore, the adaptor proteins seem to play a crucial role in the regulation of this interaction and influence the effect of PICALM on the APP trafficking. With these findings, we moved closer to the issue how PICALM influences APP processing. Modulation of

PICALM as well as the adaptor proteins can be a possible new therapeutic strategy in the attempt to find an effective treatment against AD.

Disclosures: L. Merthan: None. **B. von Einem:** None. **C. von Arnim:** None.

Nanosymposium

713. Alzheimer's Disease and Other Dementias: Abeta: Pathologic Mechanisms

Location: SDCC 33

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 713.06

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

Support: NIH R01 AG042513
NIH P01 NS074969
NIH P50 AG005681
Alzheimer's Association

Title: Phosphatase activity during sleep/wake cycles regulates APP processing and brain ISF amyloid-beta levels

Authors: *J. R. CIRRITO[1], C. E. WALLACE[2], H. EDWARDS[3]
[1]Neurol., Washington University, St. Louis, Saint Louis, MO; [2]Neurol., Washington Univ., Saint Louis, MO; [3]Washinton Univ., St. Louis, MO

Abstract: Alzheimer’s disease (AD) is initiated by the progressive accumulation of amyloid-beta (Abeta) peptide in the brain as toxic structures, such as Abeta oligomers and plaques. Evidence in both APP transgenic animal models and in humans suggests that brain Abeta levels fluctuate with the diurnal cycle; Abeta within the brain extracellular fluids are high during wakefulness and low during sleep. The diurnal fluctuation has been detected in the brain interstitial fluid (ISF) of APP transgenic mice and in the cerebrospinal fluid (CSF) of humans. In mice and in humans, sleep deprivation increases Abeta levels acutely. Chronic alterations in sleep have a similar impact on amyloid plaque accumulation in these mice. We hypothesized that sleep is altering an intracellular signaling pathway that ultimately regulates Abeta generation and secretion into the brain ISF. We used in vivo microdialysis to measure brain ISF Abeta levels every hour over several days in living APP transgenic mice while manipulating orexin receptor signaling and downstream intracellular signaling pathways, such as the extracellular regulated kinase (ERK) and phosphatases such as SHP2 and PP2A. Similar to previous studies, we detected a diurnal fluctuation in ISF Abeta levels during the sleep/wake cycle. Inhibiting Extracellular Regulated Kinase (ERK), increased ISF Abeta levels by 50% and blocked the fluctuation in ISF Abeta, suggesting that ERK plays a role in the diurnal rhythm of Abeta. Interestingly, ERK has been shown to be downstream of several neurotransmitter receptors (e.g. serotonin and NMDA receptors) which also regulate Abeta levels. SHP-2 is a phosphatase that

dephosphorylates phospho-ERK to deactivate it. Inhibition of SHP-2 reduces ISF Abeta levels and also blocks the diurnal fluctuation. Our data suggest that there is an inverse relationship between the amount of phospho-ERK and the activity of SHP-2 which determines how much Abeta is produced in response to the physiological fluctuation in sleep/wake.

Disclosures: J.R. Cirrito: None. **C.E. Wallace:** None. **H. Edwards:** None.

Nanosymposium

713. Alzheimer's Disease and Other Dementias: Abeta: Pathologic Mechanisms

Location: SDCC 33

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 713.07

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

Support: Alzheimer's and Related Diseases Research Award Fund (grant 17-5 to AN)
Owens Family Foundation (GSB)
NIH/NIA (grant RF1 AG051085 to GSB
NIH/NIA grant R21 AG052062 to SH
NIH/NIA grants P01 AG015379 and RF1 AG048080 to DYK/RET
NIH/NIA grant R01 AG014713 to DYK
NIH equipment grant S10-OD016446; AP

Title: Direct regulation of mitochondrial activity by mtorc1 unveils a novel lysosome to mitochondria signaling pathway disrupted by amyloid-β oligomers

Authors: A. NORAMBUENA[1], H. WALLRABE[1], R. CAO[2], D. BIGLER WANG[1], A. SILVA[1], Z. SVINDRYCH[3], A. PERIASAMY[1], S. HU[2], D. KIM[4], R. E. TANZI[5], *G. S. BLOOM[1]
[2]Biomed. Engin., [1]Univ. of Virginia, Charlottesville, VA; [3]Dartmouth Col., Hanover, NH; [4]Genet. and Aging Res. Unit, MIND, Massachusetts Gen. Hospital/ Harvard Med. Sch., Charlestown, MA; [5]Massachusetts Gen Hosp, Harvard Med. Sch., Charlestown, MA

Abstract: The mechanisms of mitochondrial dysfunction in Alzheimer's Disease (AD) are incompletely understood. By using fluorescence lifetime imaging that monitor changes in autofluorescence of mitochondrial coenzymes, NAD(P)H in cultured cells, and imaging oxygen metabolism in the live mouse brain (Ning et al, 2015. *Scientific Reports*. 5: 18775) with multi-parametric photoacoustic microscopy (MPAM), we uncovered a novel inter-organelle signaling pathway that regulates mitochondrial functioning and a mechanism that is disrupted in AD. In primary mouse cortical neurons and human NPC-derived neurons, nutrient-mediated activation [i.e., insulin or arginine (R) plus leucine (L)] of the lysosome-associated, protein kinase complex, mTORC1, stimulates perykarial mitochondrial activity and regulates mitochondrial DNA (mtDNA) synthesis. This effect is block by: 1) Torin1, an inhibitor of mTOR, the catalytic

subunit of mTORC1 and mTORC2; 2) knocking down Raptor, an essential mTORC1 subunit; or 3) forcing mTORC1 to associate with the plasma membrane (PM) by expressing Raptor fused to the PM targeting signal of H-Ras. Furthermore, we found that NiMA is unaffected by either knock down of S6K or eIF4E, suggesting that NiMA and protein synthesis are regulated independently by mTORC1. Likewise, NiMA was found to occur independently of mTOR interaction with mitochondria. Amyloid-β oligomers (AβOs), which activate mTORC1 at the PM, but not at lysosomes (Norambuena et al. 2017. *Alzheimer's and Dementia* 13: 152), block NiMA by a mechanism dependent on tau. Remarkably, AβO-mediated inhibition of NiMA was restored when mTORC1 was forced to lysosomes by expressing Raptor fused to the lysosomal targeting signal of Rheb. NiMA was also found to suppress mtDNA synthesis, which can be overridden by AβO-mediated activation of mTORC1 at the PM. In addition, forcing mTORC1 to lysosomes, or downregulating the activity of either of 2 endogenous lysosomal mTORC1 inhibitors, the TSC or GATOR1 complexes, leaves mitochondria insensitive to nutrient stimulation. Accordingly, NiMA was also disrupted in human fibroblasts obtained from patients affected by tuberous sclerosis, a genetic disorder triggered by dysfunctions in the TCS complex. Finally, MPAM assays showed that R plus L increases cerebral oxygen consumption *in vivo* by a mechanism sensitive to rapamycin. Collectively, these results indicate that lysosomal mTORC1 couples nutrient availability to mitochondrial activity, thus functionally connecting these organelles. NiMA represents a new mechanistic link connecting metabolic alterations to mitochondrial diseases.

Disclosures: A. Norambuena: None. **H. Wallrabe:** None. **R. Cao:** None. **D. Bigler Wang:** None. **A. Silva:** None. **Z. Svindrych:** None. **A. Periasamy:** None. **S. Hu:** None. **D. Kim:** None. **R.E. Tanzi:** None. **G.S. Bloom:** None.

Nanosymposium

713. Alzheimer's Disease and Other Dementias: Abeta: Pathologic Mechanisms

Location: SDCC 33

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 713.08

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

Support: the National Research Foundation of Korean NRF-2015M3A9E2028884

Title: Asymmetric beta-amyloid deposits leading to partial smell dysfunction by breakdown of neural reconstitution

Authors: *G. SON[1], S.-J. YOO[1,2], A. JAHANSHAHI[3], H. W. STEINBUSCH[3], K.-A. CHANG[4], Y.-H. SUH[5], C. MOON[1,2]
[1]DGIST, Daegu, Korea, Republic of; [2]Convergence Res. Advanced Ctr. for Olfaction, DGIST, Daegu, Korea, Republic of; [3]Sch. for Mental Hlth. and Neuroscience, Maastricht University, EURON, Maastricht, Netherlands; [4]Dept. of Pharmacology, Sch. of Medicine, Gachon Med.

Sch., Incheon, Korea, Republic of; [5]Dept. of Neurology, Gil Med. Center, Gachon Univ., Incheon, Korea, Republic of

Abstract: Olfactory dysfunction is considered as an unquestionable fact for patients with Alzheimer's disease (AD). Interestingly, some previous clinical studies have suggested that AD patients who suffer from smell dysfunction find it difficult to perceive only some of the presented odors. Although, this interesting symptom of AD, it has not been experimentally characterized with precise evidence. To examine the character of the AD smell dysfunction, we performed an odor detection test on 3-month 5xFAD mice, and subsequently, synaptic activity of the olfactory glomeruli was measured using calcium imaging to account for and quantify the functional activity patterns of the olfactory system. We found partial deficits of smelling and neural activity that considered as input signals of olfactory sensory neurons (OSN). To confirm the association between the diminished activity pattern of the olfactory nerve and AD-smell dysfunction, we also investigated at the peripheral olfactory synapse, distribution of oligomerized β-amyloid (Aβ) deposits known to have synaptic toxicity by immunohistologic quantification. Interestingly, our results show that the Aβ oligomers were accumulated asymmetrically, and its pattern is highly correlated with the activity decline in the olfactory system. It also demonstrated by quantifying the markers of synaptic function in the olfactory glomeruli, the decrease of TH and synaptophysin with immunohistochemistry. We also examined the turnover rate of the OSN reconstitution based on the well-balanced feature of peripheral olfactory system. Our results confirm that the Aβ asymmetry scale is consistent with the direct damage pattern of the peripheral olfactory system through the impairment of the turnover rate in the peripheral olfactory system. In summary, asymmetric destruction of the olfactory and peripheral olfactory system could provide clues to AD-specific olfactory dysfunction interpretation.

Disclosures: G. Son: None. **S. Yoo:** None. **A. Jahanshahi:** None. **H.W. Steinbusch:** None. **K. Chang:** None. **Y. Suh:** None. **C. Moon:** None.

Nanosymposium

713. Alzheimer's Disease and Other Dementias: Abeta: Pathologic Mechanisms

Location: SDCC 33

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 713.09

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

Support: NIH Grant R01AG053951

Title: Discovery of novel small-molecule inhibitor of tau oligomerization by FRET-based high-throughput screening

Authors: *C. H. LO[1], C. K. W. LIM[1], Z. DING[1], D. D. THOMAS[2,3], J. N. SACHS[1]
[1]Biomed. Engin., [2]Biochemistry, Mol. Biology, and Biophysics, Univ. of Minnesota, Minneapolis, MN; [3]Photonic Pharma, Minneapolis, MN

Abstract: We have used an innovative fluorescence resonance energy transfer (FRET)-based high-throughput screening approach to discover small molecules that disrupt toxic tau oligomers which play a significant role in tauopathy, a class of neurodegenerative diseases including Alzheimer's disease. Although many believe that neurofibrillary tangles (NFTs) are the main histopathological hallmark of these diseases, recent studies suggested that NFTs do not play the main role as toxic entities leading to progression of disease. Instead, the tau oligomer, an intermediate form of tau prior to NFTs formation, has been proposed to be the true toxic species. In this study, we developed a tau FRET biosensor expressed in living cells to monitor tau-tau interactions and to screen compounds from the NIH Clinical Collection. We used a high precision and high-throughput fluorescence lifetime screening platform to identify a small molecule that reduces FRET signal and inhibits cell death. Direct binding of small-molecule inhibitor to tau protein was characterized by surface plasmon resonance (SPR) and the binding affinity was found to be in the nanomolar range. To investigate the mechanism of action of the compound, we performed thioflavin-S (ThS) assay in cells and confirmed that the tau biosensors were absent of fibrils and the small molecule was targeting toxic tau oligomers. Biochemical method was used to show that the compounds disrupt tau-tau interactions. In addition, thioflavin-T (ThT) assay was carried out with purified tau proteins in the presence of heparin and we found that the compound neither inhibits fibril formation nor disrupts preformed fibrils. Gossypetin, a known inhibitor of fibril formation, was used as a positive control in the ThT assay. Furthermore, we tested the compound with purified tau protein FRET biosensor and found that it reduced FRET more substantially as compared to gossypetin despite no disruption of fibril was observed, indicating that the compound was disrupting tau oligomers. We have shown, for the first time, that it is possible to target toxic tau oligomers by small molecules and this strategy should be generally applicable to other intrinsically disordered proteins involved in neurodegenerative diseases.

Disclosures: C.H. Lo: None. **C.K.W. Lim:** None. **Z. Ding:** None. **D.D. Thomas:** None. **J.N. Sachs:** None.

Nanosymposium

714. Alzheimer's Disease and Other Dementias: Tau: Experimental Models

Location: SDCC 5

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 714.01

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

Support: NIH GRANT 1R01AG053060-01A1

VA GRANT 1I01 BX002478-01A1
NIH GRANT 5R01NS073899-07
FLORIDA DEPARTMENT OF HEALTH GRANT 5AZ07

Title: Enhanced tau pathology via RanBP9 and Hsp90/Hsc70 chaperone complexes

Authors: *J. A. WOO[1], T. LIU[2], C. FANG[2], C. TROTTER[2], D. KANG[2]
[2]Mol. Med., [1]USF Hlth. Byrd Inst., Tampa, FL

Abstract: Accumulation of amyloid β (Aβ) and tau represent the two major pathological hallmarks of Alzheimer's disease (AD). Despite the critical importance of Aβ accumulation as an early event in AD pathogenesis, multiple lines of evidence indicate that tau is required to mediate Aβ-induced neurotoxic signals in neurons. We have previously shown that the scaffolding protein Ran-binding protein 9 (RanBP9), which is highly elevated in brains of AD and AD mouse models, both enhances Aβ production and mediates Aβ-induced neurotoxicity. However, it is unknown whether and how RanBP9 transmits Aβ-induced neurotoxic signals to tau. Here we show for the first time that overexpression or knockdown of RanBP9 directly enhances and reduces tau levels, respectively, in vitro and in vivo. Such changes in tau levels are associated with the ability of RanBP9 to physically interact with tau and heat shock protein 90/heat shock cognate 70 (Hsp90/Hsc70) complexes. Meanwhile, both RanBP9 and tau levels are simultaneously reduced by Hsp90 or Hsc70 inhibitors, whereas overexpression or knockdown of RanBP9 significantly diminishes the anti-tau potency of Hsp90/Hsc70 inhibitors as well as Hsc70 variants (WT & E175S). Further, RanBP9 increases the capacity for Hsp90 and Hsc70 complexes to bind ATP and enhances their ATPase activities in vitro. These observations in vitroand cell lines are recapitulated in primary neurons and in vivo, as genetic reduction in RanBP9 not only ameliorates tauopathy in Tau-P301S mice but also rescues the deficits in synaptic integrity and plasticity.

Disclosures: J.A. Woo: None. **T. Liu:** None. **C. Fang:** None. **C. Trotter:** None. **D. Kang:** None.

Nanosymposium

714. Alzheimer's Disease and Other Dementias: Tau: Experimental Models

Location: SDCC 5

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 714.02

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

Support: NIH Grant 1RO1AG053060-01A1
VA Grant 1I01 BX002478-01A1
MIH Grant 5R01NS073899-07
Florida Department of Health Grant 5AZ07

Title: Distinct roles of Slingshot-1 in mitochondrial dysfunction and mitophagy

Authors: *C. FANG, J. A. WOO, T. LIU, X. ZHAO, S. CAZZARO, C. L. TROTTER, D. E. KANG
USF Hlth. Byrd Inst., Tampa, FL

Abstract: OBJECTIVE:
Slingshot-1 (SSH1), the cofilin activating phosphatase, is activated in APP/PS1 transgenic mice and is required for Aβ42-induced activation of cofilin. Activated cofilin severs F-actin to reduce dendritic spine stability and translocates to mitochondria to induce mitochondrial dysfunction. As activated mitochondrial cofilin is significantly increased in Alzheimer's disease (AD) brains, we set out to dissect the role of the SSH1-cofilin pathway in mitochondrial dysfunction and quality control (mitophagy).
METHODS:
We utilized cultured cells, primary neurons, and *SSH1-/-* mice to express combinations of p62, Optineurin, fluorescent reporter tools, SSH1 variants (FL, N461, D307), and SSH1 siRNA to assess key indices of autophagy (LC3, p62) and autophagy / mitophagy flux (GFP-mCherry-LC3; GFP-mCherry-p62, mito-keima) in conjunction with immunocytochemistry, western blotting, co-IP, and *in situ* PLA. Experiments in cells were performed with/without of Aβ42 oligomers or the mitophagy inducer FCCP.
RESULTS:
Our results indicate that SSH1 not only activates cofilin to induce mitochondrial dysfunction (loss of membrane potential and increased superoxide) but also simultaneously inhibits removal of dysfunctional mitochondria (mitophagy) as evidenced by reduced LC3 on mitochondria and reduced mitophagy flux to lysosomes (mito-keima). SSH1 knockdown produced opposite effects. The effects of SSH1 on mitochondrial dysfunction (cofilin-mediated) were separable from its effects on mitophagy, as SSH1 lacking cofilin binding (D307) was sufficient to fully inhibit mitophagy. Rather, SSH1 D307 dephosphorylated the autophagy receptor p62 on Ser403, which reduced its association with mitochondrial ubiquitin, resulting in reduced p62-mediated autophagy flux to lysosomes (GFP-mCherry-p62). SSH1 had no discernible effect on another autophagy receptor, optineurin. These results in cell lines and primary neurons were recapitulated *in vivo* in *SSH1-/-* mouse brains, where the GFP-mCherry-p62 autophagy reporter demonstrated significantly accelerated p62 autophagy flux.
CONCLUSION:
We conclude that SSH1 activation simultaneously promotes cofilin-mediated mitochondrial dysfunction and impairs p62-mediated mitophagy / autophagy, indicating a dual function on mitochondrial homeostasis via divergent mechanisms. Thus, decreasing SSH1 activity represents a potential therapeutic strategy to mitigate impaired autophagy and mitochondrial dysfunction in neurodegenerative disease.

Disclosures: C. Fang: None. **J.A. Woo:** None. **T. Liu:** None. **X. Zhao:** None. **S. Cazzaro:** None. **C.L. Trotter:** None. **D.E. Kang:** None.

Nanosymposium

714. Alzheimer's Disease and Other Dementias: Tau: Experimental Models

Location: SDCC 5

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 714.03

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH grant, R01 AG053060-01A1
Florida Health grant, 5AZ07
VA grant, 1 I01 BX002478-01A1, D.E.K.),

Title: Activated cofilin in tau-mediated microtubule dynamics and tauopahty

Authors: *D. E. KANG, J.-A. A. WOO, T. LIU, C. TROTTER, C. C. FANG, S. CAZZARO, T. KEE, K. YRIGOIN, P. LEPOCHAT, X. ZHAO, X. WANG, S. LIGGETT
USF Hlth. Byrd Inst., Tampa, FL

Abstract: Objective: In addition to the crucial importance of Aβ in the etiology of AD, it has also become clear that tau is required for the deleterious effects of Aβ. Important gaps in knowledge remain, however, in the way that Aβ pathogenically connects to tau and how tau-induced microtubule (MT) dynamics are regulated. Previous studies have shown that Aβ-induced neurotoxicity requires activation of the F-actin severing protein cofilin and that cofilin is overactivated in brains of AD patients and APP transgenic mice. In this study, we hypothesized that Aβ-induced cofilin activation represents an upstream signal that impinges on tau/MT regulation and tauopathy. **Methods:** We utilized cultured cells, primary neurons, as well as APP/PS1 and Tau-P301S mice crossed with *cofilin+/-* mice in conjunction with exogenous gene expression (transfection & rAAV), western blotting, immunohisto(cyto)chemistry, proximity ligation assays (PLA), recombinant protein-based & cell-based MT assembly assays, and electrophysiological recordings to study the role of cofilin in tau-mediated MT assembly, tauopathy, and synaptic plasticity. **Results:** We found that tau-MT complexes are reduced, and cofilin-MT complexes are increased in APP/PS1 mice, a phenotype that was reversed by genetic reduction of *cofilin*. These *in vivo* observations were supported by our observations that cofilin competes with tau for direct binding to MTs, which results in inhibition of tau-induced MT assembly *in vitro* and in cultured cells. Furthermore, genetic reduction of *cofilin* significantly ameliorated tauopathy (sarkosyl-insoluble tau & phospho-tau) and synaptic plasticity deficits (i.e. LTP & PPF) in Tau-P301S transgenic mice. The pathogenic effects of cofilin were mediated by ‘active’ but not ‘inactive’ cofilin, as the non-phosphorylable (S3A) but not phospho-mimic (S3E) cofilin selectively interacted with tubulin, destabilized MTs, and promoted tauopathy. **Conclusion:** We identified for the first time a surprising function of activated cofilin - directly interfering with tau-induced MT assembly and promoting tauopathy. These results indicate that

activation of cofilin plays a key role in the neurotoxic signaling that promotes tauopathy and MT destabilization.

Disclosures: D.E. Kang: None. **J.A. Woo:** None. **T. Liu:** None. **C. Trotter:** None. **C.C. Fang:** None. **S. Cazzaro:** None. **T. Kee:** None. **K. Yrigoin:** None. **P. LePochat:** None. **X. Zhao:** None. **X. Wang:** None. **S. Liggett:** None.

Nanosymposium

714. Alzheimer's Disease and Other Dementias: Tau: Experimental Models

Location: SDCC 5

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 714.04

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH 1RF1AG054199-01
1R01AG054672-01
1R56AG057469-01
DVT-14-320835

Title: P2X7R inhibitor blocks exosome secretion and delays proteopathic tau accumulation in P301S tau mice

Authors: *J.-C. DELPECH, Z. RUAN, A. VAN ENOO, M. BOTROS, S. IKEZU, T. IKEZU
Pharmacol. and experimental therapeutics Dept., Boston Univ., Boston, MA

Abstract: Background The P2X7 receptor (P2X7R) is an ATP-gated cation channel, highly expressed in microglia, involved in Alzheimer’s disease (AD) pathobiology. Series of studies also suggested that pharmacological inhibition or genetic deletion of P2X7R could alter exosome secretion triggered by ATP stimulation. Recently, we showed that microglia could spread tau aggregates via secretion of extracellular vesicles throughout the brain. We hypothesize that P2X7R inhibitor could inhibit exosome secretion by microglia and thus alleviate tauopathy in P301S tau transgenic mice.
Methods BV-2 murine microglial cell lines were treated with GSK1482160, a specific inhibitor of P2X7R, prior to ATP stimulation. Culture medium were collected and exosome number was measured using Nanoparticle Tracking Analysis (NTA) and CD9 ELISA. Three-months old P301S and control wild-type mice were treated with GSK1482160 (20mg/kg) or vehicle by oral gavage for 30 days. Then, hippocampal dependent memory capacity was assessed and hippocampal phosphorylated-tau (p-Tau) expression was determined by immunohistochemistry. In addition, a separated cohort of animals was generated to quantify exosome and measure hippocampal p-Tau expression by ELISA.
Results ATP stimulation of BV-2 cells significantly increased secretion of exosomes (30-150 nm), which was significantly inhibited by GSK1482160 pre-treatment in a dose-dependent

manner (IC_{50} 2.29 μM) as determined by NTA and CD9 ELISA. There was no difference in body weight between GSK1482160 and vehicle-treated groups at the endpoint. Interestingly, hippocampal p-Tau ELISA data showed that tau phosphorylation level was significantly reduced in GSK1482160-treated group as compared to vehicle-treated group (p=0.0292).
Conclusions GSK1482160 pre-treatment successfully suppresses exosome secretion by microglia *in vitro*. Its oral administration also significantly reduces Tau accumulation in the hippocampal region of P301S Tau mouse model.

Disclosures: J. Delpech: None. **Z. Ruan:** None. **A. Van Enoo:** None. **M. Botros:** None. **S. Ikezu:** None. **T. Ikezu:** None.

Nanosymposium

714. Alzheimer's Disease and Other Dementias: Tau: Experimental Models

Location: SDCC 5

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 714.05

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

Support: Department of Veterans Affairs
NIH NIGMS T32-GM-007454 Medical Genetics Postdoctoral Training Program
Bright Focus Foundation Grant A2014438S

Title: DOPA decarboxylase modulates tau-induced toxicity in a *Caenorhabditis elegans* model of tau toxicity

Authors: *R. L. KOW[1,2,3], J. M. WHEELER[6], B. C. KRAEMER[1,2,4,5]
[1]Geriatrics Res. Educ. and Clin. Ctr., Veterans Affairs Puget Sound Hlth. Care Syst., Seattle, WA; [2]Medicine, Div. of Gerontology and Geriatric Med., [3]Medicine, Div. of Med. Genet., [4]Pathology, [5]Psychiatry and Behavioral Sciences, Neurosci. Div., Univ. of Washington, Seattle, WA; [6]Seattle Inst. of Biomed. and Clin. Res., Seattle, WA

Abstract: The microtubule-associated protein tau accumulates into toxic aggregates in multiple neurodegenerative diseases such as Alzheimer’s disease and frontotemporal lobar degeneration. To aid in identifying genetic modulators of human tau-induced toxicity, we used a *Caenorhabditis elegans* model in which human tau protein is overexpressed in all *C. elegans* neurons. This causes significant motor dysfunction, progressive loss of neurons, shortened lifespan, and the accumulation of hyperphosphorylated and insoluble tau protein. We recently identified DOPA decarboxylase (DDC) as a suppressor of tau toxicity in this model. Loss of the *C. elegans* DDC gene *bas-1* ameliorated multiple phenotypes, reducing behavioral deficits and phosphorylation of tau; overexpression of BAS-1 protein enhanced the behavioral deficit. Other genes in dopamine and serotonin synthesis did not alter tau-induced toxicity on their own but were required for suppression of tau-induced toxicity by loss of *bas-1*. Currently we are

identifying other genes that regulate the ability of DDC to modulate tau-induced toxicity. We are screening kinase and phosphatase genes to see if they modulate the suppression of tau toxicity seen with loss of *bas-1/*DDC in tau transgenic *C. elegans*. Suppression of tau-induced behavioral deficits by loss of *bas-1/*DDC was blocked by the loss of protein kinase C homolog *tpa-1,* AKT homolog *akt-1,* or MAP kinases *jnk-1* and *mpk-2.* Additionally, loss of calcineurin homologs *cnb-1* and *tax-6* also blocked suppression of tau-induced toxicity by loss of *bas-1/*DDC. Our next steps are to continue screening other genes for possible roles in mediating suppression of tau-induced toxicity by loss of *bas-1/*DDC and to determine whether these mechanisms translate to mammalian systems.

Disclosures: R.L. Kow: None. **J.M. Wheeler:** None. **B.C. Kraemer:** None.

Nanosymposium

714. Alzheimer's Disease and Other Dementias: Tau: Experimental Models

Location: SDCC 5

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 714.06

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: Australian Research Council Future Fellowship: FT120100030

Title: Exploring the interaction between iron and tau in a mouse model of tauopathy

Authors: *S. S. RAO, G. MCCOLL, D. FINKELSTEIN, P. ADLARD
Florey Inst. of Neurosci. and Mental Hlth., Melbourne, Australia

Abstract: ***Background:*** There is emerging evidence implicating an interaction between iron and tau - the primary component of neurofibrillary tangles (NFTs). NFTs are a pathological hallmark of a class of neurodegenerative disorders called tauopathies, which includes Alzhimer's disease (AD). In the AD brain, iron levels are significantly elevated in the hippocampus and cortex and primarily concentrated within NFTs. Importantly, NFT accumulation correlates with the severity of neurodegeneration and iron is found to facilitate NFT formation by modulating tau phosphorylation and promoting tau aggregation. These data, together with our own work showing that tau has a role in mediating cellular iron efflux, provide evidence supporting a critical tau:iron interaction that may impact both the symptomatic presentation and progression of disease. To explore this interaction, we modulated iron levels with deferiprone (DFP, an iron chelator) in a transgenic (Tg) mouse model overexpressing mutant human tau (rTg(tau_{P301L})4510). ***Methods:*** DFP (or vehicle) was administered daily at 100mg/kg by oral gavage to 3 month old Tg or wildtype (WT) mice for 16 weeks (n=8-10/group). Brain iron levels were assessed by inductively coupled plasma mass spectrometry (ICP-MS) and tau levels by immunoblotting. ***Results:*** Iron levels in total brain homogenates were significantly reduced in DFP-treated mice compared to vehicle controls (p=0.02) and this correlated with reduced levels

of sarkosyl-insoluble tau (p=0.01). In addition, the levels of phosphorylated tau (serine 396), which is associated with the early stages of NFT formation, were significantly reduced following DFP treatment (p=0.016). In WT littermates however, although DFP reduced brain iron levels there was no change in phosphorylated tau levels. Further characterisation is underway. ***Conclusion:*** DFP reduced brain iron levels in Tg mice to a level similar to that seen in vehicle-treated WT mice, and also reduced the levels of pathological tau. This research demonstrates that there is likely to be a relationship between iron and tau, that is relevant to both disease mechanisms and also the potential treatment of neurodegeneration, which can be targeted by clinically relevant compounds like DFP. This work may pave the way for the development of a new therapeutic approach for the tauopathies.

Disclosures: S.S. Rao: None. **G. McColl:** None. **D. Finkelstein:** None. **P. Adlard:** None.

Nanosymposium

714. Alzheimer's Disease and Other Dementias: Tau: Experimental Models

Location: SDCC 5

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 714.07

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

Support: NIH Grant R01NS073899

Title: High FKBP52 levels causes tau aggregation leading to hippocampal-dependent memory impairments

Authors: *M. CRIADO MARRERO[1], N. GEBRU[1], R. BLACKBURN[1], X. WANG[2], J. D. BAKER[3], L. B. SHELTON[1], L. J. BLAIR[4], Y. VIDAL AGUIAR[1], T. SMITH[2], H. PENNY[1]
[1]Mol. Med., [2]Univ. of South Florida, Tampa, FL; [3]Mol. Med., USF Hlth., Tampa, FL; [4]Mol. Med., USF Byrd Inst., Tampa, FL

Abstract: Pathological hyperphosphorylation and aggregation of the microtubule-binding protein, Tau, are common processes associated with neurodegenerative diseases like Alzheimer's disease. Molecular chaperones with peptidyl-prolyl cis/trans isomerase (PPIase) activity are known to regulate these processes. Specifically, *in-vitro* studies have shown that the 52 kDa FK506-binding protein (FKBP52) interacts with tau inducing its oligomerization and fibril formation to promote toxicity. Thus, we hypothesized that increased expression of FKBP52 in the brain would exacerbate both oligomeric and insoluble tau formation leading to memory impairments. To study this, tau transgenic (rTg4510) and wild-type mice received bilateral hippocampal viral injections of FKBP52 AAV-9 or mCherry AAV-9 (control). Following this, we examined hippocampal-dependent memory, synaptic plasticity, tau phosphorylation status, and neuronal loss. We further used *in-vitro* studies to investigate the mechanism involved in the

FKBP52-Tau interaction. Together with previous studies, our findings suggest that FKBP52 stimulates tau pathogenesis by increasing tau oligomerization and neurotoxicity.

Disclosures: M. Criado Marrero: None. **N. Gebru:** None. **R. Blackburn:** None. **X. Wang:** None. **J.D. Baker:** None. **L.B. Shelton:** None. **L.J. Blair:** None. **Y. Vidal Aguiar:** None. **T. Smith:** None. **H. Penny:** None.

Nanosymposium

714. Alzheimer's Disease and Other Dementias: Tau: Experimental Models

Location: SDCC 5

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 714.08

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Title: Specific functional deficits in learning memory in tau transgenic mice without antibodies

Authors: *J. J. VAN DER HOVEN[1], L. S. SUH[1], A. E. VAN HUMMEL[1,2], M. PRZYBYLA[1], Y. D. KE[2], A. A. ITTNER[1], L. M. ITTNER[1,3]
[1]Dementia Res. Unit, Sch. of Med. Sci., UNSW Sydney, Sydney, Australia; [2]Motor Neuron Dis. Unit, Sch. of Med. Science, UNSW Sydney, Sydney, Australia; [3]Dementia Res. Centre, Macquarie Univ., Sydney, Australia

Abstract: Immunotherapy against tau is an emerging area of therapy development in Alzheimer's disease (AD) and related disorders with tau deposition, such as frontotemporal dementia (FTD). Others and we have shown that both passive and active vaccination against tau could improve neuropathology and, in some instances, behavioral deficits in mutant tau transgenic mouse models of AD and FTD. Both in human disease and tau transgenic mouse models, it has been recognized that there are circulating antibodies to phosphorylated tau at base line. This has prompted us to investigate the role of these autoantibodies to tau and more generally the role of antibody responses in onset and progression of tau pathology and associated functional deficits. Therefore, we use two mouse lines; Firstly, the TAU58/2 transgenic mouse model that expresses P301S mutant human tau in neurons and recapitulates histopathological and behavioral aspects of AD and FTLD. Secondly, the muMt$^{-/-}$ line with targeted deletion of the *Ighm* gene locus, resulting absence of B cells and therefore circulating antibodies. The TAU58/2 mouse line was crossbred with muMt$^{-/-}$ mice to eventually produce homozygous mice lacking antibodies. Behavioral experiments were performed to assess the deficits of the resulting TAU58/2/muMt$^{-/-}$ mice in comparison to TAU58, muMt$^{-/-}$ and non-transgenic littermates. Elevated plus maze testing for disinhibition behavior and Rotarod testing for motor phenotype was carried out at 4 months of age and showed no significant difference between genotypes. Furthermore, we assessed memory function in the Morris water maze in 8 months old mice, including consideration of search strategies using swim path analysis. Increased time to find the hidden platform were observed in the TAU58/2/muMt$^{-/-}$ mice during the learning phase when

compared to TAU58/2 mice, suggesting augmented memory deficits in TAU58/2/muMt$^{-/-}$ mice. Histological analysis revealed no significant differences in either phosphorylation state of tau, tangle pathology or neuroinflammation. Taken together, complete lack of antibodies results in augmented memory deficits in TAU58/2 transgenic mice without changes to their neuropathology.

Disclosures: J.J. Van Der Hoven: None. **L.S. Suh:** None. **A.E. van Hummel:** None. **M. Przybyla:** None. **Y.D. Ke:** None. **A.A. Ittner:** None. **L.M. Ittner:** None.

Nanosymposium

715. ALS Mechanisms

Location: SDCC 7

Time: Wednesday, November 7, 2018, 1:00 PM - 3:45 PM

Presentation Number: 715.01

Topic: C.06. Neuromuscular Diseases

Support: NMRC/OFIRG/0001/2016
NMRC/OFIRG/0042/2017
MOE2016-T2-1-024

Title: Cell-autonomous requirement of TDP-43 for oligodendrocyte survival and myelination

Authors: *S.-C. LING[1], J. WANG[1], W. HO[1], K.-A. NAVE[2]
[1]Natl. Univ. of Singapore, Singapore, Singapore; [2]Dept. of Neurogenetics, Max Planck Inst. of Exptl. Med., Gottingen, Germany

Abstract: TDP-43 aggregates in neurons and glia are the defining pathological hallmark of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), raising the possibility of glial damage in the disease pathogenesis. However, the normal physiological functions of TDP-43 in glia is largely unknown. To address how TDP-43 may be required for oligodendroglial functions, we selectively deleted TDP-43 in mature oligodendrocytes in mice. Although mice with TDP-43 deleted in oligodendrocytes are born in Mendelian ratio, they develop progressive neurological phenotypes leading to early lethality accompanied by progressive reduction in myelination. The progressive myelin reduction is, at least in part, due to the cell-autonomous RIPK1-mediated necroptosis of mature oligodendrocytes. Strikingly, enhanced proliferation of NG2-positive oligodendrocyte precursor cells within the white matter, but not the grey matter, was able to replenish the loss of mature oligodendrocytes, indicating an intrinsic regeneration capacity between the grey and white matter oligodendrocytes. By contrast, there was no loss of spinal cord motor neurons and no sign of denervation at the neuromuscular synapses in these mice. Taken together, our data demonstrates that TDP-43 is indispensable for oligodendrocyte survival and functions, and loss of TDP-43 in oligodendrocytes exert no apparent toxic effects to motor neurons.

Disclosures: S. Ling: None. **J. Wang:** None. **W. Ho:** None. **K. Nave:** None.

Nanosymposium

715. ALS Mechanisms

Location: SDCC 7

Time: Wednesday, November 7, 2018, 1:00 PM - 3:45 PM

Presentation Number: 715.02

Topic: C.06. Neuromuscular Diseases

Support: VA CDA2 #I01BX007080

Title: A genome-wide RNAi screen identifies novel mechanisms controlling TDP-43 toxicity in a *C. elegans* model of ALS and FTLD-TDP

Authors: *N. LIACHKO[1,2], A. SAXTON[1], B. C. KRAEMER[1,2]
[1]GRECC, VA Puget Sound Hlth. Care Syst., Seattle, WA; [2]Univ. of Washington, Seattle, WA

Abstract: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTLD-TDP) are severe progressive neurodegenerative diseases characterized by lesions containing aggregated, hyperphosphorylated TDP-43. Dysfunctional TDP-43 can cause these disorders, as mutations in *TARDBP*, the gene coding for TDP-43, results in a familial form of ALS. To study the cellular, molecular, and genetic underpinnings of TDP-43 mediated neurotoxicity in a tractable model system, we have developed *C. elegans* models of TDP-43 proteinopathy. Expression of familial ALS-mutant TDP-43 in all *C. elegans* neurons causes severe progressive motor dysfunction, and recapitulates some characteristic features of ALS and FTLD-TDP including decreased lifespan, neuronal degeneration, hyperphosphorylation, ubiquitination and C-terminal truncation of TDP-43, and accumulation of detergent insoluble aggregates. To identify genes and gene pathways that modify TDP-43 toxicity, we have performed an unbiased genome-wide RNAi screen for modifiers of TDP-43-driven phenotypes in *C. elegans*. 16,757 individual RNAi clones were screened, targeting 86% of the *C. elegans* genome. First pass screening identified 2,486 candidate suppressors or enhancers of TDP-43 toxicity. After the retesting of first-pass hits, 84 RNAi clones remained that consistently modified TDP-43 tg movement defects or viability. Of these, 46 suppressors were identified that improved motor function, while 38 enhancers were identified that worsened TDP-43 toxicity, resulting in paralysis, severe growth defects, or lethality of the TDP-43 tg animals. Of the TDP-43 tg modifying genes, 24 suppressors and 22 enhancers have significant homology to human genes, and fall into functional classes including energy production and metabolism, extracellular matrix and cytoskeleton genes, ion channels, nucleic acid functions, and proteostasis. These genes give new insight into cellular mechanisms regulating susceptibility to or protection against dysfunctional TDP-43, and represent new potential targets for therapeutic interventions into TDP-43 proteinopathies such as ALS and FTLD-TDP. This work was funded by a VA Career Development Award (CDA2) to N. Liachko (# I01BX007080).

Disclosures: N. Liachko: None. **A. Saxton:** None. **B.C. Kraemer:** None.

Nanosymposium

715. ALS Mechanisms

Location: SDCC 7

Time: Wednesday, November 7, 2018, 1:00 PM - 3:45 PM

Presentation Number: 715.03

Topic: C.06. Neuromuscular Diseases

Title: FUS induces neurodegeneration through its low-complexity domain in the *Drosophila* retina

Authors: *T. HASHIMOTO, T. MATSUMOTO, Y. KISHINO, K. MATSUKAWA, N. WATANABE, T. WAKABAYASHI, T. IWATSUBO
The Univ. of Tokyo, Tokyo, Japan

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that affects upper and lower motor neurons, resulting in muscular atrophy and weakness. Fused in sarcoma (FUS) gene has been identified in the pedigree with autosomal dominantly inherited familial ALS. FUS-immunoreactive neuronal cytoplasmic inclusions are the pathological hallmark of FUS-linked ALS or frontotemporal lobar degeneration. However, it remains unclear how FUS causes neurodegeneration. To gain insights into the molecular mechanism whereby FUS causes neurodegeneration, we generated transgenic *Drosophila melanogaster* overexpressing human FUS in the photoreceptor neurons (FUS tg fly), which exhibited mild retinal degeneration, e,g, vacuolation in the retina, or perturbation of ommatidial architecture. Expression of familial ALS-linked P525L mutant FUS aggravated the degeneration, which was associated with an increase in cytoplasmic localization of FUS. Notably, replacement of all tyrosine residues within the low-complexity (LC) domain, which abolished self-assembly of FUS, completely eliminated the degenerative phenotypes induced by wild-type or P525L mutant FUS. These findings suggest that FUS induces neurodegeneration through its LC domain. LC domain of FUS has been shown to be targeted for phosphorylation, although little is known about the effects of phosphorylation on FUS-induced neurodegeneration. We found that overexpression of human casein kinase I (CKI) delta, CKI epsilon, or *Drosophila* CKI epsilon, in the retina of FUS tg flies ameliorated FUS-induced retinal degeneration. Phos-tag gel electrophoresis revealed a retardation of migration of FUS polypeptides extracted from double tg flies overexpressing FUS and CKI delta, CKI epsilon, or *Drosophila* CKI epsilon, suggesting that CKI delta, or epsilon is involved in the phosphorylation of FUS. These results suggest that FUS induces neurodegeneration through its LC domain and that phosphorylation of FUS may modulate the neurodegeneration.

Disclosures: T. Matsumoto: None. **Y. Kishino:** None. **K. Matsukawa:** None. **N. Watanabe:** None. **T. Wakabayashi:** None. **T. Iwatsubo:** None.

Nanosymposium

715. ALS Mechanisms

Location: SDCC 7

Time: Wednesday, November 7, 2018, 1:00 PM - 3:45 PM

Presentation Number: 715.04

Topic: C.06. Neuromuscular Diseases

Support: R01NS085207
R01NS099320
P01NS09911
R01NS094239
U24NS078736
R01 NS082563
NS094239

Title: Stress granule assembly disrupts nucleocytoplasmic transport

Authors: *K. ZHANG[1,2], J. DAIGLE[2], K. CUNNINGHAM[3], A. N. COYNE[2], K. RUAN[1], J. C. GRIMA[4], J. D. ROTHSTEIN[5], T. E. LLOYD[6]
[1]Dept. of Neurol., Johns Hopkins University, Sch. of Med., Baltimore, MD; [2]Brain Sci. Inst., Johns Hopkins University, Sch. of Medicine,, Baltimore, MD; [3]CMM, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [4]Johns Hopkins Neurosci., Baltimore, MD; [5]Brain Sci. Inst., Johns Hopkins Univ., Baltimore, MD; [6]Neurol., Johns Hopkins Schl Med., Baltimore, MD

Abstract: Defects in nucleocytoplasmic transport have been identified as a key pathogenic event in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) mediated by a GGGGCC hexanucleotide repeat expansion in C9ORF72, the most common genetic cause of ALS/FTD. Furthermore, nucleocytoplasmic transport disruption has also been implicated in other neurodegenerative diseases with protein aggregation, suggesting a shared mechanism by which protein stress disrupts nucleocytoplasmic transport. Here, we show that cellular stress disrupts nucleocytoplasmic transport by localizing critical nucleocytoplasmic transport factors into stress granules, RNA/protein complexes that play a crucial role in ALS pathogenesis. Importantly, inhibiting stress granule assembly, such as by knocking down Ataxin-2, suppresses nucleocytoplasmic transport defects as well as neurodegeneration in C9ORF72-mediated ALS/FTD. Our findings identify a link between stress granule assembly and nucleocytoplasmic transport, two fundamental cellular processes implicated in the pathogenesis of C9ORF72-mediated ALS/FTD and other neurodegenerative diseases.

Disclosures: K. Zhang: None. **J. Daigle:** None. **K. Cunningham:** None. **A.N. Coyne:** None. **K. ruan:** None. **J.C. Grima:** None. **J.D. Rothstein:** None. **T.E. Lloyd:** None.

Nanosymposium

715. ALS Mechanisms

Location: SDCC 7

Time: Wednesday, November 7, 2018, 1:00 PM - 3:45 PM

Presentation Number: 715.05

Topic: C.06. Neuromuscular Diseases

Support: Target ALS springboard fellowship

Title: Large ventrolateral glycinergic interneurons are less excitable in a SOD1 mouse model of ALS

Authors: *K. A. QUINLAN[1,2]
[1]Biomed. and Pharmaceut. Sci., [2]George & Anne Ryan Inst. for Neurosci., Univ. of Rhode Island, Kingston, RI

Abstract: While a great deal of attention has been devoted to determining the intrinsic excitability of vulnerable populations of motoneurons in amyotrophic lateral sclerosis (ALS), few studies have investigated synaptic drive to motoneurons. This study assessed excitability of ventrolateral lumbar inhibitory interneurons at an early time point (postnatal day 6-12) using whole cell patch clamp in transverse spinal cord slices from $SOD1^{G93A}$ x GlyT2 eGFP mice. Large (input resistance <325 MOhms) GFP+ neurons were targeted, as this group includes inhibitory interneurons which are presynaptic to motoneurons (including Renshaw cells and Ia inhibitory interneurons). Active and passive properties were measured. SOD1 glycinergic interneurons (n = 16 from 10 mice) show significant dampening of intrinsic excitability compared to controls (n = 25 interneurons from 15 mice), including higher threshold voltage for action potential firing (control threshold = -41, standard deviation (SD) 4 mV; SOD1 threshold -37, SD 6mV; $p = 0.022$) and altered voltage sensitivity of persistent inward currents, including more depolarized onset and peak voltages in SOD1 interneurons (control onset = -51, SD 7mV; SOD1 onset = -45, SD 5mV; $p = 0.006$; control peak = -34, SD 6mV; SOD1 peak = -30, SD 5mV; $p = 0.017$). In conclusion, glycinergic inhibitory interneurons in SOD1 mice are less excitable and therefore are likely to spike less often and inhibit motoneurons less *in vivo*.

Disclosures: K.A. Quinlan: None.

Nanosymposium

715. ALS Mechanisms

Location: SDCC 7

Time: Wednesday, November 7, 2018, 1:00 PM - 3:45 PM

Presentation Number: 715.06

Topic: C.06. Neuromuscular Diseases

Support: Health Research Board (HRB_POR/2013/348)
Thierry Latran Foundation (FTL AP2011 PREHN)
SFI FUTURE-NEURO Research Centre 16/RC/3948 and 17/JPND/3455
Netherlands ALS Foundation
Netherlands Organization for Health Research and Development (Vici scheme)
Netherlands Organization for Health Research and Development (SOPHIA, STRENGTH, ALS-CarE project)
Netherlands Organization for Health Research and Development (Veni scheme)

Title: Small non-coding RNAs generated by the ALS-associated ribonuclease angiogenin deliver novel and accessible biomarkers of disease progression in ALS

Authors: M. C. HOGG[1], M. RAYNER[1], S. SUSDALZEW[1], M. CRIVELLO[1], I. WOODS[1], N. MONSEFI[1], A. RESLER[1], M. TROLESE[2], G. NARDO[2], C. BENDOTTI[2], L. H. VAN DEN BERG[3], M. VAN ES[3], *J. H. PREHN[1]
[1]Royal Col. of Surgeons in Ireland, Dublin, Ireland; [2]Mario Negri Inst. for Pharmacol. Res., Milan, Italy; [3]Neurol., Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: Angiogenin is a secreted RNase linked to the pathogenesis of amyotrophic lateral sclerosis (ALS) and released from motor neurons under stress conditions. Here we identify the full repertoire of angiogenin substrates in astrocytes, a main target of angiogenin's biological activity, using small RNA sequencing and a custom bioinformatic analysis pipeline. From this we identified a specific subset of tRNAs that were robustly cleaved by angiogenin within the anticodon loop. Interestingly, reads were only detected from one half of the tRNA indicating half the tRNA was preserved or protected whilst the other half was rapidly degraded during the course of the treatment. Specific isoacceptor subtypes appeared to be favoured or targeted by angiogenin (e.g. Arginine and Valine) whilst others remained intact. Angiogenin also cleaved other non-coding RNAs including small nuclear RNAs, small nucleolar RNAs, and histone RNAs. Northern blotting was used to validate tRNA cleavage by angiogenin, and custom Taqman assays were generated to recognise tiRNA fragments for high throughput quantification. As angiogenin-induced RNA cleavage constitutes an evolutionarily conserved stress response, we explored whether the identified tRNA fragments indicated disease progression in preclinical ALS models and ALS patients. tiRNAs were elevated at disease onset in slowly-progressing but not rapidly-progressing mutant $SOD1^{G93A}$ ALS mice on different genetic backgrounds,

suggesting that tiRNA formation indicates neuroprotective stress signalling. Further tiRNAs were elevated in spinal cord and serum early in disease development in a second ALS mouse model, the FUS (1-359) mice. Finally, we can show that tiRNA serum levels were also significantly higher in slowly-progressing compared to faster-progressing ALS patients, mirroring the preclinical findings. We here report the 'small RNAome' of angiogenin mediated RNA cleavage, and identify novel and accessible biomarkers of disease progression in ALS.

Disclosures: M.C. Hogg: None. **M. Rayner:** None. **S. Susdalzew:** None. **M. Crivello:** None. **I. Woods:** None. **N. Monsefi:** None. **A. Resler:** None. **M. Trolese:** None. **G. Nardo:** None. **C. Bendotti:** None. **L.H. Van Den Berg:** None. **M. van Es:** None. **J.H. Prehn:** None.

Nanosymposium

715. ALS Mechanisms

Location: SDCC 7

Time: Wednesday, November 7, 2018, 1:00 PM - 3:45 PM

Presentation Number: 715.07

Topic: C.06. Neuromuscular Diseases

Support: Target ALS
The HBI ALS Seed Grant Program

Title: Abnormal excitability and susceptibility in familial ALS iPSC derived neurons

Authors: *S. LEE[1], O. WISKOW[2], S. GHOSH[2], X. HUANG[1], K. ROET[1], B. J. WAINGER[3], B. P. BEAN[4], K. EGGAN[2], C. J. WOOLF[1]
[1]F.M. Kirby Neurobio. Ctr., Boston Children's Hosp., Boston, MA; [2]Harvard Univ., Cambridge, MA; [3]Massachusetts Gen. Hosp., Charlestown, MA; [4]Dept. of Neurobio., Harvard Med. Sch., Boston, MA

Abstract: Abnormal excitability and cell death of motor neurons are major phenotypes of amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease. We have reported previously that patient iPSC derived motor neurons that harbor the A4V mutation in superoxide dismutase 1 ($SOD1^{A4V/+}$) display hyperexcitability, ER stress, and cell death, when compared to isogenic controls. To understand the molecular mechanisms that underly how this ALS mutation causes abnormal excitability and a high susceptibility to cell death in spinal motor neurons, we first used genome editing to introduce a Hb9-GFP reporter into iPSCs to enable isolation of these cells. After differentiation, purification, and maturation in the presence of glial cells, we then after electrophysiological recording used patch-seq and patch-qPCR to compare excitability and gene expression profiles, at a single cell level. Purified $SOD1^{A4V/+}$ Hb9-GFP neurons showed both abnormal excitability and differential expression of an ion channel, compared to their isogenic controls. We are using gain- and loss-function approaches to tease out the role of the ion channel in driving the disease phenotype and its potential rescue. Patch-seq and patch-qPCR

approaches on patient iPSC derived motor neurons will help reveal, therefore, disease-related molecular mechanisms and potential novel therapeutic targets.

Disclosures: S. Lee: None. **O. Wiskow:** None. **S. Ghosh:** None. **X. Huang:** None. **K. Roet:** None. **B.J. Wainger:** None. **B.P. Bean:** None. **K. Eggan:** None. **C.J. Woolf:** None.

Nanosymposium

715. ALS Mechanisms

Location: SDCC 7

Time: Wednesday, November 7, 2018, 1:00 PM - 3:45 PM

Presentation Number: 715.08

Topic: C.06. Neuromuscular Diseases

Support: Project ALS

Title: Assessing the neuroprotective effects of cromolyn sodium in the $SOD1^{G93A}$mouse model of amyotrophic lateral sclerosis

Authors: *G. SADRI-VAKILI, E. GRANUCCI, K. MUELLER, A. GRICIUC, H. LE, A. DIOS, S. PAGANONI, J. BERRY, M. CUDKOWICZ, D. ELMALEH, R. TANZI
Dept Neurol., Massachusetts Gen. Hosp., Charlestown, MA

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. This neuroinflammation is mediated by activated microglia and reactive astrocytes which produce reactive oxygen intermediates and pro-inflammatory cytokines leading to neuronal death. Activated microglia were detected near motor neurons of $SOD1^{G93A}$ transgenic mice well before the onset of symptoms and the inflammatory response correlated with disease progression. Moreover, early stage pro-phagocytic microglia enhanced motor neuron survival, while pro-inflammatory microglia were toxic to motor neurons in the $SOD1^{G93A}$ mice. Together, these findings suggest that during ALS progression, there is a shift from the pro-phagocytic and neuroprotective to the pro-inflammatory and neurotoxic microglial activation status. Recent studies from our group have demonstrated that cromolyn sodium, an FDA approved compound, exerts neuroprotective effects in Alzheimer's disease (AD) models. Specifically, cromolyn treatment resulted in decreased levels of insoluble amyloid beta (Aβ) and increased recruitment of microglial cells around amyloid plaques, which lead to phagocytosis and removal of Aβ in a mouse model of AD. Here we tested the neuroprotective effects of cromolyn sodium in the $SOD1^{G93A}$ mice. Wild-type and transgenic age- and litter-matched male and female mice were treated with either vehicle or cromolyn (6.3 mg/kg, i.p.) starting postnatal day 60 (P60) until euthanasia. Our results demonstrate that cromolyn sodium treatment significantly delayed the onset of neurological symptoms at P120 in all mice and improved the deficits in paw grip endurance (PaGE) performance at P120 and P140. Furthermore, treatment

significantly delayed the age at paresis onset and improved PaGE performance in the male transgenic mice at P100-140. There was also a significant increase in survival in treated female transgenic mice compared to vehicle treated mice. Lastly, there was a trend towards an improvement in body weight and survival in all treated mice. Together these findings suggest that cromolyn sodium provides neuroprotection in a sex dependent manner in the $SOD1^{G93A}$ mice. Ongoing studies are assessing the effects of treatment on motor neuron counts and neuroinflammation in the spinal cord.

Disclosures: G. Sadri-Vakili: None. **E. Granucci:** None. **K. Mueller:** None. **A. Griciuc:** None. **H. Le:** None. **A. Dios:** None. **S. Paganoni:** None. **J. Berry:** None. **M. Cudkowicz:** None. **D. Elmaleh:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Chairman and CEO AZTherapies Inc. **R. Tanzi:** F. Consulting Fees (e.g., advisory boards); aid consultant and shareholder in AZ Therapies.

Nanosymposium

715. ALS Mechanisms

Location: SDCC 7

Time: Wednesday, November 7, 2018, 1:00 PM - 3:45 PM

Presentation Number: 715.09

Topic: C.06. Neuromuscular Diseases

Support: MDA 382033

Title: New mouse models of mutant CHCHD10 mitochondrial disease

Authors: C. J. ANDERSON[1], K. BREDVIK[2], S. MEADOWS[2], S. R. BURSTEIN[4], A. STEPANOVA[2], H. KAWAMATA[3], C. LUTZ[5], *G. MANFREDI[6]
[1]Feil Family Brain and Mind Res. Inst., [3]Brain and Mind Res. Inst., [2]Weill Cornell Med., New York, NY; [4]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY; [5]The Jackson Labs., Bar Harbor, ME; [6]Weill Med. Col. Cornell Univ., New York, NY

Abstract: Mutations in the coiled-coil-helix-coiled-coil-helix domain containing 10 (CHCHD10), a mitochondrial protein with unknown function, cause autosomal dominant forms of familial amyotrophic lateral sclerosis (ALS), frontotemporal dementia, Parkinson disease, and myopathy. To investigate the pathogenic role of CHCHD10 *in vivo*, we have generated CHCHD10 knock out (KO) mice and mutant (S55L) CHCHD10 knock in (KI) mice. CHCHD10 KO lack behavioral abnormalities and have a normal lifespan, suggesting that mice can adapt to the loss of CHCHD10. Instead, mutant S55L KI mice show progressive body weight loss, motor deficits, and die prematurely. Homozygote mice show earlier disease onset and fatal outcome than heterozygote mice, suggesting a gene dosage effect. Interestingly, young S55L females die during pregnancy due to a fatal dilative cardiomyopathy. Gross pathology revealed significant

reductions in skeletal muscle and cardiac mass. We investigated tissue pathology of S55L KI mice in the CNS, skeletal muscle, and heart, which are the most affected tissues in CHCHD10 mutant patients and found marked vacuolization in skeletal muscle and heart, while in the brain, where CHCHD10 is expressed mostly in dopaminergic neurons, we found altered protein localization. S55L KI mice have drastically elevated CHCHD10 levels in heart mitochondria, which is accompanied by altered mitochondrial function, with decreased respiration and ATP synthesis. Importantly, transcriptomic analyses of the heart of S55L KI mice indicate that the mutant protein causes a profound integrated mitochondrial stress response with elevation of enzymes of one carbon metabolism, and stress-related proteins, such as ATF4 and ATF5 as well as the mitochondrial disease biomarkers FGF21 and Gdf15. These results obtained in the first mouse model of CHCHD10 mutations associated with human disease suggest that pathogenic mutations in CHCHD10 alter the normal functions of the protein and cause a toxic gain of function that damages mitochondria and causes a systemic form of mitochondrial disease.

Disclosures: C.J. Anderson: None. **K. Bredvik:** None. **S. Meadows:** None. **S.R. Burstein:** None. **A. Stepanova:** None. **H. Kawamata:** None. **C. Lutz:** None. **G. Manfredi:** None.

Nanosymposium

715. ALS Mechanisms

Location: SDCC 7

Time: Wednesday, November 7, 2018, 1:00 PM - 3:45 PM

Presentation Number: 715.10

Topic: C.06. Neuromuscular Diseases

Support: Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship (Parent F31)
National Science Foundation Graduate Research Fellowship
NIH
NINDS
Packard Center for ALS Research
Johns Hopkins Solomon H. Snyder Department of Neuroscience Graduate Program
Johns Hopkins Brain Science Institute

Title: Loss of o-glcnac contributes to nuclear pore complex defects in als/ftd and sals

Authors: *J. GRIMA[1], J. D. ROTHSTEIN[2]
[1]Neurosci., Johns Hopkins University, Sch. of Med., Baltimore, MD; [2]Brain Sci. Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: A mutation in gene C9orf72 is the most common genetic cause of familial and sporadic Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD). Our group and others simultaneously showed that dysfunction in nucleocytoplasmic transport may be a

fundamental pathway for C9orf72-ALS/FTD pathogenesis. The efficient and selective trafficking of macromolecules between the nucleus and cytoplasm is a critical task regulated by nuclear pore complexes (NPCs). We now present data that the NPC is compromised not only in models of C9orf72-ALS/FTD but also sporadic ALS (sALS), suggesting that NPC dysfunction may underlie the majority ALS. More specifically, we have surveyed the NPC in several mouse models, iPSC neurons, a drosophila model, and human brain tissue using confocal microscopy, siRNAs, proteomics, transcriptomics, and a genetic screen. We have identified a unique set of NPC subunits (NUPs) and other transport machinery that are particularly affected, with the majority of these being components of nuclear import machinery that have FG-repeats and/or the O-GlcNAc post-translational modification. We show that O-GlcNAc is severely depleted in models of ALS and pharmacological or siRNA depletion of O-GlcNAc recapitulates many aspects of the disease including nuclear loss of TDP43 and cytoplasmic mislocalization of unique NUPs. Finally, we can mitigate cell toxicity and NPC pathology when increasing levels of O-GlcNAc. This data suggests that NPC dysfunction may be a common insult in the majority of ALS and that disruption of nuclear import machinery partially due to a loss of O-GlcNAc may be the first domino to fall in the disease cascade.

Disclosures: J. Grima: None. **J.D. Rothstein:** None.

Nanosymposium

715. ALS Mechanisms

Location: SDCC 7

Time: Wednesday, November 7, 2018, 1:00 PM - 3:45 PM

Presentation Number: 715.11

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant 5R01NS100023
NSF Graduate Research Fellowship Program

Title: Skeletal muscle-driven mechanisms of motor neuron degeneration in SBMA

Authors: *A. GROMOVA[1,2], H. C. MIRANDA[1], A. R. LA SPADA[2]
[1]UC San Diego, La Jolla, CA; [2]Duke Univ., Durham, NC

Abstract: Spinal and bulbar muscular atrophy (SBMA) is an X-linked neuromuscular disease, the pathogenic hallmark of which is the loss of lower motor neurons. It is caused by repeat expansions of the CAG codon (translated into glutamine, [Q]) in the first exon of the androgen receptor *(AR)* gene. Motor neuron degeneration in SBMA leads to progressive muscle weakness, with no disease-modifying therapy currently available. Using transgenic mice (BAC fxAR121) where expression of mutant human AR containing 121 CAG repeats can be excised in a tissue-specific manner by Cre recombinase, our lab demonstrated that expression of pathogenic polyQ-AR in skeletal muscle is necessary for motor neuron degeneration. Human skeletal muscle actin

(HSA, a muscle specific gene)-Cre/BAC fxAR121 bigenic mice, which express pathogenic polyQ-AR in all tissues except skeletal muscle, exhibit complete rescue of functional motor defects, spinal cord neuron degeneration, weight loss, and shortened lifespan, that occur in singly transgenic BAC fxAR121 littermates. These findings implicate skeletal muscle as a driver of neurodegeneration in SBMA, but the causal molecular pathways and specific mechanisms remain unknown. Furthermore, it is unclear if the disease process and associated mechanisms can be recapitulated in a human cell context. To address these questions, we have established an induced pluripotent stem cell (iPSC)-based model in which highly pure skeletal myotubes or motor neurons are derived from SBMA patient or control cells (from 3 donors each). In line with previous work showing polyQ-AR in skeletal muscle in mice is required for motor neuron degeneration, conditioned media from iPSC-derived SBMA myotubes induces an increase in TUNEL staining in iPSC-derived motor neurons. As AR is a transcription factor, we have completed an RNA-seq study of iPSC-derived myotubes to begin to determine potential mechanisms of skeletal muscle-driven neurodegeneration. Transcriptome analysis of SBMA myotubes identified several upregulated transcripts coding for secreted proteins, including metabolic regulators and inflammatory factors. Characterization of these factors and their role in SBMA pathogenesis may yield pathways responsible for skeletal muscle-mediated motor neuron toxicity and previously unknown therapeutic targets for neuromuscular disorders.

Disclosures: A. Gromova: None. **H.C. Miranda:** None. **A.R. La Spada:** None.

Nanosymposium

716. Brain Injury: From Animal Models to Physiology, Behavior, and Treatments

Location: SDCC 4

Time: Wednesday, November 7, 2018, 1:00 PM - 4:00 PM

Presentation Number: 716.01

Topic: C.10. Brain Injury and Trauma

Support: CNRM Grant Support

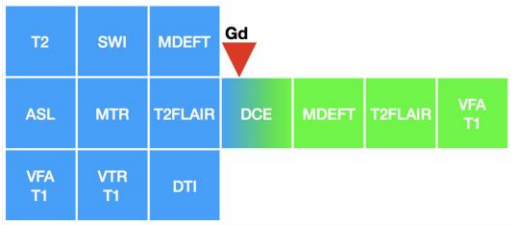
Title: MRI markers of brain injury in a ferret model of closed head rotation and acceleration

Authors: *E. B. HUTCHINSON[1,2], S. KING[1], Y. KIM[3,2], A. KOROTCOV[4,2], A. BOSOMTWI[4,2], L. D. REYES[1,2], S. C. SCHWERIN[3,2], S. L. JULIANO[3], B. DARDZINSKI[4], C. PIERPAOLI[1]
[1]Quantitative Med. Imaging Section, NIBIB, NIH, Bethesda, MD; [2]Henry M. Jackson Fndn., Bethesda, MD; [3]APG, [4]Radiology, USUHS, Bethesda, MD

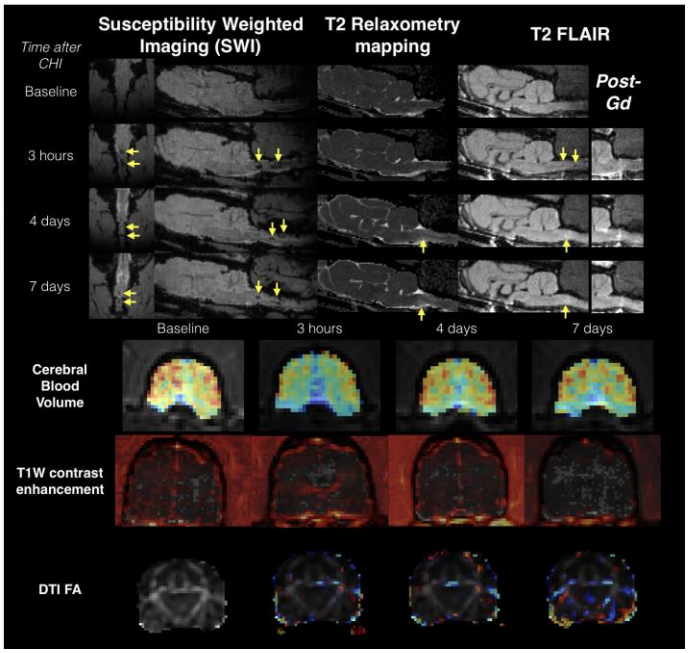
Abstract: Introduction: In order for experimental animal models of traumatic brain injury (TBI) to have a translationally relevant impact, they must faithfully recapitulate key features of human TBI. In the current study a closed head injury (CHI) model of engineered rotation and acceleration was adapted for use in the ferret - a species with folded cortex and relatively high

white matter volume. Longitudinal in-vivo MRI was performed using a comprehensive battery of scans based on the listed MRI markers for human TBI in the NIH common data element (CDE) registry. The objective was to determine if MRI abnormalities could be detected at different times following injury in the ferret and which among these are in common with with human imaging markers.

Methods: Four adult male ferrets were administered CHI to varying degrees (1 control, 1 severe, 2 mild) using a specially designed device. Serial brain scans were collected at baseline, 3 hours, 1 week and 4 weeks following CHI, using a comprehensive MRI battery including: T2 mapping, susceptibility weighted imaging (SWI), arterial spin labeling (ASL), magnetization transfer ratio (MTR), diffusion tensor imaging (DTI), dynamic contrast enhancement (DCE) during Gadolinium (Gd) injection, pre/post Gd T1-mapping, pre/post Gd T1W high-resolution imaging and pre/post Gd T2FLAIR. By comparison with the baseline images, MRI abnormalities were identified and compared with the CDE MRI markers.



	CDE tier		Demonstrated in fCHIMERA
T2W	1	✓	Hyperintense foci during the chronic period
SWI	1	✓	Focal hypointensities consistent with microhemorhage
DWI	1	X	No major change in diffusivity at 3h
T2-FLAIR	1	~	Focal hyperintensities, No indication of meningeal involvement
DTI	2	✓	Reduced FA for midline structures
PWI	3	✓	Acute leakage of Gd into parenchyma, BBB disruption
ASL	3	✓	Acute decrease in CBF, recovery in chronic period



Results: As demonstrated in the figure, several MRI markers were identified following severe CHI in the ferret including SWI hypointensity, T2 enhancement, Gd leakage, reduced CBF and reduced DTI fractional anisotropy in the white matter. The presence of these abnormalities in mild TBI was more subtle.

Conclusions: Closed head injury in the ferret appears to provide a TBI model with similar MRI outcomes as observed in humans. By inducing a translationally relevant biomechanical injury in a species with human-similar anatomic features and assessing MRI markers as outcome measures, this paradigm may provide a crucial bridge between basic and clinical TBI research.

Disclosures: E.B. Hutchinson: None. **S. King:** None. **Y. Kim:** None. **A. Korotcov:** None. **A. Bosomtwi:** None. **L.D. Reyes:** None. **S.C. Schwerin:** None. **S.L. Juliano:** None. **B. Dardzinski:** None. **C. Pierpaoli:** None.

Nanosymposium

716. Brain Injury: From Animal Models to Physiology, Behavior, and Treatments

Location: SDCC 4

Time: Wednesday, November 7, 2018, 1:00 PM - 4:00 PM

Presentation Number: 716.02

Topic: C.10. Brain Injury and Trauma

Support: Eranet Neuron TRAINS
Fondation des Gueules Cassées

Title: Locomotor adaptations in a mouse model of controlled cortical impact

Authors: *S. LEMARCHANT[1], G. COURTAND[1], M. A. MAYORGA RODRIGUEZ[1], L. CARDOIT[1], M. WOLFF[1], F. E. PERRIN[2], G. BARRIÈRE[1]
[1]INCIA, CNRS UMR5287, Bordeaux Cedex, France; [2]INSERM U 1198, Univ. of Montpellier, Montpellier, France

Abstract: Traumatic brain injury (TBI) represents a major cause of disability and mortality worldwide. The limited capacity of the CNS to self-repair after injury eventually leads to chronic devastating functional impairments regardless of the primary origin of the injury. Therefore, there is an urgent need to characterize local and remote modifications leading to sensorimotor dysfunctions after TBI. For that purpose, adult male mice were subjected to a craniectomy followed by either a mild or a severe controlled cortical impact (CCI) onto the right parietal cortex delivered by an electromagnetic impactor device. Sham-operated mice were subjected to the same surgery except the impact. Spontaneous locomotor activity (open-field) and gait pattern (treadmill) are performed at several time points up to 2 months post-injury. Additionally, learning and memory are tested by using the novel object recognition test at 2 months post injury. Brains and spinal cords are collected afterwards for ex vivo magnetic resonance imaging and immunohistochemistry. Our preliminary data show that spontaneous locomotor activity was significantly reduced in mice with severe CCI compared with sham mice at 1 dpi (decrease of the total distance, the average speed and the number of rearings; increase of the motionless time), but not at 14, 28 and 58 dpi. However, the number of entries in the center of the arena was significantly reduced in the chronic phase after severe CCI, suggesting a sustained anxiety. No differences in the parameters listed above were modified in mild CCI mice at any time points. In parallel, we have performed analyses of the gait pattern; mice are placed on a treadmill and the speed is adjusted for each mouse. We have analyzed the linear relation between the stance (extension) or the swing (flexion) durations and the cycle duration. Our results show modifications of gait pattern signatures that indicate adaptations of locomotor networks after CCI. For instance: 1) significant differences of linear regressions between sham and CCI mice (mild and severe) during the acute (4 dpi) and the chronic (59 dpi) phases, 2) asymetrical gait signatures between the right and the left forelimbs in mild and severe CCI mice during the acute

phase, 3) asymetrical gait signatures between the right and the left hindlimbs in CCI mice during the chronic phase, which indicates locomotor plasticity over time after CCI. To conclude, we have evidenced short and long-term locomotor adaptations after either mild or severe CCI in mice. We are currently investigating local and remote alterations/modifications (cell death, neuroinflammation, neuroplasticity) that may cause sensorimotor dysfunctions after TBI.

Disclosures: S. Lemarchant: None. **G. Courtand:** None. **M.A. Mayorga Rodriguez:** None. **L. Cardoit:** None. **M. Wolff:** None. **F.E. Perrin:** None. **G. Barrière:** None.

Nanosymposium

716. Brain Injury: From Animal Models to Physiology, Behavior, and Treatments

Location: SDCC 4

Time: Wednesday, November 7, 2018, 1:00 PM - 4:00 PM

Presentation Number: 716.03

Topic: C.10. Brain Injury and Trauma

Support: Veterans Health Administration, Office of Research and Development, Rehabilitation Research and Development (I01RX001520)
Assistant Secretary of Defense for Health Affairs through the Congressionally Directed Gulf War Illness Research Program (W81XWH-16-1-0626)
Florida Department of Health James and Esther King Biomedical Research Program (4KB14)
The Bay Pines Foundation
Veterans Bio-Medical Research Institute

Title: Gene expression, morphological, and behavioral changes associated with a mouse model of mild repetitive TBI and treatment with activators of Nrf2 and PPAR-γ transcription factors

Authors: *W. A. RATLIFF[1,2], D. QUBTY[3], T. MICHAELS[1], C. M. SMITH[1], C. G. PICK[3], B. A. CITRON[4,2]
[1]Bay Pines VA Healthcare Syst., Bay Pines, FL; [2]Dept. of Mol. Med., Univ. of South Florida Morsani Col. of Med., Tampa, FL; [3]Tel Aviv Univ., Tel Aviv, Israel; [4]Lab. of Mol. Biol., VA New Jersey Hlth. Care Syst., East Orange, NJ

Abstract: The incidence of traumatic brain injury (TBI) is estimated at 0.5% per year worldwide, with a much higher frequency among service personnel and athletes. The majority of TBIs are mild and these can result in deleterious cognitive effects for which there is currently no effective treatment. Moreover, repetitive mild head injuries, common in military and athletic activities, have produced more severe consequences. We have demonstrated improved outcomes in both *in vitro* and *in vivo* models of brain injury following treatment with tert-butylhydroquinone (tBHQ) by activation of the inflammatory responsive transcription factor, Nrf2, and downstream neuroprotective factors. Additionally, the PPAR-γ agonist, pioglitazone,

has been shown to have neuroprotective effects in models of neurodegenerative disease and TBI. In an effort to better understand the underlying mechanisms of injury, and how to treat it, we tested mice receiving closed head injuries once per week for 5 weeks along with potentially synergistic treatment by tert-butylhydroquinone (tBHQ) and pioglitazone. At acute and chronic times we evaluated gene expression, cognitive changes, and immunohistochemistry for microglial changes (Iba1) and lipid peroxidation (4-hydroxynonenal). mRNA samples from the ipsilateral hippocampi one day post-injury were evaluated with Affymetrix GeneChip Arrays. Our initial examination (4 groups, n=6 per group) indicated that genes displayed a variety of expression patterns. For example, dysregulations after injuries alone included upregulation of G-protein coupled receptor 3 (Gpr3) and downregulation of aminolevulinic acid synthase (Alas2). After injuries, the transcription factor modulation caused elevation of cysteine-rich secretory protein LCCL domain containing 2 (Crispld2) and lowering of erythroid differentiation regulator 1 (Erdr1) expression. Some genes that were decreased by the injury were increased by the treatment, e.g., SRY (sex determining region Y)-box 3 (Sox3), and certain genes, like ankyrin repeat and SOCS box-containing 6 (Asb6), were induced by the injury and reduced by the treatment. Two months post-injury, we have identified morphological changes within the microglia, while microglia from treated mice appear normal. Behaviorally, we have shown that object recognition memory is impaired two months following injury and that this is ameliorated by treatment. Through these approaches, we hope to better define inflammatory responsive transcription factor signaling pathways and identify factors that could be targeted to produce neuroprotection and improve outcomes for TBI patients.

Disclosures: W.A. Ratliff: None. **D. Qubty:** None. **T. Michaels:** None. **C.M. Smith:** None. **C.G. Pick:** None. **B.A. Citron:** None.

Nanosymposium

716. Brain Injury: From Animal Models to Physiology, Behavior, and Treatments

Location: SDCC 4

Time: Wednesday, November 7, 2018, 1:00 PM - 4:00 PM

Presentation Number: 716.04

Topic: C.10. Brain Injury and Trauma

Support: NINDS R56-NS-090311
NINDS P30-NS-045758
T32-DE-01-4320

Title: Traumatic brain injury-induced neuronal damage induces cortical rod microglia that promote persistent neuroinflammation

Authors: *K. G. WITCHER[1], C. BRAY[2], J. DZIABIS[2], D. B. MCKIM[3], B. BENNER[2], R. ROWE[5], P. G. POPOVICH[4], J. LIFSHITZ[6], O. KOKIKO-COCHRAN[2], D. EIFERMAN[2], J. P. GODBOUT[7]

[1]Dept. of Neurosci., [2]Neurosci., Ohio State Univ., Columbus, OH; [4]Dept. of Neurosci., [3]The Ohio State Univ., Columbus, OH; [5]Child Hlth., Univ. of Arizona Col. of Med. Phoenix, Phoenix, AZ; [6]Child Hlth. - Phoenix, Univ. of Arizona/Phoenix Children's Hosp., Phoenix, AZ; [7]Neurosci., Ohio State Univ. Dept. of Neurosci., Columbus, OH

Abstract: Microglia are important immune responders to traumatic brain injury (TBI) and these responses may be neuroprotective or maladaptive. For example, diffuse TBI results in a unique population of elongated and rod-shaped microglia in the cerebral cortex, but their contribution to inflammation and pathophysiology is unclear. The purpose of this study was to determine the origin and function of rod microglia after diffuse TBI, induced by midline fluid percussion injury (mFPI), in mice. We confirmed that Iba1+ rod microglia were present and formed elongated trains in the somatosensory cortex 7 days post-injury (dpi). This corresponded with upregulation of genes related to neuronal injury (Csf1, Atf3) and glial reactivity (Ccl2, Trem2, Gfap) in the lateral cortex 3 and 7 dpi. Furthermore, bone marrow chimerism and BrdU pulse-chase experiments revealed that rod microglia were derived from resident microglia with limited proliferation. Novel data show that TBI-induced rod microglia were in close proximity to axotomized (ATF3+) neurons, spatially overlapped with dense (GFAP+) astrogliosis, and aligned with apical pyramidal dendrites. To better understand the activation profile of microglia and rod microglia 7 dpi, microglia were eliminated prior to TBI by CSF1R antagonism (PLX5622). PLX5622 administration eliminated ~98% of microglia by histology and reduced cortical gene expression of microglial signature genes (Cx3cr1, Tgfbr1, Csf1r) at baseline. Following TBI, microglial elimination did not affect neuronal axotomy, but attenuated rod microglial formation and astrogliosis. Furthermore, nanoString analysis of cortical gene expression showed prolonged neuroinflammation that was ablated by PLX5622 administration. Diffuse TBI caused both acute (8h) and prolonged (7d) changes in inflammatory gene expression. Inflammatory cytokines (Il1b, Il6) were increased 8h post-injury, while chemokines were highly expressed at both 8h and 7d post-injury; TBI-induced increases in cytokine and chemokine signaling was prevented by microglial elimination. Notably, there was a unique microglia-dependent inflammatory signature that persisted 7dpi but was not present at 8h. This response included diverse signaling cascades, including complement factors, interferon-responsive proteins, phagocytosis, and pattern-recognition receptors. Taken together, microglia respond directly to cortical neurons injured by TBI, align along their apical dendrites, and function to augment astrocyte activation and promote persistent neuroinflammation.

Disclosures: K.G. Witcher: None. **C. Bray:** None. **J. Dziabis:** None. **D.B. McKim:** None. **B. Benner:** None. **R. Rowe:** None. **P.G. Popovich:** None. **J. Lifshitz:** None. **O. Kokiko-Cochran:** None. **D. Eiferman:** None. **J.P. Godbout:** None.

Nanosymposium

716. Brain Injury: From Animal Models to Physiology, Behavior, and Treatments

Location: SDCC 4

Time: Wednesday, November 7, 2018, 1:00 PM - 4:00 PM

Presentation Number: 716.05

Topic: C.10. Brain Injury and Trauma

Support: Western University's BrainsCAN initiative

Title: Repetitive closed-skull traumatic brain injury in mice leads to long-term axonal injury and cognitive impairments

Authors: *A. BROWN[1], X. XU[2], M. COWAN[2], F. BERALDO[2], A. L. SCHRANZ[2], P. MCCUNN[2], M. J. DALEY[2], T. BUSSEY[3], R. BARTHA[3], M. PRADO[3]
[1]Biotherapeutics Res., Robarts Res. Inst., London, ON, Canada; [2]Robarts Res. Inst., Univ. of Western Ontario, London, ON, Canada; [3]Robarts Reseaarch Inst., Univ. of western Ontario, London, ON, Canada

Abstract: Repetitive mild traumatic brain injury (mTBI) is an important medical concern for active sports and military personnel. Many patients with a history of repeated concussion suffer long-lasting neurobehavioral impairments. In the present study, we developed and characterized a mouse model of multiple mTBI that reflected the long-term cognitive deficits, pathological features and metabolic changes seen in this patient population. C57B6 mice received 5 mild closed-skull impacts, using a controlled cortical impactor, equipped with a custom-made silicon tip. Each impact was separated by a 24h rest interval. The concussed mice showed deficits in sustained attention in the 5-Choice Serial Reaction Time Test at 6 weeks post-concussion. In contrast, pairwise visual discrimination and reversal, which can be used to determine cognitive flexibility was normal when compared to sham concussed mice. Moreover, we uncovered significant memory loss in the Morris Water Maze Retention test at 20 weeks post-concussion. Prominent axonal damage was observed at 48 h and up to 10 weeks after injury. Reactive microglia and astrocytes adjacent to the areas of axonal damage were prominent from 48h to 4 weeks post-concussion. The histopathology, cognitive deficits, and abnormalities seen on magnetic resonance spectroscopy and diffusion tensor imaging are similar to those described in concussed patients validating both the experimental model and the biomarkers being used.

Disclosures: A. Brown: None. **X. Xu:** None. **M. Cowan:** None. **F. Beraldo:** None. **A.L. Schranz:** None. **P. McCunn:** None. **M.J. Daley:** None. **T. Bussey:** None. **R. Bartha:** None. **M. Prado:** None.

Nanosymposium

716. Brain Injury: From Animal Models to Physiology, Behavior, and Treatments

Location: SDCC 4

Time: Wednesday, November 7, 2018, 1:00 PM - 4:00 PM

Presentation Number: 716.06

Topic: C.10. Brain Injury and Trauma

Support: NINDS R56-N5090311

Title: Examining sleep disruption as an immune stressor after traumatic brain injury

Authors: *O. KOKIKO-COCHRAN[1], J. KUMAR[1], K. G. WITCHER[2], R. ATLURI[1], J. VELASQUEZ[1], C. GAFFNEY[1], J. FONTANA[1], J. GODBOUT[1]
[1]Neurosci., [2]Dept. of Neurosci., Ohio State Univ., Columbus, OH

Abstract: Accumulating evidence shows that traumatic brain injury (TBI) impairs the ability to restore homeostasis in response to a stressor, reflecting dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis. As a result, normal everyday stressors elicit intense “wear and tear” or “allostatic load” on the body and substantially influence outcome after brain injury. We hypothesize that sleep disruption is a physiologically relevant stressor that engages the HPA-axis after TBI, and upon a dysregulated stress response, promotes increased neuroinflammation, neuropathology, and behavioral impairment. Reactive microglia can drive neuronal injury and the spreading of progressive neurodegeneration through the brain. Thus, we predict that they are the primary effector cells that exacerbate neuroinflammation and pathology. Equal numbers of male and female C57BL/6 mice aged 2 months received lateral fluid percussion TBI or sham injury. Half of the mice in each group were exposed to 4 hours of sleep disruption for 3 consecutive days post-injury (DPI). For the first time we show that the plasma corticosterone (CORT) response to sleep disruption is blunted in TBI mice compared to sham mice; illustrating that sleep disruption is a potent stressor and CORT-mediated negative feedback is compromised after brain injury. This response is associated with enhanced neuroinflammation in the injured brain, including cortical Iba1 reactivity, expression of inflammatory cytokines, and leukocyte recruitment to the brain. Alterations in the neuroinflammatory environment persist at 7DPI, suggesting that acute sleep disruption promotes delayed alterations in cytokine expression. Together, these data provide new insight into the dynamic interplay between TBI, sleep disruption, and neuropathology. Our results support the hypothesis that sleep disruption is an immune stressor that significantly alters outcome.

Disclosures: O. Kokiko-Cochran: None. **J. Kumar:** None. **K.G. Witcher:** None. **R. Atluri:** None. **J. Velasquez:** None. **C. Gaffney:** None. **J. Fontana:** None. **J. Godbout:** None.

Nanosymposium

716. Brain Injury: From Animal Models to Physiology, Behavior, and Treatments

Location: SDCC 4

Time: Wednesday, November 7, 2018, 1:00 PM - 4:00 PM

Presentation Number: 716.07

Topic: C.10. Brain Injury and Trauma

Title: Newly developed high-throughput screening assay identifies Berberine as a potential drug to protect blood-brain barrier from toxic stresses

Authors: *Y. SUZUKI[1], K. KADOYA[1], T. ENDO[1], Y. MATSUI[1], Y. RUFEI[1], T. ASANO[1], S. NAKAGAWA[2], N. IWASAKI[1]
[1]Orthopaedic Surgery, Hokkaido Univ., Sapporo, Japan; [2]Dept. of Med. Pharmacology, Grad. Sch. of Biomed. Sci., Nagasaki Univ., Nagasaki, Japan

Abstract: INTRODUCTION: Although accumulated evidences show that disruption of blood-brain barrier (BBB) contributes to the pathological mechanisms in many disease conditions in central nervous system (CNS), the therapeutic strategy to protect BBB functions from harmful stresses remains to be developed. The purposes of the current study are 1) to develop high-throughput screening assay (HTSA) for identifying candidate drugs to protect human brain endothelial cells (ECs) from oxidative stress, 2) to identify potential drugs to protect BBB functions from toxic stresses in CNS disease conditions and 3) to verify the protective effect of candidate drugs in mouse brain injury model. METHODS: Human brain EC cells (hCMEC/D3) on 96 well plates were incubated with various concentrations of hydrogen peroxide (H_2O_2) for 6 hours, and viability, cytotoxicity, and live/dead ratios were measured to determine the optimal condition for the HTSA. 1600 existing drugs were screened using this newly developed HTSA, followed by subsequent tests of dose dependency and oxygen-glucose deprivation (OGD). Then, mixture of ECs, astrocytes, and pericytes from rat brains were cultured with or without a candidate drug under the OGD condition and trans-endothelial electrical resistance (TEER) and Na-F permeability were measured. Finally, to determine whether a candidate drug can actually protect BBB function after brain injury, C57BL/6 adult mice received intraperitoneal injections of a candidate drug or control, followed by cortex injury by wire-knife one day later. Next day, subjects were perfused and brain sections were immunolabeled for IgG.RESULTS and DISCUSSION: 450μM was determined as an optimal concentration of H_2O_2 for HTSA, based on the fact that its Z'-factor, S/B ratio, and CV were 0.75, 2.9, and 4% respectively. Actual HTS identified 48 existing drugs as candidates for BBB protection, and subsequent tests revealed that Berberine, an alkaloid compound extracted from natural herb, protected human ECs from the OGD stress in dose dependent manner. Moreover, Berberine maintained the TEER and the Na-F permeability significantly more than a control under the OGD condition. Further, subjects treated with Berberine had significantly smaller IgG positive area than control subjects after cortex injury, indicating its BBB protection effect. Collectively, these findings indicate that the newly

developed HTSA can successfully identify candidate drugs to protect human brain ECs from toxic stresses and identifies Berberine as a potential drug to protect BBB functions from brain injury. Currently, further screening is ongoing to identify other potential drugs to protect BBB functions.

Disclosures: Y. Suzuki: None. **K. Kadoya:** None. **T. Endo:** None. **Y. Matsui:** None. **Y. Rufei:** None. **T. Asano:** None. **S. Nakagawa:** None. **N. Iwasaki:** None.

Nanosymposium

716. Brain Injury: From Animal Models to Physiology, Behavior, and Treatments

Location: SDCC 4

Time: Wednesday, November 7, 2018, 1:00 PM - 4:00 PM

Presentation Number: 716.08

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NS50465
NIH Grant DK104363
NIH Grant NS103088

Title: The pivotal action of the gut-brain axis on brain trauma pathogenesis

Authors: *F. GOMEZ-PINILLA[1], S. D. REGE[1], L. ROYES[3], Z. YING[2]
[1]Integrative Biol. and Physiol., [2]Dept of Integrative Biol. and Physiol., UCLA, Los Angeles, CA; [3]Federal Univ. of Santa Maria, Santa Maria, Brazil

Abstract: Traumatic brain injury (TBI) results in high rates of morbidity and mortality in sports, military and domestic environments. Although clinical evidence indicates that TBI has profound effects on peripheral metabolism, underlying mechanisms are poorly understood. TBI research has primarily focused on the CNS, and little is known about the peripheral alterations that may compromise brain metabolic homeostasis and inflammation and exacerbate the pathophysiology of TBI. The liver plays a major role in control of homeostasis and pathogenesis, particularly affecting synthesis of lipids and proteins used across the body and brain. Sham animals exposed to fructose consumption for 3 weeks (15% w/v, 3wks) before moderate fluid percussion injury (FPI) onset, showed no alterations in peripheral metabolism. However, fructose consumption potentiated an increase in plasma insulin and a decrease in glucose tolerance in animals exposed to FPI. Consumption of fructose under the threshold for establishment of metabolic syndrome (MetS) exacerbates the effects of TBI on deterioration of peripheral metabolism. These effects were evident as increase in inflammatory cascade, disruption in oxidative and cell energy homeostasis and interference with components of GH/IGF1 axis in the liver, thereby worsening the TBI pathology. These effects of TBI and fructose seem to engage the hypothalamic neuroendocrine axis with resulting effects on an inflammatory cascade involving hepatic TLR4. In addition, fructose fed TBI animals had elevated markers of lipid peroxidation (4HNE), and

reduced markers of cell energy homeostasis (uMitCK) as well as reduced hepatic insulin signaling proteins (InR, IRS1) and growth hormone signaling proteins (GHR, IGF-1R). These results reveal that the effects caused by TBI are not limited to the CNS, and that fructose promotes a stage of metabolic dysfunction that potentiates the effects of TBI on systemic metabolism. Fructose is abundant in the Western diet and a major cause of MetS, diabetes, and obesity. Chronic exposure to fructose has been associated with protracted brain plasticity and function, assumingly secondary to MetS. Our results show that a short period of fructose consumption poses a risk for the outcome of TBI, with subsequent effects on the progress of the pathophysiology of TBI. These studies are particularly significant on the light of recent studies showing the pervasive effects of fructose and TBI on many genes associated with important neurological and psychiatric disorders (Meng et al., eBiomedicine, 2016, 2017). (supported by NIH R01NS50465).

Disclosures: F. Gomez-Pinilla: None. **S.D. Rege:** None. **L. Royes:** None. **Z. Ying:** None.

Nanosymposium

716. Brain Injury: From Animal Models to Physiology, Behavior, and Treatments

Location: SDCC 4

Time: Wednesday, November 7, 2018, 1:00 PM - 4:00 PM

Presentation Number: 716.09

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NS094834
AHA Grant 14SDG20490359
AHA Grant 16PRE27790122
NIH Grant AG047296
NIH Grant HL093554

Title: Effects of acute insulin-induced hypoglycemia on cerebral microvascular function

Authors: *W. R. EVANS[1,2], J. A. SPERLING[1], V. N. SURE[1], S. S. SAKAMURI[1], P. SPENCER[1], R. MOSTANY[1,2], D. W. BUSIJA[1,2], P. V. G. KATAKAM[1,2]
[1]Pharmacol., Tulane Univ. Sch. of Med., New Orleans, LA; [2]Tulane Brain Inst., Tulane Univ., New Orleans, LA

Abstract: Objective. Hypoglycemia (HG) is a dreaded side effect of insulin therapy and is directly related to increased morbidity of stroke in patients with diabetes (DM). In addition, HG has been shown to aggravate the already compromised cerebral vasculature due to DM. Our objective is to determine the effect of acute HG on the cerebral microvasculature of healthy mice.
Methods. C57Bl/6 mice (male and female) were surgically prepared for in vivo two-photon laser scanning microscopy (2PLSM) by implanting a glass sealed craniotomy over the somatosensory

cortex. A custom titanium bar was incorporated into the acrylic for head-fixing during imaging under isoflurane anesthesia. Cerebral vasculature was visualized by injecting FITC-dextran 40 kDa i.v. and the fluoroprobe was excited with a tunable Ti:sapphire laser set to 910 nm. HG was induced by 0.8-1 U/kg Humulin-R i.p. to achieve a drop of blood glucose from 198 ± 17 mg/dL to 66 ± 8 mg/dL by 45 minutes (n=5 animals; $p<0.05$). Mice were held in HG for additional 45 min-hr during 2PLSM imaging sessions. In addition, cerebral microvessels (40-300 microns in length) were isolated by filtration and gradient separation from homogenates of saline perfused brains of mice with and without HG exposure and oxygen consumption rates (OCR) of microvessels *ex vivo* were determined by Agilent Seahorse XFe Analyzer using mito stress test kit.

Results. Acute HG did not change the blood-brain barrier permeability. However, increased red blood cell (RBC) velocity and increased RBC traffic in cerebral microvessels under HG with increased number of cells/second (149 ± 7 before and 170 ± 7 after HG, $p < 0.05$, N = 5 animals, n = 57 micro-vessels). Similarly, microvascular diameter was increased under acute HG (3.36 ± 0.07 microns before and 3.73 ± 0.08 microns after HG, $p< 0.05$, N = 5 animals, n = 57 micro-vessels). OCRs (pmol/min/mg protein) determined in microvessels showed that HG reduced the maximal respiration (2380 ± 200 untreated versus 1790 ± 80 in HG; $p<0.026$) and reserve respiratory capacity (590 ± 60 untreated versus 380 ± 30 in HG; $p<0.016$) although basal and ATP-linked respiration leak remained unaffected (n=5 mice each group and 6-8 wells per group).

Conclusions. Thus, HG leads to increased microvascular dilation and blood flow accompanied by diminished mitochondrial reserve respiratory capacity. We conclude that HG-induced cerebral microvascular vasodilation may be mediated by altered mitochondrial function.

Disclosures: W.R. Evans: None. **J.A. Sperling:** None. **V.N. Sure:** None. **S.S. Sakamuri:** None. **P. Spencer:** None. **R. Mostany:** None. **D.W. Busija:** None. **P.V.G. Katakam:** None.

Nanosymposium

716. Brain Injury: From Animal Models to Physiology, Behavior, and Treatments

Location: SDCC 4

Time: Wednesday, November 7, 2018, 1:00 PM - 4:00 PM

Presentation Number: 716.10

Topic: C.10. Brain Injury and Trauma

Support: DoD CDMRP grant W81XWH-15-1-0284
DoD CDMRP grant W81XWH-13-1-0284

Title: Augmenting M-current as a treatment for traumatic brain injury

Authors: *F. A. VIGIL, E. BOZDEMIR, V. BUGAY, L. ESPINOZA, R. J. VERAZA, S. H. CHUN, D. M. HOLSTEIN, I. SANCHEZ, M. HOBBS, J. D. LECHLEITER, R. BRENNER, M. S. SHAPIRO
Univ. of Texas Hlth. San Antonio, San Antonio, TX

Abstract: Traumatic brain injury (TBI) is a risk factor for the development of epilepsy. TBI can trigger the development of post-traumatic seizures due to increase in neuronal excitability. TBI-induced hyperexcitability leads to energy depletion and cellular death. As a result, inflammatory response intensifies leading to more cell death and worst outcome for the patient. We will present data that supports the hypothesis that reducing neuronal excitability by augmenting M-current before the process of epileptogenesis commences, moderates or prevents deleterious effects that follow TBI. Using a model of blunt TBI, we pharmacologically enhanced currents from M-type K+ channels, which play a dominant role in limiting neuronal excitability, injecting one dose (i.p. 1mg/kg) of the anti-convulsant drug, Retigabine (RTG), 30 min after injury. We then studied TBI-induced seizures and abnormal cortical activity (video/EEG recording), metabolic stress (lactate/pyruvate ratio), cell death (IVIS), blood-brain barrier increase permeability (IVIS) and immunologic response (immunoblotting and immunohistochemistry). We also tested the effects of TBI and RTG treatment in the expression of different isoforms of M-type channels (qRT-PCR). Experimenters were blind to animal/sample treatment. After TBI, 5 out of 15 vehicle only-treated mice displayed post-traumatic seizures, whereas no animal treated with RTG (n=10) had seizures. Additionally, when the same animals were challenged with pilocarpine (3X, 75 mg/kg) RTG treatment significantly reduced the occurrence of cortical epileptiform abnormal spike activities. RTG treatment also decreased TBI-induced rise in cortical lactate/pyruvate ratio (n=5-6 per group), a marker for energy depletion. We also observed that RTG treatment significantly reduced cell death in the cortex of TBI subjected animals (n=6-7 per group). Finally, RTG treatment also reduced TBI-induced inflammation (n=10-17 per group), increase in blood-brain barrier permeability (n=5-6 per group), and the activation of cell death pathways (n=13-17 per group). RTG treatment combined with TBI induced an increase in cortical KCNQ2, but not KCNQ3, mRNA levels (n=7-9 per group). Together these results support that KCNQ/M channel-activating drugs may serve as a novel therapeutic avenue for TBI. We will also present preliminary experiments with in vivo two-photon imaging of Ca+ and glutamate. These experiments show the occurrence of TBI-induced neuronal hyperexcitability and that M-current augmentation with new, more potent and specific drug reduced the TBI-induced excitability, in our model. This work is supported by DoD grants W81XWH-13/15-1-0284.

Disclosures: F.A. Vigil: None. **E. Bozdemir:** None. **V. Bugay:** None. **L. Espinoza:** None. **R.J. Veraza:** None. **S.H. Chun:** None. **D.M. Holstein:** None. **I. Sanchez:** None. **M. Hobbs:** None. **J.D. Lechleiter:** None. **R. Brenner:** None. **M.S. Shapiro:** None.

Nanosymposium

716. Brain Injury: From Animal Models to Physiology, Behavior, and Treatments

Location: SDCC 4

Time: Wednesday, November 7, 2018, 1:00 PM - 4:00 PM

Presentation Number: 716.11

Topic: C.10. Brain Injury and Trauma

Support: NIH/NIA Grant RO1 AG054025
NIH/NIDS Grant RO1 NS094557

Title: Soluble tau strains after TBI ?

Authors: *A. BITTAR, T. F. HASAN, N. BHATT, R. AL LAHHAM, S. A. MCALLEN, A. ELLSWORTH, M. CARRETERO-MURILLO, R. KAYED
Neurol., UTMB, Galveston, TX

Abstract: It is unknown what underlies the development of different neurodegenerative pathologies after TBI. Since TBI induced pathology (CTE) is majorly a tauopathy, toxic forms of tau most likely play a role in the development of post-TBI pathology and the related late-life dementias. TBI-induced tau aggregates include phosphorylated-tau, soluble and insoluble oligomeric aggregates. Knowing that soluble tau oligomers are the most toxic species of tau aggregates, it becomes crucial to characterize the toxicity, strain like characteristics, and propagation of soluble tau aggregates from different TBI(s). *In-vitro* Biochemical and biophysical analyses show that soluble oligomeric tau oligomers derived from mouse brains exposed to different TBI paradigms represent distinct strains with different morphology, and cytotoxicity potentials using established methods. In addition, we recently showed that TBI-brain derived tau can propagate *in-vivo*. Therefore, we evaluated the effects of the soluble tau aggregates on LTP impairment (brain slice preparation) as well as on mouse behavior (novel object recognition, rotarod, and open field*)* using wild type and htau mice. TBI brain-derived oligomeric aggregates were isolated from 1) SB-24Hr sacrificed at 24 hours after a 50 psi single blast treatment, 2) SB-3W sacrificed at 3 weeks after a 50 psi single blast treatment, 3) RB-24Hr sacrificed at 24 hours after repeated blast treatment (6 blasts over two weeks), 4) SHAM sacrificed at 24 hours following sham TBI. For electrophysiological analyses, acute brain slices from C57/B6 mice were incubated for 1 hour with one of the four TBI brain-derived tau oligomers (50 nM). The same samples were also injected bilaterally via ICV route in 6 months old wild type mice (C57/B6) (1 µl both sides), and behavior was tested at 2 weeks and 2 months after treatment. The different TBI brain-derived tau oligomers showed differential LTP impairment, primary neuronal toxicity profiles and internalization. To our knowledge, this is the first evidence that soluble tau oligomers derived from different TBI(s) form distinct strains which might be relevant to the different tauopathies. Well-characterized disease-relevant strains in TBI will lay the foundation for determining the most toxic and important strains for the development of CTE and TBI-induced late-life neurodegenerative diseases, thereby allowing for the creation of novel diagnostic and therapeutic strategies specifically tailored against the most toxic tau oligomeric strains.

Disclosures: A. Bittar: None. **T.F. Hasan:** None. **N. Bhatt:** None. **R. Al Lahham:** None. **S.A. McAllen:** None. **A. Ellsworth:** None. **M. Carretero-Murillo:** None. **R. Kayed:** None.

Nanosymposium

716. Brain Injury: From Animal Models to Physiology, Behavior, and Treatments

Location: SDCC 4

Time: Wednesday, November 7, 2018, 1:00 PM - 4:00 PM

Presentation Number: 716.12

Topic: C.10. Brain Injury and Trauma

Support: Special Coordination Funds for Promoting Science and Technology from the MEXT the Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) from AMED

Title: CRMP2-binding compound accelerates motor function recovery after cortical damage

Authors: *S. JITSUKI[1,2], H. ABE[2], W. NAKAJIMA[2], H. MASUYAMA[3], T. OKUDA[3], T. TAKAHASHI[2]
[2]Physiol., [1]Yokohama City Univ. Grad. Sch. of Med., Yokohama, Japan; [3]Pharmacol. reseach, Toyama Chem. Co., Ltd., Toyama, Japan

Abstract: Brain damage mainly caused by stroke is a severe neurological condition, which may lead to paralysis and compromise work capacity and self-care. No pharmacological intervention that could foster recovery and complement current rehabilitation has yet been established as effective. Restoration of motor impairment after brain damage is considered to be the result of compensative neural plasticity in intact brain regions, mediated by the reorganization of cortical motor maps. Experience-dependent synaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic-acid) receptor (AMPAR) delivery underlies behaviors that require neural plasticity such as learning. We found that a small compound, edonerpic-maleate (also known as T-817MA), facilitated experience-driven synaptic glutamate AMPA receptor delivery and resulted in the acceleration of motor function recovery after motor cortex cryoinjury in mice in a training-dependent manner through cortical reorganization. Edonerpic bound to collapsin-response-mediator-protein 2 (CRMP2), a downstream molecule of semaphorin, and is thought to be related to synaptic plasticity and learning. Edonerpic failed to facilitate experience-driven synaptic glutamate AMPA receptor delivery and augment recovery in CRMP2-deficient mice. Thus, edonerpic-maleate, a neural plasticity enhancer, could be a clinically potent small compound to accelerate rehabilitation after brain damage.

Disclosures: **S. Jitsuki:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Toyama Chemical Co., Ltd.. **H. Abe:** None. **W. Nakajima:** None. **H. Masuyama:** None. **T. Okuda:** None. **T. Takahashi:** None.

Nanosymposium

717. Pain Imaging and Perception

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 717.01

Topic: D.03. Somatosensation: Pain

Support: NIDCR 5R01DE022746-02

Title: Corticostriatal plasticity in the transition to chronic pain: Effects of levodopa

Authors: *D. RECKZIEGEL[1,2], M. GHANTOUS[2], T. ABDULLAH[2], R. JABAKHANJI[2], T. J. SCHNITZER[2], A. APKARIAN[2]
[1]Physiol., [2]Northwestern Univ., Chicago, IL

Abstract: Learning mechanisms give rise to the transition from acute to chronic pain and render the pain to become more emotional. Here we aim to further explore the idea that persistent pain, following an inciting injury, leads to an aversive learning signal that reorganizes the brain into a chronic pain state. By blocking the emotional/motivational learning response triggered by peripheral nerve injury in a critical time window, we expect to reduce the chances of transition from sub-acute to chronic pain. In an animal model of neuropathic pain, we previously showed that a combination of dopamine and Naproxen blocked the transition to persistent pain. Here, we test this in humans and hypothesize that early treatment with Carbidopa-Levodopa plus Naproxen in individuals with sub-acute back pain (SBP) will decrease related reorganization and block transition to chronic back pain.
Six month, double-blind, randomized, placebo plus Naproxen-controlled, three-arm, trial of the pharmacological treatment Carbidopa-Levodopa plus Naproxen for individuals with SBP. 125 individuals with sub-acute low back pain were screened and had baseline assessments including MRI brain scans and pain and psychological questionnaires. Participants were classified between high and low risk of developing chronic pain, based on their baseline brain scan. Those at high risk were randomized to receive 12 weeks of either active or control treatment, whereas those at low risk were simply observed and did not receive treatment. A flexible dose scheme was used, starting at 12.5mg-50mg Carbidopa-Levodopa TID, which, depending on the percentage change in pain intensity from baseline at week 4 and 8, could be titrated up first to 25mg-100mg and later to 50mg-200mg. Naproxen dose was 250mg TID. The criteria for recovery was 20% or more reduction in pain intensity from baseline to 6 months. Fischer's exact test at p<0.1 was set a priori to be considered significant. Sixty participants completed study participation, with 22 on the study medication arm, 28 on the control drug arm and 10 being observational only. Around 75% of the entire population receiving treatment were classified as “recovered” at 6 months. Treatment with Carbidopa-Levodopa plus Naproxen did not yield superior recovery rates than the control combination drug.

Our preliminary findings indicate that treatment combination of dopamine plus Naproxen was not superior to the combination of placebo plus Naproxen in blocking the transition from sub-acute to persistent pain. The differential effects of treatment on brain reorganization and the circuitry changes that occur with the change in pain condition are currently under investigation.

Disclosures: D. Reckziegel: None. **M. Ghantous:** None. **T. Abdullah:** None. **R. Jabakhanji:** None. **T.J. Schnitzer:** None. **A. Apkarian:** None.

Nanosymposium

717. Pain Imaging and Perception

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 717.02

Topic: D.03. Somatosensation: Pain

Support: IBS-R015-D1

Title: An fMRI signature of tonic pain based on whole-brain functional connectivity

Authors: *J.-J. LEE[1], H.-J. KIM[1], M. CEKO[2], B.-Y. PARK[1], M. ROY[3], T. D. WAGER[4], C.-W. WOO[1]
[1]Ctr. For Neurosci. Imaging Res. (CNIR), Inst. For Basic Sci., Suwon, Korea, Republic of; [2]ICS, Boulder, CO; [3]Dept. of Psychology, McGill Univ., Montreal, QC, Canada; [4]Psychology and Neurosci., Univ. of Colorado Boulder Dept. of Psychology and Neurosci., Boulder, CO

Abstract: Recent advances in functional neuroimaging, such as functional magnetic resonance imaging (fMRI), has opened up a unique opportunity to measure pain objectively based on brain features without relying on self-report. However, the brain-based marker development efforts have been limited to modeling acute pain with fMRI activation patterns, though their potential for clinical translation is unclear. Here we developed an fMRI signature of tonic pain using machine learning approach to identify multivariate functional connectivity patterns sensitive and specific to tonic pain intensity. The signature showed high sensitivity in predicting within-individual tonic pain ratings (r = 0.47 - 0.64) across three different studies involving a total of 110 participants (Studies 1-3). In addition, the signature demonstrated high specificity in discriminating tonic pain from other aversive conditions including bitter taste and aversive odor (accuracy = 76 - 90%). Furthermore, the tonic pain signature explained between-patients variability of pain scores and predicted placebo-induced analgesia in three clinical pain studies (Studies 4-6, N = 185). This study provides a promising brain-based biomarker for tonic pain that holds high potential for clinical translation.

Disclosures: J. Lee: None. **H. Kim:** None. **M. Ceko:** None. **B. Park:** None. **M. Roy:** None. **T.D. Wager:** None. **C. Woo:** None.

Nanosymposium

717. Pain Imaging and Perception

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 717.03

Topic: D.03. Somatosensation: Pain

Support: NIH Grant 5 R01 DA035484-03
NIH Grant 5 R01 MH076136-10

Title: Brain representation of nociception is local while pain experience is distributed

Authors: *B. PETRE[1], L. Y. ATLAS[3], S. GEUTER[4], L. KOBAN[1], A. KRISHNAN[2], M. LÓPEZ-SOLÀ[5], M. ROY[6], C.-W. WOO[1], T. D. WAGER[7]
[2]Inst. of Cognitive Sci., [1]Univ. of Colorado Boulder, Boulder, CO; [3]NIH (NCCIH, NIDA), Bethesda, MD; [4]Johns Hopkins Univ., Baltimore, MD; [5]Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [6]Dept. of Psychology, McGill Univ., Montreal, QC, Canada; [7]Psychology and Neurosci., Univ. of Colorado Boulder Dept. of Psychology and Neurosci., Boulder, CO

Abstract: Multivoxel pattern analyses (MVPA) of fMRI data can provide information about the brain representations underlying perception, affect, and more. In pain, MVPA-derived biomarkers capture pain-predictive brain information that is both stimulus-dependent and stimulus-independent. There are reasons to believe that the neural codes for these are in fact distinct: Nociception is a bottom-up sensory response processed in local centers, whereas pain is a context-dependent, conscious experience. Like other forms of conscious experience, it may depend on integrated activity across systems. Representational architectures are hypothesized to reflect this distinction.
Here, we investigate these architectures in 217 healthy subjects across 7 previously published studies. These studies combine acute noxious thermal stimulation with a variety of expectation and contextual pain manipulations. First, we identify stimulus-dependent and -independent pain representation patterns using a novel hierarchical MVPA method optimized for multi-study fMRI biomarker development. These whole brain signatures were trained on 12180 trial-level images. They are divisible into 186 discrete cortical and subcortical regions, each with their own unique local stimulus-dependent and stimulus-independent pain-related signals. The overall composite predictive maps are reconstructed through an optimal reweighting of these regions using Bayesian regression. Two regression models with different priors are used to formalize the concepts of distributed vs. local pain representation, yielding distributed or sparse models, respectively. Estimates of generalization performance are obtained using between-study cross-validation.
The results show that stimulus-dependent pain representation is preferentially localized to a handful of brain areas largely circumscribed by regions targeted by nociceptive afferents (and

included in the canonical “pain matrix”). A composite of local representations predicted 49% of the variance in stimulus intensity dependent pain ratings, 23% more of the variance than did distributed patterns, (range across 5 hold out studies: [-15%, 43%] more). A composite of distributed representations predicted 4% of the trial-by-trial variance in stimulus independent pain (residuals of pain report after removing stimulus related variance), 2.4% more than local composites (range: [-2.5%, 15%]). Thus, stimulus response is localized while stimulus-independent pain representation is distributed. This topological contrast provides a lens through which to understand pain as both a sensory response and unified conscious experience.

Disclosures: B. Petre: None. **L.Y. Atlas:** None. **S. Geuter:** None. **L. Koban:** None. **A. Krishnan:** None. **M. López-Solà:** None. **M. Roy:** None. **C. Woo:** None. **T.D. Wager:** None.

Nanosymposium

717. Pain Imaging and Perception

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 717.04

Topic: D.03. Somatosensation: Pain

Support: SFB936/A06
ERC-2010-AdG_20100407

Title: Opioid analgesia in the human central pain system

Authors: *A. TINNERMANN[1], C. SPRENGER[2], C. BÜCHEL[1]
[1]Dept. of Systems Neurosci., Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany; [2]Dept. of Engin., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Background and aims Remifentanil is a strong opioid agonist that exerts its analgesic action through opioid receptors in the central nervous pain system. To assess opioid effects in the entire central pain system, we investigated BOLD responses related to opioid-mediated analgesia from the spinal cord to the brain. Furthermore, we investigated if expectations modulate the analgesic effect of remifentanil. **Methods** Eighty-five healthy, male volunteers participated in the heat pain experiment that were randomly assigned to one of three experimental groups. One group received the opioid agonist remifentanil in an open-label manner (N = 28) whereas the other two groups received either saline solution (N = 28) or remifentanil (N = 29) in a blind manner. An anesthesiologist administered the remifentanil intravenously for approximately 30 minutes at a dose of 0.05 µg/kg/min. To assess neural correlates of opioid analgesia in the entire central pain system, BOLD responses were simultaneously recorded in the brain and spinal cord using a newly established combined cortico-spinal functional MRI method. The MRI experiment comprised a baseline and an infusion phase. Both phases included 32 heat pain stimuli with a duration of 15 seconds that

were applied on the left volar forearm using a thermode. Individual pain ratings were assessed after every heat stimulus and some trials included an additional online rating scale where participants rated painfulness during the entire heat stimulus. **Results** Pain ratings in both remifentanil groups were significantly reduced compared to the saline group ($t = 5.9$, $p < 0.001$). However, pain reduction in the open-label and blind remifentanil group did not differ significantly. Activation in pain-processing areas such as the insula and secondary somatosensory cortex (SII) was reduced whereas activity in the medial prefrontal cortex and hippocampus was increased under opioid analgesia. Individual analgesia ratings correlated positively with activity in the insula, thalamus, SII and periaqueductal gray whereas analgesia ratings correlated negatively with activity in the medial prefrontal cortex. Activity in the medial prefrontal cortex and insula furthermore mediated analgesia ratings between the three experimental groups. Moreover, dynamic analgesia ratings correlated with Neurological Pain Signature (NPS) responses. **Conclusions** The opioid remifentanil reduces brain activity in pain-processing areas. Furthermore, BOLD and NPS responses correlate with individual pain ratings.

Disclosures: A. Tinnermann: None. **C. Sprenger:** None. **C. Büchel:** None.

Nanosymposium

717. Pain Imaging and Perception

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 717.05

Topic: D.03. Somatosensation: Pain

Support: NCCIH Grant 5P01AT006663-03

Title: Reduced hyperalgesia and increased dorsolateral prefrontal cortex response following acupuncture is associated with analgesia in low back pain

Authors: K. ISENBURG[1], I. A. MAWLA[2], J. LEE[1], J. GERBER[1], J. KIM[3], H. KIM[3], S.-T. CHAN[1], R. GOLLUB[1], J. KONG[1], B. ROSEN[1], *V. NAPADOW[1]
[1]Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp., Charlestown, MA; [2]Neurosci. Grad. Program, Univ. of Michigan Med. Sch., Ann Arbor, MI; [3]Div. of Clin. Res., Korea Inst. of Oriental Med., Yuseong-gu, Korea, Republic of

Abstract: Chronic low back pain (cLBP) has been associated with aberrant brain processing and hyperalgesia. Several non-pharmacological therapies have shown promise for cLBP, including acupuncture. However, the brain-based mechanisms supporting reduced hyperalgesia and clinical outcomes are unknown. We conducted a longitudinal neuroimaging study with brain response to evoked pressure pain before and after treatment with real versus non-insertive needle and non-needle forms of sham acupuncture. We enrolled 33 healthy controls (HC) and 63 cLBP patients (33 male, 40.3 ± 11.7 (M ± SD) years), with the latter randomized to four treatment arms

(verum, sham non-penetrating Streitberger needles, mock-laser, and usual care control). Patients received six treatments over 4 weeks with LBP intensity ratings (0-100, NRS) collected prior and after each treatment. At baseline and post-intervention, brain response to evoked leg cuff pain (calibrated to 40/100) was assessed with BOLD functional Magnetic Resonance Imaging (fMRI) at 3T. Post-therapy assessment used the same pressure as baseline. Correlation analyses linked mean changes in clinical LBP intensity with 1) post-intervention changes in brain response to cuff pain and 2) baseline pain catastrophizing (PCS) score. Compared to HC, cLBP patients reported 40/100 pain at lower cuff pressures ($p<0.05$), suggesting hyperalgesia. A 3 (GROUP) x 6 (TIME) repeated measures ANOVA found a significant GROUP effect for within-session reduction in LBP ($p<0.005$), and post-hoc testing found reduced LBP only for verum acupuncture. For verum acupuncture, baseline PCS predicted within-session LBP change (i.e. higher PCS was associated with less pronounced clinical pain reduction, $p=0.01$). Moreover, within-session change in LBP was correlated with post-intervention change in cuff pain ratings for verum acupuncture only ($r=0.55$, $p = 0.02$), and with increased pain-evoked activation in right dorsolateral Prefrontal Cortex (dlPFC, $p._{corrected}<0.05$). Thus, cLBP patients treated by verum acupuncture showed greater within-session LBP improvement, which was linked with 1) reduced hyperalgesia and 2) increased pain-evoked activation in the dlPFC, a brain region previously implicated in inhibitory control of nociceptive information. Individuals with chronic pain have shown compromised dlPFC structure and/or function and acupuncture may facilitate greater cortical anti-nociceptive modulation, leading to reduced hyperalgesia and clinical pain.

Disclosures: K. Isenburg: None. **I.A. Mawla:** None. **J. Lee:** None. **J. Gerber:** None. **J. Kim:** None. **H. Kim:** None. **S. Chan:** None. **R. Gollub:** None. **J. Kong:** None. **B. Rosen:** None. **V. Napadow:** None.

Nanosymposium

717. Pain Imaging and Perception

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 717.06

Topic: D.03. Somatosensation: Pain

Support: NIH-NCCIH grant R61-AT009306
Norwegian Research Council /Marie Sklodowska-Curie Actions (FRICON/COFUND-240553/F20)
Korea Institute of Oriental Medicine (KIOM)

Title: Brain concordance between patients and clinicians underpins non-verbal communication, positive affect, and treatment analgesia - a fMRI hyperscanning study

Authors: *D.-M. ELLINGSEN[1,2], K. ISENBURG[1], C. JUNG[1,3], J. LEE[1], J. GERBER[1], I. A. MAWLA[4], R. SCLOCCO[1], R. R. EDWARDS[5], J. KELLEY[6], I. KIRSCH[7], V. NAPADOW[1]

[1]Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hospital, Harvard Med. Sc, Charlestown, MA; [2]Dept. of Psychology, Univ. of Oslo, Oslo, Norway; [3]KM Fundamental Res. Div., Korea Inst. of Oriental Med., Daejeon, Korea, Republic of; [4]Neurosci. Grad. Program, Univ. of Michigan Med. Sch., Ann Arbor, MI; [5]Brigham and Women's Hosp., Boston, MA; [6]Endicott Col., Beverely, MA; [7]Harvard Med. Sch., Boston, MA

Abstract: Patient-clinician interactions can shape patients' clinical outcomes such as pain relief, but the underlying brain mechanisms are unknown. We used functional Magnetic Resonance Imaging (fMRI) to simultaneously record brain activity in patient-clinician dyads who interacted via video transfer, during clinician-initiated treatment of patients' pain. We hypothesized that spatiotemporal concordance in activation of social mirroring circuitry, i.e. ventrolateral prefrontal cortex (vlPFC), anterior Insula (aINS), and temporoparietal junction (TPJ) during pain treatment underpins placebo analgesia and non-verbal communication. We enrolled patients with chronic pain (fibromyalgia) and clinicians (acupuncturists). Each patient was matched with a clinician participant (n=32 dyads). During block-design fMRI using multiband BOLD at both 3T scanners, patients received 12 moderately painful cuff pressures to the left leg (15 s), while the clinician used a button box to control (real/sham, double-blind) electro-acupuncture stimulation (EA) to reduce cuff pain. Participants rated self-pain (patients) or vicarious pain of the patient (clinicians) after each stimulus block. Patients' pain was significantly decreased during both real and sham EA treatment compared to overt no-treatment (cuff pressure was identical for all stimulus blocks). Clinicians rated vicarious pain as decreased with treatment, relative to no treatment. Moreover, patients' placebo analgesia (i.e. no-treat - treat) correlated with clinicians' perceived efficacy (no-treat - treat). A conjunction analysis of patients' (evoked pain+treatment) and clinicians (observing pain+treating) brain response demonstrated activation of vlPFC, aINS, and TPJ, for both patients and clinicians. Using TPJ ROI extraction of trial-by-trial fMRI response, we found that patient-clinician concordance (r-to-z transformed trial-by-trial correlations between patients and clinicians) correlated with higher patient-reported in-scanner measures of therapeutic alliance 'frequency of eye contact', 'comfort of seeing the acupuncturist', and stronger patient-rated placebo analgesia. TPJ activity is central in empathic concern and social mirroring, and brain-to-brain coupling of TPJ activity between patients and clinicians may support psychosocially facilitated analgesia.

Disclosures: D. Ellingsen: None. **K. Isenburg:** None. **C. Jung:** None. **J. Lee:** None. **J. Gerber:** None. **I.A. Mawla:** None. **R. Sclocco:** None. **R.R. Edwards:** None. **J. Kelley:** None. **I. Kirsch:** None. **V. Napadow:** None.

Nanosymposium

717. Pain Imaging and Perception

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 717.07

Topic: D.03. Somatosensation: Pain

Support: NCCIH (R01-AT007987)
NINDS (NS035115)

Title: Hippocampal shape as a potential biomarker for sex dimorphism in chronic pain

Authors: *T. B. ABDULLAH[1], D. RECKZIEGEL[2], E. VACHON-PRESSEAU[3], L. HUANG[4], T. SCHNITZER[5], A. APKARIAN[3]
[1]Physiol., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [2]Physiol., [4]Phyisology, [5]Physcial Med. and Rehabil., [3]Northwestern University, Feinberg Sch. of Med., Chicago, IL

Abstract: Aim of Investigation: It is well-established that sex differences exist in the prevalence and severity of chronic pain conditions. However, potential neural circuits mediating this effect remain largely unknown. One important region critically involved in the predisposition to, and presenting abnormalities in, chronic pain is the hippocampus. Given its hormone-dependent functions and its known sex-specific responses to stress, the hippocampus was examined as a potential marker for sex dimorphism in chronic pain. Given the complex formation of the region, we hypothesize that measurements of hippocampal shape would be indicative of neurological sex dimorphism in chronic pain, as these may reveal subtle changes in structure at the sub-regional level. **Methods:** Data included in the analyses were from 275 patients in two clinical trials with populations differing primarily in duration of back pain: 108 participants with subacute lower back pain, and 167 chronic lower back pain patients (CBP, having pain for at least 6 months). Data from each study were analyzed independently. High-resolution T1-weighted brain images (Siemens, 3T) were subjected to subcortical segmentation using *FMRIB's integrate registration and segmentation tool* (FSL FIRST). The segmentations were checked for accuracy before extracting the right and left hippocampal meshes for each subject. These were next projected onto a group average surface mask to calculate the displacement values for each of the vertices of the mesh, for each subject. FSL's *randomise* tool for nonparametric permutation inference was used to test for differences between sexes in each group, with threshold-free cluster enhancement (TFCE) at a family-wise error rate of $P \leq 0.05$ considered significant.**Results:** In the CBP group, vertex-wise representations revealed significant differences between males and females in the right hippocampus, traversing along the longitudinal axis. More specifically, CBP females displayed right hippocampal extraversion throughout the extent of anterior and posterior hippocampus (CBP_male= -0.25 +/- 0.095; CBP_female =0.268 +/- 0.068; T-stat = -4.38, $p<.0001$). No significant effect was observed on either left or right hippocampal shape in the SBP group.**Conclusions**: Here we present sex-dependent hippocampal morphological differences in lower back pain populations that display similar levels of pain intensity, but differ in their duration-based classification (chronic, subacute). Given that SBP did not exhibit sex-dependent hippocampal distortions, these results indicate that the observed shape distortions in CBP may be sex-specific consequences of living with chronic pain.

Disclosures: T.B. Abdullah: None. **D. Reckziegel:** None. **E. Vachon-Presseau:** None. **L. Huang:** None. **T. Schnitzer:** None. **A. Apkarian:** None.

Nanosymposium

717. Pain Imaging and Perception

Location: SDCC 30E

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 717.08

Topic: D.03. Somatosensation: Pain

Support: Wellcome Trust (COLL JLARAXR)
European Research Council (Consolidator Grant PAINSTRAT)

Title: Slow neural oscillation tracks dynamic nociceptive input and correlates with individual pain perception

Authors: *Y. GUO[1], R. J. BUFACCHI[1], M. MOAYEDI[2], G. IANNETTI[1]
[1]Dept. of Neuroscience, Physiol. and Pharmacol., Univ. Col. London, London, United Kingdom; [2]Fac. of Dent., Univ. of Toronto, Toronto, ON, Canada

Abstract: The brain responses elicited by fast-rising transient nociceptive stimuli causing pain are widely recorded. They are composed by a mixture of neural activities encoding specific features of the peripheral nociceptive input, as well as non-specific neural activities encoding stimulus saliency. Since the saliency-related component dominates, the usefulness of fast-rising stimuli in understanding the brain processing of nociceptive input is limited. Therefore, the use of extremely slow-rising nociceptive stimuli causing pain holds promise to identify more pain-specific neural activities. In this study we delivered both nociceptive and auditory stimuli at 0.1 Hz during simultaneous recording of 128-channel EEG. To control for the confound of ratings, participants either did or did not rate the perceived stimulus intensity on a visual analogues scale. Our results demonstrate that the human brain builds a dynamic representation of the rhythmic structure of continuous nociceptive input through both frequency and phase modulation of slow neural oscillation. The entrained slow oscillation closely correlated with interindividual variability in ongoing painful percept. Although cortical oscillations could entrain to the slow rhythm in nociception, they showed no similar effect when the same rhythm was presented in audition, exhibiting modality difference for the entrainment to external dynamics at this long-time scale. We propose that the entrained slow oscillation may function as an internal reference frame that provides the potential for predictive modulation of neural processing of time-varying nociceptive inputs.

Disclosures: Y. Guo: None. **R.J. Bufacchi:** None. **M. Moayedi:** None. **G. Iannetti:** None.

Nanosymposium

718. Vestibular Systems: VOR, Locomotion, and Gaze

Location: SDCC 2

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 718.01

Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant P20 GM103650

Title: Visual-vestibular conflict detection is better during active than passive head movement

Authors: *P. R. MACNEILAGE[1], M. MOROZ[1], I. GARZORZ[3], E. FOLMER[2]
[1]Psychology, Cognitive and Brain Sciences, Neurosci., [2]Computer Sci., Univ. of Nevada, Reno, Reno, NV; [3]Grad. Sch. of Systemic Neurosci., Ludwig-Maximilian Univ. of Munich, Munich, Germany

Abstract: Head movement relative to the visible earth-fixed environment gives rise to congruent vestibular and visual optic flow signals. The resulting percept of a stationary, earth-fixed visual environment depends on mechanisms that compare visual and vestibular signals to evaluate their congruence. Here we investigate the efficiency of these comparison mechanisms during active and passive head movement by modifying the gain on visual motion relative to head movement on individual trials and asking subjects to report whether the gain was too low or too high. Low and high gains result in percepts of the environment moving with or against head movement, respectively. Fitting a psychometric function to the resulting data yields the range of gains that are compatible with perception of a stationary visual environment, referred to by Wallach as the Range of Immobility. Experiments were conducted using a head-mounted display capable of rendering visual scene motion contingent on head motion with virtually zero latency. Human subjects were run in conditions in which they completed active head rotations of ~15 degs and also in conditions where identical head movement trajectories were presented passively while subjects were seated on a rotating chair with their heads fixed relative to their bodies. In addition, performance was compared between conditions in which subjects fixated either a head-fixed or scene-fixed fixation point. Performance was better during active than passive head movement, likely due to increased precision on the head movement estimate arising from motor prediction and neck proprioception. Performance was also better during scene-fixed than head-fixed fixation, perhaps due to decreased velocity of retinal image motion and increased precision on the estimate of retinal image motion under these conditions.

Disclosures: P.R. MacNeilage: None. **M. Moroz:** None. **I. Garzorz:** None. **E. Folmer:** None.

Nanosymposium

718. Vestibular Systems: VOR, Locomotion, and Gaze

Location: SDCC 2

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 718.02

Topic: D.06. Auditory & Vestibular Systems

Support: NSERC Discovery Grant (Canada)

Title: Traditional analysis of VOR nystagmus results in weak diagnostic features

Authors: *H. GALIANA[1], H. L. SMITH[2]
[1]Mcgill Univ. Fac Med., Montreal, QC, Canada; [2]OTL-ENT/Royal Victoria Hosp., McGill Univ. Hlth. Centers, Montreal, QC, Canada

Abstract: Traditional approaches to the analysis of ocular nystagmus focus on the slow phases of reflex nystagmus to find a slow-phase (SP) 'envelope' of eye velocity during the vestibulo-ocular reflex (VOR), optokinetic nystagmus (OKN), or target pursuit (TP) velocity. Here we focus on the VOR to illustrate the issues. For example: To characterize the VOR, nystagmus velocity is computed, and a fit is produced through all *slow-phase segments* (ignoring fast phases) to parameterize the dynamics (gain/phase or gain/time constant) of the VOR response during step or harmonic passive head rotation. These approaches are only valid if the assumption of a perfect 'neural integrator' (NI) in the ocular motoneural pathway (D.A. Robinson) is satisfied. With small NI time constants (<3s), the envelope metrics are very labile and fast-phases affect the slow-phase time profile. Envelope decay during constant head rotation could range from 30s to 4s time constants, just by changing the alertness level of a test subject, and with it, the fast phase frequency and end-points. We recommend instead that slow-phase velocities be examined in the context of their local data (initial conditions, head velocity) to extract robust VOR dynamics despite variations in fast phases. Examples will be provided from simulated and experimental data. This approach is robust and repeatable, unless the reflex itself has changed its slow phase dynamics with context (FP rate, vestibular NL, range of head velocity). In this case, a single non-linear model of the VOR would describe the reflex well regardless of FP rate. As a result, a more accurate set of norms for any ocular reflex will need to be determined from ensembles of control and patient responses supporting clinical diagnosis by attending physicians. These norms will not necessarily match the current norms from envelopes, but separation of healthy from deficient responses should be much clearer over a large population. The same arguments against envelope methods apply to all ocular nystagmus responses (VOR, OKN, pursuit), and to any movement trajectory that imbeds two modes of dynamics during tracking (head, hand reaching⋯).

Disclosures: H. Galiana: None. **H.L. Smith:** None.

Nanosymposium

718. Vestibular Systems: VOR, Locomotion, and Gaze

Location: SDCC 2

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 718.03

Topic: D.06. Auditory & Vestibular Systems

Support: NIH N01-DC-6-005,
NIH R01 DC014002-01,
NIH RR00166

Title: Control of gaze shifts evaluated with a vestibular prosthesis

Authors: *J. O. PHILLIPS[1], E. CHUNG[2], L. LING[1], A. NOWACK[1], K. NIE[3], J. RUBINSTEIN[1]
[1]Oto-HNS, [2]Neurobio., [3]Bioengineering, Univ. of Washington, Seattle, WA

Abstract: Introduction: Large amplitude gaze shifts are accomplished by combined eye and head movements. Previous studies suggest that vestibular information is either gated or modulated during a gaze shift and may be used to reconstruct dynamic eye position in space to produce accurate gaze movements. To further address this question, we perturbed vestibular feedback during active gaze shifts in monkeys by stimulating the vestibular end organ with a chronically implanted vestibular prosthesis. Methods: 2 rhesus monkeys were implanted with a vestibular neuroprosthesis, with stimulation sites in individual semicircular canals, controlled remotely from a PC computer via an RF link. Eye and head movements were recorded with chronically implanted scleral and head coils. Animals were trained to make head unrestrained gaze shifts to stepped point targets in complete darkness. During the gaze shift, the natural vestibular input was perturbed with the addition of an electrically induced “fictive” head movement, produced by biphasic pulse train stimulation with the vestibular prosthesis. The target was eliminated during the gaze shift to remove any visual feedback. Results: Stimulation produced large perturbations in eye and head position before, after and during gaze shifts. During natural gaze shifts, the size of the eye or gaze velocity perturbation was heavily influenced by the direction of the natural gaze shift, the time of the stimulation relative to gaze start or end, and the stimulation pulse frequency or current amplitude. The perturbation always had the same direction, aligned with the stimulated canal plane, and latency, approximately 20 ms after stimulation onset. After stimulation offset, there was a compensatory gaze shift which realigned the eye with its earlier trajectory. This realignment resulted in gaze shifts that were accurate, despite the fact that there were large perturbations in eye, head and gaze movement due to stimulation. Conclusion: These results suggest that sensory input from the vestibular system contributes to the gaze movement during combined gaze shift. However, vestibular information is not used to calculate gaze

position dynamically during an ongoing movement. Rather, the trajectory of a gaze shift is preprogrammed, and presumably maintained with an internal model of eye position in space.

Disclosures: **J.O. Phillips:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); U of Washington. **E. Chung:** None. **L. Ling:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); U of Washington. **A. Nowack:** None. **K. Nie:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); U of Washington. **J. Rubinstein:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); U of Washington. F. Consulting Fees (e.g., advisory boards); Cochlear Ltd..

Nanosymposium

718. Vestibular Systems: VOR, Locomotion, and Gaze

Location: SDCC 2

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 718.04

Topic: D.06. Auditory & Vestibular Systems

Support: the Ministry of Internal Affairs and Communications, Japan (H29 0155-0149)
the Foreign Researcher Invitation Program, National Institute of Information and Communications Technology (NICT), Japan
JSPS KAKENHI (16H01524)

Title: Multi-dimensional vestibular self-motion system in the human brain

Authors: ***N. HAGURA**[1,2], K. AOYAMA[4], H. BAN[5,2], A. YOKOI[5,2], Y. IKEGAYA[6,5], T. MAEDA[3,5], H. ANDO[3,5], E. R. FERRÈ[7,3]
[1]CiNet, Suita-Shi, Japan; [2]Grad. Sch. of Frontier Biosci., [3]Grad. Sch. of Information Sci. and Technol., Osaka Univ., Osaka, Japan; [4]Grad. Sch. of information Sci. and Technol., Univ. of Tokyo, Tokyo, Japan; [5]Ctr. for Information and Neural Networks, Natl. Inst. of Information and Communication Technol., Suita-Shi, Japan; [6]Grad Sch. Pharma Sci, Univ. Tokyo, Tokyo, Japan; [7]Dept. of Psychology, Royal Holloway Univ. of London, Egham, United Kingdom

Abstract: As we move through the world, a stream of sensory information informs the brain about the motion of the head with respect to the surrounding environment. The vestibular system is particularly important for sensing self-motion. Head rotation (angular velocity) is coded by the three semicircular canals, while head translation (linear acceleration) is detected by the otoliths. Although rotation and translation can provide an accurate percept of self-motion, where and how they are represented in the human brain is still unclear. Since these self-motions can co-exist independently (i.e. feeling the roll rotation while moving forward), we predicted that rotation and

translation motions are independently represented in the brain, within the fronto-parietal vestibular network. Here we combined methods for eliciting virtual head motion sensations (rotation and translation) with fMRI to identify brain areas representing head rotation and translation. A four-pole Galvanic Vestibular Stimulation (GVS) was used in the fMRI scanner (n=16) to stimulate the vestibular organs and evoke virtual left-right roll rotation and forward-back translation sensations. In particular, the electrical current passing between the mastoids electrodes activates the vestibular organs inducing a perception of left-right head roll sensation, while the current passing between mastoids and temples evoked a forward-backward head translation sensation. To control for non-specific transcutaneous effects of GVS, we delivered a sham stimulation by placing two electrodes at the base of the neck, which does not induce any movement sensation. Voxel by voxel univariate analysis revealed GVS induced activations in the bilateral inferior parietal, premotor/anterior insula and prefrontal cortices. These areas are known to receive direct projections from the vestibular organs through vestibular nucleus. Furthermore, using a multi-voxel-pattern classification analysis, we confirmed that each of these areas reliably possess information about the four types of virtual head motions (left-right roll and forward-back translation). The described pattern of brain responses was vestibular input specific; such results were absent in sham stimulation condition. Finally, when the head roll and translation sensations were induced simultaneously, the activity pattern in the fronto-parietal vestibular network was well described by the weighted sum of the sole roll and translation GVS induced brain activity patterns. Our study demonstrates that roll and translation form independent representation within the cortical vestibular network in the human brain.

Disclosures: N. Hagura: None. **K. Aoyama:** None. **H. Ban:** None. **A. Yokoi:** None. **Y. Ikegaya:** None. **T. Maeda:** None. **H. Ando:** None. **E.R. Ferrè:** None.

Nanosymposium

718. Vestibular Systems: VOR, Locomotion, and Gaze

Location: SDCC 2

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 718.05

Topic: D.06. Auditory & Vestibular Systems

Support: NIDCD R01 DC006685
NIDCD R21 DC016443

Title: Pulsed ultrasound stimulates vestibular organs and evokes phase locked action potentials

Authors: *M. M. IVERSEN, B. R. POPE, R. D. RABBITT
Bioengineering, Univ. of Utah, Salt Lake City, UT

Abstract: Introduction
Neural encoding of gravito-inertial acceleration by inner ear vestibular organs primarily uses

action potential firing rate modulation (rate code) to transmit traditional low frequency vestibular information [1], and action potential timing (phase locking) to transmit high frequency sound, acceleration, and vibration [2]. We recently demonstrated that phase locked responses can be preferentially evoked in vestibular organs by delivering brief packets of low intensity focused ultrasound (LiFU) to the semicircular canal crista, utricular macula or saccular macula [3]. In the present work we examined amplitude- and frequency-dependent phased locked responses of individual vestibular afferents to pulsed LiFU stimuli with the goals of quantifying the high frequency temporal code evoked in vestibular organs by pulsed acoustic radiation stimuli. Results have relevance to applications of LiFU to remote vestibular stimulation, as well as quantifying coding of high frequency stimuli by vestibular organs.

Methods

Focused 5 MHz ultrasound was applied to the vestibular organs in discrete packets with repetition rates of 0.1-2000 Hz. Single-unit afferent neurons were recorded and analyzed for phase-locking strength (vector strength) and timing (stimulus-triggered histograms) across a range of ultrasound amplitudes. Background discharge statistics were recorded to examine correlates with temporal coding properties of individual organs.

Results

Vestibular afferent neurons with irregular interspike intervals at rest, responded to pulsed ultrasound with high vector strength to ultrasound pulses. Afferents innervating the otolith organs responded with higher strength than afferents innervating cristae. Responses in otolith organs mimic those elicited by high frequency vibrational acceleration.

Conclusion

Vestibular end organ sensitivity to pulsed LiFU is the result of the acoustic radiation force acting to deflect sensory hair bundles as shown previously [3]. Responses are stronger in the otolith organs due to the acoustic radiation force generated by the high impedance mismatch between the otolithic mass and surrounding tissues. Action potential timing analysis shows that phase-locking of vestibular afferents is independent of stimulus amplitude. This has similarly been demonstrated in auditory spiral ganglion neurons. Amplitude independence suggests the standard noisy integrate-and-fire model used to describe neural firing is incomplete in describing phase-locking in vestibular afferent neurons [1].

References

[1] SG Sadeghi, *J Neurosci* (2007)
[2] IS Curthoys, *Brain Res Bull* (2012)
[3] MM Iversen, *J Acoust Soc Am* (2017)

Disclosures: M.M. Iversen: None. **B.R. Pope:** None. **R.D. Rabbitt:** None.

Nanosymposium

718. Vestibular Systems: VOR, Locomotion, and Gaze

Location: SDCC 2

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 718.06

Topic: D.06. Auditory & Vestibular Systems

Support: VA RR&D Merit Award to AGH

Title: Using Manganese enhanced magnetic resonance imaging (MEMRI) to assess calcium dependent activity in linear acceleration detection pathways following Otolith stimulation

Authors: *A. HOLT[1,2], S. KALLAKURI[1], A. CACACE[3], A. APAWU[1], M. HALI[1], R. BRAUN[1]
[1]Wayne State Univ. Sch. of Med., Detroit, MI; [2]John D. Dingell VAMC, Detroit, MI; [3]Wayne State Univ. Communication Sci. and Disorders, Detroit, MI

Abstract: Manganese enhanced magnetic resonance imaging (MEMRI) is a powerful imaging paradigm that has been used both in vitro and in vivo for mapping neuronal pathways and objectively evaluating spatial and temporal dynamics of neuronal activity. Manganese is a paramagnetic contrast agent that acts as a calcium surrogate and accumulates in active neurons, primarily through voltage-gated calcium channels. Therefore, MEMRI can be used to appraise calcium channel function and quantify neuronal activity. While auditory, visual, and olfactory systems have begun to be evaluated with MEMRI, studies of the vestibular and balance pathways have been limited. Using short bursts of linear acceleration (jerks) known to stimulate otolith organs and produce short latency vestibular evoked potentials (VsEPs), we assess manganese uptake in central vestibular nuclei (lateral, medial, superior, and spinal vestibular nuclei) as well as related cerebellar nuclei in adult Sprague Dawley rats. The current MEMRI data reveal significant manganese uptake in central vestibular nuclei 24 hours after administration, which has returned to baseline levels within two weeks. In addition, there is differential manganese uptake in rats with jerk stimulation compared to those without. These results may provide important clues regarding mono and disynaptic excitatory and inhibitory inputs to central vestibular neurons and help to clarify contributions of central neurons to VsEP waveforms. In the future MEMRI can be used in longitudinal experimental designs to evaluate models of vestibular dysfunction resulting from noise over exposure.

Disclosures: A. Holt: None. **S. Kallakuri:** None. **A. Cacace:** None. **A. Apawu:** None. **M. Hali:** None. **R. Braun:** None.

Nanosymposium

718. Vestibular Systems: VOR, Locomotion, and Gaze

Location: SDCC 2

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 718.07

Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant DC012775

Title: Learned preference drives locomotor development in zebrafish

Authors: *D. E. EHRLICH, D. SCHOPPIK
Neurosci. and Physiol., NYU Langone Med. Ctr., New York, NY

Abstract: Animals optimize their movements by selecting among numerous, redundant options. To what extent does learning of such movement preferences contribute to the development of locomotion? We employed an underwater model to reduce physical constraints, finding that swimming matures in larval zebrafish due to a learned preference for effective kinematics. We discovered that larvae could climb in one of two ways: by rotating their bodies upwards and climbing with thrust, or remaining horizontal and using their pectoral fins to generate lift. With development, larvae transitioned from body rotation to fin-mediated climbing, but at all ages made the steepest climbs by pairing both synergistcally. The youngest swimmers were therefore capable of using their fins but did not yet prefer them. We made computer simulations to identify putative criteria by which larvae might contrast the two swimming modes, and found that fin use facilitated balance near horizontal. Empirically, preference for fin use was abolished in mutants with congenitally impaired balance sense due to peripheral vestibular lesion. We conclude larvae typically rely on feedback about balance to select between redundant modes of swimming. These data reveal that growing fish learn to favor their fins using the balance sense, and establish a critical role for movement preference in locomotor development.

Disclosures: D.E. Ehrlich: None. **D. Schoppik:** None.

Nanosymposium

719. Vision: Extrastriate Cortex

Location: SDCC 23

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 719.01

Topic: D.07. Vision

Support: NWO Grant #452.17.012
NWO Grant #452.08.008
FCT Grant #IF/01405/2014

Title: A network of topographic maps for visual event timing in human association cortex

Authors: *B. M. HARVEY[1], S. O. DUMOULIN[2,1,3], A. FRACASSO[4,5,6], J. M. PAUL[1]
[1]Utrecht Univ., Utrecht, Netherlands; [2]Spinoza Ctr. For Neuroimaging, Amsterdam, Netherlands; [3]VU Univ., Amsterdam, Netherlands; [4]Spinoza Ctr. for Neuroimaging, Amsterdam, Netherlands; [5]Univ. of Glasgow, Glasgow, United Kingdom; [6]Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: Introduction: Precise quantification of the timing of short, sub-second events is vital to understanding and interacting with our complex, dynamic environment. However, despite the central role of timing in perception and action planning, it remains unclear how the brain encodes and represents sensory event timing. Converging evidence from psychophysical adaptation, neurophysiology of motor planning and computational modelling suggests the presence of tuned neural responses to specific event durations. We therefore hypothesized that neural populations in the human brain may exhibit tuned responses to visual event timing. Methods: We acquired ultra-high field (7T) fMRI data while showing subjects visual events (a circle appearing and disappearing) that gradually varied the time between circle appearance and disappearance (duration) and/or the time between consecutive circle appearances (period, i.e. 1/frequency). We summarized the fMRI responses to these events using neural models tuned to duration and period, following a population receptive field (pRF) modeling approach. Results: Models tuned to event duration captured fMRI responses well in five widely-separated areas of temporo-occipital, superior parietal and frontal cortex. Within these areas, preferences for event duration and period progressed gradually across the cortical surface, forming topographic maps of event timing preferences. These timing maps largely overlap with a network of numerosity maps that we recently described. However, these timing maps are largely lateralized to the left hemisphere, while numerosity maps are largely lateralized to the right. Conclusion: Neural populations tuned to specific event timings, organized into topographic maps, suggest the neural representation of visual event timing is similar to that of both sensory spaces and other quantities, such as numerosity and object size. Their temporo-occipital, superior parietal and frontal locations suggest roles in visual motion processing, multisensory integration and sensory-motor transformations respectively.

Disclosures: B.M. Harvey: None. **S.O. Dumoulin:** None. **A. Fracasso:** None. **J.M. Paul:** None.

Nanosymposium

719. Vision: Extrastriate Cortex

Location: SDCC 23

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 719.02

Topic: D.07. Vision

Support: NIH Grant F32 EY026785 to author AW
NIH grant R01 EY12925 to authors JP and GB

Title: Capacity limits for word recognition in brain and behavior

Authors: *A. L. WHITE[1], J. PALMER[1], J. D. YEATMAN[2], G. M. BOYNTON[1]
[1]Dept. of Psychology, [2]Inst. for Learning & Brain Sci. and Dept. of Speech & Hearing Sci., Univ. of Washington, Seattle, WA

Abstract: *Background*: Vision begins with parallel processing: the retinas and early visual cortex can encode many stimulus elements at once. If parallel processing continued all the way through the system, observers would be able to recognize multiple objects simultaneously. At the other extreme, a serial bottleneck would allow only one object to be recognized at a time, severely impairing performance when attention must be divided. We recently found that the cost of divided spatial attention on visual word recognition is consistent with such a serial processing model: observers can recognize only one of two words in a brief masked display (White, Palmer & Boynton, *Psychological Science* 2018).
Question: Here we investigate the neural basis of that capacity limit in visual word recognition: where in the brain is the bottleneck? Specifically, we tested whether dividing (compared to focusing) spatial attention reduces the magnitudes of BOLD responses to words in early visual areas and in word-selective regions of ventral occipito-temporal (VOT) cortex (i.e., the "visual word form area", VWFA).
Methods & Results: During fMRI scanning, observers viewed masked pairs of words - one to either side of fixation - and performed a semantic categorization task. On some trials, the word on only one side was cued as task-relevant (focused attention). On other trials, both words were cued as relevant (divided attention). In early visual areas, responses were higher when the contralateral word was relevant than when the ipsilateral word was relevant, consistent with prior fMRI studies on spatial attention. Extending prior work, we found the same selective attention effect in VOT areas. Moreover, responses in all regions of interest were just as high when both words were relevant as when only the contralateral word relevant, despite the fact that observers could only recognize one of the two words per trial.
Conclusion: This dissociation between the attentional effects on behavior and on neuronal activity suggests that the source of the capacity limit in word recognition is not in early visual

cortex or in word-selective VOT cortex. Instead, we propose that the bottleneck lies in downstream brain areas responsible for later stages of processing.

Disclosures: A.L. White: None. **J. Palmer:** None. **J.D. Yeatman:** None. **G.M. Boynton:** None.

Nanosymposium

719. Vision: Extrastriate Cortex

Location: SDCC 23

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 719.03

Topic: D.07. Vision

Support: NIH Grant 1RF1MH114277-01

Title: Bayesian modeling of fMRI data to infer neural subpopulation tuning functions in visual cortex

Authors: *R. A. COWELL[1], P. SADIL[2], J. SERENCES[3], D. E. HUBER[1]
[1]Psychological and Brain Sci., Univ. of Massachusetts, Amherst, MA; [2]Univ. of Massachusetts Amherst, Amherst, MA; [3]Psychology, UCSD, La Jolla, CA

Abstract: The results of fMRI studies are assumed to indicate the function of different cortical areas. However, fMRI voxels typically contain at least a million neurons, which likely differ in their responses. Thus, fMRI data may be misleading with regard to the activity of separate neural subpopulations within a voxel. Forward encoding models (FEMs; Brouwer and Heeger, 2009, 2011) address this limitation by assuming that all neural subpopulations exhibit the same tuning function in all conditions, differing only in terms of the magnitude of response for different conditions (i.e., regression analysis). However, we know from single cell recording studies that many manipulations (e.g., attending versus not attending) change the shape of the neural tuning function. We developed a hierarchical Bayesian model that subsumes the FEM (i.e., the FEM is a special case), by simultaneously inferring the shape of the tuning function in different conditions as well as the response magnitude of each subpopulation for a given voxel. We present a simple test of this model in visual cortex. We applied to model to changes in visual contrast, which is a manipulation known (from electrophysiology) to change the magnitude but not the shape of neural tuning functions (i.e., multiplicative gain). Although the voxel tuning functions suggested a change of shape, the Bayesian model correctly recovered a change in multiplicative gain without a change in shape. This technique is potentially applicable to any fMRI study of modulations in visual cortical responses that tests multiple points along a well-established dimension of variation (e.g., orientation, speed of motion, isoluminant hue, etc.).

Disclosures: R.A. Cowell: None. **P. Sadil:** None. **J. Serences:** None. **D.E. Huber:** None.

Nanosymposium

719. Vision: Extrastriate Cortex

Location: SDCC 23

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 719.04

Topic: D.07. Vision

Support: China Scholarship Council (CSC)

Title: Topographic numerosity maps dynamically adjust to the presented numerosity range

Authors: *Y. CAI[1,2], J. A. VAN DIJK[1,3], W. ZUIDERBAAN[1], W. VAN DER ZWAAG[1], B. M. HARVEY[3], S. O. DUMOULIN[1,2,3]
[1]Spinoza Ctr. for Neuroimaging, Amsterdam, Netherlands; [2]Exptl. and Applied Psychology, VU Univ. Amsterdam, Amsterdam, Netherlands; [3]Exptl. Psychology, Helmholtz Institude, Utrecht Univ., Utrecht, Netherlands

Abstract: Introduction
Numerosity, the set size of a group of visual items, helps guide human and animal behavior and decisions. For small numerosities (< 8), we have described neural populations responding to specific numerosities organized in systematic topographic maps, analogous to primary sensory and motor cortical maps (Harvey et al, 2013, 2017). However, different mechanisms are thought to underlie the perception of small and large numerosities. Consequently, it is not clear how or whether these numerosity maps respond to larger numerosities. Here, we investigate the neural representation of larger numerosities.
Method
We used ultra-high field fMRI at 7T to measure responses elicited by viewing different numerosities. Numerosity stimuli consisted of a group of dots with a constant total dot area presented in the central 2 degrees (radius) of the visual field. The small numerosity range stimuli consisted of 1 to 7 dots with baseline periods of 20 dots. Large numerosities ranged from 1 to 64 dots with a baseline of 512 dots. During stimulus presentation, participants responded when white dots were shown rather than black: No numerosity judgments were required. We summarized the fMRI signals using a logarithmic Gaussian function with two parameters, preferred numerosity and tuning width. The residual sum of squares between the predicted and measured fMRI signals (R^2) was used to quantify explained signal variance. This analysis is analogous to the conventional population receptive field (pRF) analysis of visual field maps (Dumoulin & Wendell, 2008).
Results
Within the same network of topographic numerosity maps, we found neural populations tuned to either small or large numerosities depending on the range shown. Numerosity preferences derived from viewing small and large numerosity ranges were well correlated ($r > 0.8$), though

significantly higher when measured with the large range.
Discussion
While perception of small and large numerosity stimuli differ in many aspects, we show that both ranges elicit responses in the same numerosity maps. Our results suggest that neuronal populations in topographic numerosity maps dynamically adjust their numerosity tuning to follow the presented numerosity range.

Disclosures: Y. Cai: None. **J.A. van Dijk:** None. **W. Zuiderbaan:** None. **W. van der Zwaag:** None. **B.M. Harvey:** None. **S.O. Dumoulin:** None.

Nanosymposium

719. Vision: Extrastriate Cortex

Location: SDCC 23

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 719.05

Topic: D.07. Vision

Support: ERC 310809
James S. McDonnell Foundation 220020284

Title: The mapping of the brain's mind eye in the absence of visual experience: A population receptive field mapping of the soundscape space

Authors: *S. HOFSTETTER[1], W. ZUIDERBAAN[2], S. O. DUMOULIN[3], A. AMEDI[4]
[1]Med. Neurobio., The Hebrew Univ., Jerusalem, Israel; [2]Spinoza Ctr. for Neuroimaging, Amsterdam, Netherlands; [3]Spinoza Ctr. for Neuroimaging, Amsterdam Zuidoost, Netherlands; [4]Dept. of Develop. Med. Neurobio., Fac. of Med. Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Studies showed that blind participants trained in visual-to-auditory sensory substitution devices (SSDs) were able to recognize and to specifically activate many of the known categories in the high-order visual streams. But how is this learned experience integrated in the brain? Does the visual-to-auditory input follow similar organizational principles as the natural senses? Here we studied a proficient EyEMusic-SSDcongenitally blind user using population receptive field (pRF) mapping, a method for imaging retinotopic maps. The EyEMusic-SSD algorithm reads the image from left to right and forms a soundscape of the image where the X and Y axes are represented by time and pitch in pentatonic-scale, respectively (Fig 1A; adapted from Dumuolin 2008). The pRF analysis modeled the receptive fields from the time series data with a 2D Gaussian, estimating the center (x0,y0) and size of the pRFs in relation to the provided stimuli. The variance explained by the model (R^2) points to significant activations in the auditory, occipital, and parietal cortices (Fig 1B). Full "tonotopic" maps of musical pitch-elevation (y axis)were found in bilateral A1, showing organized maps of the EyeMusic's notes (Fig 1C). Moreover, topographical maps of the soundscape field were found in

the right lateral occipital (LO), right medial occipital cortex, and right parietal-occipital cortex (PO). Full topographic maps of timing of the stimuli (x axis)were shown in the same regions in the right LO and right PO. Notably, in the right PO, the maps of the two axes overlapped (Fig 1D). Conceptually, this proposes that the learned soundscape field may be analyzed in a similar way to how the two dimensions of retinotopy, eccentricity and polar angle, span the visual field. Our results revealed dedicated topographic maps in several regions, from primary visual cortex to high-order areas, corresponding to one or both axes of the learned 2D space that is conveyed by the EyeMusic SSD. This case study suggests that in adulthood novel topographic maps can develop following extensive training in topographic sensory experiences.

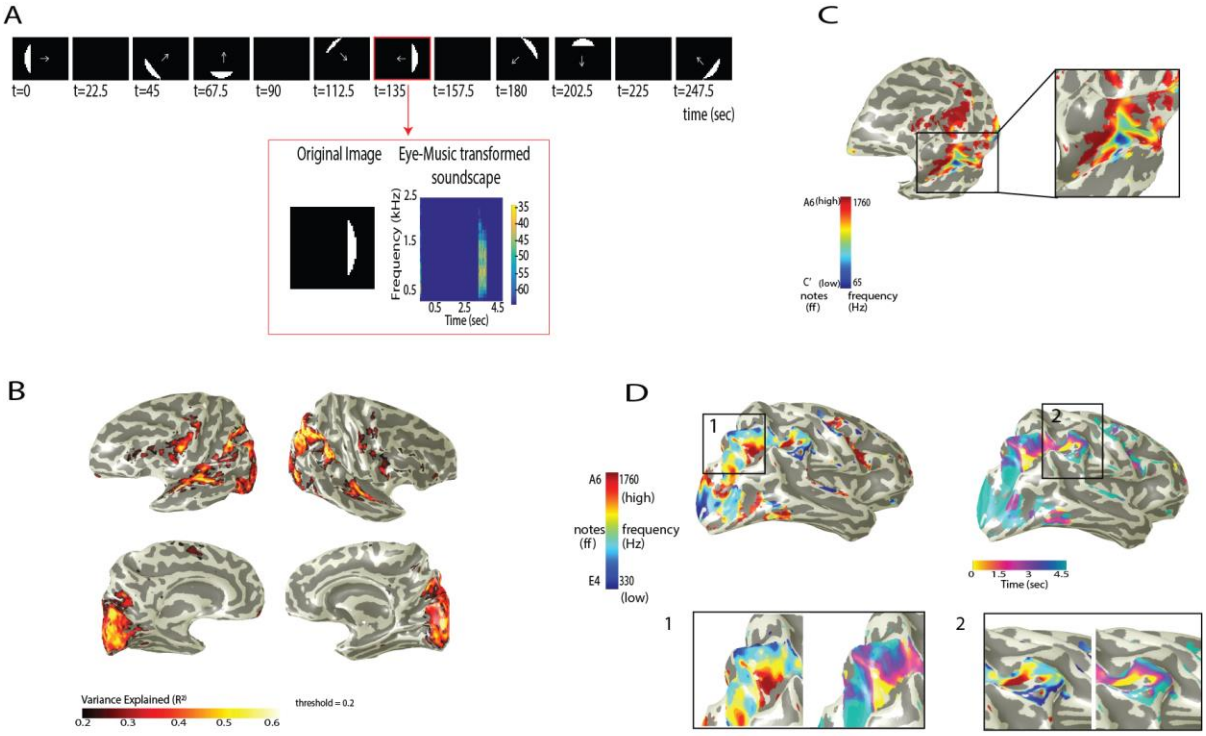


Figure Legend:

A. Illustration of stimulus sequence. Visual bars were conveyed with the visual-to-auditory EyEMsuic-SSD. Within one imaging scan the bars sweep through the soundscape-field in 8 different orientations, as indicated by the arrows. One bar is shown in its corresponding soundscape-field.
B. Maps of the variance explained (R^2) by the pRF model are displayed on inflated cortical surface at a threshold of R^2>0.2 .
C. Topographic maps found in left auditory cortex for the EyEMusic's pitch in pentatonic scale.
D. Topographical maps of the soundscape-space: Overlapping maps of both axes, musical pitch (y) and timing of the stimulus (x), were found in the parietal-occipital cortex (1,2) . ff indicates the fundamental frequency of the EyEMusic notes.

Disclosures: W. Zuiderbaan: None. **S.O. Dumoulin:** None. **A. Amedi:** None.

Nanosymposium

719. Vision: Extrastriate Cortex

Location: SDCC 23

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 719.06

Topic: D.07. Vision

Support: NIH Grant P41 EB015894
NIH Grant P30 NS076408
NIH Grant S10 RR026783
NIH Grant S10 OD017974-01
W. M. Keck Foundation

Title: Differential representation of object category information across lateral and medial ventral temporal cortex revealed with ultra-high-resolution fMRI

Authors: *E. MARGALIT[1], K. JAMISON[3,4], K. S. WEINER[5,6], L. VIZIOLI[4], R. ZHANG[4], K. N. KAY[4], K. GRILL-SPECTOR[2]
[1]Neurosciences Grad. Program, [2]Psychology, Stanford Univ., Stanford, CA; [3]Weill Cornell Med. Col., New York, NY; [4]Radiology, Univ. of Minnesota Twin Cities, Minneapolis, MN; [5]Psychology, [6]Helen Wills Neurosci. Inst., UC Berkeley, Berkeley, CA

Abstract: Visual object categories are represented in a reliable topology within ventral temporal cortex (VTC): neural representations of object category in lateral VTC are different from those in medial VTC. Despite this regularity, it is presently unknown if the two regions (a) represent object category at the same level of abstraction and (b) illustrate differences in representational structure at the same spatial scale. To fill this gap, we measured responses in 7 participants in medial and lateral VTC to 10 object categories from five domains (written characters, bodies, faces, places, and objects) at a spatial resolution of 0.8 mm using fMRI at 7T (Fig 1A). These measurements afford dense sampling of visual cortex both parallel to the cortical surface and through cortical depth. To compare to standard fMRI, we also resampled the data to 2.4mm (Fig 1-right). For each subject and anatomical subdivision, we computed (1) pairwise correlations between distributed responses in each of three cortical depths to different items of either the same category (within-category correlations) or different categories (between-category correlations), (2) the difference between within-domain correlations and between-domain correlations (domain discriminability), and (3) the difference between within-category correlations and between-category correlations within a given domain (category discriminability). Results suggest that domain discriminability is stronger in lateral VTC than in medial VTC ($F(1,6) = 22.2$, $p < .01$) whereas category discriminability is higher in medial VTC than in lateral VTC ($F(1,6) = 42.8$, $p < .001$; Fig 1B). This difference in representational structure in the lateral and medial subdivisions of VTC was stable across cortical depth and also evident after downsampling to 2.4mm. Our analyses suggest that lateral and medial VTC represent categories at different levels of abstraction and that the spatial scale of this representational structure is larger than 0.8mm.

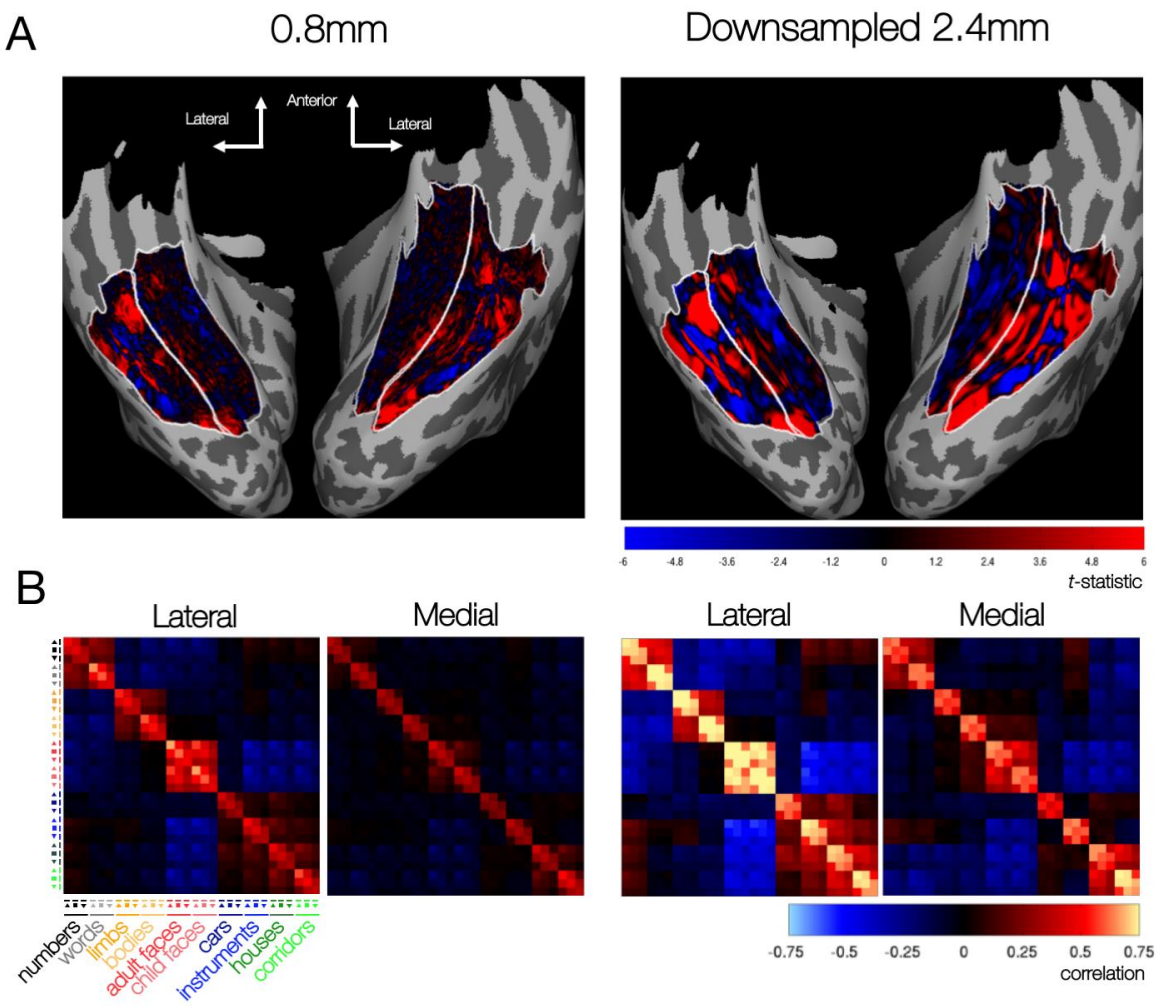


Figure 1: **A)** Maps of selectivity for an example object category, words, in the most superficial sampling depth of one subject's anatomically-defined VTC. The white boundaries delineate lateral and medial VTC. t-statistics are shown for each vertex for high-resolution data (left) and downsampled medium-resolution data (right). **B)** Group average representational similarity matrices derived from each object category at each of three sampling depths. Matrices are ordered first by depth (superficial, middle, deep), then by category (numbers, words, limbs, etc.).

Disclosures: E. Margalit: None. **K. Jamison:** None. **K.S. Weiner:** None. **L. Vizioli:** None. **R. Zhang:** None. **K.N. Kay:** None. **K. Grill-Spector:** None.

Nanosymposium

719. Vision: Extrastriate Cortex

Location: SDCC 23

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 719.07

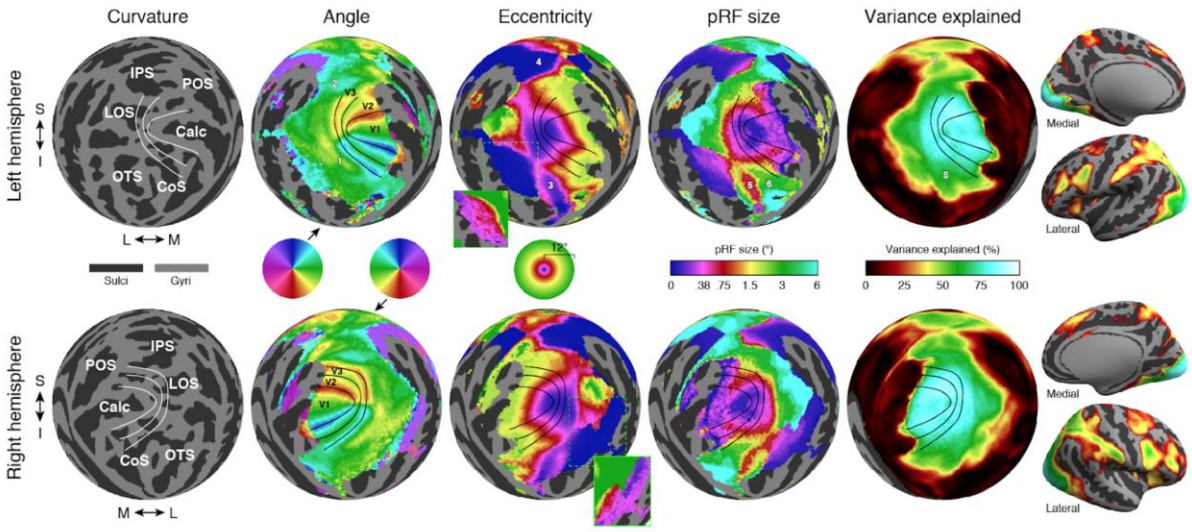
Topic: D.07. Vision

Support: NIH Grant 1U54MH091657 (Human Connectome Project)
NIBIB Grant P41 EB015894
NINDS Grant P30 NS076408
NIH Grant EY027401

Title: The human connectome project 7t retinotopy dataset: A freely available resource of human visual organization

Authors: *N. C. BENSON[1], K. W. JAMISON[3], M. J. ARCARO[4], A. T. VU[5], M. F. GLASSER[6], D. C. VAN ESSEN[7], K. UGURBIL[8], J. WINAWER[2], K. N. KAY[9]
[1]Dept. of Psychology, [2]Psychology, New York Univ., New York, NY; [3]Radiology, Weill Cornell Med. Col., New York, NY; [4]Neurobio., Harvard Med. Sch., Boston, MA; [5]Radiology, VA Med. Ctr., San Francisco, CA; [6]Dept. of Anat. & Neurobio., Washington Univ. Sch. of Med., Saint Louis, MO; [7]Washington Univ. Sch. Med., Saint Louis, MO; [8]Radiology, Univ. of Minnesota, Minneapolis, MN; [9]Radiology, Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: Topographic maps are one of the primary modes of sensory organization in the brain. Retinotopic maps of the visual field tile as much as one quarter of human cortex and have served the neuroscience community as a model system for cortical organization. Recently, efforts to characterize human brain organization have culminated in the Human Connectome Project (Van Essen et al., 2013; DOI:10.1016/j.neuroimage.2013.05.041), which included retinotopic mapping in 181 human subjects, as measured via 7T fMRI. Here, we present population receptive field (pRF) results for all 181 subjects as well as a group-average pseudo-subject. We find that over 40% of the cortical surface is responsive in the mapping paradigm (group-average pRF variance explained > 10%), including large portions of parietal and frontal cortex. Distinct foveal representations (eccentricity < 1°) are present in large swaths of parietal and ventral temporal cortex, and make up about half of responsive cortex. Split-half reliability analyses indicate that pRF solutions are highly reliable within individual subjects. The group-average results agree well with previously published parcellations of early and intermediate visual areas. The HCP 7T Retinotopy Dataset is unique in its size and quality, and provides a valuable resource for sensory neuroscience. The dataset and pRF solutions are freely available on an Open Science Framework web site (https://osf.io/bw9ec/) and the BALSA database (https://balsa.wustl.edu/study/show/9Zkk).



Disclosures: N.C. Benson: None. **K.W. Jamison:** None. **M.J. Arcaro:** None. **A.T. Vu:** None. **M.F. Glasser:** None. **D.C. Van Essen:** None. **K. Ugurbil:** None. **J. Winawer:** None. **K.N. Kay:** None.

Nanosymposium

719. Vision: Extrastriate Cortex

Location: SDCC 23

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 719.08

Topic: D.07. Vision

Support: HBP 172779-01

Title: Decoding counterfactual information in extrastriate cortex during visual room navigation with 3T and 7T fMRI after immersion training in virtual reality

Authors: A. PATON, Y. LAZAROVA, L. PETRO, *L. MUCKLI
Univ. of Glasgow, Glasgow, United Kingdom

Abstract: When you navigate your home, you do so with certainty that when you open your bedroom door, you will enter your bedroom. Underlying this knowledge are top down predictions driven by learning, experience and familiarity. Visual cognition relies heavily on top down predictions to contextualise incoming sensory information with this prior knowledge. However not all predictions are driven by immediate sensory information. When we engage in counterfactual thought processes such as mind-wandering, mental simulation or prospective thought, the brain generates predictions over longer time frames. To ensure our subjects had strong internal models of the same familiar environment, we created an immersive and richly

contextual 3D virtual house environment presented using a virtual reality headset. Subjects were able to freely explore four rooms prior to the fMRI experiment (kitchen, bedroom, office, game room). Each room contained contextually congruent objects that subjects could interact with. In a 3T fMRI experiment subjects (N=20) viewed trials containing a text cue of direction (left or right), followed by a video clip of exiting one room, followed by a video clip of entering a second room. Video clips had the lower right quadrant occluded which renders the corresponding retinotopic patch of cortex unstimulated by scene information, and therefore processing only cortical feedback signals. During the first video clip, subjects responded as to what the upcoming room would be, based on the prior directional cue. We find that during the second sequence we can decode what subjects are viewing from both feedforward (FF) and feedback (FB) voxels in V1, V2 and V3. In the first sequence we can decode not only what subjects are viewing from FF voxels in V1, V2 and V3 but also what subjects are expecting to view from FB voxels in V2 and V3. We also find classifier performance to be attenuated relative to the second sequence, suggestive of interference due to perceptual decoupling. We conclude that during counterfactual thinking extrastriate cortex is utilised by the brain to perform internalised mental simulations of the past and future. During perceptual decoupling, visual sensory information is still available to early visual cortex although as a weakened signal, and is likely still being monitored during counterfactual processes. We intend to explore this further to investigate whether by changing the task we can also read out information about the past. We also intend to investigate counterfactual processing using 7T fMRI to explore how both sensory driven prediction and counterfactual information can co-exist in different layers of cortex.

Disclosures: A. Paton: None. **Y. Lazarova:** None. **L. Petro:** None. **L. Muckli:** None.

Nanosymposium

720. Neural Activity Patterns for Speech and Sign Language in Disease and Health

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 720.01

Topic: E.04. Voluntary Movements

Title: Self-monitoring in l1 and l2 speech production: An meg study

Authors: *S. BAKST, C. A. NIZIOLEK
Communication Sci. and Disorders, Univ. of Wisconsin–Madison, Madison, WI

Abstract: We listen to ourselves while talking, comparing our acoustic output to an internal auditory representation of how our speech should sound. Because these representations of speech targets are weaker in a second language (L2), self-monitoring may be less successful, resulting in more varied, less native-like speech.
In the current study, participants were recorded producing monosyllabic words in L1 (English) and L2 (French) during a magnetoencephalography (MEG) scan. The vowels tested were English

{i, ɛ, æ} ("Eve", "eff", "add") and French {i, ɛ, œ} ("Yves", "hais", "oeuf"). Because native speakers are sensitive to the natural acoustic variability in their productions, they can steer deviant productions towards their auditory targets while speaking (Niziolek et al. 2013). This corrective behavior is evident in the magnitude and direction of the trajectories of vowel formants throughout an utterance. The speakers in the present study showed such corrective behavior while speaking L1, but in L2, utterances were both more acoustically variable and showed less self-correction. Further, the most variability and least corrective behavior was found for [œ], the only vowel not found in English. In L1, acoustic variability is positively correlated with self-correction, but the increased acoustic variability in L2 vowels did not trigger commensurate self-correction. These results indicate that weakened representations of speech targets in L2 impair the ability to self-correct.
Learning an L2 is also associated with structural differences in the brain; beginners show increased structural connectivity between hemispheres compared with monolinguals and more proficient bilinguals (Xiang et al. 2015). Here, we investigated functional differences while speaking and listening to acoustically-matched productions played over headphones in L1 and L2. Neuroimaging studies have previously shown that the auditory cortical response to hearing one's own speech during L1 production is suppressed in comparison with silent listening to those same productions (Houde et al. 2002; Niziolek et al. 2013). Preliminary analyses of MEG data show left auditory cortical suppression in both L1 and L2, providing evidence of self-monitoring in both languages. However, there was a tendency for a difference in laterality: while the cortical response to self-produced speech in L1 was highly left-lateralized, in L2 there was less lateralization in both speaking and listening. Our findings suggest greater recruitment of right hemisphere during both speaking and listening in adult L2 learners, which may be related to observed structural changes accompanying language learning.

Disclosures: C.A. Niziolek: None.

Nanosymposium

720. Neural Activity Patterns for Speech and Sign Language in Disease and Health

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 720.02

Topic: E.04. Voluntary Movements

Title: Neural correlates of sign language and spoken language revealed by electrocorticography

Authors: J. SHUM[1,3], L. FANDA[1,3], B. MAHMOOD[1,3], D. FRIEDMAN[1,3], P. DUGAN[1,3], W. DOYLE[2,3], O. DEVINSKY[1,3], *A. FLINKER[1,3]
[1]Neurol., [2]Neurosurg., NYU, New York, NY; [3]NYU Comprehensive Epilepsy Ctr., New york, NY

Abstract: The cortical dynamics underlying speech and sign language production remain poorly understood. Here we report a unique case of a neurosurgical patient with intact hearing and bilingual in English and American sign language. The patient suffered from pharmaco-resistant epilepsy requiring surgical implantation of electrodes to clinically identify seizure onset zones. During lulls in clinical treatment we administered a battery of cognitive tasks designed to mirror clinical paradigms employed during electrical stimulation mapping which remains the gold standard to identify eloquent cortex. Electrocorticographic (ECoG) recordings during the five production tasks can functionally track neural activity from stimulus presentation through speech and sign output under multiple cognitive demands. Here we describe the neural propagation maps during both speech and sign language output. The tasks involved visual naming, word reading, auditory repetition, auditory naming, and auditory comprehension. We focused our analyses on changes in high gamma activity (70 - 150 Hz) during the tasks, as high gamma activation has been previously shown to robustly track single trial cortical activity and correlates with neural population firing rates and fMRI BOLD responses. The patient also underwent electrical stimulation mapping using similar language tasks of visual naming, auditory naming, and auditory comprehension, as part of his clinical work up to identify eloquent cortex. We identified brain regions with high gamma activation during our language tasks in both spoken English and sign language. In addition we identified discrete regions in the frontal, temporal, parietal, and occipital cortices with sign language specific responses compared to spoken English and provide evidence for temporal propagation of neural activity from post-central to occipital cortices during sign language production. These results are the first report in the literature, to our knowledge, of direct cortical recordings in a hearing native signer, bilingual in spoken English and sign language since birth and provide a unique window into the cortical underpinnings of sign language production.

Disclosures: J. Shum: None. **L. Fanda:** None. **B. Mahmood:** None. **D. Friedman:** None. **P. Dugan:** None. **W. Doyle:** None. **O. Devinsky:** None. **A. Flinker:** None.

Nanosymposium

720. Neural Activity Patterns for Speech and Sign Language in Disease and Health

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 720.03

Topic: E.04. Voluntary Movements

Support: ALS Association Milton Safenowitz Postdoctoral Fellowship
Larry and Pamela Garlick Foundation; Samuel and Betsy Reeves
NIDCD R01DC009899, R01DC014034
Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N9288C, A2295R, B6453R)
Executive Committee on Research (ECOR) of Massachusetts General Hospital

The Executive Committee on Research (ECOR) of Massachusetts General Hospital
NICHD-NCMRR (R01HD077220)

Title: Single neuron population dynamics in dorsal motor cortex during human speech

Authors: *S. D. STAVISKY[1,2], F. R. WILLETT[1,2], B. A. MURPHY[5,6], P. REZAII[1], W. D. MEMBERG[5,6], B. WALTER[6,7], J. A. SWEET[6,8], J. P. MILLER[6], R. F. KIRSCH[5,6], L. R. HOCHBERG[9,10,11,12], A. B. AJIBOYE[5,6], K. V. SHENOY[13,3,4], J. M. HENDERSON[1,3,4]
[1]Neurosurg., [2]Electrical Engin., [3]Stanford Neurosci. Inst., [4]Bio-X Program, Stanford Univ., Stanford, CA; [5]Dept. of Biomed. Engin., Case Western Reserve Univ., Cleveland, OH; [6]FES Center, Rehab. R&D Service, Louis Stokes Cleveland Dept. of Veterans Affairs Med. Ctr., Cleveland, OH; [7]Dept. of Neurol., [8]Dept. of Neurosurg., Univ. Hosp. Cleveland Med. Ctr., Cleveland, OH; [9]VA RR&D Ctr. for Neurorestoration and Neurotechnology, Dept. of VA Med. Ctr., Providence, RI; [10]Sch. of Engin., Brown Univ., Providence, RI; [11]Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA; [12]Dept. of Neurol., Harvard Med. Sch., Boston, MA; [13]EE, BioE & Neurobio., Howard Hughes Med. Inst. - Stanford Univ., Stanford, CA

Abstract: Speaking is one of the most complex and uniquely human movement behaviors, but its neural correlates are difficult to study. Measuring neural population activity at action potential resolution is critical for a deeper mechanistic understanding of speech production and disorders, and for developing high performance speech neural prostheses. Unfortunately, the challenges of intracortical recording and the lack of an animal model have restricted previous speech studies to the coarser resolution of ECoG or to small numbers of penetrating electrodes.

We had the opportunity to record neuronal ensemble activity from two 96 electrode arrays chronically implanted in the 'hand knob' area of dorsal motor cortex of two BrainGate2 pilot BCI clinical trial participants (T5, T8) during speech. Both participants had tetraplegia due to cervical spinal cord injury; they performed phoneme and word speaking tasks in response to auditory prompts. Despite recording from an area thought of as primarily involved in controlling hand and arm movements, we found robust activation during speech: 74 (T5) and 47 (T8) electrodes' firing rates significantly modulated during production of at least one phoneme. A classifier could predict which of ten short words (or silence) was spoken using a combination of binned threshold crossings and high frequency LFP power with 83.5% (T5) and 61.5% (T8) accuracy (chance is 9.1%). Of the 24 sortable single units, 21 also responded during orofacial movements, suggesting that this activity reflects control of the speech articulators.

We found that two population dynamics motifs previously reported in motor cortex during arm movements were also significant features of speech-related activity. First, firing rates obeyed rotatory dynamics as described in monkeys (Churchland 2012) and humans (Pandarinath 2015). Neural state space rotation explained 61% of the variance in T5's top 6 PCs ($p < 0.001$ using Elsayed 2017 test; T8: 15%, not significant). Second, in both participants a large component of the population activity immediately following the movement go cue was highly invariant across different words, similar to Kaufman 2016's finding about monkey reaching conditions. The largest condition-independent component explained 60% (T5) and 16% (T8) of the variance in the top 8 demixed PCs.

The ability to record single neuron resolution activity from the same sensors already being used

in BCI trials provides an entry point for studying motor cortical population dynamics during human speech. Here we demonstrate the utility of this approach by showing that there are conserved motor cortical dynamics motifs across reaching, grasping, pedaling - and now speaking.

Disclosures: S.D. Stavisky: None. **F.R. Willett:** None. **B.A. Murphy:** None. **P. Rezaii:** None. **W.D. Memberg:** None. **B. Walter:** None. **J.A. Sweet:** None. **J.P. Miller:** None. **R.F. Kirsch:** None. **L.R. Hochberg:** None. **A.B. Ajiboye:** None. **K.V. Shenoy:** F. Consulting Fees (e.g., advisory boards); Neuralink Corp., CTRL-Labs, Inc. MIND-X Inc., Inscopix Inc., Heal, Inc. These entities did not support this work. **J.M. Henderson:** F. Consulting Fees (e.g., advisory boards); J.M.H. serves on Medical / Scientific Advisory Boards of Circuit Therapeutics, Enspire DBS, and Neuropace. These entities did not support this work..

Nanosymposium

720. Neural Activity Patterns for Speech and Sign Language in Disease and Health

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 720.04

Topic: E.04. Voluntary Movements

Support: NIH Grant 1U01NS098969-01

Title: Cortical and subcortical representations of consonant articulatory features

Authors: *A. CHRABASZCZ[1,1], W. J. NEUMANN[2], O. STRETCU[3], W. J. LIPSKI[1], A. BUSH[1], C. DASTOLFO-HROMACK[1], D. WANG[1], D. J. CRAMMOND[1], S. SHAIMAN[1], M. W. DICKEY[1], L. L. HOLT[3], R. S. TURNER[1], J. A. FIEZ[1], M. RICHARDSON[1]
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Charité - Universitätsmedizin Berlin, Berlin, Germany; [3]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Speech production constitutes a complex motor behavior involving precise coordination of orofacial, laryngeal and respiratory muscles. Studies on the localization of speech in the brain point to the somatotopic organization of the sensorimotor cortex (SMC) for speech articulation, wherein articulatory features of speech sounds are mapped onto the cortical motor regions subserving corresponding articulators (Bouchard et al., 2013; Conant et al., 2018). While neural representations of speech movements have been vastly explored at the cortical level using various methods, it is still largely unknown how the basal ganglia are involved in speech production. To compare how speech and articulatory features are encoded at the cortical and subcortical levels, we analyzed local field potentials (LFP) from electrocorticography (ECoG) and subthalamic nucleus (STN) macroelectrode recordings of 11 Parkinson's patients undergoing awake implantation of deep brain stimulation electrodes. The task included reading aloud 3-phoneme words and pseudowords presented on the computer screen, and was administered at

different STN recording depths. The analysis focused on the productions of the word-initial consonants involving the lips or the tongue as primary articulators. We extracted the high-gamma (HG) frequency component (60-150Hz) from the LFPs and normalized the amplitude changes by transforming to z-scores relative to baseline. A significant speech-related increase in HG activity was found in 195 out of 198 ECoG electrodes, and 84 out of 88 STN recording locations ($p<.01$, FDR corrected). The cortical HG response was broadly distributed over the perisylvian regions; the subcortical HG response was significantly affected by the dorsal-ventral position of the macroelectrodes, with greater HG power observed dorsally ($t(80.12)=2.9$, $p=.005$). The HG response in 29% of the ECoG locations exhibited a significant effect of the articulator type (tongue or lips) ($p<.01$, FDR corrected). Topography was consistent with previous findings showing that consonants involving the tongue are encoded in the ventral regions of the SMC, while consonants involving the lips are mapped onto more dorsal regions. The HG response in 27% of the STN recording locations showed a significant articulator effect; but without topographical specificity. The results provide evidence for cortical and subcortical involvement in speech production at the level of articulatory features, but indicate that the two structures may represent speech-related movement differently.

Disclosures: A. Chrabaszcz: None. **W.J. Neumann:** None. **O. Stretcu:** None. **W.J. Lipski:** None. **A. Bush:** None. **C. Dastolfo-Hromack:** None. **D. Wang:** None. **D.J. Crammond:** None. **S. Shaiman:** None. **M.W. Dickey:** None. **L.L. Holt:** None. **R.S. Turner:** None. **J.A. Fiez:** None. **M. Richardson:** None.

Nanosymposium

720. Neural Activity Patterns for Speech and Sign Language in Disease and Health

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 720.05

Topic: E.03. Basal Ganglia

Support: NIH Grant NS098969

Title: Local field potentials in the human subthalamic nucleus predict scaling of speech production

Authors: *C. A. DASTOLFO-HROMACK[1], A. ALHOURANI[4], W. J. LIPSKI[5], D. J. CRAMMOND[1], S. SHAIMAN[1], M. W. DICKEY[1], L. L. HOLT[7], R. S. TURNER[2], J. A. FIEZ[6], M. RICHARDSON[3]
[2]Dept. of Neurobio., [3]Neurolog. Surgery, [1]Univ. of Pittsburgh, Pittsburgh, PA; [4]Univ. of Louisville, Louisville, KY; [5]Dept. of Neurosurg., [6]Univ. Pittsburgh, Pittsburgh, PA; [7]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The basal ganglia have been implicated in speech motor control, but their role is unclear. In limb movement tasks, intra-operative electrophysiology studies reveal a role for basal ganglia in movement scaling. Here, we explore the relationship between an indirect measure of scaling in speech articulation (acoustic formant-frequency ratio) and population-scale neuronal signals from the human subthalamic nucleus (STN). Local field potentials (LFP's) were recorded from the macroelectrode as 14 patients with Parkinson's disease (PD) underwent intra-operative recording during STN deep brain stimulation (DBS) implant surgery. Patients read aloud a list of consonant-vowel-consonant words as their utterances were recorded for acoustic analysis. LFP's were separated into canonical spectral bands and analyzed for changes relative to baseline recordings. Using correlation and mixed effects models, we examined the relationship of theta, beta and gamma band power (z-scores) with the formant ratio (FR), an acoustic measurement of the second formant frequency (F2) during /i/ versus /u/ (as in *he* vs. *who*) that provides a relative estimate of the amplitude of tongue movement during articulation. Compared to baseline, theta power (4-8 Hz) significantly increased following the visual cue, low beta power (13-20 Hz) and high beta power (20-30 Hz) decreased following the visual cue, and gamma power (50-90 Hz) increased during speech. The average theta band z-score during speech was significantly correlated with FR ($r = 0.337$ $p = 0.0415$), as was low beta ($r = -0.53$ $p = 0.00068$); high beta was only correlated to FR with non-parametric analysis (spearman's rho = -0.451, $p = 0.0051$). Gamma power however did not correlate significantly with FR. We then applied mixed effects models across the task using each band as a fixed effect, and subject and recording session as random effects. The effect of theta power in predicting FR was significant for time points during speech [0.0725 s - 0.13 s, peak beta = 0.057]; low beta power was also significant 0.26 s before speech onset to 0.7 s after speech onset; high beta power was also significant across the task. Effects remained significant when including the Unified Parkinson's Disease Rating Scale as a random effect (theta: fixed effect = 0.059, $p = 0.001$; low beta: fixed effect = -0.048, $p < 0.026$). These results provide evidence that the STN participates in speech articulation and contributes to scaling of articulatory movements. Theta and beta oscillations may contribute synergistically to speech scaling These relationships may represent theoretical 'internal models' of movement, and have implications for treatment of speech deficits with DBS.

Disclosures: C.A. Dastolfo-Hromack: None. **A. Alhourani:** None. **W.J. Lipski:** None. **D.J. Crammond:** None. **S. Shaiman:** None. **M.W. Dickey:** None. **L.L. Holt:** None. **R.S. Turner:** None. **J.A. Fiez:** None. **M. Richardson:** None.

Nanosymposium

720. Neural Activity Patterns for Speech and Sign Language in Disease and Health

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 720.06

Topic: E.03. Basal Ganglia

Support: NIH Grant 5U01NS098969-02

Title: Neuronal firing in the subthalamic nucleus encodes chunks in speech sequences

Authors: *W. J. LIPSKI[1], M. RICHARDSON[2], A. BUSH[2], D. WANG[2], C. DASTOLFO-HROMACK[3], A. CHRABASZCZ[3], D. J. CRAMMOND[2], S. SHAIMAN[3], R. S. TURNER[4], J. A. FIEZ[3]
[1]Dept. of Neurosurg., Univ. Pittsburgh, Pittsburgh, PA; [2]Neurolog. Surgery, [4]Dept. of Neurobio., [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The basal ganglia has been implicated in the implementation of "chunking" of motor sequences that may contribute to learning and execution of complex behaviors. This mechanism is thought to facilitate an efficient representation of complex motor sequences as well as their optimization during learning. Speech can be understood in terms of sequence chunks at several hierarchical levels of representation: (1) individual articulator movements (2) phonemes (3) syllables and (4) syllable sequences. To investigate the involvement of the subthalamic nucleus (STN) in encoding these speech chunks, we recorded extracellular single- and multi-unit activity from the STN of Parkinson's disease patients undergoing deep brain stimulation electrode implantation. Subjects listened to audio recordings of consonant-vowel syllable triplets presented through earphones, and repeated them during STN recordings and simultaneous electrocorticographic (ECoG) recordings from sensorimotor cortex. We hypothesized that STN neuronal activity is patterned to designate the boundaries and the duration of individual speech productions at these levels of granularity; and that phase synchronization between STN spiking and oscillatory activity in sensorimotor cortex is modulated throughout the execution of a motor sequence. Consistent with our previous findings, we observed that speech production induced both increases (165 ± 11% of baseline firing rate in 24 units) and decreases (68 ± 3% of baseline firing rate in 23 units) in the firing rate of STN neurons (55 units recorded from 6 subjects). Furthermore, we observed that speech-related firing rate increases were either phasic (i.e. temporally aligned with one or more individual syllables in the spoken response) or tonic (i.e. temporally aligned with the entire spoken response), while speech-related firing rate decreases were always tonic. This finding provides preliminary evidence for STN encoding of motor chunks at the syllable- and syllable sequence-level. In addition, we observed phase synchronization between STN spiking and oscillatory activity in sensorimotor cortex at rest. Further analyses will address speech-related changes in cortico-subthalamic phase synchronization, and the encoding of motor sequence chunks in these networks.

Disclosures: W.J. Lipski: None. **M. Richardson:** None. **A. Bush:** None. **D. Wang:** None. **C. Dastolfo-Hromack:** None. **A. Chrabaszcz:** None. **D.J. Crammond:** None. **S. Shaiman:** None. **R.S. Turner:** None. **J.A. Fiez:** None.

Nanosymposium

720. Neural Activity Patterns for Speech and Sign Language in Disease and Health

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 720.07

Topic: E.04. Voluntary Movements

Support: NIH Grant R21DC014525
NIH Grant R01DC013979
Grant from the National Spasmodic Dysphonia Association
AAO-HNSF resident research grant to Molly Naunheim

Title: Neural correlates of aberrant vocal motor control in spasmodic dysphonia

Authors: *H. KOTHARE[1], S. L. SCHNEIDER[1], K. C. YUNG[2], L. B. HINKLEY[1], D. MIZUIRI[1], S. HONMA[1], C. GARRETT[1], M. NAUNHEIM[1], M. S. COUREY[3], S. S. NAGARAJAN[1], J. F. HOUDE[1]
[1]Univ. of California, San Francisco, San Francisco, CA; [2]San Francisco Voice & Swallowing, San Francisco, CA; [3]Mount Sinai Hlth. Syst., New York, NY

Abstract: Spasmodic dysphonia (SD) is a debilitating disorder of voicing where the laryngeal muscles are intermittently in spasm and are dystonic. This prevents the vocal folds from vibrating efficiently and results in involuntary interruptions during speech. The underlying causes of SD remain largely unknown. Prior imaging studies have found aberrant activity in the CNS during SD phonation. However, these studies could not resolve whether SD involves impairment of preparatory, feedforward aspects of vocal control or instead involves abnormal processing of sensory feedback during phonation. To investigate this question, we used Magnetoencephalography (MEG) to monitor neural activity and associated behavioural responses time-locked to glottal onset, phonation onset, and onset of pitch feedback perturbations in adductor SD (AdSD) patients and matched controls.
MEG scanning was performed in 17 patients and 12 controls. Four additional patients participated only in speech psychophysics studies without imaging. Data from 2 patients and 1 control had to be excluded because of large dental or movement artefacts. During scanning, subjects were prompted to start vocalising the vowel /ɑ/ and hold it for the duration of the prompt (2.4 s). Glottal onset was recorded using surface electromyography of pre-phonatory laryngeal muscular activity. On every trial, between 200ms and 500ms after voice onset, the pitch of their auditory feedback was briefly perturbed by +/- 100 cents for a period of 400ms and vocal responses to this change were recorded. We examined induced beta-band (12-30 Hz) neural oscillations over sensorimotor cortices in patients and controls and performed non-parametric statistical tests to observe group differences.
Patients showed an elongated interval between laryngeal movement onset and phonatory onset as

well as abnormal pitch perturbation responses. Prior to glottal onset, patients showed reduced task-induced beta band suppression over the left laryngeal motor cortex, left ventral premotor cortex and left inferior frontal gyrus, and enhanced suppression bilaterally in the parietal lobe, especially around the angular gyrus . This abnormal activity in patients near the angular gyrus persisted after glottal onset. Additionally, after phonation onset, patients had increased bilateral suppression around the postcentral gyrus. Following the onset of an auditory feedback perturbation, patients showed increased bilateral frontal lobe suppression. The results suggest that AdSD patients not only have abnormal responses to sensory feedback during phonation, but also have impaired feedforward, preparatory vocal control prior to phonation.

Disclosures: S.L. Schneider: None. **K.C. Yung:** None. **L.B. Hinkley:** None. **D. Mizuiri:** None. **S. Honma:** None. **C. Garrett:** None. **M. Naunheim:** None. **M.S. Courey:** None. **S.S. Nagarajan:** None. **J.F. Houde:** None.

Nanosymposium

720. Neural Activity Patterns for Speech and Sign Language in Disease and Health

Location: SDCC 30B

Time: Wednesday, November 7, 2018, 1:00 PM - 3:00 PM

Presentation Number: 720.08

Topic: E.04. Voluntary Movements

Support: NIH Grant R01-DC015260-02

Title: Effect of STN-DBS on sensorimotor integration mechanisms of voice motor control in Parkinson’s disease

Authors: *R. BEHROOZMAND[1], K. JOHARI[2], J. D. GREENLEE, M.D.[3]
[1]Communication Sci. and Disorders, Univ. of South Carolina, Irmo, SC; [2]Univ. of South Carolina, Columbia, SC; [3]Dept Neurosurg, Univ. Iowa, Iowa City, IA

Abstract: The present study investigated the effects of subthalamic nucleus (STN) deep brain stimulation (DBS) on the sensorimotor integration mechanisms of voice motor control in Parkinson’s disease (PD). A total of ten PD patients with bilateral implantation were tested under STN-DBS ON vs. OFF while they performed a vowel vocalization task in an altered auditory feedback (AAF) paradigm. EEG recordings were conducted to measure neurophysiological modulation of cortical neural activities during the vocalization task. During each vocalization, the auditory feedback was altered by a randomized upward (+100 cents) or downward (-100 cents) pitch-shift stimulus, and compensatory vocal responses to AAF along with band-specific power of neural activities were extracted as the behavioral and neurophysiological measures of sensorimotor integration for vocal pitch motor control, respectively. We found that the magnitude of compensatory vocal responses was significantly suppressed for STN-DBS ON vs. OFF only in response to downward pitch-shift stimuli. However, no such effect was observed for

vocal responses to upward pitch-shift alterations in the auditory feedback. In addition, the power of cortical neural activities was found to be significantly suppressed for STN-DBS ON vs. OFF predominantly within the Beta frequency band (~15-25 Hz), and this band-specific modulation of neural activities was correlated with the suppression of compensatory vocal responses to AAF. These findings provide supporting evidence for STN-DBS induced modulation of sensorimotor integration mechanisms of vocalization motor control. Based on these findings, we propose that suppression of pathological Beta band neural oscillations as a result of STN-DBS may ameliorate deficits in sensorimotor integration mechanisms of vocalization pitch motor control in PD. Our findings suggest that suppression of Beta oscillations can leads to the generation of stable vocal responses with smaller magnitudes that are less susceptible to pitch alterations in the auditory feedback. In conclusion, data from the present study suggest that specific aspects related to motor control of vocalization pitch is improved by STN-DBS in patients with PD. These results have important clinical implications for understanding the effect of STN-DBS implantation on voice motor control in PD patients.

Disclosures: R. Behroozmand: None. **K. Johari:** None. **J.D. Greenlee:** None.

Nanosymposium

721. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC 24

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 721.01

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH-1 MH106640
Vetran's Affairs-Sioux Falls
CBBRe- University of South Dakota
University of South Dakota- Board of Regents

Title: Carbamoylated erythropoietin produces antidepressant-like effects in male and female BALB/c mice

Authors: *D. SAMPATH[1], J. MCWHIRT[2], M. SATHYANESAN[1], S. S. NEWTON[2]
[1]Div. of Basic Biomed. Sci., [2]Univ. of South Dakota, Vermillion, SD

Abstract: Introduction: Major depressive disorder and related illnesses are globally prevalent, with a greater risk for suicidality if untreated. It also disrupts mental and social wellbeing. The drugs that are currently prescribed to treat depression have limited efficacy and only 40% of the patients respond to these medications. Furthermore, there is a delay of 3 or more weeks before a reduction in symptoms. The use of trophic factors for treating mood disorders is based on neurobiological evidence from clinical and preclinical investigations. Brain derived neurotrophic factor (BDNF) emerged as an attractive therapeutic candidate but clinical testing is hampered by

its inability to cross the blood-brain barrier (BBB). Erythropoietin (EPO), widely prescribed for anemia, also has robust neurotrophic actions in the CNS. Although EPO's antidepressant activity has been successfully demonstrated in multiple clinical trials, its inherent ability to elevate RBC counts and other hematological actions preclude development as a mainstream CNS drug. A chemically engineered derivative, carbamoylated EPO (CEPO), has no hematological activity but retains the neurotrophic actions of EPO. CEPO appeared to be an ideal candidate to test as an antidepressant. **Objectives**: To evaluate the antidepressant properties of CEPO in established antidepressant-responsive rodent behavioral assays. **Methods**: All experiments were conducted after obtaining prior approval from the institutional OLAR-IACUC committee, University of South Dakota. Adult male and female BALB/c mice were used for this study. CEPO (30 µgrams/ kg BWT) or veh was administered intraperitoneally for 4 days before the test of novelty induced hypophagia and subsequently at five hours before testing in forced swim test (FST), tail suspension test (TST) and open field test (OFT) . To obtain mechanistic insight we are examining the expression of neurotrophic factors such as BDNF, neuritin and VGF, which independently produce behavioral effects and are also regulated by EPO. **Results**: Administration of CEPO at 30 µgrams/ kg BWT, for 5 days produced significant effects in male and female mice across 3 behavioral assays. Further validation of CEPO's antidepressant activity will be conducted in a stress model. **Acknowledgement:** NIMH-1 MH106640; Veteran's Affairs -Sioux Falls; CBBRe- University of South Dakota; University of South Dakota- Board of Regents.

Disclosures: D. Sampath: None. **J. McWhirt:** None. **M. Sathyanesan:** None. **S.S. Newton:** None.

Nanosymposium

721. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC 24

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 721.02

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH grant MH107615 to T.D.G.
Harrington Discovery Institute Scholar-Innovator grand to T.D.G.
NARSAD Young Investigator award to P.Z.
NIMH Psychoactive Drug Screen Program Contract # HHSN-271-2008-025C

Title: Ketamine's (2R,6R)-hydroxynorketamine metabolite exerts mGluR2-dependent antidepressant actions

Authors: *P. ZANOS[1], J. N. HIGHLAND[2], P. GEORGIOU[4], X. KANG[5], C. A. ZARATE, JR[6], T. D. GOULD[3]
[1]Univ. of Maryland, Baltimore, MD; [2]Program in Toxicology, [3]Dept Psychiat, Univ. of Maryland

Sch. of Med., Baltimore, MD; [4]Univ. of Maryland, Baltimore, Baltimore, MD; [5]NIMH Psychoactive Drug Screening Program, Dept. of Pharmacol. and Div. of Chem. Biol. and Medicinal Chemistry, Univ. of North Carolina Chapel Hill Med. Sch., Chapel Hill, NC; [6]Div. Intramural Res. Program, NIMH, Bethesda, MD

Abstract: Ketamine alleviates depressive symptoms in treatment-resistant depressed patients within hours following a single infusion and this effect typically persists for many days. In preclinical animal tests, metabotropic glutamate receptor 2/3 (mGluR2/3) antagonists exert rapid and sustained antidepressant actions, similar to ketamine. Based upon their similar rapid antidepressant actions we hypothesized that convergent mechanisms exist between ketamine and mGluR2/3 antagonists. Using both pharmacological manipulations, as well as genetic knockout mice, we examined the role of mGluR2 and mGluR3 receptors in the antidepressant behavioral actions of ketamine and its active metabolite, (*2R,6R*)-hydroxynorketamine (HNK). This approach was complemented by *in vivo* quantitative electroencephalographic measurements to assess for high-frequency gamma oscillation changes following (*2R,6R*)-HNK administration to mGluR2 and mGluR3 knockout mice or following a pre-treatment with an mGluR2/3 agonist. Ketamine and (*2R,6R*)-HNK prevented mGluR2 agonist-induced hyperthermia. Combined sub-threshold doses of the mGluR2/3 antagonist LY341495 and (*2R,6R*)-HNK induced a synergistic effect to exert robust antidepressant behavioral actions. Furthermore, we found that activity of mGluR2, but not mGluR3, receptors is involved in the antidepressant actions of both ketamine and (*2R,6R*)-HNK, since these actions were absent in mGluR2, but not mGluR3, knockout mice and were prevented by pre-treatment an mGluR2/3 agonist. (*2R,6R*)-HNK-induced increases in gamma EEG power were also absent in mGluR2, but not mGluR3, knockout mice and in mice pre-treated with an mGluR2/3 agonist (LY379268). *In vitro* functional assays found that (*2R,6R*)-HNK does not exert agonist or antagonist activity on the mGluR2 or the mGluR3 receptors suggesting that convergent mechanisms are either upstream or downstream of mGluR2 activity. These findings highlight the presence of a common mechanism underlying the antidepressant actions of ketamine/(*2R,6R*)-HNK and mGluR2 antagonists. Our data also support the existence of a convergent pathway underlying rapid antidepressant efficacy, which might involve enhanced high-frequency gamma activity. Moreover, our data support the use of drugs with mGluR2 antagonist activity in experimental therapeutic trials either alone or in combination with ketamine or (*2R,6R*)-HNK for treatment-resistant depression.

Disclosures: P. Zanos: Other; P.Z. is listed as co-author in patent applications related to the pharmacology and use of (2S,6S)- and (2R,6R)-hydroxynorketamine in the treatment of mood disorders. **J.N. Highland:** None. **P. Georgiou:** None. **X. Kang:** None. **C.A. Zarate:** Other; C.A.Z. is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation., C.A.Z. is also listed as co-author in a patent applications related to the pharmacology and use of (2S,6S)- and (2R,6R)-hydroxynorketamine in the treatment of mood disorders. **T.D. Gould:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); T.D.G. has received research funding from Janssen Pharmaceuticals and Roche Pharmaceuticals during the preceding three years. F. Consulting Fees (e.g., advisory boards); T.D.G. has received consulting fees from Janssen Pharmaceuticals. Other; T.D.G. is

listed as co-author in a patent applications related to the pharmacology and use of (2S,6S)- and (2R,6R)-hydroxynorketamine in the treatment of mood disorders.

Nanosymposium

721. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC 24

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 721.03

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: ETSU RDC major grant
NIH AG029493
Quillen College of Medicine

Title: CNTF promotes and reduces depressive-like behavior in female and male mice, respectively

Authors: *C. JIA[1], R. W. BROWN[3], H. M. MALONE[2], K. C. BURGESS[2], W. D. GILL[2], M. P. KEASEY[2], T. HAGG[1]
[1]Dept. of Biomed. Sci., [2]East Tennessee State Univ., Johnson City, TN; [3]East Tennessee State Univ. Dept. of Biomed. Sci., Johnson City, TN

Abstract: Ciliary neurotrophic factor (CNTF) is produced by astrocytes and promotes neurogenesis and neuroprotection. Little is known about the role of CNTF in affective behavior. We investigated whether CNTF affects depressive- and anxiety-like behavior in 3-4 month old mice using a battery of tests. Female wildtype CNTF+/+ (C57BL/6 background) mice had a longer immobility time in the forced swim test than male CNTF+/+ littermates, indicating that females more readily develop learned helplessness. Female CNTF+/+ mice had longer immobility times than female CNTF-/- littermates. In contrast, male CNTF+/+ mice displayed less immobility time than male CNTF-/- littermates. Together these data indicate that CNTF increases learned helplessness in females but reduces it in males. These differences were not due to motor deficits. Further, female CNTF-/- mice had a higher sucrose preference than female CNTF+/+ mice, suggesting that CNTF in females promotes behavioral anhedonia. To determine whether CNTF is involved in hormone-regulated learned helplessness mice were gonadectomized. Naïve female wildtype mice had more CNTF in the hypothalamus and amygdala than male mice, which may contribute to the greater depressive-like behavior in females. Ovariectomy (OVX) increased CNTF expression in the amygdala, as well as the immobility time, but this did not occur in CNTF-/- mice. This suggests that ovarian hormones inhibit CNTF expression in the amygdala and that OVX-induced learned helplessness is mediated entirely by CNTF. In vitro, progesterone but not 17-β estradiol inhibited CNTF expression in C6 astroglioma cells. In female mice, progesterone blocked the OVX-induced increase in immobility time in CNTF+/+ but not CNTF-/- mice, suggesting that progesterone-

mediated inhibition of CNTF, possibly in the amygdala, is one of the underlying mechanisms of OVX-induced depressive-like behavior. Castration did not alter CNTF expression in males, nor their learned helplessness, indicating a hormone-independent mechanism of depressive behavior. CNTF did not play a role in anxiety-like behavior tested by elevated T maze. This study reveals a novel CNTF-mediated mechanism in female depressive-like behavior and points to opportunities for sex-specific treatments for depression.

Disclosures: C. Jia: None. **R.W. Brown:** None. **H.M. Malone:** None. **K.C. Burgess:** None. **W.D. Gill:** None. **M.P. Keasey:** None. **T. Hagg:** None.

Nanosymposium

721. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC 24

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 721.04

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: National Science Foundation of China (81673625)

Title: Impairment of hippocampal PKA-CREB and NMDA signaling in a novel model for long-term depressive behaviors, and repaired selectively with antidepressants

Authors: *G. CHEN, Z. ZOU, W. XUE, X. ZHOU
Nanjing Univ. of Chinese Med., Jiangsu, China

Abstract: Major depressive disorder is chracterized with the long-term depressive condition, which however has not well modeled using many existing paradigms. This hampered the assessment of the long-term therapeutic effects of an antidepressant. Here we developed an easily controlled protocol for intermittent learned helplessness (iLH) which resulted in at least for 1 month post termination of the stress. Using the model, we compared the efficacy of conventional antidepressant fluoxetine and Yueju pill, a traditional Chinese medicine formulated to treat syndromes of mood disorders, and investigated the role of neural plasticity associated with PKA- (protein kinase A-) CREB (cAMP response element binding protein) and NMDA (N-methyl-D-aspartate) signaling. We showed that a single low dose of Yueju demonstrated antidepressant effects in tests of tail suspension, forced swim, and novelty-suppressed feeding. Repeated administration of Yueju following iLH remarkably alleviated all of depressive-like symptoms measured, whereas fluoxetine only showed a minor improvement. In the hippocampus, Yueju and fluoxetine both normalized brain-derived neurotrophic factor (BDNF) and PKA level. Only Yueju, not fluoxetine, rescued the deficits in CREB signaling. Furthermore, The iLH upregulated the expression of NMDA receptor subunits NR1, NR2A, and NR2B, which were all attenuated by Yueju. An intracerebraventricular administration of NMDA blunted the antidepressant effect of Yueju. These findings supported the antidepressant efficacy of repeated

routine dose of Yueju in a long-term depression model and the critical role of CREB and NMDA signaling.

Disclosures: G. Chen: None. **Z. Zou:** None. **W. Xue:** None. **X. Zhou:** None.

Nanosymposium

721. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC 24

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 721.05

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH grant MH-094268 Silvio O. Conte center
NIH grant DA-040127
JST PRESTO grant JPMJPR14M6

Title: Influence of adolescent stress on regulation of the HPA axis and postpartum behaviors

Authors: S. LOCKHART, J. L. PAYNE, *M. NIWA, A. SAWA
Psychiaty and Behavioral Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Adverse events in early life have a major, and often irreparable, effect on adult behaviors. Mood disturbance and cognitive impairment during the postpartum period are common and serious mental health problems that affect not only mothers, but also their children. These psychiatric disturbances may be augmented by early life stress, but its mechanism remains elusive. In the present study, we tested how adolescent psychosocial stress alters first-time mothers' behavioral patterns related to mood and social cognition in the postpartum period. We observed in mice that exposure to three-week isolation stress during late adolescence produced a sustained elevation of plasma glucocorticoids, potentially from a lack of negative feedback of the hypothalamic-pituitary-adrenal (HPA) axis, that occurred soon after delivery. We also observed subsequent behavioral deficits at one-week postpartum, but not immediately after delivery in mice. These behavioral deficits were prolonged at least for three weeks after delivery. The onset of behavioral changes coincided with the sustained increase in plasma glucocorticoids in mice exposed to adolescent stress, but not those without the adolescent stress. To determine whether the aberrantly sustained elevation of glucocorticoids during the postpartum period caused the postpartum behavioral deficits, we used a selective glucocorticoid receptor antagonist and found an amelioration of the behavioral deficits. To further elucidate the mechanisms that account for the deficits of the HPA axis, we administered dexamethasone to suppress adrenocorticotropic hormone and glucocorticoid release, but observed a lack of suppression only in postpartum mice that experienced adolescent stress. These results suggest that there is a disruption of negative feedback of the HPA axis in the stressed mice that is not present in non-stressed mice. We also measured plasma samples from pregnant women with a history of a mood disorder to assess

glucocorticoid levels throughout pregnancy and the postpartum period. Our study provides insight into how adolescent psychosocial stress can lead to enduring physiological effects that may influence postpartum behaviors in adulthood.

Disclosures: S. Lockhart: None. **J.L. Payne:** None. **M. Niwa:** None. **A. Sawa:** None.

Nanosymposium

721. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC 24

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 721.06

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Neuroimaging based prediction of individual treatment outcome with DLPFC-rTMS in depression: A machine learning approach

Authors: *R. CASH[1], L. COCCHI[2], R. ANDERSON[1], A. ZALESKY[3], P. FITZGERALD[1]
[1]Monash Alfred Psychiatry Res. Ctr., Melbourne, Australia; [2]Mental Hlth., QIMR Berghofer, Herston, Australia; [3]Melbourne Neuropsychiatry Ctr., Melbourne, Australia

Abstract: The neurobiology of major depressive disorder (MDD) remains incompletely understood and many patients fail to respond to first-line treatment. Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex has emerged as a promising therapy for treatment resistant depression. However, the cost, time taken to establish treatment success, and heterogeneity of treatment response highlight a pressing need for biomarkers of treatment outcome, especially for patients at risk of suicide. Resting state functional magnetic resonance imaging (rsfMRI) has shown significant promise in identifying functional connectivity abnormalities in depression and recent animal work suggests that signal amplitude (or power) may be a feature of neural dynamics that provides orthogonal information to functional connectivity. We explored BOLD power abnormalities in MDD and whether multivariate machine learning (ML) incorporating connectivity and power features could predict treatment outcome. RsfMRI data was collected in 47 MDD patients prior to 4-6 weeks of rTMS treatment and in 29 healthy individuals. We identified novel and striking reductions in BOLD signal power in patients compared to healthy individuals, which localised to brain areas implicated in the pathophysiology of depression and proposed mechanism of rTMS treatment response. Moreover, BOLD power correlated with rTMS treatment outcome. Functional connectivity in the default mode and affective networks also correlated with treatment outcome. Our ML approach integrating default mode and affective connectivity and power features could classify treatment response with 85-95% accuracy. This provides a novel, physiologically plausible, transparent and comparatively simple ML approach incorporating few core neurobiological features of MDD for the accurate classification of DLPFC-rTMS treatment outcome which may prove clinically

useful. Moreover, these data identify reduced BOLD signal power as novel feature in the neurobiological signature of depression.

Disclosures: L. Cocchi: None. **R. Anderson:** None. **A. Zalesky:** None. **P. Fitzgerald:** None.

Nanosymposium

721. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC 24

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 721.07

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: MH105623

Title: Antidepressant effects of the ketamine metabolite hydroxynorketamine

Authors: *C. A. BROWNE[1], H. A. WULF[1], C. A. ZARATE, JR[2], I. LUCKI[1]
[1]Pharmacol. & Mol. Therapeut., Uniformed Services Univ., Bethesda, MD; [2]Div. Intramural Res. Program, NIMH, Bethesda, MD

Abstract: Major Depression Disorder (MDD) is one of the leading causes of disability and functional impairment worldwide. Characterized by persistent negative mood and anhedonia, only 30-50% of patients achieve remission of their symptoms in response to their first antidepressant drug. Ketamine is an N-methyl D-aspartate (NMDA) receptor antagonist that demonstrates robust antidepressant effects in treatment-resistant patients at subanesthetic doses within hours of infusion. Despite its potential to treat MDD, its inherent psychomimetic effects and abuse liability may limit ketamine's widespread use. Development of a ketamine-like compound that does not produce side effects would be of significant clinical value. Emerging evidence from preclinical studies suggest that ketamine's metabolite hydroxynorketamine (HNK) can produce ketamine-like antidepressant activity without side effects. The studies reported here were conducted to corroborate this hypothesis.
The behavioral effects of ketamine (10 mg/kg) and the R and S enantiomers of HNK (10 mg/kg) were compared with saline and the antidepressant desipramine (20 mg/kg) in 8 - 12-week-old C57BL/6J mice. Antidepressant-like activity, measured as decreased immobility in the forced swim test (FST), was examined 24 h, 7 and 14 days post dosing, using a regimen (3 injections, 48 h apart) adapted from clinical trial procedures for treatment-resistant subjects. The behavioral effects of HNK were compared with the motoric and analgesic effects of ketamine in locomotor activity and hot plate (55°C) assays respectively.
R-HNK ($p<0.01$) and S-HNK ($p<0.01$) exerted an immediate antidepressant-like response in the mouse FST, comparable to that of ketamine. At 7 days, ketamine ($p<0.05$), R-HNK ($p<0.001$), and S-HNK ($p<0.001$) produced marked reductions in immobility, these effects were not evident 14 days post treatment. Unlike ketamine, HNK did not alter the latency of mice to withdraw their

hind paw in the hot plate test, or evoke hyperactivity immediately following administration. These data confirm the antidepressant-like activity of HNK and determine that HNK is not active in tasks where ketamine's behavioral effects are mediated through NMDA receptors. HNK has potential as a novel, fast-acting antidepressant that may be able to fill an important treatment gap for MDD.

Disclosures: C.A. Browne: None. **H.A. Wulf:** None. **C.A. Zarate:** A. Employment/Salary (full or part-time):; National Institute of Health. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr Zarate is listed a co-inventor on a patent for the use of ketamine and its metabolites in the treatment of depression, anxiety, anhedonia, suicidal ideation and post-traumatic stress disorders., Dr. Zarate has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government.. **I. Lucki:** None.

Nanosymposium

721. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC 24

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 721.08

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: XPro1595 supplied by Inmune Bio

Title: Antidepressant and anxiolytic effects of tumor necrosis factor inhibition with XPro1595 in a rodent model of antidepressant-resistance

Authors: *J. PRICE, D. MALTAIS[1], K. BUTTERS[1], S. MCGEE[2], S. J. TYE[3]
[1]Mayo Clin., Rochester, MN; [2]Sch. of Med., Deakin Univ., Geelong, Australia; [3]Univ. of Queensland, Brisbane, Australia

Abstract: Background: Factors contributing to antidepressant-resistance remain unclear. However, inflammation is being increasingly associated with poor outcome to first line treatments. The aim of this project was to examine the antidepressant and anxiolytic effect of XPro1595, a novel agent that selectively blocks soluble Tumor Necrosis Factor (TNF) from binding to the TNF receptor, in a rodent model of adrenocorticotrophic hormone (ACTH)-induced antidepressant treatment-resistance.
Methods: To establish an antidepressant-resistant phenotype, male Wistar rats were administered ACTH (100ug/day, 14 days) in combination with XPro1595 (10mg/kg; 2 days; n=38) or control vehicle saline (0.9%; n=28). An additional cohort was administered saline in combination with XPro1595 (n=30) or saline (n=26). Rats were then subjected to open field (6 minutes) and forced swim tests (6 minutes), or elevated zero maze testing (15 minutes). 30 minutes after behavioral testing, rats were euthanized and cardiac blood and brain tissue were immediately collected.

Enzyme-linked-immusorbent assays (ELISAs) were performed to detect CRP in blood samples. Results: XPro1595 significantly reduced immobility time during the forced swim test in animals pre-treated with ACTH ($p<0.05$), but not saline (p=n.s.). Open field testing did not reveal significant pre-existing differences in locomotor activity between groups (p=n.s.), thereby reinforcing the validity of forced swim test outcomes. Anxiolytic effects of XPro1595 were observed across both treatment groups; XPro1595 significantly increased time spent in the open arms of the elevated zero maze for animals pre-treated with either ACTH ($p<0.01$) or saline ($p<0.05$). Additionally, Xpro1595 was observed to significantly reduce CRP in rats pre-treated with ACTH ($p<0.05$), but not saline (p=n.s.).
Conclusions: These results suggest an important relationship between soluble TNF and antidepressant outcomes. Here, XPro1595 has demonstrated a capability in producing antidepressant- and anxiolytic-like behavioral effects, while lowering CRP levels in rats modelling antidepressant treatment-resistance.

Disclosures: J. Price: None. **D. Maltais:** None. **K. Butters:** None. **S. McGee:** None. **S.J. Tye:** None.

Nanosymposium

721. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC 24

Time: Wednesday, November 7, 2018, 1:00 PM - 3:15 PM

Presentation Number: 721.09

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CIHR (Y.T.W., A.G.P.)
UBC Graduate Four Year Fellowship

Title: Extending the characterization of the Wistar-Kyoto genetic model of depression in the context of ketamine's antidepressant properties

Authors: *L. ALEKSANDROVA[1], C. J. BURKE[5], G. L. DALTON[2], D. R. EUSTON[5], S. M. PELLIS[5], S. B. FLORESCO[2], Y. T. WANG[3], A. G. PHILLIPS[4]
[1]Neurosci., [2]Psychology, [3]Neurol., [4]Psychiatry, Univ. of British Columbia, Vancouver, BC, Canada; [5]Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada

Abstract: Background. The Wistar-Kyoto (WKY) rat exhibits a high physiological susceptibility to stress and displays preclinical symptoms of depression. The present study extends the range of domains affected in the WKY rat model to include aspects of motivation and cognition, ultrasonic social vocalization, as well as synaptic plasticity. Methods. We utilized a battery of behavioural tests, including the forced swim test (FST), progressive ratio (PR) schedule of reinforcement, probabilistic reversal learning (PRL) task, object location recognition (OLR) test, as well as measuring social interaction (SI) and ultrasonic vocalizations (USVs) during

anticipation of SI. WKYs were further characterized in terms of their antidepressant response to ketamine (5-10mg/kg, ip), as well as hippocampal (HPC) synaptic transmission and plasticity using in vivo field recordings and western blotting. Results. WKYs exhibited pronounced impairments across all behavioural tests as compared to normal Wistar controls, including increased FST immobility ("despair"), lower PR break point (lower motivation/effort), various PRL deficits (altered sensitivity to positive/negative feedback), deficient discrimination in the OLR test (impaired long-term spatial memory), social withdrawal as well as an altered USV profile (deficient social communication/hedonic function). In addition, WKY rats displayed impaired CA1 long-term potentiation (LTP) in vivo. Importantly, ketamine, which produced significant rapid (30min) and sustained (24h-7d) antidepressant effects in the FST, also acutely restored the impaired HPC LTP in WKYs at 3.5h after injection, leading to a subsequent increase in CA1 basal transmission and HPC AMPAR subunit surface expression at 24h. Conclusions. The depressive-like phenotype of the WKY rat more closely parallels the complex range of functional domains that define clinical depression, including aspects of motivation and cognition rarely studied in preclinical models of depression. Accordingly, this project illustrates the feasibility of utilizing a comprehensive battery of preclinical tests related to emotional reactivity, motivation and cognition in animal models of depression. The functional relevance of the impaired HPC LTP in WKYs and its modulation by ketamine is currently under investigation. Ketamine's effects on HPC synaptic plasticity and AMPAR expression may mediate/ contribute to its general mechanism of action as an antidepressant or could be more specifically related to hippocampal-dependent processes, such as spatial learning and memory.

Disclosures: L. Aleksandrova: None. **C.J. Burke:** None. **G.L. Dalton:** None. **D.R. Euston:** None. **S.M. Pellis:** None. **S.B. Floresco:** None. **Y.T. Wang:** None. **A.G. Phillips:** None.

Nanosymposium

722. Looking For Biological Interventions for Cocaine Use Disorder

Location: SDCC 1

Time: Wednesday, November 7, 2018, 1:00 PM - 3:30 PM

Presentation Number: 722.01

Topic: G.08. Drugs of Abuse and Addiction

Support: Rubicon 446-14-015
1K01DA043615-01A1
R01MH090134
R01DA041528
U01DA041174

Title: Resting-state connectivity defines neurobiological subtypes underlying different cognitive-emotional profiles in cocaine addiction

Authors: *A. ZILVERSTAND[1], P. CURTIN[2], M. A. PARVAZ[3], A. B. KONOVA[4], C. M. LISTON[5], N. ALIA-KLEIN[3], R. Z. GOLDSTEIN[3]
[1]Psychiatry, [2]Envrn. Med. & Publ. Hlth., [3]Psychiatry and Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]Ctr. for Neural Sci., New York Univ., New York, NY; [5]Psychiatry and Neurosci., Weill Cornell Med. Col., New York, NY

Abstract: Background: We applied data-driven methods to discover neurobiological subtypes of cocaine addiction based on individuals' brain function alone. We hypothesized that different neurobiological subtypes would be associated with different cognitive-emotional functioning.
Methods: We acquired a resting-state scan from 42 individuals with cocaine addiction and 32 healthy controls and applied Graph theory methods to extract functional connectivity (Global Efficiency) from 638 brain regions. The average Global Efficiency of 16 large-scale brain networks was input into an unsupervised classifier (self-organizing map), which generated a similarity map of the brain connectivity of all participants. K-centroid clustering was applied to detect subgroups within this map. We then characterized the cognitive-emotional functioning of the discovered neurobiological subtypes post-hoc by statistically comparing their reward reactivity [measured by the Multidimensional Personality Questionnaire (MPQ): Positive Emotionality scale (MPQ-PEM); % risky choice after wins in a novel Risk-Value Decision Making Task], inhibitory control capacity [measured by the MPQ: Constraint scale (MPQ-CON); Stop Signal Reaction time (SSRT) in a Stop Signal Reaction Time Task] and clinical characteristics (derived from a Structured Clinical Interview).
Results: We identified four neurobiological subtypes, two of which contained 90% of the cocaine users (and 6% of controls, diagnostic accuracy = 92%). The first cocaine user subtype (N=20), who demonstrated increased salience network (insula/dACC) connectivity also showed increased reward sensitivity and seeking (MPQ-PEM and % risky choice after wins, $p<0.05$ corrected for multiple comparisons). The second cocaine user subtype (N=20), who showed increased motor network connectivity (M1) also showed reduced constraint and impaired motor inhibition (MPQ-CON and SSRT, $p<0.05$ corrected). These neural-behavioral impairments were dissociated, with the "reward reactive" subtype showing normal inhibitory control/motor network connectivity (compared to controls) and the "low constraint" subtype demonstrating normal reward reactivity/salience network connectivity. The two cocaine subtypes did not differ in recency/chronicity of cocaine use.
Conclusions: Results suggest different underlying mechanisms in each subtype, rather than differences in addiction severity. These findings have important implications for developing individually targeted treatments for cocaine addiction that could differentially focus on normalizing impaired inhibitory control/execution of action or drug cue hyper-reactivity.

Disclosures: A. Zilverstand: None. **P. Curtin:** None. **M.A. Parvaz:** None. **A.B. Konova:** None. **C.M. Liston:** None. **N. Alia-Klein:** None. **R.Z. Goldstein:** None.

Nanosymposium

722. Looking For Biological Interventions for Cocaine Use Disorder

Location: SDCC 1

Time: Wednesday, November 7, 2018, 1:00 PM - 3:30 PM

Presentation Number: 722.02

Topic: G.08. Drugs of Abuse and Addiction

Support: PHS DA016511
DA006214
4T32ES007148

Title: Serotonin and norepinephrine signaling in dorsal CA1 drive sex differences in persistent cocaine-seeking

Authors: *A. S. KOHTZ[1], J. ZHAO[2], G. S. ASTON-JONES[3]
[1]Neurosci., [2]Brain Hlth. Inst., Piscataway, NJ; [3]Brain Hlth. Inst., Rutgers Univ., Piscataway, NJ

Abstract: The initiation of abstinence from a chronically self-administered drug is a stressful event. Cocaine-seeking on the first day that an expected drug is absent (extinction day 1, ED1) is reduced in males and females by blocking 5-HT signaling in dorsal hippocampus CA1 (CA1), or by blocking CA1 norepinephrine (NE) in females only. **Hypothesis**: The experience of ED1 can substantially influence later relapse behavior, and dorsal raphe serotonin (DR 5HT) and locus coeruleus NE (LC-NE) signaling to CA1 are involved in this influence of early abstinence on later abstinence. Control rats were either saline or aCSF administered. All n=8/group. **Serotonin:** We inhibited 5HT1A/1B receptors (via WAY100,635 plus GR127935, vs saline), or DR input (via DREADDs, CNO vs aCSF), in CA1 on ED1 and tested cocaine-seeking persistence after 2 weeks in the home cage. Our results indicate that inhibition of DR projections, or 5HT1A/1B signaling in CA1 on ED1 decreased drug-seeking on ED1, and also persistently decreased cocaine-seeking after 2 weeks in the home cage. These data confirm that 5-HT signaling in CA1 is involved in the impact of initial abstinence on later (persistent) drug-seeking after additional abstinence. We then inhibited 5HT1A or 5HT1B receptors in CA1 during conditioned place preference for cocaine, to examine mechanisms involved in persistent effects of ED1 manipulations. Administration of a 5HT1B antagonist alone immediately prior to testing transiently decreased drug-associated memory performance in CPP, whereas administration of a 5HT1A antagonist on test day had no effect on memory but blocked CPP on a test 24h later. **Norepinephrine:** Antagonism of β-adrenergic signaling in the CA1 with betaxolol plus ICI-118,551 (β1 and β2 antagonists) on ED1 reduced persistent cocaine-seeking in females only. Inhibition of the LC-NE projection to CA1 with a PRSx8 promoter-driven hM4Di DREADD (to limit expression to NE neurons) decreased ED1 seeking and persistence in females, but had no effect in males. Interestingly, activation of LC-NE to CA1 via a similar hM3Dq DREADD on ED1 increased seeking on ED1 in males, and decreased seeking persistence in females. We

found that activation of the LC-NE to CA1 pathway induced anxiogenic behavior (elevated plus maze) in both males and females, without altering motor behavior. **Conclusions:** DR inputs to CA1 on ED1 augments recall of the drug-associated context, whereas LC inputs to CA1 on ED1 drives stress encoding, increasing seeking-persistence in females only. Thus, treatments that inhibit 5HT-dependent memory and LC-dependent stress responses during initial abstinence may facilitate later maintenance of abstinence.

Disclosures: A.S. Kohtz: None. **J. Zhao:** None. **G.S. Aston-Jones:** None.

Nanosymposium

722. Looking For Biological Interventions for Cocaine Use Disorder

Location: SDCC 1

Time: Wednesday, November 7, 2018, 1:00 PM - 3:30 PM

Presentation Number: 722.03

Topic: G.08. Drugs of Abuse and Addiction

Support: P30 DA029925

Title: Pharmacological versus genetic ablation of b-arrestin2 signaling at the ghrelin receptor: Differential effect on cocaine-induced hyperlocomotion

Authors: *K. TOTH[1,4], L. M. SLOSKY[1], T. EVRON[1], N. M. URS[1,5], P. BOONE[1], M. G. CARON[1,2,3], L. S. BARAK[1]
[1]Cell Biol., [2]Neurobio., [3]Med., Duke Univ., Durham, NC; [4]Pharmaceut. Sci., Campbell Univ., Buies Creek, NC; [5]Pharmacol. and Therapeut., Univ. of Florida, Gainesville, FL

Abstract: Many highly abused drugs like the psychostimulant cocaine increase brain dopamine and produce hyperlocomotion in experimental animal models of addictive behaviors. The G protein-coupled ghrelin receptor (GHSR1a) is an endogenous regulator of brain dopamine signaling in mammals and thus a promising target for treating drug abuse. GHSR1a(s) signal through G protein and β-arrestin mediated pathways that independently converge on dopamine signaling. Therefore, functionally selective drugs that selectively modulate only one of the two GHSR1a signaling arms could provide non-redundant therapeutic outcomes. Additionally, because GHSR1a/β-arrestin signaling affects cocaine-induced synaptic plasticity, a fundamental role for β-arrestin signaling may arise during the formation of drug-associated behaviors. We have investigated the GHSR1a/β-arrestin signaling arm *in cellulo* by bioluminescence resonance energy transfer (BRET) and *in vivo* with C57BL/6J background mice by open field locomotion studies. In cells, GHSR1a formed more stable complexes with β-arrestin2 than with β-arrestin1, and the β-arrestin2 interaction was determined using the kinase inhibitor, Compound 101, to be G protein receptor kinase2 dependent. In full body β-arrestin2 KO mice, brain-conditional β-arrestin2 KO mice, and the wild-type littermates of these mice, we evaluated the effects of GHSR1a antagonism on cocaine sensitization. KO and wild-type mice both exhibited

comparable levels of locomotor sensitization following repeated cocaine exposure (20 mg/kg, i.p. for 5 days). In contrast, cocaine-induced hyperlocomotion was attenuated only in wild-type mice by the GHSR1a antagonist YIL781 (10 mg/kg, i.p.) and not in the β-arrestin-2 KO mice. These data suggest that the attenuation of hyperlocomotion is β-arrestin2-dependent and G-protein independent and indicate that the short-term consequences of pharmacologic ablation of β-arrestin2 pathway activity differs from permanent genetic ablation. Moreover, this study supports the development and therapeutic use of novel functionally selective ligands in targeting GHSR1a signaling as well as GPCR signaling in general.

Disclosures: K. Toth: None. **L.M. Slosky:** None. **T. Evron:** None. **N.M. Urs:** None. **P. Boone:** None. **M.G. Caron:** None. **L.S. Barak:** None.

Nanosymposium

722. Looking For Biological Interventions for Cocaine Use Disorder

Location: SDCC 1

Time: Wednesday, November 7, 2018, 1:00 PM - 3:30 PM

Presentation Number: 722.04

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA044308

Title: Administration of granulocyte-colony stimulating factor protects against cocaine-seeking in a rodent model

Authors: *R. S. HOFFORD[1], N. L. MERVOSH[1], E. G. PECK[2], E. S. CALIPARI[3], D. D. KIRALY[2,1]
[1]Dept. of Psychiatry, [2]Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Dept. of Pharmacol., Vanderbilt Univ. Sch. of Med., Nashville, TN

Abstract: Psychostimulant use disorder remains a significant health burden in the United States and around the world. Currently, there are no FDA-approved treatments for this condition and candidate pharmaceuticals have had limited efficacy and unwanted side effects. Hence, identifying novel targets for the treatment of cocaine addiction is extremely urgent. Given the chronic relapsing-remitting nature of addiction, it is especially important to identify therapeutics that are effective when administered during drug-free periods that may reduce propensity to relapse. Recently, our lab and others have identified neuroimmune signaling pathways as key contributors to the addiction process. We have shown that signaling of one cytokine in particular, granulocyte-colony stimulating factor (G-CSF), is necessary for formation of cocaine conditioned place preference in mice. For the current set of studies, we sought to determine if G-CSF signaling could be utilized to reduce reinstatement behaviors and, therefore, might be a viable translational treatment strategy. Male Sprague-Dawley rats were trained to stably self-administer cocaine (0.8 mg/kg/infusion) before undergoing a combined extinction/abstinence

paradigm, where rats underwent periods of both extinction and abstinence before consecutive cue- and cocaine prime-induced reinstatement tests. On the day following the last self-administration session, rats underwent extinction training for five days, where active lever presses no longer resulted in cocaine infusion or cue presentation, followed by an abstinence period where rats remained in their home cages. Daily injections of vehicle (1x PBS) or G-CSF (50 ug/kg, i.p.) were given to rats either: a) 30 minutes before each extinction session or b) during abstinence and 30 minutes before each reinstatement test. When administered during extinction, G-CSF decreased cue-induced reinstatement. However, when administered during abstinence and reinstatement, G-CSF attenuated both cue- and cocaine-primed reinstatement. While more work needs to be done to understand the underlying neural mechanisms responsible, these studies suggest that G-CSF could be used as a treatment to attenuate cocaine-seeking when administered during drug-free periods.

Disclosures: R.S. Hofford: None. **N.L. Mervosh:** None. **E.G. Peck:** None. **E.S. Calipari:** None. **D.D. Kiraly:** None.

Nanosymposium

722. Looking For Biological Interventions for Cocaine Use Disorder

Location: SDCC 1

Time: Wednesday, November 7, 2018, 1:00 PM - 3:30 PM

Presentation Number: 722.05

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA 5R01DA037216-04
VA Merit Award

Title: Assessing the role of ASIC1A in cocaine self-administration in mice

Authors: *R. J. TAUGHER[1,3], A. GHOBBEH[1,3], M. M. CONLON[1,3], R. T. LALUMIERE[2], J. A. WEMMIE[1,3]
[1]Psychiatry, [2]Dept. of Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA; [3]Veteran's Affairs Med. Ctr., Iowa City, IA

Abstract: Drug abuse is difficult to treat and relapse is common. An incomplete understanding of the mechanisms underlying drug seeking hinders development of novel therapies. Our recent work suggests that the acid-sensing ion channel-1A (ASIC1A) may be a potential therapeutic target. ASIC1A is a cation channel activated by extracellular acidosis. It is expressed postsynaptically, where it is activated by protons released during neurotransmission. ASIC1A is abundantly expressed in the nucleus accumbens (NAc), a region implicated in cocaine-evoked plasticity and behavior. Our previous study found that ASIC1A regulates glutamatergic transmission and dendritic spine morphology in the NAc. This study also found that manipulations of ASIC1A altered cocaine-reinforced behaviors. In mice, ASIC1A disruption

boosted cocaine conditioned place preference; in rats, overexpression of ASIC1A in NAc attenuated cocaine self-administration. Together, these studies suggest that ASIC1A opposes cocaine seeking. The goal of the current study is to take advantage of existing tools for manipulating ASIC1A in mice to further characterize the role of ASIC1A in cocaine self-administration. We hypothesized that ASIC1A disruption will increase cocaine seeking. Consistent with this hypothesis, our results suggest that *Asic1a*$^{-/-}$ mice self-administer more cocaine than *Asic1a*$^{+/+}$ controls. In future studies, this technique will enable us to assess craving and relapse in mice. Because animals control their own dosing in self-administration it is thought to more closely parallel human substance abuse. Ultimately, these studies, along with parallel physiological studies, will provide insight into the therapeutic potential of targeting brain pH or ASIC1A for the treatment of substance use disorders.

Disclosures: R.J. Taugher: None. **A. Ghobbeh:** None. **M.M. Conlon:** None. **R.T. LaLumiere:** None. **J.A. Wemmie:** None.

Nanosymposium

722. Looking For Biological Interventions for Cocaine Use Disorder

Location: SDCC 1

Time: Wednesday, November 7, 2018, 1:00 PM - 3:30 PM

Presentation Number: 722.06

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA 032898

Title: Learning to resist drugs through transient suppression of dopaminergic activity

Authors: *P. J. VENTO[1], D. PULLMANN[1], J. TOMBERLIN[2], S. L. BLACK[2], T. C. JHOU[1]
[1]Med. Univ. of South Carolina, Charleston, SC; [2]Col. of Charleston, Charleston, SC

Abstract: Addictive and compulsive disorders are marked by aberrant decision-making and an inability to suppress inappropriate and often dangerous behaviors. While most healthy individuals shift strategies when outcomes become less than optimal, humans addicts along with rodent models of addiction display resistance to the suppressive effect of punishment on reward seeking. While increased dopamine (DA) activity has been strongly implicated in reinforcement and approach behavior, far less is known about how reductions in DA-ergic activity guide avoidance and behavioral inhibition. The rostromedial tegmental nucleus (RMTg) is activated by a wide range of aversive stimuli, as well as many drugs of abuse, and provides a major inhibitory input to midbrain DA neurons, and we recently found that inhibition of RMTg projections to the DA-ergic ventral tegmental area (VTA) causes persistent food seeking in the presence of an aversive footshock. Given this role for the RMTg in behavioral inhibition, we hypothesized that the RMTg-VTA pathway may be similarly important in suppressing drug-seeking behavior. To test this, we developed a punished cocaine seeking model in which rats trained to lever press for

cocaine infusions received concurrent punishment in the form of brief footshock that gradually increased in intensity until rats effectively inhibited drug seeking. We found that inactivation of RMTg projections to the VTA using inhibitory *designer receptors exclusively activated by designer drugs* (Gi DREADDs) increased the maximum shock rats would endure to receive cocaine infusion, an effect analogous to the punishment resistance observed after protracted drug use. To test whether RMTg stimulation alone, in the absence of footshock, was sufficient to suppress cocaine self-administration, we next used an optogenetic approach to stimulate RMTg projections to the VTA using a temporal pattern designed to mimic the shock experiment above. Although stimulation of the RMTg-VTA pathway was not sufficient to reduce cocaine self-administration, it completely blocked cue-induced reinstatement during subsequent test sessions nearly two weeks later. Together, these results suggest that the RMTg may serve as a particularly useful target for producing enduring reductions in drug craving.

Disclosures: P.J. Vento: None. **D. Pullmann:** None. **J. Tomberlin:** None. **S.L. Black:** None. **T.C. Jhou:** None.

Nanosymposium

722. Looking For Biological Interventions for Cocaine Use Disorder

Location: SDCC 1

Time: Wednesday, November 7, 2018, 1:00 PM - 3:30 PM

Presentation Number: 722.07

Topic: G.08. Drugs of Abuse and Addiction

Support: Fyssen Foundation Post-doctoral grant
NIH DA 003906
NIH DA 12513

Title: Accumbens brain-derived neurotrophic factor (BDNF) transmission inhibits cocaine seeking

Authors: *A.-C. BOBADILLA, C. GARCIA-KELLER, V. CHAREUNSOUK, J. HYDE, D. MEDINA CAMACHO, J. HEINSBROEK, P. KALIVAS
Dept. of Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: Brain-derived neurotrophic factor (BDNF) regulates a variety of physiological processes, and several studies have explored the role of BDNF in addiction-related brain regions like the nucleus accumbens core (NAcore). We sought to understand the rapid effects of endogenous BDNF on cocaine seeking. Rats were trained to self-administer cocaine and extinguished. We then microinjected two inhibitors of BDNF stimulation of tropomyosin receptor kinase B (TrkB), the non-competitive receptor antagonist ANA-12, and TrkB/Fc, a fusion protein that binds BDNF and prevents TrkB stimulation. Blocking TrkB or inactivating BDNF in NAcore potentiated active lever pressing, showing that endogenous BDNF tone was

present and supplying inhibitory tone on cue-induced reinstatement. To determine if exogenous BDNF also negatively regulated reinstatement, BDNF was microinjected into NAcore 15 min before cue-induced reinstatement. BDNF decreased cocaine seeking through TrkB receptor binding, but had no effect on inactive lever pressing, spontaneous or cocaine-induced locomotion, or on reinstated sucrose seeking. BDNF-infusion potentiated within trial extinction when microinjected in the NAcore during cue- and context+cue induced reinstatement, and the inhibition of lever pressing lasted at least 3 days post injection. Although decreased reinstatement endured for three days when BDNF was administered prior to a reinstatement session, when microinjected before an extinction session or in the home cage, BDNF did not alter subsequent cued-reinstatement. Together, these data show that endogenous BDNF acts on TrKB to provide inhibitory tone on reinstated cocaine seeking, and this effect was recapitulated by exogenous BDNF.

Disclosures: A. Bobadilla: 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.; Fyssen Foundation; NIDA. **C. Garcia-Keller:** None. **V. Chareunsouk:** None. **J. Hyde:** None. **D. Medina Camacho:** None. **J. Heinsbroek:** None. **P. Kalivas:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH DA 003906 and DA12513.

Nanosymposium

722. Looking For Biological Interventions for Cocaine Use Disorder

Location: SDCC 1

Time: Wednesday, November 7, 2018, 1:00 PM - 3:30 PM

Presentation Number: 722.08

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA044308
NARSAD Young Investigator Grant

Title: Depletion of the gut microbiome differentially affects the development and persistence of cocaine sensitization

Authors: *K. R. MECKEL, N. L. MERVOSH, D. D. KIRALY
Psychiatry/Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Addiction to cocaine and other drugs of abuse represents a public health crisis leading to substantial social and economic cost. Despite this, there are currently no FDA-approved medications for treatment of psychostimulant use disorders. In recent years, there has been increasing evidence that the bacterial composition of the gut microbiome significantly affects

brain and behavior. Our lab has previously demonstrated that depletion of the gut microbiota significantly affects the formation of conditioned place preference and locomotor sensitization. While previous studies have seen effects in the period immediately after cocaine, there has been no study into the effects of microbiome manipulation during drug abstinence and challenge. For this study, C57BL/6 mice were treated with a prolonged course of non-absorbable antibiotics in the drinking water and compared with untreated controls. After two weeks of treatment, animals were administered saline or cocaine (10 mg/kg i.p.) for five days to promote development of cocaine sensitization. Animals were then returned to their home cages for 28 days of withdrawal before being administered a challenge dose of saline or cocaine (5 mg/kg i.p.), and their locomotor activity monitored. Animals were sacrificed 60 minutes following drug administration; cecal contents were collected for 16S rRNA sequencing and metabolomics analysis, and nucleus accumbens tissue was dissected and processed for RNA sequencing. As we had seen previously, antibiotic-treated mice showed no significant difference in locomotor sensitization to cocaine at the 10 mg/kg dose. However, antibiotic-treated mice exhibited significantly decreased persistence of locomotor sensitization when given a cocaine challenge (5mg/kg) after prolonged withdrawal. These results are contrary to our previous finding that antibiotic-treated mice develop increased sensitization at the 5mg/kg dose, and suggest that fluctuations in the gut microbiome may be playing different roles in the development and persistence of cocaine sensitization. Studies are underway to determine how ongoing changes in the gut microbiota and its metabolites alter gene expression in the nucleus accumbens and ultimately influence the development and persistence of addictive behaviors in response to cocaine.

Disclosures: K.R. Meckel: None. **N.L. Mervosh:** None. **D.D. Kiraly:** None.

Nanosymposium

722. Looking For Biological Interventions for Cocaine Use Disorder

Location: SDCC 1

Time: Wednesday, November 7, 2018, 1:00 PM - 3:30 PM

Presentation Number: 722.09

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant R01-DA031734

Title: CRF enhances a behavioral index of cocaine-seeking via CRF-R_2 in the nucleus accumbens core

Authors: *M. Z. LEONARD[1], H. COVINGTON[2], K. MICZEK[2]
[2]Psychology, [1]Tufts Univ., Medford, MA

Abstract: Adverse life events often precipitate the initiation of- and relapse to- cocaine use in drug-dependent individuals. For example, acute stressors can potently exacerbate the extent to

which drug-related stimuli elicit craving to seek and procure drug, perhaps via peptidergic modulation of mesolimbic dopamine circuitry. Indeed, dopaminergic signaling within nucleus accumbens core (NAcc) is critical to guiding motivated behavior in response to rewarding or aversive stimuli. Therefore, the present studies were designed to examine the extent to which pharmacological manipulation of the stress peptide corticotropin releasing factor (CRF) within the NAcc alters responding for cocaine in the presence of conditioned stimuli. Additionally, we aimed to characterize parameters under which CRF recruits dopamine transmission within the NAcc. To that end, male Long-Evans rats were trained to self-administer cocaine intravenously under a chained schedule of reinforcement (FI-FR) in order to dissociate appetitive ('drug-seeking') from consummatory ('drug-taking') behavior. Completion of a fixed interval (5min.) was followed by 10 min of continuous reinforcement (0.4mg/kg cocaine; FR1) on another lever. After training, rats were microinjected with CRF (50 or 500ng/side) into the NAcc prior to self-administration sessions. Microinfusion of CRF dose-dependently increased responding during the fixed-interval link of the chained schedule, but did not affect subsequent cocaine intake. These effects were CRF-R2-dependent, as CRF-potentiated responding was prevented by pretreatment with Astressin-2B, but not CP376395. Moreover, when administered alone, A2B moderately suppressed cocaine-seeking responses. Parallel microdialysis experiments revealed that CRF infusion into the NAcc is sufficient to elicit a modest increase in extracellular dopamine. In addition to clarifying these CRF-DA interactions, ongoing studies aim to extend neurochemical analyses to assess phasic CRF activity within the NAcc in response to cocaine-predictive cues, and subsequent drug consumption. Taken together these data suggest a role for CRF-R2 in modulating appetitive drug-seeking behavior, perhaps via interactions with NAcc DA, which may offer insight into the substrates of stress-potentiated relapse.

Disclosures: M.Z. Leonard: None. **H. Covington:** None. **K. Miczek:** None.

Nanosymposium

722. Looking For Biological Interventions for Cocaine Use Disorder

Location: SDCC 1

Time: Wednesday, November 7, 2018, 1:00 PM - 3:30 PM

Presentation Number: 722.10

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant F31DA042505
NIH Grant DA031900

Title: Susceptibility to traumatic stress accelerates the development of cocaine-associated dopamine transients and drives cocaine use vulnerability

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: Post-traumatic stress disorder (PTSD) and cocaine use disorder are highly co-morbid psychiatric conditions, with PTSD onset generally occurring prior to the development of cocaine use disorder. Thus, it appears that development of PTSD drives cocaine use vulnerability. We recently characterized a model of PTSD using predator odor stress with segregation of subjects as susceptible or resilient based on elevated plus maze behavior and context avoidance. Using this model, paired with in vivo freely moving fast scan cyclic voltammetry, we measured differences in phasic dopamine signaling (1) in response to a single injection of cocaine, (2) in response to repeated cues that predict the delivery of cocaine injections, and (3) in response to cocaine-paired cues in the absence of a cocaine delivery. In addition, we examined differences in the acquisition of cocaine self-administration behavior across groups. Together, our results suggest that the experience of traumatic stress increases the rate at which phasic dopamine signals entrain to cocaine-associated cues, and that this engenders vulnerability to developing cocaine use disorder following traumatic stress.

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

Nanosymposium

723. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques

Location: SDCC 25

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 723.01

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: ANR Grant ANR-15-CE16-0007

Title: SponGee and SpiCee, genetically encoded tools for cell-specific and subcellular manipulation of cGMP and calcium *in vivo*

Authors: *X. NICOL[1,2,4], O. ROS[3], K. LOULIER[5], S. RIBES[3], S. COUVET[3], Y. ZAGAR[3], A. AGHAIE[6], D. LADARRÉ[7], A. LOUAIL[3], S. BAUDET[3], C. PETIT[6], Z. LENKEI[7], Y. MECHULAM[8]
[1]Inst. de la Vision, CNRS, Paris, France; [3]Inst. de la Vision, [2]Sorbonne Univ., Paris, France; [4]Inserm, Paris, France; [5]UPMC / Inst. De La Vision, PARIS, France; [6]Unite Genetique & Physiologie Audition, Paris, France; [7]ESPCI-ParisTech, Paris, France; [8]Lab. de Biochimie, Ecole Polytechnique, Palaiseau, France

Abstract: Second messengers are mid-point relays in signaling cascades governing a wide range of cellular functions. Calcium is central in multiple cellular responses ranging from metabolism and survival to vesicle release and motility. The blockade of calcium signals currently relies on pharmacological strategies to block calcium influx into the cell or chelate extracellular or intracellular calcium. Since calcium is crucial for a wide range of signaling pathways and for the function of a wide range of components of the extracellular matrix, those strategies lack cellular

specificity and are plagued with a variety of side effects when applied to patients. Similarly, cGMP is involved in a wide range of signaling pathways and cellular processes including neurotransmission, calcium homeostasis, phototransduction, lipid metabolism and cation channel activity. The diversity of these processes suggests that cGMP signals are tightly controlled in space and time to achieve specific modulation of its downstream pathways. However, manipulating cGMP is mostly achieved using pharmacological approaches either altering the synthesis or degradation of this cyclic nucleotide, or manipulating downstream signaling pathways. These techniques lack both cellular and subcellular specificity.
We have developed SponGee and SpiCee, a pair of genetically-encoded buffers that alter physiological changes in the concentration of cGMP and calcium respectively. These tools enable disrupting signaling cascades with cellular and subcellular resolution. We provide evidence that SponGee and SpiCee, both in soluble form or targeted to lipid rafts are able to locally buffer changes in the respective second messenger concentration and to alter downstream cellular processes including axon pathfinding events. In contrast, SponGee and SpiCee excluded from lipid rafts do not affect the behavior of axons exposed to repellent guidance cues. When *in utero* electroporated in the developing brain, SponGee and SpiCee interfere with the migration of newly generated cortical neurons *in vivo* and highlights a non-cell autonomous impact of second messenger manipulation. SponGee and SpiCee pave the way to investigate subcellularly-localized signaling *in vivo*, combined with cellular resolution and to directly manipulate these second messengers for therapeutic use.

Disclosures: **X. Nicol:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CNRS. **O. Ros:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sorbonne Université. **K. Loulier:** None. **S. Ribes:** None. **S. Couvet:** None. **Y. Zagar:** None. **A. Aghaie:** None. **D. Ladarré:** None. **A. Louail:** None. **S. Baudet:** None. **C. Petit:** None. **Z. Lenkei:** None. **Y. Mechulam:** None.

Nanosymposium

723. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques

Location: SDCC 25

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 723.02

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: CREST from JST

Title: Development of a single cell analysis tool for neurological disorders on 2D planar-patch-clamp plate with positional information

Authors: ***S. ISHIGAKI**[1], H. UNO[2], Z.-H. WANG[2], Y. UKITA[3], R. BHARDWAJ[4], T. TUE[4], S. HASHIMOTO[5], T. OKA[6], K. KAWAHARA[6], Y. TAKAMURA[4], T. URISU[2], G. SOBUE[1]

[1]Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan; [2]Nagoya Univ. Inst. of Innovation for Future Society, Nagoya, Japan; [3]Dept. of Interdisciplinary Res., Grad. Sch. of Univ. of Yamanashi, Kofu, Japan; [4]Japan Advanced Inst. of Sci. and Technol., Nomi, Japan; [5]Grad Sch. of Med. Sci, Kanazawa Univ., Kanazawa, Japan; [6]World fusion Inc, Tokyo, Japan

Abstract: The recent advance in the technology of single cell analysis has brought a large impact, especially on the area of oncology. For instances, it uncovers the intratumoural heterogeneity which is now recognized as a central hallmark of cancer. However, the device based on microfluidics methods has a limitation of application in neuroscience due to technical difficulties in cell separation. The goal of this research is to develop a technical base for the comprehensive analysis of biomolecules in single cells on 2D plane, such as primary neurons, in keeping with the positional information of the cells. Furthermore, the device equips both the planar patch clamp and the micro pore which allow us to analyse both neuronal activity and its transcriptome profiles. For the purpose, we are developing the array of cell-analysis-units which extract the cytoplasm using micro actuators, to hand out the extract to RNAseq analysis. We preliminarily analyzed a single cell with or without GFP expression positioned on the micro pore of the planar patch clamp chip by suction (5 kPa) through the micro pore. During the suction rapid decrease of the fluorescence intensity in a cell was observed. The transcriptome profiles of single cells were analyzed by qPCR and RNAseq analysis. We confirmed that the majority of the mRNA in the single cell was recovered through the pore. Furthermore, rat primary hippocampal neurons infected with lentivirus expressing shRNA against a gene of interest were successfully cultured on the developed planar patch clamp chip. We will further analyze the extract from single cells of primary neuronal and/or glial cell culture, which can allow us to detect transcriptome heterogeneity in various certain disease or stress conditions.

Disclosures: S. Ishigaki: None. **H. Uno:** None. **Z. Wang:** None. **Y. Ukita:** None. **R. Bhardwaj:** None. **T. Tue:** None. **S. Hashimoto:** None. **T. Oka:** None. **K. Kawahara:** None. **Y. Takamura:** None. **T. Urisu:** None. **G. Sobue:** None.

Nanosymposium

723. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques

Location: SDCC 25

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 723.03

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: American University Faculty Research Support Grant
American University Startup Funding
T32 DA 007268
R01 DA 11697
R37EB003320

Title: LC-MS/MS method to detect neurotransmitters during cocaine and amphetamine administration

Authors: *A. G. ZESTOS[1], R. T. KENNEDY[2], M. E. GNEGY[3]
[1]Chem., American Univ., Washington, DC; [2]Chem., [3]Pharmacol., Univ. of Michigan, Ann Arbor, MI

Abstract: We have pioneered a liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay that can detect 24 neurochemicals simultaneously from microdialysate samples in freely behaving animals. The method utilizes a 4-minute gradient to detect important neurotransmitters such as dopamine, serotonin, norepinephrine, and others. This assay is immensely important in monitoring neurotransmitters in microdialysate fractions under specific behavioral and pharmacological stimuli. We have applied this method to study the effects of therapeutics for amphetamine and cocaine abuse. Previous work has shown that protein kinase C (PKC)-β inhibitors, enzastaurin and ruboxistaurin, have attenuated amphetamine stimulated-dopamine efflux and hyperlocomotion using *in vivo* microdialysis and LC-MS/MS for detection. Furthermore, perfusing 1 μM ruboxistaurin directly into the core of the nucleus accumbens via retrodialysis has decreased cocaine-stimulated increases in extracellular dopamine. Since cocaine is not known to activate PKC, it is hypothesized that ruboxistaurin could possibly be acting on the D2-autoreceptor, perhaps as an agonist. To test this hypothesis, we perfused 100 μM raclopride, a D2-autoreceptor antagonist, to block the D2 autoreceptor. Upon administering ruboxistaurin and the vehicle, ruboxistaurin only slightly attenuated cocaine-stimulated increases in extracellular dopamine. However, upon perfusing 5 μM raclopride before, ruboxistaurin or vehicle, there was no significant effect on cocaine-stimulated increases in extracellular dopamine. We hypothesize that if raclopride blocks the D2-autoreceptor before ruboxistaurin can act on D2, then the effect of ruboxistaurin on the D2-autoreceptor is negligible. Ruboxistaurin does have a significant effect on attenuating amphetamine-stimulated dopamine efflux even in the presence of raclopride, suggesting that PKC inhibition is the dominant mechanism of amphetamine action rather than D2-inhibition.

Disclosures: A.G. Zestos: None. **R.T. Kennedy:** None. **M.E. Gnegy:** None.

Nanosymposium

723. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques

Location: SDCC 25

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 723.04

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Swedish research council AR-MH-2016-01997
Parkinson's Disease Foundation International Research Grant (PDF-IRG-1303)

Title: Using AAV capsid engineering, molecular barcodes and spatial transcriptomics to dissect circuit repair in Parkinson's disease

Authors: *T. BJORKLUND[1], M. DAVIDSSON[1], P. ALDRIN-KIRK[1], M. HARTNOR[1], J. RAJOVA[1], A. HEUER[1], T. CARDOSO[2], S. NOLBRANT[2], M. PARMAR[2]
[1]Mol. Neuromodulation, Wallenberg Neurosci., Lund, Sweden; [2]Developmental and Regenerative Neurobiology, Lund University, Lund, Sweden, Lund, Sweden

Abstract: Brain repair using embryonic stem cell (ESC) transplantation in Parkinson's disease has shown great promise as a future treatment option. However, little is known what directs maturation and circuit integration. In this study, we have transplanted human ESC-derived dopaminergic neurons into a 6-OHDA lesioned rat model and utilized retrograde infectivity of novel AAV's together with molecular barcodes in combination with mono-synaptic rabies tracing to answer these outstanding questions. Establishment of the tracing starter population is generated through the Retrograde infectivity of the transplant using a Cre-inducible, FLP expressing AAV virus. As only the transplanted neurons express the Cre recombinase, this two-factor approach enable us to trace connectivity to only transplanted neurons which have managed to grow axons which regenerate the correct nigro-striatal circuitry. Using this novel barcoded AAV vector-induced tracing approach, followed by Spatial Transcriptomics mapping, we here present a more precise method to evaluate vector transport, vector function and mapping connectivity in the brain which provides significant advancement over current state-of-the-art. Using the ST technology, we have here deeply analyzed the maturation of hESC-derived DA neurons and compared them to both the intact midbrain DA-system and a reference single cell RNA-sequencing data set covering both human DA neuron development and midbrain neurons. With this approach, we show that the utilized differentiation protocol generates DA neurons which very closely mirrors a nigral gene expression with few genes originating from DA neurons from the ventral tegmental area. In addition, we show that nigral transplantation of identical hESC derived neurons receive distinctly different afferent input depending on the graft innervation pattern, suggesting a previously unknown directed circuit integration.

Disclosures: T. Bjorklund: None. **M. Davidsson:** None. **P. Aldrin-Kirk:** None. **M. Hartnor:** None. **J. Rajova:** None. **A. Heuer:** None. **T. Cardoso:** None. **S. Nolbrant:** None. **M. Parmar:** None.

Nanosymposium

723. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques

Location: SDCC 25

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 723.05

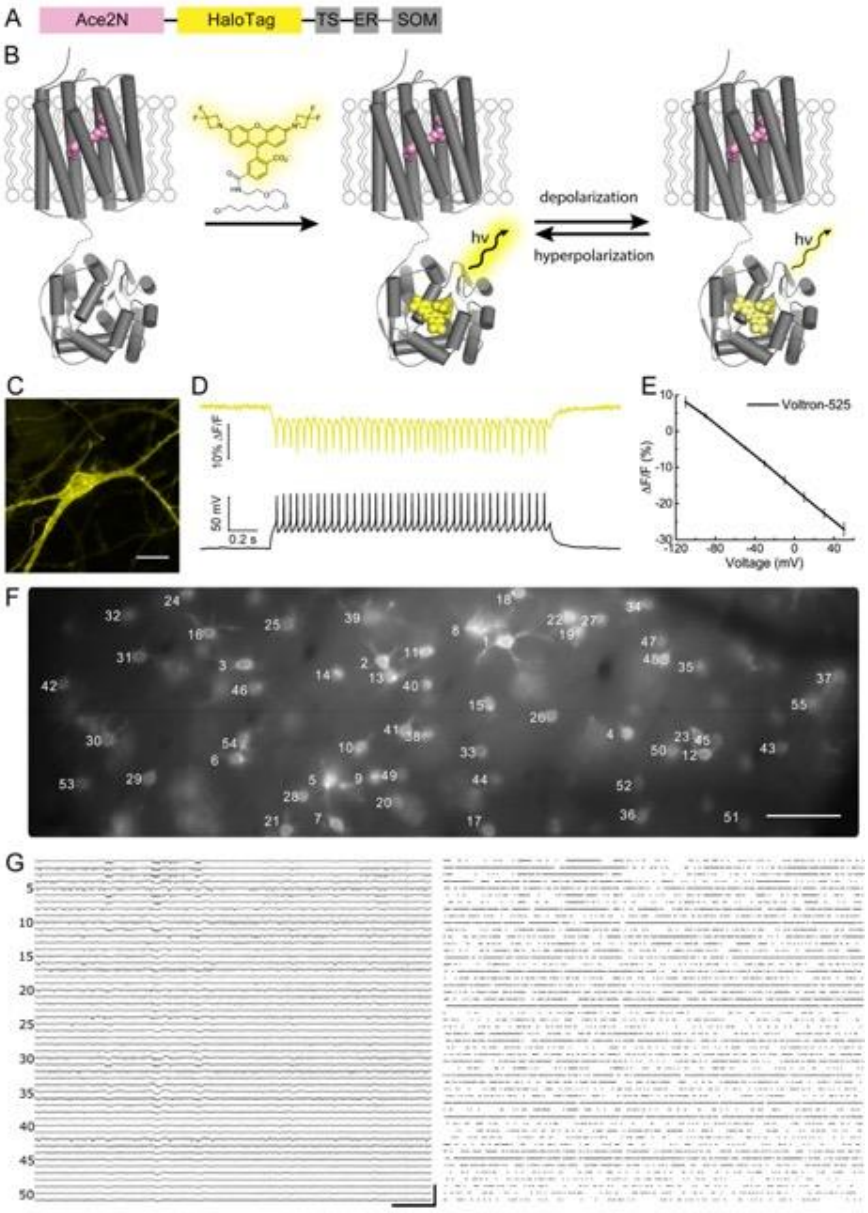
Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: HHMI

Title: Engineering chemigenetic voltage indicators for *in vivo* voltage imaging

Authors: *A. S. ABDELFATTAH[1], T. KAWASHIMA[1], A. SINGH[1], O. NOVAK[1], H. LIU[1], Y. SHUAI[1], Y.-C. HUANG[2], B.-J. LIN[2], R. PATEL[1], J. J. MACKLIN[1], T.-W. CHEN[2], G. C. TURNER[1], Z. LIU[1], M. KOYAMA[1], D. S. KIM[3], K. SVOBODA[4], M. B. AHRENS[5], L. D. LAVIS[1], E. R. SCHREITER[6]
[1]HHMI Janelia Res. Campus, Ashburn, VA; [2]Natl. Yang-Ming Univ., Taipei, Taiwan; [3]Janelia Farm Res. Campus, Howard Hughes Med. Inst., Ashburn, VA; [4]HHMI / Janelia Farm Res. Campus, Ashburn, VA; [5]Janelia Res. Campus / HHMI, Ashburn, VA; [6]Howard Hughes Med. Institute, Janelia Farm Res. Campus, Ashburn, VA

Abstract: Voltage imaging using genetically encoded fluorescent voltage indicators (GEVIs) is a powerful approach for recording neuronal activity with high spatial and temporal resolution. However, this method inherently requires high acquisition rate and intense illumination, which can lead to rapid photobleaching of the indicator. Current GEVI designs are based on fluorescent proteins and the intrinsic brightness and photostability of these chromophores limits their utility. To address this issue, we engineered a GEVI, called Voltron, that utilizes bright and photostable dyes together with self-labeling protein tags. In our design, a self-labeling protein tag (e.g HaloTag or SNAP-tag) is fused to microbial rhodopsin voltage sensor domains and can be targeted to specific cell types followed by specific labeling via in vivo delivery of dye-ligands. Voltage-dependent fluorescence changes rely on energy transfer (FRET) between the dye emission and rhodopsin absorption. Voltron is significantly brighter and more photostable than existing GEVIs, extending productive imaging time by more than 10 times. Using Voltron, we can now record spiking and subthreshold activity of tens of neurons simultaneously in awake behaving mice and larval zebrafish over timescales of 10-20 minutes. Additionally, we describe how amino acid substitutions and electrophysiology recordings during the course of Voltron evolution led to novel mechanistic insights into the indicator function. This allowed us to rationally control opsin absorption with membrane potential changes for Voltron and the broad class of rhodopsin-based GEVIs.
Fig. 1 (A-B) Schematic of Voltron sequence and function (C) Hippocampal neuron expressing Voltron labeled with JF-525 (D) Single-trial recording of action potentials using Voltron (E) Voltron fluorescence change as a function of membrane voltage. (F) Mouse visual cortex expressing Cre-dependent soma targeted Voltron (G) Left: Raw intensity traces from neurons labelled in E. Scalebars: 50% ΔF/F, 20s. Right: Spike rasters from ΔF/F traces on left.



Disclosures: A.S. Abdelfattah: None. **T. Kawashima:** None. **A. Singh:** None. **O. Novak:** None. **H. Liu:** None. **Y. Shuai:** None. **Y. Huang:** None. **B. Lin:** None. **R. Patel:** None. **J.J. Macklin:** None. **T. Chen:** None. **G.C. Turner:** None. **Z. Liu:** None. **M. Koyama:** None. **D.S. Kim:** None. **K. Svoboda:** None. **M.B. Ahrens:** None. **L.D. Lavis:** None. **E.R. Schreiter:** None.

Nanosymposium

723. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques

Location: SDCC 25

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 723.06

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH intramural research grant

Title: Real-time and label-free electronic measurements of enzyme activity and kinetics

Authors: A. BALIJEPALLI[1], N. B. GUROS[1,3], R. C. ROBERT[1], A. CARDONE[2,4], N. D. AMIN[5], S. ZHANG[1,7], *H. C. PANT[6], C. A. RICHTER[1], S. T. LE[1,7], J. B. KLAUDA[3]
[1]Engin. Physics Div., [2]Software and Systems Div., Natl. Inst. of Standards and Technol., Gaithersburg, MD; [3]Dept. of Chem. and Biomolecular Engin., [4]Univ. of Maryland Inst. for Advanced Computer Studies, Univ. of Maryland, College Park, MD; [5]NINDS, [6]LNC NINDS, NIH, Bethesda, MD; [7]Theiss Res., La Jolla, CA

Abstract: We have developed new electronic sensors that are label-free, highly sensitive and time-resolved enabling the measurements of both the activity and kinetics of enzymes in a single assay. We applied the technique to the measurement of the pathological proline directed kinase complex Cdk5/p25 that is implicated in neurodegenerative conditions such as Alzheimer's disease (AD). As an initial proof of concept, the activity of the pathological complex was measured to be 17.5±1.3 μM and found to be statistically consistent with the ^{32}P-ATP assay. Furthermore, time-series measurements of kinase mediated phosphorylation exhibited enzyme limited behavior at short times and returned a kinetic rate constant of 0.18±0.02 per min[1,2] when modeled with a first-order rate law. Furthermore, the measurements were performed with a kinase concentration that was 5-fold lower than that used in traditional kinetic assays. Cdk5 mediated phosphorylation results in the release of a proton (causing a small change in pH) during ATP hydrolysis and the transfer of a single phosphate group to either a serine or threonine residue immediately preceding a proline[3]. We measured the resulting change in solution pH with dual-gated field-effect transistors that were fabricated with atomically thin semi-conducting films placed on oxide substrates and encapsulated with an ionic liquid. The high polarizability of the ionic liquid caused a strong amplification of the measured signal, allowing the devices to operate near their theoretical limits. This in turn allowed the detection of pH changes with 100-fold higher sensitivity than state-of-the-art techniques[4] during enzyme mediated phosphorylation as a reporter of enzyme function. Finally, the signal-to-noise ratio (SNR) of the measurements are more than an order of magnitude higher than state-of-the-art ion sensitive field effect transistors (ISFET) allowing a low limit of detection of 0.001 pH units[5].
(1) *Biochemistry* **2008**, *47*, 8367-8377.(2) *J. Biol. Chem.* **2002**, *277*, 44525-44530.(3) *Sci Rep* **2015**, *5*, 8687. (4) *ACS Nano* **2017**, *11*, 7142-7147.(5) *NATURE* **2011**, *475*, 348-352.

Disclosures: A. Balijepalli: None. **N.B. Guros:** None. **R.C. Robert:** None. **A. Cardone:** None. **N.D. Amin:** None. **S. Zhang:** None. **H.C. Pant:** None. **C.A. Richter:** None. **S.T. Le:** None. **J.B. Klauda:** None.

Nanosymposium

723. Molecular, Biochemical, and Genetic Techniques: Molecular Techniques

Location: SDCC 25

Time: Wednesday, November 7, 2018, 1:00 PM - 2:45 PM

Presentation Number: 723.07

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Brain INITIATIVE R24MH106107

Title: Investigating the molecular and cellular mechanisms of ultrasonic neuromodulation

Authors: *S. YOO[1], M. SHAPIRO[2]
[1]Div. of Chem. and Chem. Engin., [2]Caltech, Pasadena, CA

Abstract: Ultrasonic neuromodulation has great potential as a non-invasive technology for basic neuroscience research and translational applications, because the ultrasound can be transmitted through the skull and focused at deep brain regions to control neural activity. Recently, low frequency ultrasound (250~500 kHz) has been used to modulate the neural activity in various models including primate and human. However, the molecular and cellular mechanisms of such modulation are still unknown, and recent reports of indirect auditory side-effects heighten the need to demonstrate and understand the biophysical mechanisms of direct ultrasonic neuromodulation at the molecular and cellular levels.
In order to avoid indirect artifacts in intact brain during the sonication, primary cortical neurons were placed on acoustically transparent substrate and genetically modified to express fluorescent calcium or voltage sensors. These neurons were subjected to ultrasound stimulation at 300 kHz, and optical responses indicating action potential firing were monitored by a high speed sCMOS camera.
We found that ultrasound at intensities above 6 W/cm^2 (I_{SPPA}) and pulse duration above 200 ms (continuous wave), within the range reported in primate and human studies, can induce reliable neural responses without cellular damage. Control measurements indicate that these responses are not caused by changes in temperature, do not require cavitation in the media and are not associated with membrane poration or cell death. Molecular perturbations show that responses to ultrasound do not require synaptic transmission, but are amplified in each cell by voltage gated sodium and L-and T-type calcium channels. Furthermore, detailed analysis of response kinetics revealed that latency of the neural responses is on the order of 50 ms, which decreases with higher intensity. Additional pharmacological and genetical knockdown studies found that ultrasound triggers calcium entry from extracellular media and release from endoplasmic reticulum, and activates specific mechanosensitive calcium channels to generate bursting

responses.
In summary, our study provides direct evidence of ultrasonic neuromodulation under carefully controlled conditions, eliminates several potential mechanisms, and provides a platform to study the specific cellular and molecular processes underlying this important technology.

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