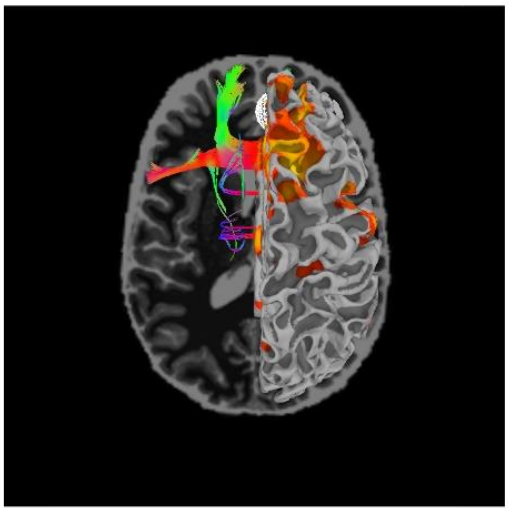
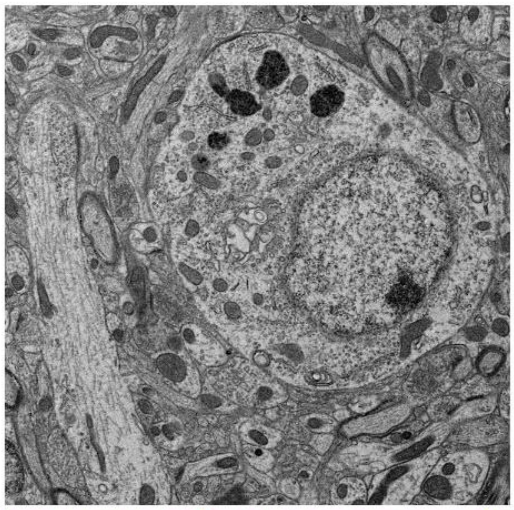
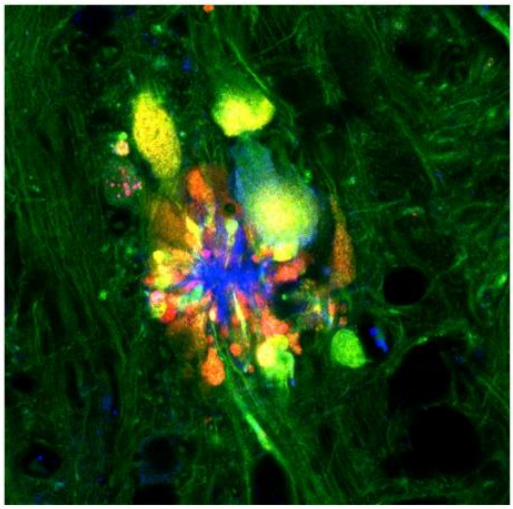
The Nathan Kline Institute Presents Science Day 2023



May 16th, 2023

1-5 PM

Brought to you by the Community Building Committee

Melissa Alldred
Pam Butler
Alex Franco
Renee Hartig
Ying Jiang
Amanda Labuza
Annette Moreno
Brian Russ
Rob Sears
Emily Stern
Catia Teixeira
Sharifa Williams

NKI Science Day

1:00-1:15 *Welcome and Introduction*

1:15-1:30 *Expression profiling and bioinformatics of homogeneous populations of frontal cortex pyramidal neurons from Alzheimer's disease and age-matched controls*
Amanda Labuza, PhD
Postdoctoral Fellow, Center for Dementia Research, NYUGSOM and NKI

1:30-1:45 *Early-Life Prefrontal Cortex Inhibition and Early-Life Stress Led to Long-Lasting Behavioral, Transcriptional, and Physiological Impairments*
Edenia C. Menezes, PhD
Postdoctoral Fellow, Emotional Brain Institute, NKI

1:45-2:00 *Examining Sex Differences in Emotion Regulation and Affect Intensity*
Zamfira Parincu, BS
Research Assistant, Clinical Research NKI

2:00-2:15 *The Omnipresence of the Sensorimotor-Association Axis Within the Human Connectome*
Karl-Heinz Nenning, PhD
Research Scientist, Center for Biomedical Imaging and Neuromodulation, NKI

2:15-2:30 *Attributions of Everyday Discrimination Experiences to Intersecting Statuses: Prevalence and Correlates with Stress*
Navin Sanichar, MPH
Doctoral Candidate, Social Solutions and Research Division, NKI
NKI

2:30-2:40 *Closing Remarks*

2:40-3:10 *Refreshments and Poster Placements*

3:15-5:00 *Poster Presentations (* indicates presenting author)*

Abstracts Presentations:

1. *Expression profiling and bioinformatics of homogeneous populations of frontal cortex pyramidal neurons from Alzheimer's disease and age-matched controls.*

Amanda Labuza*, Melissa J. Alldred, Harshitha Pidikiti, Adriana Heguy, Paul D. Coleman, Elliott J. Mufson, and Stephen D. Ginsberg

A daunting and unfulfilled challenge is understanding the complex pathobiology underlying Alzheimer's disease (AD). AD is an irreversible, age-related neurodegenerative brain disorder affecting an estimated 6.2 million Americans responsible for the gradual and insidious failure of cognitive function. AD is now a recognized spectrum disorder with pathology onset decades prior to clinical symptoms. Currently, confirmed diagnosis requires postmortem neuropathological evaluation. So far, FDA approved treatments have not arrested or prevented the onset of AD. Therefore, there is an urgent need to identify molecular and cellular mechanism(s) underlying AD, which would lead to novel therapeutics. There are several 'omics approaches under development to evaluate changes at transcriptomic, proteomic, and metabolomic levels associated with AD. Accordingly, RNA sequencing (RNA-seq) provides an index of expressed genes as well as noncoding RNAs (ncRNAs) within a given cellular population. However, a limitation is that bulk-tissue resolution masks complex alterations occurring across different cell types. Here, we applied single population RNA-seq using laser capture microdissection (LCM) to isolated Nissl-stained layer III or V pyramidal neurons from the superior frontal gyrus (BA22) from postmortem human brain tissue obtained from clinically and pathologically characterized AD (n=3; 2M/1F) and age-matched nondemented control cases (n=3; 2M/1F). A total of 600-900 Nissl-stained pyramidal neurons from each lamina were collected via LCM, RNA was isolated, converted to RNA-seq cDNA libraries, and analyzed on the Illumina NovaSeq platform at an average sequencing depth of 63 million reads per sample. Preliminary bioinformatic pathway analyses including IPA, KEGG, GO, and WGCNA were used to identify changes in differently expressed genes (DEGs) and canonical pathways between the AD and age-matched control cases. A total of 1,147 and 740 DEGs ($p<0.05$) were found between AD and controls in layer III and V, respectively. Differences in DEGs between laminae suggest studying single populations can unveil new targets previously masked when assaying admixed neuronal and non-neuronal cell types. By generating and examining molecular fingerprints of vulnerable AD cortical neurons, we expect to discover mechanistic changes via targeted and unbiased pathway analyses to help explain circuit degeneration and inform novel therapeutic strategies.

2. *Early-Life Prefrontal Cortex Inhibition and Early-Life Stress Led to Long-Lasting Behavioral, Transcriptional, and Physiological Impairments*

Edenia C. Menezes*, Heather Geiger, Fabiula F. de Abreu, Melissa Alldred, Cátia M. Teixeira

The brain contains interconnected circuits which are neither completed at birth or invariant across life, essential for life-long adaptive features like continuous learning and memory. However, this plasticity, especially when associated with severe adverse factors during early-life, can lead to the derailment of normative brain development and contribute to the etiology of behavioral deficits. In extreme cases of childhood adversity, institutional rearing where the infants were deprived of caregiver contact, cognitive deficits, and dysregulated prefrontal cortex (PFC) function were found. Our laboratory recently showed that pups` cortical activity is influenced by maternal presence. Using local field potential (LFP) recording in behaving rat pups, we observed that LFP power decreases when the mother is absent of the nest in comparison to when she is present. Whether PFC activity during early-life is causal to behavioral outcomes in the adult is not known. Hypothesis: In this study we hypothesize that transient inhibition of the PFC during early-life leads to long-lasting dysregulation of PFC function and behavioral alterations in the adult that mimic the ones observed in maternal separation (MS). Here we also hypothesized that PFC excitation during MS can prevent cognitive deficits and dysregulation of PFC induced by MS. Methods: We performed single-nucleus RNAseq with hashing to contrast the PFC transcriptome of MS animals with that of standard reared animals. To transiently inhibit of excite PFC in early-life we used chemogenetics. Animals were injected with excitatory or inhibitory DREADDs at P1 (or control), injected with CNO or vehicle from P2-P17,

and behavioral and physiological measures were collected during adulthood. Results: Using snRNAseq, we found changes in cell type proportions in MS similar to the ones seen in more immature brains. More, we observed that the proportion of oligodendrocytes in adult-MS animals was similar to infant animals. Furthermore, we found that most of the differentially expressed genes between MS and standard reared animals was in interneurons, affecting pathways related to GABAergic, glutamatergic, and serotonergic functions. We found that MS and transient inhibition of PFC activity during early life affect adult cognition (in object recognition and delayed-non-match-to-sample), while excitation of PFC during MS rescues this cognitive deficit. Interestingly, both maternal separation and early-life prefrontal cortex inhibition led to changes in physiological responses in prefrontal activity to GABAergic and serotonergic antagonists that were similar to the responses of more immature brains. These changes were rescued by PFC excitation during MS. Conclusion: This study suggests that MS or transient inhibition of PFC leads to the behavioral deficits, while the excitation of PFC during can prevent deficit caused by MS.

3. *Examining Sex Differences in Emotion Regulation and Affect Intensity*

Zamfira Parincu*, Kathryn T. Evans, Allison M. Sparpana, Elizabeth F. Sullivan, Katherine A. Collins, Matthew J. Hoptman, and Dan V. Iosifescu

Background: Expressive suppression (pushing negative thoughts and feelings from awareness) and cognitive reappraisal (reframing a negative stimulus to reduce negative emotions) are two emotion regulation strategies that seem to have opposing associations with mood and anxiety psychopathology. Depression and anxiety severity are positively associated with suppression and negatively associated with cognitive reappraisal. Existing literature suggests that women report utilizing more varied emotion regulation strategies than men and are more likely to be diagnosed with anxiety and depressive disorders. Here, we leverage data from a community sample to better understand the relationship between sex, affect, and emotion regulation strategies: when faced with a negative experience, men will report more expressive suppression than women, and women will report more emotion reappraisal than men.

Methods: Data from the Nathan Kline Institute Rockland Sample was analyzed (n=185, age=30.94 ±7.4, sex=62% female). Subjects completed the Emotional Regulation Questionnaire (ERQ), which measures the style of emotion regulation (cognitive reappraisal and expressive suppression), and the Affect Intensity Measure (AIM), which measures Negative Intensity, Positive Intensity, Negative Affectivity, and Positive Affectivity. Hierarchical and forward stepwise linear regression analyses were used to investigate the relationships between emotion regulation, affect intensity, and sex.

Results: Negative intensity of emotion was positively associated with expressive suppression and age (R2=.04, p=.02). Strength of positive emotion predicted likelihood of emotion reappraisal for both men and women (R2=.095, p=.01). Strength of negative emotions was positively associated with age (R2=.062, p=.03) and predicted how much women (but not men) in general suppress emotions (R2=.061, p=.009).

Conclusions: In line with existing research, this study found that women use more emotion regulation strategies. These results also suggest that women use more expressive suppression when faced with negative affect, perhaps due to greater use of automatic emotion regulation in men or more stereotyped thinking in women, as previous studies suggest. Considering that many psychopathologies are characterized by poor emotion regulation, clinicians may benefit from understanding how sex differences play a role in decreasing negative affect, which is key to improving well-being.

4. *The Omnipresence of the Sensorimotor-Association Axis Within the Human Connectome*

Karl-Heinz Nenning*, Ting Xu, Alexandre R. Franco, Khena Swallow, Arielle Tambini, Daniel S. Margulies, Jonathan Smallwood, Stanley J. Colcombe, and Michael P. Milham

Low-dimensional representations are increasingly used to study meaningful organizational principles within the human brain. Most notably, the sensorimotor-association axis consistently explains the most variance in the human connectome as its so-called principal gradient, suggesting that it represents a fundamental organizational principle. While recent work indicates these low dimensional representations are relatively robust, they are limited by modeling only certain aspects of the functional connectivity

structure. To date, the majority of studies have restricted these approaches to the strongest connections in the brain, treating weaker or negative connections as noise despite evidence of meaningful structure among them. The present work examines connectivity gradients of the human connectome across a full range of connectivity strengths and explores the implications for outcomes of individual differences, identifying potential dependencies on thresholds and opportunities to improve prediction tasks. Interestingly, the sensorimotor-association axis emerged as the principal gradient of the human connectome across the entire range of connectivity levels. Moreover, the principal gradient of connections at intermediate strengths encoded individual differences, better followed individual-specific anatomical features, and was also more predictive of intelligence. Taken together, our results add to evidence of the sensorimotor-association axis as a fundamental principle of the brain's functional organization, since it is evident even in the connectivity structure of more lenient connectivity thresholds. These more loosely coupled connections further appear to contain valuable and potentially important information that could be used to improve our understanding of individual differences, diagnosis, and the prediction of treatment outcomes.

5. *Attributions of Everyday Discrimination Experiences to Intersecting Statuses: Prevalence and Correlates with Stress*

Kerstin Pahl, Sharifa Williams, Navin Sanichar*, Crystal Lewis and Marilena Lekas

Background: Experiences of discrimination/stigma related to different social statuses are associated with health disparities via multiple pathways, including stress. This study examined intersections of stigma attributions using the Everyday Discrimination Scale (EDS) adapted to attributing each discriminatory experience to up to three different statuses and explored their relationships with psychosocial stress in Black and Latinx adults.

Methods: We used the method of k¬-means clustering to identify combinations of intersecting statuses of attributions (e.g., gender, race, ancestry) for each of the eight EDS items among 160 Black and Latinx adults. We then described the identified clusters and examined between-cluster differences with respect to sociodemographic characteristics and psychosocial stress.

Results. Four clusters (CLs) represented participants reporting the lowest levels of discriminations and, thus, the fewest attributions (CL1; n=59); those most frequently attributing discrimination to race, then gender, then SES (CL2; n=68); those heavily attributing discrimination to ancestry, then race, then gender (CL3; n=11), and those predominantly attributing discrimination to race, then a physical characteristic, than gender (CL4; n=22). Cluster membership differed by race/ethnicity, such that Latinx participants were most prevalent in CL1 and Black participants in CL2 (□2(3) = 13.92, $p < 0.01$). There were also between-cluster differences in perceived stress, such that participants in CL2 and CL4 reported significantly ($p<0.05$) more stressful life events than participants in CL 1 (CL1 mean=2.05; CL2 mean=3.63; CL3 mean=4.09; CL4 mean=4.59). Similarly, participants in CL2 and CL4 experienced higher ($p<0.05$) levels of daily hassles than participants in CL1 (CL1 mean = 11.8; CL2 mean=19.2; CL3 mean=20.3; CL4 mean=22.4).

Conclusions: Findings highlight 1) the salience of race and gender in discrimination experiences among Black and Latinx adults, 2) their intersections with other potentially stigmatizing statuses (i.e., ancestry and physical attributes), and 3) the associations of these intersecting statuses with psychosocial stress. Understanding how stigmatizing statuses intersect is an important first step to examining how discrimination works to generate stress and undermine health in among individuals of color.

Abstracts Posters:

1. *Estimates of Total Neuron Number Show That Neonatal Ethanol Causes Immediate and Lasting Neuron Loss in Cortical and Subcortical Areas*

John* Smiley, Cynthia Bleiwas, Brandon Marino, Prerana Vaddi, Stephanie Canals-Baker, Don Wilson and Mariko Saito

In neonatal brain development there is a period of normal apoptotic cell death that regulates adult neuron number. At approximately the same period, ethanol exposure can cause a dramatic spike in apoptotic cell death. While ethanol-induced apoptosis has been shown to reduce adult neuron number, questions remain about the regional selectivity of the ethanol effect, and whether the brain might have some capacity to overcome the initial neuron loss. The present study used stereological cell counting to compare cumulative neuron loss 8 hours after postnatal day 7 (P7) ethanol treatment to that of animals left to mature to adulthood (P70). Across several brain regions we found that the reduction of total neuron number after 8 hours was as large as that of adult animals. Comparison between regions revealed that some areas are more vulnerable, with neuron loss in the anterior thalamic nuclei > dorsal subiculum > medial septum/ vertical diagonal band > dorsal lateral geniculate > cingulate cortex > mammillary bodies > whole neocortex. In contrast to estimates of total neuron number, estimates of apoptotic cell number in Nissl-stained sections at 8 hours after ethanol treatment provided a less reliable predictor of adult neuron loss. The findings show that ethanol-induced neonatal apoptosis often causes immediate neuron deficits that persist in adulthood, and furthermore suggests that the brain may have limited capacity to compensate for ethanol-induced neuron loss.

2. *Odor Discrimination and Identification in Schizophrenia: Relationship to mRNA in Lymphocytes and MATRCIS Battery scores*

Robert C. Smith*, Henry Sershen, Mary Youseff, AnMei Chen, Abel Lajtha, Hua Jin, Mimei Zhang, Alexandro Guidotti, and John M Davis

Background: Patients with schizophrenic have been reported to show deficits in various measures odor perception but odor discrimination has not been standardly assessed. DNA methylation and GABAergic input have been implicated in biochemical process controlling odor in animal studies, but this has not been investigated in human studies. Some studies have related cognitive deficits in schizophrenia to odor deficits but none have used the MATRICS battery to investigate this question.

Methods: In a study of DNA methylation and GABAergic mRNAs in lymphocytes we also measured odor identification and discrimination with the Sniff and Sticks battery in 58 patients with chronic schizophrenia (CSZ) and 48 non-psychiatric controls (NPC). mRNAs in lymphocytes were assessed by qPCR using TaQMan probes. Cognition was assessed by the MATRICS battery in CSZ and NPC and symptoms in CSZ were assessed by PANSS scale. The relationship of odor deficits to mRNA levels and MATRICS scores and symptoms was explored by correlation analysis.

Results: CSZ showed significant deficits compared to NPC in odor identification ($P = 0.011$, Cohen's $d=0.50$)), but much larger deficits in discrimination ($P<0.001$, $d=1.01$). In step down regression analysis odor discrimination but not odor identification had significant β weight for classify patients into the CSZ vs NPC group. There were significant negative correlations ($r=-33$ to $-.68$) of odor identification with DNMT1 mRNAs, and significant negative correlations with odor discrimination and GABAergic mRNAs in CSZ subjects ($-.38$ to $-.42$). Odor discrimination scores correlated significantly ($P=.02$ to $P=.009$) with several Matrics Domain scores in CSZ subjects but not NPC; there was a sex effect and these correlations were stronger in female than male CSZ.

Conclusion: Odor discrimination deficits, which has not been consistently evaluated in schizophrenia studies, showed the strongest differentiation between patients with schizophrenia and controls. This is the first study to report relationship between odor deficits and DNMT and GABAergic mRNAs in human subjects. However, the negative correlations of odor scores with lymphocyte mRNA levels may not necessarily reflect neuronal processes.

3. *BT75, A Novel Rarα Agonist, Inhibits Neuroinflammation in Experimental Models of Alzheimer's Disease Through AKT/NF-Kb Pathway and M1-To-M2 Phenotypic Polarization of Microglia*

Xiuli Zhang*, Subbanna Shivakumar, Colin Williams, Stefanie Canals-Baker, Donald A. Wilson, Bhaskar C. Das, and Mariko Saito

Alzheimer's disease (AD), the most common form of dementia, is a terminal, progressive disorder leading to memory loss, personality changes and the inability to communicate. BT75, a boron-containing retinoid, is a novel retinoic acid receptor (RAR)α agonist synthesized by our research group. Previous studies indicate that activation of retinoic acid (RA) signaling pathway may attenuate progression of AD. Presently, we aim to examine the anti-inflammatory effect of BT75 using cell culture and AD mouse model. SIM-A9 (muse microglial cell line) cells were pretreated with different doses of BT75 (1μM - 25μM) and stimulated by LPS. Griess reaction method for the detection of Nitric Oxide (NO) and ELISA was applied for the detection of inflammatory factors. The cell viability was detected by MTT method. The target proteins involved in the cell signal pathway were determined by Western blot. Results showed that BT75 attenuated the cytotoxicity induced by high dose of LPS in SIM-A9 cells and suppressed the releases of nitric oxide (NO) and IL-1β in cell culture medium induced by LPS in SIM-A9 cells. BMS195614, a specific RARα antagonist blocked the inhibition of NO production of BT75, indicating that BT75 inhibited LPS-induced NO production at least partially through RARα signaling pathway. Moreover, BT75 inhibited p-AKT and p-NF-κB expression induced by LPS. In addition, BT75 promoted M1-to-M2 phenotypic polarization in microglia. For in vivo study, C57BL/6 mice were intracerebroventricularly injected with streptozotocin (STZ) at 3mg/kg body weight to induce AD-like icv-STZ model. BT75 (5mg/kg body weight) was given to icv-STZ mice with intraperitoneal injection for 3 weeks. Sham mice were intraperitoneally given vehicle or BT75 (5mg/kg body weight) separately. Immunofluorescence staining on mouse brain sections was performed for the detection of GFAP-positive astrocyte and Iba1-positive microglia. Western blot assay was done for the detection of target proteins like synaptophysin, nNOS and P-Tau. The results indicated that BT75 inhibited glial cell activation and p-Tau expression in the hippocampus of icv-STZ mice. BT75 also increased synaptophysin and decreased nNOS expression in the hippocampus of icv-STZ mice. Taken together, BT75-inhibited neuroinflammation may be mediated by AKT/NF-κB pathway and microglia polarization in LPS-stimulated SIM-A9 cells and BT75 possessed neuroprotective effects against the STZ-induced AD model mice via inhibition of glial cell activation. Thus, BT75 is a promising neuroprotective agent worthy of further development into AD treatment. Supported by NIAAA R21AA027374 and NIAAA R01AA023181

4. *Withdrawn*

5. *The Role of The Hippocampus in Maternal Suppression of Infant Fear*

Alejandra Urquieta Pinaya* And Regina Sullivan

Children use parents as a safe-base. Animal research shows this safety-signal suppresses amygdala and fear (social buffering); maltreatment disrupts this. We hypothesize that hippocampus codes parent-safety and maltreatment disrupts it. Rat pups were adversity-reared or control-reared from postnatal-day (PN)8-12. PN18/PN28 testing used threat (0.5mA footshock) with/without the mother and assessed 2-DG hippocampal activity. PN18 immature hippocampus was not responsive to threat nor buffering, but was following maltreatment. PN28 showed the reverse.

6. *Olfacto-Spatial Episodic Memory Circuits in the Rat: From Engagement to Acquisition to Expression*

Colin Williams*, Nadine Ravel, and Don Wilson

A focus of our lab is how networks change based on 1) behavioral demands on a millisecond scale, and 2) internal state such as sleep/wake cycles on a minute to hour scale, and how pathology and early adverse events can modify these network dynamics to impact behavior. As an example, here we explore how engaging in an episodic memory task, and learning and expressing those episodic memories, affects network connectivity within a large cortical-subcortical network using multisite local field potential recordings in freely moving adult rats. We find large changes in network connectivity evoked by simple

engagement in the task compared to spontaneous periods of disengagement and grooming. Important connectivity nodes emergent during engagement include sensory cortex and orbitofrontal cortex. By comparing connectivity early versus late in acquisition (two "engaged" states) we find a shift to association and entorhinal cortices and hippocampus as major nodes. Interestingly, error trials show the least difference in connectivity patterns from disengagement.

7. *Hippocampal Mossy Cells Exhibit Some of The Earliest Signs of Increased Excitability in the Tg2576 Model of Alzheimer's Disease Neuropathology*

David Alcantara-Gonzalez*, Chiara Criscuolo, Justin J Botterill, Meghan Kennedy, and Helen E Scharfman

Background: Alzheimer's disease (AD) is a neurodegenerative illness characterized by progressive accumulation of amyloid beta (Aβ) and neurofibrillary tangles, with cognitive impairment and altered neural activity. Hyperexcitability in the early stages of AD contribute to Aβ accumulation and cognitive impairment, aggravating the progression of AD. However, the hyperexcitability origin is not clear. This study aimed to test whether mossy cells (MCs), an excitatory cell of the hippocampal dentate gyrus, show increased excitability at early stages of AD and contribute to the increased network excitability generation. Indeed, alterations of MCs contribute to hyperexcitability and cognitive impairment in epilepsy. However, the role of MCs in AD has not been substantially explored.

Methods: Intrinsic and synaptic properties of MCs and granule cells (GCs) from WT and Tg2576 mice at early ages (1-2 m.o.) were characterized by whole-cell patch-clamp recordings. Synaptic properties included the frequency and amplitude of spontaneous excitatory postsynaptic potentials (EPSPs) and excitatory and inhibitory postsynaptic currents (EPSCs and IPSCs). Deterioration in MCs morphology was evaluated using Nissl staining and GluR2/3 labeling by light- and confocal microscopy. Aβ deposition was evaluated using the McSA1 antibody.

Results: Tg2576 GCs did not have any significant difference in their intrinsic properties, as we shown previously in mice ∼3 m.o. However, an enhanced excitatory and inhibitory input to GCs, depicted by augmented IPSC (7.16 vs 14.04 events/s) and NMDA-mediated EPSC frequencies (0.81 vs 1.41 events/s) were found. Interestingly, Tg2576 MCs had an augmented EPSP frequency (5.75 vs 9.44 events/s), and their intrinsic properties showed a depolarized RMP (-72.88 vs -58.36 mV), and reduced rheobase (145.56 vs 47.14 pA), AP amplitude (98.14 vs 76.66 mV), time-to-peak (552.75 vs 266.16 ms) and maximum rise (171.44 vs 88.68 mV/ms) and decay slopes (-61.17 vs -42.38 mV/ms). The correlation between #APs and current injected showed Tg2576 MCs fired significantly more APs (SEZD = 0.34; z = 2.48). Tg2576 MCs showed robust intracellular Aβ aggregation without any significant morphological change.

Conclusions: MCs changes in excitability and early accumulation of Aβ suggest that MCs could be the cause of increased excitability occurring later in GCs. In this manner, MCs could be an important contributor to AD.

8. *Leveraging Computational Approaches to Map the Signaling from Mitochondrial Dysfunction to Clinical Outcomes in Subjects with Amnestic Mild Cognitive Impairments and Early Alzheimer's Disease*

Betty Bigio*, Ricardo Lima-Filho, Olivia Barnhill, Felipe K. Sudo, Claudia Drummond, Naima Assunção, Bart Vanderborght, Fernanda Tovar-Moll, Paulo Mattos, Sergio T. Ferreira, Fernanda G. De Felice, Mychael V. Lourenco, and Carla Nasca

The current translational work is an outgrowth of a mechanistic framework in rodents characterized by decreased levels of the pivotal mitochondrial metabolite acetyl-L-carnitine (LAC) with the corresponding cognitive deficits and depressive-like behavior (Neuron 2017, 10.1016/j.neuron.2017.09.020, PNAS 2013, 10.1073/pnas.1216100110). Here, we used computational approaches and ultraperformance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS) to ascertain the role of this mitochondrial signaling pathway in subjects with cognitive impairments (CI), and potential sex differences in these mechanisms. We used available plasma samples from a well-characterized cohort of subjects with CI (i.e.: subjects with Alzheimer's disease AD and amnestic mild cognitive

impairments aMCI) and in age- and sex-matched cognitively healthy controls (HC) as we described in our prior reports (Nature Medicine 2019, 10.1038/s41591-018-0275-4). Our new findings showed decreased levels of LAC in subjects with CI as compared to age- and sex-matched HC, with important sex differences in carnitine levels. The degree of carnitine deficiency reflected the severity of cognitive dysfunction as assessed by using the Mini Mental Status Exam (MMSE). Using computational approaches, we found that the integration of these mitochondrial measures with canonical biomarkers (CSF levels of Ab42 and total Tau) improves diagnostic accuracy. The current findings of sex differences in carnitine deficiency in subjects with aMCI and AD suggest a possible sex-specific mitochondrial phenotype of vulnerability to AD characterized by greater severity of cognitive dysfunction. These findings compel further research on the potential role of LAC-related mitochondrial metabolism as an innovative target to identify sex-specific clinical phenotypes of AD risk and pathophysiology for more effective treatment of cognitive dysfunction.
Supported by National Institute on Aging (NIA) through the Early Adversity & Later Life Reversibility Pilot Grant to CN under Award Number R24AG06517

9. *Autolysosomal Acidification Failure as a Primary Driver of Amyloid Pathogenesis in Alzheimer Disease Elevated*

Ju-Hyun Lee*, Dun-Sheng Yang, Chris N. Goulbourne, Eunju Im, Philip Stavrides, Anna Pensalfini, Han Chan, Cedric Bouchet-Marquis, Cynthia Bleiwas, Martin J. Berg, Chunfeng Huo, James Peddy, Monika Pawlik, Efrat Levy, Mala Rao, Mathias Staufenbiel, and Ralph A. Nixon

Genetic evidence has increasingly linked lysosome dysfunction to an impaired autophagy-lysosomal pathway (ALP) flux in Alzheimer disease (AD) although the relationship of these abnormalities to other pathologies is unclear. In our recent investigation on the origin of impaired autophagic flux in AD, we established the critical early role of defective lysosomes in multiple AD models. To assess in vivo alterations of autophagy and ALP vesicle acidification, we expressed thy-1 promoter driven eGFP-mRFP-LC3 (tfLC3) specifically in neurons of mouse (TRGL) and crossed with multiple AD mouse models. We discovered that autophagy dysfunction in these models arise from exceptionally early failure of autolysosome/lysosome acidification, which then drives downstream AD pathogenesis. Extreme autophagic stress in compromised but still intact neurons associated with markedly lowered vATPase activity and cause AVs containing toxic APP metabolites, Aβ/β-CTFs, to pack into huge blebs and protrude from the perikaryon membrane. These tfLC3 and lysosome maker positive blebs surrounding a perikaryon, especially when the nucleus is DAPI-stained blue, resemble petals of a flower (PANTHOS: Poisonous + ANTHOS: flower) given to this unique pattern in AD mouse models. Most notably, AVs also coalesce with ER related tubules and yield fibrillar β-amyloid within these tubules. Later lysosomal membrane permeabilization, cathepsin release, and lysosomal cell death ensue accompanied by microglial invasion and plaque expansion from recruited neurons. Collectively, amyloid immunoreactivity within these intact neurons assumes the appearance of amyloid-plaques and, indeed, their eventual death transforms them into extracellular plaque lesions. 3D ultrastructural serial reconstruction and quantitative analysis confirms that neurons undergoing this transformation are the principal source of β-amyloid-plaques in APP-AD models. These results suggest that improper acidification of the autolysosome is important for AD pathogenesis and restoration of its acidification will be beneficial as a therapeutic approach.

10. *Elevated Suicidal Ideation in Schizophrenia is Associated with Urgency*

Matthew J. Hoptman*, Molly K. Irvin, Allison M. Sparpana, Elizabeth F. Sullivan, Zamfira Parincu, Katherine A. Collins, Umit Tural, and Dan Iosifescu

Suicidal ideation and behavior (SIB) is highly elevated in schizophrenia, with 10% of patients dying by suicide. The mechanisms underlying SIB in schizophrenia are poorly understood; but we have hypothesized that it may relate to poor emotion regulation. Here we examined relationships between scores on the Beck Scale for Suicidal Ideation (BSSI) and emotion-related impulsivity (urgency) in 21 people with schizophrenia. Urgency was measured with the Urgency, (Lack of) Planning, (Lack of) Perseverance, and Sensation seeking scale (UPPS-P). Participants showed a significant positive correlation between BSSI scores and both positive and negative urgency ($r_s > .58$, $ps < .0006$). Both measures correlated with positive

scores as measured by the Positive and Negative Syndrome Scale, but the relationship between BSSI persisted above and beyond the psychopathology measure. Our results are consistent with the hypothesis that problems with emotion related impulsivity in schizophrenia are associated with suicidal ideation.

11. *Fundamental Cause of Bio-Chirality: Space-Time Symmetry: Molecular Aging*

Victor V. Dyakin*

In humans, age-associated degrading changes, widely observed in molecular and cellular processes underly the time-dependent decline in spatial navigation, time perception, cognitive and psychological abilities, and memory. Cross-talk of biological, cognitive, and psychological clocks provides an integrative contribution to healthy and advanced aging. At the molecular level, genome, proteome, and lipidome instability are widely recognized as the primary causal factors in aging. We narrow attention to the roles of protein aging linked to prevalent amino acids chirality, enzymatic and spontaneous (non-enzymatic) post-translational modifications (PTMs SP), and non-equilibrium phase transitions. The homochirality of protein synthesis, resulting in the steady-state non-equilibrium condition of protein structure, makes them prone to multiple types of enzymatic and spontaneous PTMs, including racemization and isomerization. Spontaneous racemization leads to the loss of the balanced prevalent chirality. Advanced biological aging related to irreversible PTMs SP has been associated with the nontrivial interplay between somatic (molecular aging) and mental (psychological aging) health conditions. Through stress response systems (SRS), the environmental and psychological stressors contribute to the age-associated "collapse" of protein homochirality. The role of prevalent protein chirality and entropy of protein folding in biological aging is mainly overlooked. In a more generalized context, the time-dependent shift from enzymatic to the non-enzymatic transformation of biochirality might represent an important and yet underappreciated hallmark of aging. We provide the experimental arguments in support of the racemization theory of aging.

12. *Early-Life Environmental Factors Regulating Serotonergic-Dopaminergic Interaction and Adult Behavior*

Fabiula Francisca De Abreu*, Edenia Cunha Menezes, And Catia Martins Teixeira

Many neuropsychiatric disorders have developmental origins in which susceptibility to disease is restricted to narrow developmental windows; the perinatal period is a highly plastic time in which environmental factors can derail the normal development of the brain. Serotonin and dopamine are two key regulators of mood, reward-seeking and motivated behavior; several environmental factors have been shown to alter serotonin levels during development and lead to behavioral deficits in the adult. Here we present how changes in serotonin levels during development, produced by early-life administration of the SSRI fluoxetine, affect the dopaminergic system and lead to deficits in motivation later in life. We will further show that these deficits can be rescued by modulating the dopaminergic system.

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13. *A Modified Density-Based Method to Separate Brain-Derived Extracellular Vesicles Shines a Light on Their Heterogeneity and Neuropathological Potential*

Pasquale D'Acunzo*, Tal Hargash, Rocío Pérez-González, Chris N Goulbourne, Monika Pawlik, and Efrat Levy

Brain-derived extracellular vesicles (EVs) are a heterogenous population of vesicles that can be isolated from the extracellular matrix of neuronal tissues. Two main EVs subpopulations have been identified to date: microvesicles, which bud directly from the plasmalemma, and exosomes, which are released upon the fusion of late endosomes/ multivesicular bodies with the plasma membrane. EVs contribute to cellular functions such as cell-to-cell communication and waste removal, but their roles in neuronal pathophysiology are not clearly understood.

Previously, we have developed a method to isolate EVs from human and murine brain tissues using a sucrose density step-gradient. Sucrose gradients, however, do not allow to separate different subpopulations of EVs. Here, we demonstrate that by using an iodixanol-based step-gradient we are able to enhance the separation of the brain EVs, leading to a more pronounced differentiation of EVs subtypes. Our improved protocol led to the formation of eight fractions corresponding to different densities that were analyzed by Western blotting, transmission electron microscopy (TEM), cryogenic electron microscopy (cryoEM), and nanoparticle tracking analysis (NTA).

Our data revealed that 1) lighter fractions contain mainly large, single-membrane, electron-lucent vesicles and show enrichment of microvesicular markers, 2) moderately dense fractions contain smaller, single-membrane, mainly electron-dense vesicles and carry exosomal markers, and 3) dense fractions contain electron-dense double-membrane vesicles similar in size to exosomes that bear mitochondrial markers. Furthermore, we were able to describe a new class of EVs that bear mitochondrial but not exosomal nor microvesicular proteins, that we name 'mitovesicles'. Purification and analysis of homogeneous populations of EVs are of key interest because of their possible involvement in the propagation of neurodegenerative pathologies such as Alzheimer's Disease.

14. *Counterconditioning of Response-Produced Safety Signals is Highly Context-Dependent in Female Rats*

Lindsay Laughlin*, Shanna Samels, Danielle Moloney, Erika Andrade, Robert Sears, and Chris Cain

In signaled active avoidance (SigAA), rats are presented with a warning stimulus (WS; e.g. sound) that predicts an aversive unconditioned stimulus (US; e.g. footshock). Performance of the avoidance response (AR) terminates the WS, prevents the US, and produces new feedback stimuli. Failure to perform the AR results in WS-US pairings, transforming the WS into a conditioned threat. The reinforcement mechanism in SigAA is unknown, though prominent models suggest negative reinforcement is key (WS-termination or US-omission). Another possibility is that positive reinforcement contributes to instrumental avoidance, via response-produced stimuli that become safety signals due to negative correlations with the WS and US. To examine this, we designed a shuttlebox SigAA task with an explicit feedback stimulus (5s tone) and an outcome-devaluation procedure involving Pavlovian counterconditioning of the feedback-tone in separate chambers (40 tones & shocks, paired or unpaired). Final tests involved 15 WS presentations in the shuttleboxes (no WS-termination, shock or feedback tones). In male rats, avoidance behavior after moderate training (5 sessions) was strongly suppressed by devaluation and freezing to the WS reemerged. These effects were absent after 20 sessions of training, consistent with appetitive studies showing that overtraining results in habitual behavior that is no longer dependent on outcome value. Subsequent tests confirmed that devaluation was effective in male rats, who displayed high freezing to the feedback-tone in multiple contexts (counterconditioning boxes, shuttleboxes, and a novel open field). A different profile was observed in female rats using identical procedures. Devaluation effects were absent after both moderate training and overtraining. Females showed high freezing to the feedback-tone in the counterconditioning boxes, confirming that devaluation was effective. However, very low freezing to the same cue was observed in the shuttleboxes and open field, suggesting that expression of this learning is context-dependent. To circumvent this context-dependence of devaluation, counterconditioning was next conducted in the shuttleboxes with the door blocked, followed by avoidance testing with the door open (females only). Devaluation effects were again absent. Subsequent tests in the shuttleboxes revealed high freezing to the devalued tone only when the door was blocked. In the final experiments, avoidance behavior collapsed when training, devaluation and testing all occurred in the shuttleboxes with the door open. Taken together, these data suggest that response-produced safety signals contribute to positive reinforcement of goal-directed avoidance in male rats. The unusually strong context-dependence of counterconditioning in females means that other methods like contingency degradation may be necessary to explore mechanisms of goal-directed vs. habitual avoidance in females. This novel context effect may also help explain why anxiety disorders characterized by avoidance are more prevalent in females: devaluation of an avoidance outcome may not weaken goal-directed avoidance in other contexts.

15. *Exploring The Impact of Gender Role Nonconformity on Depressive Symptoms: Masculinity as a Potential Protective Factor*

Allison M. Sparpana*, Elizabeth F. Sullivan, Zamfira Parincu, Molly K. Irvin, Molly S. Arnold, Umit Tural, Katherine A. Collins, Matthew J. Hoptman, and Dan V. Iosifescu

Background: Uncertainty remains about the psychological implications of gender role nonconformity (GRNC), defined as men endorsing or performing femininity and women endorsing or performing masculinity. Previous studies have indicated that variance in gender presentation is associated with negative mental health outcomes. Homophobic stigmatization and internalized homophobia partially mediate this association, suggesting it is not GRNC itself that causes distress, but perceived reactions to it. Here, we test the hypothesis that people reporting higher levels of GRNC experience increased symptoms of depression.

Methods: We analyzed data from the Nathan Kline Institute Rockland Sample. 781 subjects (age=49.0 ± 17.4, sex=67% female) completed the Sex Role Identity Scale (SRIS) and the Trauma Symptom Checklist (TSC-40). GRNC and several subtypes were quantified by SRIS questions—behavioral GRNC (B-GRNC) was assessed using the question "How feminine/masculine do you act or behave?," subjective GRNC (S-GRNC) was assessed using the question "How feminine/masculine do you think you are?," and perceived GRNC (P-GRNC) was assessed with "How feminine/masculine do you think you appear and come across to others?" A composite variable including all three subtypes was created to assess overall GRNC. Depression was measured with the relevant TSC-40 subscale. We performed correlational analyses and a bootstrap quantile regression to explore the relationships between GRNC and its subtypes and depression.

Results: For male subjects, depression symptoms were significantly positively correlated with GRNC ($r_s(256) = .20$, $p = .001$), B-GRNC ($r_s(256) = .17$, $p = .005$), S-GRNC ($r_s(256) = .18$, $p = .003$), and P-GRNC ($r_s(256) = .17$, $p = .008$). For female subjects, depressive symptoms were significantly positively correlated with GRNC ($r_s(521) = .10$, $p = .019$), B-GRNC ($r_s(521) = .14$, $p = .002$), and P-GRNC ($r_s(521) = .10$, $p = .027$). For all subjects, GRNC significantly and positive predicted depressive symptoms ($B = 1.44361$, $SE = 0.37219$, $p = 0.00011$). S-GRNC masculinity scores significantly but negatively predicted depressive symptoms ($B = -0.90226$, $SE = 0.41269$, $p = 0.02910$).

Conclusion: GRNC and many of its subtypes are significantly associated with depressive symptoms, suggesting that those with higher levels of GRNC experience increased depressive symptoms. Interestingly, those who think they are more masculine, regardless of sex, experience decreased depressive symptoms. Perhaps this is due to masculine people being socialized to express depressive symptoms less. It could also be that masculinity is revered in a patriarchal society and is therefore protective against depressive symptoms. While limited by the secondary analyses conducted, these results have clinical significance; practitioners should be aware that patients experiencing and exhibiting GRNC may need additional support. Future research should identify potential mediators such as discrimination and social support.

16. *For the Sake of Safety: Orexinergic Modulation of VTA for Avoiding Threats*

Cristina Siller-Perez*, Erika C. Andrade, Christopher K. Cain, Joseph LeDoux, and Robert M. Sears

Identifying the neuromodulatory mechanisms that orchestrate survival behaviors is of critical importance to understanding anxiety- and stress-coping in health and disease. Perifornical (PFH) and lateral hypothalamus (LH) neurons expressing orexin (hypocretin) peptides project throughout the brain and mediate functions critical for survival behaviors including vigilance, attention, and action selection. Here we assessed the role of a key hypothalamic orexin system target using a model of proactive threat-coping behavior—signaled active avoidance (SigAA). Based on appetitive studies and physiology findings, we hypothesized that orexin would invigorate safety seeking via projections to a central hub in the reward pathway, the ventral tegmental area (VTA). Sprague Dawley rats received infusions of an orexin-specific viral vector containing an inhibitory opsin (AAV1-Ple112-Arch3.0-eYFP) into the PFH/LH, and optic fibers were implanted in the VTA. Following a 6-8-week incubation, rats were trained in the SigAA task. Animals received one Pavlovian trial (60 s white noise warning signal (WS) paired with an inescapable foot-shock (1.0/0.7 mA males/females; 0.5 s). For all remaining trials, if animals shuttled during the WS (an avoidance

response), a feedback (FB) tone was delivered (5 s, 80 dB) and indicated the animals were safe from harm (a safety signal). Failures to shuttle during the WS resulted in shock, identical to trial 1. Rats received 15 trials per day until reaching criterion (80% successful avoidance) after which they were subjected to daily shock-free avoidance tests. Orexin VTA axon terminals were inhibited (green laser 532 nm, 10 mW) during FB stimulus presentations only. On the first day, latencies and avoidance responses were unimpaired. However, inhibition on subsequent days increased latencies and impaired avoidance. These results suggest that 1) the FB cue is a reinforcer, perhaps through its association with safety, and 2) orexin communication with VTA is essential for safety-reinforced avoidance. Future studies will uncover the orexin system's role in adaptive coping behaviors and provide support for novel treatments of maladaptive coping, including active coping therapy combined with drugs to target the orexin system.

17. Distress Tolerance: A Potential Indicator for Disordered Eating Risk

Kathryn T. Evans*, Elizabeth F. Sullivan, Zamfira Parincu, Allison M. Sparpana, Matthew J. Hoptman, Katherine A. Collins, and Dan V. Iosifescu

Distress tolerance (DT), the ability to withstand negative emotional states, has been long associated with issues in regulation emotions as well as having implications on decision making. Specifically, previous research has found associations between low DT and increased disordered eating behaviors, specifically bingeing behavior. Eating behaviors were classified into two categories: restrictive eating and disinhibition of eating behaviors according to the Three-Factor Eating Questionnaire (TFEQ). Despite this, the link between DT and different facets of eating behavior has not yet been determined and calls for additional research. We hypothesize that the DT will be positively related to restrictive behaviors but negatively associated with disinhibition.

Methods: Data from the Nathan Kline Institute Rockland Sample were analyzed (n= 2445, sex= 59.1% female, age= 37.43 ± 22.71). All participants in this study completed the TFEQ, as well as the Behavioral Indicator of Resiliency to Distress (BIRD), a task measuring DT. Regressions and linear stepwise regressions were conducted to investigate the relationship between eating and DT.

RESULTS: Overall there was a positive relationship between latency on the DT task and disinhibition in eating behaviors (R^2= .021, p< .001), but not restrictive eating (R^2= .001, p= .748). There was a positive relationship between total score on the DT task and disinhibition in eating behavior (R^2= .023, p<.001), but not restrictive eating (R^2= .001, p= .364). A model including latency and total score on DT task significantly predicted eating disinhibition [$F(2, 655)=9.97$, $p<0.001$, adj. $R^2=0.03$]

Discussion: Results indicate a relationship between DT and disinhibition of control around food. These findings within the context of prior research have interesting implications for the treatment and risk assessment of binge and overeating behavior generally. Clinically, these results indicate that DT should play an important role in the future assessment of disordered eating behaviors and those who may be at risk of developing them.

18. Analysis of Extracellular Vesicles Using the Bigfoot Cell Sorter

Yohan Kim* and Efrat Levy

Extracellular vesicles (EVs) are nanoscale phospholipid bilayer membrane-bound vesicles containing lipids, proteins, and RNAs that are released by cells into tissue extracellular space, biological fluids, and conditioned culture media. EVs in the brain play a functional role in intercellular communicators and are associated with multiple types of brain disorders. Research into single EVs is an area of growing interest due to the many potential uses of these vesicles as therapeutic agents, as diagnostic and theragnostic biomarkers, and as regulators of cellular biology. Flow cytometry is currently developed as a promising tool for thorough single-EV studies. The majority of EVs, however, are below the detection sensitivity of most commercially available flow cytometers. To overcome these obstacles, we purchased the Bigfoot cell sorter, which is equipped with a small particle detector. Here, we present the successful detection of single exosomes and mitovesicles derived from mouse brains using membrane dye staining and optimized fluorescent antibody labeling. Encouraged by our preliminary success, we are exploring

methods for the analysis and sorting of different subtypes of EVs in order to expand our understanding of EV biology in the brain as well as the use of EVs as biomarkers for patients with neurological disorders.

19. *Differential Neurobiology of Sensory Over-Responsivity in ASD and OCD: A Preliminary Analysis*
Lucia Tu*, Katherine A. Collins, Melissa M. Breland, Molly Ludlow, Alexis Lieval, Russell H. Tobe, and Emily R. Stern

Autistic individuals and those with Obsessive-Compulsive Disorder (OCD) often report subjective sensory over-responsivity (SOR)—a rapid, intense, and/or durable responses to sensory stimuli. To our knowledge, the shared and differential neurobiology of SOR in Autism Spectrum Disorder (ASD) and OCD has not been thoroughly investigated.

Objectives: To investigate sensory profile differences across ASD and OCD. To investigate neural correlates of SOR via resting state functional magnetic resonance imaging.

Methods: Participants: Data were analyzed from 10 autistic participants without OCD (age 26.4 [5.4], range 19-36), 27 participants with OCD but not ASD (age 26.2 [5.1], range 19-36), and 22 neurotypical (NT) participants without psychiatric diagnosis (age 24.6 [3.1], range 20-31), confirmed via semi-structured psychiatric research diagnostic interview. Autistic participants met Autism Diagnostic Observation Schedule (ADOS-2) instrument classification of ASD. Participants with major medical, neurologic, or comorbid psychiatric diagnosis (e.g., bipolar or schizophrenia spectrum disorder) were excluded. All three groups were sex- (all male) and age-matched. Use of psychiatric medication was permitted in autistic and OCD cohorts.

Methods: MRI Scanning: Participants were scanned on a 3.0T Siemens TIM Trio with a 32-channel head coil. Resting-state functional scans were acquired using a high-resolution multiband-accelerated echo-planar sequence for full brain coverage. Preprocessing of functional data was performed using Statistical Parametric Mapping (SPM) v.12 and python and included: gradient distortion correction, realignment of functional images, normalization to MNI template, and 6-mm FWHM spatial smoothing.

Methods: Measures: The Adolescent and Adult Sensory Profile (AASP) (Brown & Dunn, 2002; Dunn, 2001) is a self-report questionnaire assessing responses to everyday sensory experiences. Following prior work, SOR was calculated using the AASP Sensory Sensitivity and Sensation Avoiding quadrant scores (Podoly et al., 2022).

Methods: Analyses: Between-group comparisons on SOR scores were performed using one-way ANOVAs. Resting-state functional connectivity analysis was performed using the Conn toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). Functional connectivity analyses focused on global connectivity which measures, for each participant, the connectivity between a given voxel and every other voxel in gray matter, with higher connectivity reflecting greater neural centrality or "hubness" (Martuzzi et al., 2011; Whitfield-Gabrieli & Nieto-Castanon, 2012) in an area. Group-level analyses interrogated the relationship between SOR scores and global connectivity within the ASD and OCD groups separately using regression. Preliminary connectivity results were thresholded at voxelwise $p < .005$ (uncorrected).

Results: SOR scores were significantly different between the participant groups, $F(2, 56) = 12.076$, $p < .0001$. Tukey post-hoc analysis revealed that both autistic ($M = 2.5$, $SD = 0.5$) and OCD participants ($M = 2.6$, $SD = 0.6$) had significantly higher SOR scores than NT participants ($M = 1.9$, $SD = 0.4$) ($p \leq .005$ for both). Autistic and OCD participants did not differ in SOR scores ($p = .963$). Analysis of global connectivity indicated that SOR scores were associated with medial orbitofrontal connectivity in OCD but sensorimotor connectivity in autistic participants.

Conclusions: Autistic individuals and those with OCD reported increased SOR compared to neurotypical control participants. While OCD and autistic participants were similar behaviorally, SOR was associated with distinct group-specific resting-state functional architecture. Overall, findings support SOR as a shared behavioral phenotype in ASD and OCD that may be driven by differential neural circuitry.

20. *Identifying Urge Suppression Subtypes in Obsessive-Compulsive Disorder using Latent Profile Analysis*
Goi Khia Eng*, Alessandro S. De Nadai, Katherine Collins, Nicolette Recchia, Pearl Kravets, Russell H. Tobe, Dan V. Iosifescu, Laura B. Bragdon, and Emily R. Stern

Obsessive-compulsive disorder (OCD) is characterized by a wide range of symptoms. Many patients with OCD experience uncomfortable or aversive sensory-based urges ("sensory phenomena") in addition to, or instead, of a concrete fear. These sensory-based urges are thought to be phenomenologically and neurobiologically related to everyday "urges-for-action", such as the urge to blink or scratch. Using an urge-to-blink paradigm as a model for sensory-based urges, we previously reported that OCD patients were less successful than controls in suppressing eyeblinks. Here we further investigated variability within OCD patients in urge suppression success and its association with clinical characteristics and neural activation.

Method: 82 patients with OCD and 38 controls performed an fMRI eyeblink-suppression task with eyeblinks measured using eye-tracking. The severity of both overall symptoms and sensory phenomena was assessed through the completion of the Yale-Brown Obsessive-Compulsive Scale and University of São Paulo's Sensory Phenomena Scale, respectively. Erroneous blinks during suppression were analyzed using latent profile analysis conducted via Mplus (version 8). All controls were assigned into a single cluster that is separated from patients and patients were freely assigned to model-estimated clusters. Brain-imaging data were analyzed using SPM12, and cluster threshold was estimated using AFNI's 3dClustSim with mixed-model spatial autocorrelation function using 10,000 Monte Carlo simulations to achieve a whole-brain corrected threshold of $p<.05$ (cluster-wise) at $p<.005$ (voxel-wise).

Results: A four-cluster solution emerged (Entropy=.83). Erroneous blinks during suppression were lowest in the OCD_Cluster1_Lo group (n=19), moderate in the OCD_Cluster2_Mod group (n=49), and highest in the OCD_Cluster3_Hi group (n=14; $p<.001$). Patient groups did not differ in overall OCD severity ($p>.05$), but OCD_Cluster3_Hi had higher sensory phenomena than the other two patient groups ($p<.05$). Compared with OCD_Cluster1_Lo, OCD_Cluster2_Mod and OCD_Cluster3_Hi had greater activations during suppression in regions including the insula, supramarginal gyrus/postcentral gyrus, precentral gyrus, parahippocampal gyrus, and superior temporal gyrus. OCD_Cluster3_Hi also had reduced activations in the middle frontal gyrus than OCD_Cluster2_Mod during suppression.

Discussion: While previous research has demonstrated that individuals with OCD were generally less successful in suppressing sensory-based urges compared with controls, results from our study revealed variability in urge-suppression success within patients that was associated with severity of sensory phenomena and neural activations associated with sensorimotor areas and interoception. Hyperactivity in these regions during suppression, as found in moderate- and high- erroneous blink groups, may reflect greater physiological sensation of the urge, leading to greater difficulty in suppressing the build-up of the urge to blink during suppression. Additionally, hypoactivity in the middle frontal gyrus observed during suppression in the subgroup of patients with most severe sensory phenomena and highest erroneous blinks may indicate reduced ability to inhibit blinks in the face of increasing urge.

Conclusion: We found heterogeneity within OCD patients in eyeblink suppression that is associated with clinical severity and neural activation. Future research could target a subset of OCD patients with the aim of developing interventions to improve urge suppression and pathological urge sensation.

21. *Sensory Over-Responsivity and Resting State fMRI Global Connectivity in Obsessive-Compulsive Disorder*

Nicolette L. Recchia*, Pearl Kravets, Amanda N. Belanger, Laura B. Bragdon, Goi Khia Eng, Katherine A. Collins, and Emily R. Stern

Sensory over-responsivity (SOR) is characterized by the avoidance of and/or hypersensitivity to sensory stimuli. Patients with obsessive-compulsive disorder (OCD) exhibit elevated SOR compared to healthy controls, and greater SOR is associated with higher symptom severity and functional impairment within patients. Despite the importance of SOR in OCD, there is a lack of research regarding its neurobiology. The current study investigated the neural correlates of SOR in OCD using measures of resting state functional connectivity.

Methods: One hundred twenty-six individuals with OCD (44 men, 82 females) and 86 healthy controls (39 men, 47 females) completed the Adolescent/Adult Sensory Profile (AASP). SOR was calculated as the average of the sensory sensitivity (i.e. excessive and strong response to sensory stimuli) and sensation avoiding (i.e. engaging in behaviors in order to actively avoid sensory stimuli) subscales. We conducted an independent samples t-test to evaluate group differences in SOR. OCD participants

underwent an 8-minute resting-state scan with eyes open in a 3T MRI scanner. Correlations between SOR and global connectivity, which is a measure of connectivity between each voxel and the rest of the brain (or "hubness"), were conducted within the OCD group using the CONN-fMRI Functional Connectivity Toolbox for SPM (v.20b).

Results: Individuals with OCD (M = 2.75, SD = .557) had significantly greater SOR scores compared to healthy controls (M = 1.89, SD = .378) [t (210) = 13.412, p<.001]. Greater global connectivity in the medial orbitofrontal cortex (OFC) was positively associated with SOR scores within the OCD group (whole-brain cluster-level familywise error correction p < .05, voxelwise threshold p < .005) such that OCD patients with higher SOR exhibited greater "hubness" of the medial OFC than patients with lower SOR.

Discussion: The finding of elevated SOR scores in patients compared to healthy controls is consistent with those of previous correlational studies and support a hypothesis that SOR is a feature of abnormal sensory processing in OCD. Our analysis of resting state functional connectivity data in patients with OCD found greater global connectivity in the medial OFC to be associated with elevated SOR scores. The medial OFC is a region of the classic cortical-striatal-thalamic-cortical (CSTC) model for OCD that has been shown to be involved in reward processing, emotion, and decision making. The involvement of the OFC raises the intriguing possibility that SOR in OCD relates more to an affective reaction to sensory stimuli rather than to a primary sensory deficit involving sensory cortices

Conclusion: SOR is elevated in OCD and is associated with abnormal OFC functioning. Further research examining the relationship between SOR and other neural and behavioral characteristics in OCD will be needed to fully characterize the nature of these experiences.

22. *Development of Isoproterenol Derivatives to Restore Lysosomal Ph and Defective Proteostasis in Alzheimer's Disease*

Sandeep Malampati*, Eunju Im, Ju-Hyun Lee, Philip Stavrides, Chris N. Goulbourne, Panaiyur S. Mohan, Bhaskar C. Das, Ralph A. Nixon

Maintaining optimal lysosomal pH preserves neuronal proteostasis and is predicted to extend an individual's lifespan. Poor lysosome acidification causes lysosomal functional failure and is deemed to be a major contributing factor to the pathological progression of Alzheimer's disease (AD), Parkinson's disease (PD), and other neurodegenerative disorders. In AD, the lysosomal vacuolar ATPase complex (v-ATPase) is impaired in pumping protons from the cytosol to the lysosomal lumen due to the inherited presenilin-1 familial Alzheimer's disease (PSEN1-FAD) mutations. The resultant defect in acidification impedes proteolysis resulting in substrate accumulation. We previously identified that the non-selective β-adrenergic receptor agonist Isoproterenol can restore the pH of the lysosome. Using the Isoproterenol pharmacophore, we have designed, synthesized, and screened a total of 33 compounds in 3 separate batches and screened for the ability of compounds to restore lysosome pH and function in PSEN1 knock-out blastocysts, Out of these compounds, we have identified C3, BT-595, BT-597, BT-787, and BT-790 as capable of restoring the lysosomal pH, promoting the cathepsin-D, cathepsin-B, proteolytic activities, and promoting autophagy flux in both PSEN1-FAD-246E fibroblasts and PSEN1 knock-out blastocysts. The β-adrenergic receptor blocker Propanolol, β2-adrenergic receptor specific blocker butaxamine and protein kinase A inhibitor H89 blocked the lysosomal pH restoration induced by BT-787 and BT-790, confirming that the test compounds are acting through β-adrenergic receptors. In the N2a cells carrying amyloid precursor protein Swedish (APPswe) mutation, we found that BT-787 and BT-790 could reduce the APP C-terminal fragments (APP-CTFs) level. These two compounds induced Cathepsin-D and proteolytic activities renewal in PS1-KO blastocysts as well as the reduction of APP-CTFs level in N2a-Swe-APP was prevented when co-treated with v-ATPase inhibitor Concanamycin-A. Also, in the lysosome fraction of PSEN1-FAD-246E fibroblasts treated with BT-790, the v-ATPase activity was significantly restored. These experimental results indicate that activating β-adrenergic receptors restored lysosomal pH by activating v-ATPase and promoting the clearance of autophagy vesicles. BT-790 is being advanced for further evaluation of its efficacy and for therapeutic intervention in AD.

23. *Analysis of Electrophysiological Markers and Correlated Components of Neural Responses to Discourse Coherence*

Kurt Masiello*

Constructing meaning from spoken language is invaluable for learning, social interaction, and communication. In clinical populations with developmental disorders of speech comprehension, the severity of disruption can persist and vary from limiting occupational opportunities to lower performance outcomes. Previous research has reported an event-related potential (ERP) neural positivity over right hemisphere lateral anterior sites in response to semantic and discourse processing. Although useful as a marker for clinical populations of autism spectrum disorder (ASD) and developmental language disorder (DLD), little is understood about the dynamics and neural sources of this biological marker. In addition to traditional methods of ERP analysis, this investigation utilizes methods for analyzing correlated components to determine meaningful sources of neural activity during language processing shared across this population of healthy adults. Based on previously published findings by Neumann et al. (2014), it was hypothesized in the current study that a positivity index of discourse processing would be detected at right lateral anterior sites starting 600 ms after sentence onset and persisting for 300 ms. The current study replicated previous findings and confirms that a persistent positivity is detectable for 300 ms over right lateral anterior sites during late-stage semantic processing. This positivity was shown to be sensitive to word-type in the sentence-initial position, resulting in a 100 ms delay of the LAP response onset time from 700-1000 ms. The results of this analysis also revealed a significant positivity at parietal sites when listening to discourse, which started 1000 ms following sentence onset and persisted for 200 ms. In addition, a significant negativity when listening to discourse over right lateral anterior sites started at 1000 ms following sentence onset and persisted for 200 ms. The results from this study reveal a more complex, biphasic dynamic of potentiation not observed in previous findings which had an epoch limit <1000 ms following sentence onset. The correlated components of evoked responses were determined using inter-subject correlation (ISC) and found to be consistent with the pattern observed for ERPs. The current study confirmed that correlation is stronger for coherent, ordered sentences when compared with randomly-ordered sentences, or with nonsense syllabic speech. These findings suggest a novel understanding of the processes involved in the neural construction of coherent discourse comprehension.

24. *Molecular and Functional Analyses of Glycosylated Cannabinoid-1 Receptors in the Frontal Cortex*

Sanjay Awathale*, Sandeep Alapati, Beat Lutz, and Vinod K. Yaragudri

A significant advancement has been made in delineating the molecular mechanisms of cannabinoid type 1 (CB1) receptor-mediated signaling in normal physiology and disease conditions. However, the post-translational modifications of CB1 receptors and their functional significance are still understudied. In this study, we characterized different forms of glycosylated and non-glycosylated CB1 receptors in the frontal cortex of mice by western blot, immunofluorescence, and agonist-stimulated G-protein coupling methods.

We identified seven forms of CB1 receptors in the synaptic membrane fraction with apparent molecular weights of 31, 48, 50, 51, and 55 kDa using two specific antibodies and brain tissue devoid of CB1 receptors. Both 48 and 55 kDa forms are highly expressed compared to the others. In addition, incubation of samples at increased temperatures resulted in aggregation and formation of many other CB1 receptor forms at higher molecular weights thereby depleting the receptor abundance at lower molecular weights. Immunofluorescence studies revealed the presence of the highly glycosylated CB1 receptors (55 kDa) mainly in the plasma membrane of the cell body which are partially co-localized with the antibody that recognizes receptors at lower molecular weights. These specific immunolabelings were absent in the frontal cortex of CB1 receptor-deficient mice. The enzyme peptide:N-glycosidase F (PNGase F) markedly reduced the CB1 receptor immunoreactivity at 48 and 55 kDa resulting in the detection of CB1 receptors at 31, 34, 37, 46, and 48 kDa. This deglycosylation led to the reduction of the CB1 receptor-mediated G-protein activation. Taken together, our findings suggest the existence of CB1 receptors in highly glycosylated forms

at molecular weights around 48-55 kDa and that the non-glycosylated form is present at a much lower molecular weight (~31 kDa) than previously recognized. The deglycosylation diminishes the ligand-induced G-protein activation of the CB1 receptors in the frontal cortex. Thus, the dysregulation of glycosylation of CB1 receptors may play an important role in the etiology of mental disorders.

25. *Bioinformatic Analysis of Single Population RNA-Sequencing (RNA-seq) From Neurons Obtained from Mouse and Postmortem Human Brains*

Harshitha Pidikiti*, Melissa J. Alldred, Amanda Labuza, and Stephen D. Ginsberg

Bioinformatics is an interdisciplinary field that combines the knowledge of mathematics, biology, and computer science. While there are many computational tools available publicly for performing the necessary steps between raw reads and gene identification, often specific datasets will require custom-designed computational approaches for rigorous analyses. Unbiased qualitative and quantitative analysis will result in a more comprehensive understanding of biological variation in the datasets. Bioinformatics has constant growth in new methodologies that result in more detailed and comprehensive data mining. The computational tools developed for the analysis of single population RNA-Seq data obtained from neurons microisolated via laser capture microdissection from mouse and postmortem human brains are described herein. We employ tools including FastQC for quality control, Trimmomatic to remove adapter contamination, and STAR Aligner to align RNA sequences to the reference genome. Quantitative assessments of the sequence reads are performed by Picard and RSEM. The Variance Partition package is used for the differential expression analysis of the data. Differentially expressed genes (DEGs) are identified and pathway analyses using Ingenuity Pathway Analysis (IPA), Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analysis, among others are enabled. We utilize these tools to identify DEGs and pathways for hypothesis testing within vulnerable neurons, with the goal of elucidating novel pathways and novel therapeutic targets during onset and disease progression of Alzheimer's disease and Down syndrome for discovery science and therapeutic intervention.

26. *Interictal Spikes in Animal Models of Alzheimer's Disease: Dominance of the Dentate Gyrus and Cholinergic Control by Medial Septum*

Christos Lisgaras* and Helen E. Scharfman

Objective: Interictal spikes (IIS) are a common type of abnormal electrical activity in animal models of Alzheimer's disease (AD) and AD patients. The brain regions where IIS are largest and occur first are not known but are important because such data would suggest where IIS originate. Here we asked whether the origin of IIS is along the cortical-CA1-dentate gyrus (DG) dorso-ventral axis based on the evidence that these areas exhibit hyperexcitability in AD models. We also tested the hypothesis that silencing the medial septohippocampal cholinergic neurons selectively would reduce IIS because of data showing that medial septal (MS) cholinergic neurons are overactive when IIS typically occur.

Methods: We used 3 models of AD, Tg2576 mice, presenilin 2 knockout mice, and the Ts65Dn model of Down's syndrome. To selectively silence MS cholinergic neurons, Tg2576 mice were bred with ChAT-Cre mice and offspring mice were injected in the MS with AAV encoding inhibitory designer receptors exclusively activated by designer drugs. We recorded EEG along the cortical-CA1-DG axis using silicon probes during wakefulness, slow-wave sleep (SWS) and rapid eye movement (REM) sleep. IIS amplitude was quantified along the cortical-CA1-DG axis.

Results: We detected IIS in all transgenic mice but not age-matched controls. IIS were detectable throughout the cortical-CA1-DG axis although IIS amplitude varied. In all 3 models, the amplitudes of IIS were significantly greater in the DG granule cell layer vs. CA1 pyramidal layer or overlying cortex. Selective chemogenetic silencing of MS cholinergic neurons significantly reduced IIS frequency during REM sleep without affecting the overall duration or number of REM sleep bouts.

Significance: Maximal IIS amplitude in the DG of 3 AD mouse models suggests that the DG could be one of the areas where IIS originate in AD models. Selectively reducing MS cholinergic tone could be a new strategy to reduce IIS in AD.

27. *Stability of Dentate Gyrus Mossy Fiber BDNF Protein Expression with Age and Resistance of Granule Cells to Alzheimer's Disease Neuropathology in a Mouse Model*

Chiara Criscuolo*, Elissavet Chartampila, and Helen E. Scharfman

It is well known that the neurotrophin brain-derived neurotrophic factor (BDNF) plays an important role in the developing CNS and in adulthood. In adults, BDNF contributes significantly to several normal functions, and deficits in BDNF have been implicated in disorders such as Alzheimer's disease (AD). Hippocampal BDNF levels in AD patients and AD animal models have often shown a decline, suggesting that reduced BDNF contributes to the disease. However, the location where hippocampal BDNF protein is most highly expressed, and plays a critical role in memory, the mossy fiber (MF) axons of dentate gyrus (DG) granule cells (GCs), has been poorly studied, and never in a controlled experimental situation like an animal model allows. Therefore, we examined MF BDNF protein in the Tg2576 mouse model of AD neuropathology. Tg2576 and wild type (WT) of both sexes were examined at 2-3 months of age, when amyloid β (Aβ) is present in neurons but plaques are absent, and 11-20 months, after plaque accumulation. Similar to past studies in WT mice, MF BDNF protein expression was strong compared to other hippocampal layers. Moreover, MF BDNF protein in female mice correlated with the stages of the estrous cycle. These results were true in both Tg2576 and WT. Surprisingly, there was no significant decline with age in either genotype or sex, suggesting a notable exception to the idea that reduced hippocampal BDNF contributes to AD. Notably, we found a correlation between MF BDNF protein and GC ΔFosB, a transcription factor that increases when neuronal activity has been elevated for the previous 1-2 weeks. Remarkably, there was relatively little evidence of intracellular Aβ in GCs even at old ages compared to pyramidal cells, using antibodies to Aβ (McSA1; 6E10; 4G8). Taking together these results suggest that MF BDNF may remain stable in Tg2576 due to increased GC neuronal activity, since BDNF expression is activity-dependent. In addition, the resistance of Tg2576 GCs to Aβ accumulation even in aged mice provides insight into AD resilience.

28. *The Prevalence of Supra- and Subthreshold Neural Responses Across Thalamocortical Circuits to Motor and Environmental Sensory Events*

Monica-Noelle* O'Connell, Annamarie Barczak, Chase Mackey, Sam Neymotin, Kieran Mackin, Tammy McGinnis, Peter Lakatos, and Charles Schroeder

Over the past four decades it has become well recognized that many brain regions, if not all, are capable of processing or being influenced by more than just one modality. Preferred modality stimuli result in suprathreshold evoked responses which are characterized by transient changes in the firing rates of neuronal ensembles and are due to specific driving type inputs that transmit stimulus specific information about the sensory environment. Neural responses to non-preferred modality stimuli, on the other hand, are typified by an absence of an evoked response but do exhibit a subthreshold modulation of ongoing neural excitability, which results in a frequency-specific increase in phase coherence across trials. This type of modulatory response can alter the representation of driving-type information related to preferred modality stimuli through an enhancement or suppression of activity. The main goal of this study was to delineate these driving and modulatory type brain circuits by examining and characterizing response types related to auditory, visual, and motor events as they occur across multiple cortical and thalamic structures. To accomplish this, we used linear array multielectrodes to record neuroelectric activity from auditory cortex (core and belt), motor cortex, auditory thalamic nucleus, visual thalamic nucleus and pulvinar (a multisensory thalamic nucleus), in awake macaque monkeys. A survey of response profiles specific to auditory, visual, and motor (saccades) events across these areas revealed groups of structures that are part of a driving circuit for a specific modality event, and others that belong to modulatory circuits. As anticipated, we found that saccades modulate neuronal excitability at all hierarchical levels examined.

29. *Salivary Uric Acid Reactivity to Discrimination Stress and Associations with Cardiometabolic Risk*

Sharifa Z. Williams*, Douglas Granger, Kennedy Blevins, Natalie Green, and Kerstin Pahl*

Background: Black and Latinx Americans are at disproportionate risk for cardiovascular disease (CVD) and metabolic syndrome. A well-documented pathway to these adverse health outcomes is psychosocial stress. Racism and racial discrimination are significant sources of stress for Black and Latinx Americans that potentially contribute to CVD. Salivary uric acid (sUA), a biomarker known to be associated with CVD and metabolic syndrome, has recently demonstrated stress reactivity.

Methods: We examined whether sUA showed reactivity related to a discrimination stressor and whether baseline sUA and sUA reactivity were associated with CVD and metabolic syndrome risk in 160 Black and Latinx adults. Saliva was collected before and after participants wrote about a personal experience of racial discrimination. Path analysis examined relationships between baseline sUA, sUA reactivity, BMI, and cardiometabolic outcomes (heart rate, systolic and diastolic blood pressure, and HbA1c).

Results: sUA showed reactivity to the discrimination stressor. There was an association between baseline sUA and systolic blood pressure, as well as sUA reactivity and heart rate and HbA1c. There was also an association between baseline sUA and outcomes of heart rate and HbA1c mediated by sUA reactivity, and between BMI and systolic blood pressure mediated by baseline sUA.

Conclusions: Results demonstrate that sUA is reactive to discrimination stress. Further, both higher baseline sUA and reactivity are linked with CVD and metabolic syndrome risk. These findings provide preliminary evidence suggesting that elevated uric acid levels may be a mechanism by which racism-based stress affects CVD and metabolic syndrome risk in Black and Latinx Americans.

30. The Lasting Effects of Racism-Related Stress: A Qualitative Study

Daniela Galvez*, Kerstin Pahl, Muazzez Melike Aksoy, Pedro Batista, Linda Capobianco, Pamela, Montano Arteaga, Naomi Pharr, and Helen-Maria Lekas

Background: In the context of a cohort study that has been examining the impact of social determinants, including racial/ethnic discrimination, on physical and mental health for three decades, we collected brief write-ups on experiences of racial discrimination from 160 Black and Latinx adult study participants. These write-ups were intended to elicit a stress response to be measured through self report and biological indicators. However, a content analysis of the write-ups revealed critical insights about the chronic and pernicious mental health effects of exposure to racism. This analysis can contribute to the debate about the reliability of existing tools to assess the health effects of racism, a highly critical issue given the current sociopolitical climate in the US.

Methods: The write-ups were collected between 08/2018 and 3/2020. Participants were asked to write about a personal experience of racial discrimination or one they had witnessed, and rate how stressful this experience was when it occurred and after writing about it using a 1-10 scale. The analysis was conducted by a multiracial and multidisciplinary team of eight coders. Following an iterative coding process, the team developed a coding scheme that pertained to the following domains: (1) context where the racist event took place; (2) time when the event occurred (childhood or adulthood); (3) personal experience vs. witnessing: who was exposed to racism; (4) response: how did the writer respond to the event; and (5) description of race/ethnicity: ways of referring to race/ethnicity.

Results: The emerging analytic themes are the following:

(1) racism's ubiquity, from the public to the private spheres,
(2) racism's protracted adverse effect on mental well-being,
(3) vicarious racism's adverse impact,
(4) range of coping strategies, from cognitive (e.g., discrediting the perpetrators) to behavioral (e.g., seeking justice through legal venues),
(5) resilience's protective effect, and
(6) explicit and implicit discussions of racism, impact on mental wellbeing. Do we have the language to talk about such experiences?

Conclusions: This study's brief write ups generated a plethora of insights that can inform survey design and scale development to assess the effects of racism on mental wellbeing.

31. A Novel Realistic Variable Resolution Approach to Infer Functional Brain Networks

Eduardo Gonzalez-Moreira*, Deirel Paz-Linares, F Xavier Castellanos, and Alexandre R. Franco

Inferring cortical sources from electromagnetic observations is essential for understanding their cognitive and behavioral correlates. Estimating such putative brain sources from magnetoencephalography (MEG) data would provide the topographic map of power amplitude variations corresponding to large-scale cortical network oscillatory activity emerging at distinct time and spectral scales. However, identifying functional brain networks across multiple rhythms (frequency bands) involves solving a challenging inverse problem. Here we introduce a novel inverse solution approach, spectral structured sparse Bayesian learning (ssSBL), for neural functional connectivity inference. In the ssSBL approach, different simultaneously active areas can be identified, even if they are close to each other, throughout the maximum a posteriori as $\hat{\iota} = \max\{P(\iota|v,\Omega)\}$, where v represents the voltage fluctuation in sensor space which directly reflects the macroscopic neural currents ι at gray matter points or sources in the time domain, and Ω represents the set of hyperparameters. In this work, we use MEG data to evaluate the ssSBL performance. The MEG and fMRI datasets were downloaded from the Human Connectome Project release. This high-quality data represents a unique opportunity for validating new ESI methods. The validation methodology was focused on the functional connectivity matrix estimated for neural regions over the cortical surface. To evaluate the similarity of MEG and fMRI functional connectivity maps, we estimated the Sorensen-Dice similarity coefficient, widely used for similarity comparison between brain functional connectivity matrices. We achieved promising results within the initial validation of the ssSBL approach. The ssSBL high-quality results will allow the scientific community to perform complex connectivity analyses with minimal information loss, transforming the discovery of novel brain-cognition-behavior relationships in electrophysiological data.

32. *Using AI-driven platform to Detect Negative Symptoms of Schizophrenia Through Facial and Acoustic Analysis*

Anzalee Khan*, Jean-Pierre Lindenmayer, Vikram Ramanarayanan, Kothare Hardik, David Paulter, Mohan Parak, Benedicto Parker, David Suendermann-Oeft, and Christian Yavorsky

Background: The automatic analysis of facial and acoustic expressions is an evolving field that finds several clinical applications. One of these applications is the study of facial and speech productions in individuals with schizophrenia, which is a major indication of negative symptoms of this illness. One feature of Negative symptoms is the reduction of facial movements and emotional facial expressions and is a transdiagnostic feature of schizophrenia. Current methods of assessing negative symptoms depend on verbal report from patients and/or caregivers and a clinical interview. These interviews can be insensitive to change in treatment, subjective, requires extensive training and subject to cultural disparities. Facial and speech changes in negative symptom may be difficult to track and quantify with only interview methods. With passive (real-world) data collection, combined with patented algorithms and machine learning, we are starting to see examples of AI-driven biosensors that can predict early signs of diseases in advance of an actual event. Similarly, digital therapeutics platforms can be used to supplement clinical interviews for more objective and precise measurements. This study assesses whether a novel artificial intelligence (AI) system analyzing facial and acoustic features improve measurement of negative symptoms in schizophrenia.

Method: Hospitalized inpatients with schizophrenia (SZ: n = 35) and demographically matched healthy controls (HC: n = 31) completed a brief 8-minute assessment using the AI-driven platform. Each participant was rated twice by the same clinician within one week period in order to assess for test-retest reliability. For the AI software, participants were each provided a valence-neutral sentence to read; participants then be engaged in free speech where they were asked open ended probes designed to be emotionally-ambiguous in valence and content (e.g., tell me about yourself?). For the SZ group, at the first visit, AI vocal/speech software, PANSS, BNSS, CDSS, CGI-S, AIMS, SAS, BARS was performed. Concurrent, convergent, divergent and discriminative validity were assessed. For the HC group, individuals received the AI vocal/speech software. All individuals were asked to assess user experience as measured by the SUTAQ (Service User Technology Assessment Questionnaire). Mann–Whitney test was used for comparison of AI features. Accuracy, sensitivity, specificity, and area under receiver operating characteristics-curve were measured as discriminatory indices of classifications.

Results: The mean age of individuals with SZ was 41.29 (10.34) and the HC group was 40.22 (8.32), and the mean PANSS total score at Time 1 was 80.23 (10.11). Comparison of all the extracted features (54 facial and acoustic metrics) between SZ and the HC groups found 39 features to be significantly different ($p < 0.001$) mostly belonging to speech features (syllable alternating motion rate, loudness/articulation, speaking rate and pauses) and some facial features (e.g., average jaw acceleration, lip aperture). Session duration for the AI software was a mean of 8:42 min (min = 5:01 min, max = 13:39 min). Significant correlations were observed between PANSS Motor Retardation and the AI software speaking rate ($r = -0.706$) and average jaw acceleration ($r = -0.801$), PANSS Active Social Avoidance and syllable alternating motion rate ($r = -0.800$), PANSS Marder Negative symptom score pauses during speech ($r = -0.525$), BNSS Blunted Affect Vocal Expression, and Blunted Affect Expressive Gestures with the AI software speaking rate ($r = -0.759$). Most SZ (85.71%) and HC (93.75%) reported satisfaction with the AI-driven platform. Accuracy of classifying SZ from HC was 89.29%.

Conclusions: Speech and facial AI technology could supplement negative symptoms clinical interviews as it affords precision of measurement of negative symptoms.

33. *Immersive, Mindfulness-Based Virtual Reality (VR) to Improve Aggressive Behaviors in an Inpatient Setting*

Anzalee Khan, Brianna Fitapelli, Seth Eaton, Jean-Pierre Lindenmayer, Nanea Reeves, and Theresa Abad*

Background: Aggressive behavior in individuals with schizophrenia is a multifactorial issue with severe health and social consequences. Virtual reality (VR) appears to be a unique possibility as a mindfulness-based intervention, which has been used as an adjunctive treatment for a variety of mental health conditions. The main objective of the present study is to explore the feasibility and the potential benefits of using mindfulness-based VR in participants with schizophrenia and aggressive behaviors.

Methods: This is a randomized controlled trial comparing the effect of engaging with the self-guided auditory mindfulness meditation app 'Headspace' (HS-MM) to a self-guided virtual reality mindfulness program 'TRIPP' (TRIPP-VR), for a period of 6 weeks, using a cohort of inpatient participants diagnosed with schizophrenia with a history of aggressive behavior. The Excitement Component of the Positive and Negative Syndrome Scale (PANSS-EC), the Oxford Mood Scale (OMS), the State Trait Anxiety Index (STAI) were administered at baseline and after 6 weeks of the interventions. The number of aggressive incidents before and after the intervention was also assessed. Following the intervention, all participants completed the Mobile Application Rating Scale (MARS). Eighteen participants (HS-MM n = 20, TRIPP-VR n = 20) were enrolled.

Results: MBT-VR with TRIPP showed a significantly larger reduction in PANSS Excitement Factor scores compared to the MBT with Headspace ($F=2.964$, 95% CI -5.1418, -0.7864, $p=0.04$); MBT-VR was significantly better than MBT with Headspace at reducing PANSS Positive total score with an estimate=-4.1692, 95% CI -7.7318, -0.6067, p=-0.03. MBT-VR was significantly better than MBT with Headspace at reducing PANSS Marder Hostility Factor with estimate=-2.6359, 95% CI -4.8179, -0.4539, p=-0.03. MBT-VR was significantly better than MBT with Headspace at reducing the number of aggressive episodes with estimate=-0.6823, 95% CI -1.30, -0.062, p=-0.03.

Conclusions: MBT using an immersive VR shows significant improvement over MBT with an auditory only component (Headspace) in decreasing aggressive behaviors as measured by number of aggressive episodes and the PANSS Excitement factor. Participants found both programs engaging, but MBT VR participants reported higher acceptability and aesthetics.

34. *Computerized Cognitive and Social Cognition Training for Impulsive Aggression in Schizophrenia*

Anzalee Khan, Jean-Pierre Lindenmayer*, Beverly Insel, Mary Seddo, Ecem Demirl, Kayla DeFazio, Mark Sullivan, Matthew J. Hoptman and Anthony O. Ahmed

Background: Schizophrenia is associated with an elevated risk for impulsive aggression for which there are few psychosocial treatment options. Neurocognitive and social cognitive deficits have been associated with aggression with social cognitive deficits seemingly a more proximal contributor. The current study examined the effects of combining computerized cognitive and social

cognition treatment of impulsive aggression among inpatients with chronic schizophrenia and schizoaffective disorder and a history of aggression compared to cognitive remediation treatment alone.

Methods: The two-center study randomized 130 participants to receive 36 sessions of either a combination of cognitive remediation and social cognition treatment or cognitive remediation plus a computer-based control. Participants had at least one aggressive incident within the past year or a Life History of Aggression (LHA) score of 5 or more. Participants completed measures of neurocognition, social cognition, symptom severity, and aggression at baseline and endpoint.

Results: Study participants were mostly male (84.5%), had a mean age 34.9 years, and 11.5 years of education. Both Cognitive Remediation Training (CRT) plus Social Cognition Training (SCT) and CRT plus control groups were associated with significant reductions in aggression measures with no group differences except on a block of the Taylor Aggression Paradigm (TAP), a behavioral task of aggression which favored the CRT plus SCT group. Both groups showed significant improvements in neurocognition and social cognition measures with CRT plus SCT being associated with greater improvements.

Conclusion: CRT proved to be an effective non-pharmacological treatment in reducing impulsive aggression in schizophrenia inpatient participants with a history of aggressive episodes. The addition of social cognitive training did not enhance this anti-aggression treatment effect but did augment the CRT effect on cognitive functions, on emotion recognition and on mentalizing capacity of our participants.

35. *Understanding Against Medical Advice Discharges from the Emergency Department: Opportunities for Enhancing Quality and Equity in Medical Care*

Helen-Maria Lekas, Kerstin Pahl, Navin Sanichar*, Jay Brenner and Crystal Lewis

Background: Leaving the Emergency Department (ED) against medical advice (AMA) is associated with high ED readmission, and morbidity/mortality rates. Psychosocially-vulnerable patients (i.e., Black, young men, uninsured or Medicaid insured, with behavioral health conditions) experience the highest rates of AMA discharges. Understanding how providers manage AMA discharges can likely inform strategies to reduce health inequities.

Methods: In 2020, Web-based surveys (n=109) among ED providers (physicians, NPs, PAs, and nurses) in upstate New York ascertained reasons on why patients leave AMA, including those that are patient-related and provider/hospital-related. Regression analysis was used to assess the relationship between confidence in managing AMA events (AMA confidence) and (1) engaging in shared-decision making (SDM), and (2) medical regard for with patients who leave AMA. Additionally, New York State Statewide Planning and Research Cooperative System (SPARCS) database was analyzed to further examine disparities in AMA discharges.

Results: Providers were mostly male (56.4%) and non-Latinx White (76.2%) (average age=36.9). Most providers (65.1%) attributed AMA discharges to both patient and provider/hospital reasons and one-third (34.9%) reported provider/hospital factors reasons only. After adjustment, providers with AMA confidence had significantly higher: (1) SDH scores, and (2) medical regard for AMA patients ($p<0.001$). While non-Latinx Black patients represented 25.9% of all ED visits, they disproportionately represented 36.4% of AMA discharges.

Conclusion: Examining ED providers' AMA perceptions and experiences elucidated their engagement in SDM and tendency for high medical regard for patients, core features of person-centered care. Further research on AMA discharge may inform effective health equity strategies.

36. *Journal Club Corner: "Addressing racial and phenotypic bias in human neuroscience methods", Nature Neuroscience April 2022*

Anushka Thummalapenta* and Anna MacKay Brandt

Electroencephalogram is a powerful research technique in neuroscience that is used to collect brain activity as participants engage in a variety of tasks. The newest study in the NKI-Rockland research program has added EEG to its characterization. In April 2022 a perspective was published in Nature Neuroscience addressing racial and phenotypic bias in human neuroscience methods

(https://doi.org/10.1038/s41593-022-01046-0). In this presentation we will review the major points of the perspective that: 1) review historical racial bias in science, 2) consider ways that racial bias can persist without explicit exclusion but instead by ignoring differences that are present, 3) propose ways to avoid or minimize racial bias within neuroscience methods moving forward. We welcome critical evaluation and discussion of this perspective and impressions based on experiences within our own research communities.

37. *FloD: A New Method to Quantify Bulk Flow in Brain Extracellular Space*

Jan Hrabe* and Sabina Hrabetova

Brain can be viewed as a porous medium. From this point of view, brain cells form a "solid" phase while extracellular space (ECS) forms a "liquid" phase that fills the pores between them. The brain ECS has fundamental importance for brain function. It serves as a reservoir for ions and a channel for transport of biologically significant molecules, including the clearance of harmful metabolites. It has been suggested that bulk flow of the interstitial fluid, rather than diffusion, is the dominant mechanism of ECS transport, especially for the removal of harmful substances. However, this idea has yet to be experimentally supported. An early attempt using radiotracers to measure bulk flow in a normal brain tissue found flow only in white matter and no flow in gray matter. Here we propose a flow detection method (FloD) to directly evaluate the bulk flow of interstitial fluid in vivo. The respective contributions of the diffusion and the bulk flow to the transport of molecules in ECS could thus be determined experimentally.

38. *Cortical Oscillation Events in a Multiscale Model of The Auditory Thalamocortical Pathway*

Erica Y Griffith*, Salvador Dura-Bernal, Annamaria Barczak, Noelle O'Connell, Tammy McGinnis, William W Lytton, and Samuel A Neymotin

We developed a biophysically-detailed model of the macaque auditory thalamocortical pathway, with medial geniculate body (MGB), thalamic reticular nuclei (TRN), and a column of primary auditory cortex (A1). This model used the NEURON simulator and NetPyNE modeling tool to integrate information at the subcellular, cellular, and circuit-level scales, from synapse characteristics to cell electrophysiology to long-range, local and dendritic connectivity. We used this model to reproduce cortical oscillations observed in macaque non-human primate (NHP) A1. We found that oscillations emerged spontaneously in the model and were comparable to those recorded in vivo. Individual oscillation events were detected in current source density (CSD) data from in silico and in vivo resting state recordings. These events were then classified by laminar region (supragranular, granular, infragranular) and frequency band (delta, theta, alpha, beta, gamma). To see if we reproduced physiologically realistic oscillation events in silico, we compared the duration, number of cycles, and peak frequency of oscillation events in the model and NHP datasets. These properties showed similar average values and overlapping distributions across frequency bands and laminar regions. We also compiled several examples of individual oscillation events from model and NHP which matched across all of these features. Having reproduced realistic oscillation events in silico, we used a supragranular theta oscillation event to demonstrate that the model can decipher the contributions of distinct neuronal populations to the overall CSD signal. This analysis revealed that the layer 4 spiny stellate and pyramidal tract cells, and the layer 5A intratelencephalic cells (IT5A), made the strongest contributions to the CSD signal during the oscillation. The contribution of IT5A was particularly interesting, since IT5A cell bodies were located 350-650 um below the electrode where the oscillation was recorded, suggesting that IT5A apical dendrite currents generated a substantial component of the detected oscillation. We also examined the corresponding spiking activity in these populations, and observed gamma band activity in the spike rate spectrograms, demonstrating a cross-frequency interaction often observed in oscillations, but with the added benefit of cell-type specificity. Overall, our model provides a valuable framework for integrating and reproducing experimental data in auditory circuits. Here we demonstrate this with respect to cortical oscillation events, and highlight how the model's biological detail can be used to examine the origins of complex cortical activity.

39. *REVISIT-C: A Multicenter, NIMH Funded, Randomized Clinical Trial to Examine the Effects of Clozapine Vs TAU for Prevention of Violence in Schizophrenia: Preliminary Methodological Findings*

Jean-Pierre Lindenmayer, Malathi Perugula*, Amir Meftah, Tania Sultana, Theresa Abad, Benedicto Parker, and Anzalee Khan

Background: Although most individuals with psychosis are not violent and most violence is committed by non-psychotic individuals, many studies support an elevated risk of violence in individuals with psychosis. Additional research is needed to better understand the relationship between psychosis and violence, as well as to investigate the potential benefits of clozapine in reducing violent behaviors. Clozapine usage in individuals with psychosis is very low due to lack of evidence from a definitive randomized clinical trial (RCT) in outpatients in the community, concerns about potential side effects, and the need for strict monitoring (i.e., REMS). To date, no large effectiveness clinical trial has analyzed the effects of clozapine on violent behavior in community settings, which was recognized by NIMH in funding this study. This study was designed to ensure liberal enrollment criteria, retention criteria, and flexible treatment criteria for the evaluation of the effects of clozapine vs. treatment as usual (TAU) on the risk for violent acts.

Methods: This is a randomized, single blind, open-label, 6-month clinical trial in adults with schizophrenia or schizoaffective disorder with a central coordinating site (NYSPI, New York, NY) and 7 clinical sites with extensive experience in the management of psychosis using clozapine. 280 individuals aged 18-65 with schizophrenia with recent history of violent acts will be randomized in this 2-arm, parallel-group, 24-week, blinded rater trial. Participants are recruited from the community and hospitals by referral and randomized to clozapine or TAU. The inclusion criteria require participants to have committed a minor or serious act of violence in the last 6 months as measured by the MacArthur Community Violence Interview (MCVI) and be appropriate for treatment with either clozapine or TAU. There are weekly visits including ANC for clozapine participants, vital Signs for TAU participants, and research assessments at Weeks 4, 8, 16, and 24. All study raters must undergo a comprehensive training program for the PANSS, CGI for Aggression, MCVI and diagnostic and motor assessments implemented by the Manhattan Psychiatric Center (MPC) site. Raters are blinded for the MCVI, PANSS, CGI (both CGI and CGI-A), and PSAP. On a weekly basis, all scores for the PANSS, MCVI and CGI for Aggression are compared for data validation (i.e., consistency checks between and across scales) by the MPC rater coordination site. The Data and Safety Monitoring Board (DSMB), under NIMH supervision, reviews all SAEs and violent episodes. All participants have access to the PharmCAT program, which is an evidence-based intervention that incorporates environmental supports, including signs and checklists to assist with participant medication adherence.

Results: Since enrollment began in 2022, 57 participants were consented and 33 were randomized. Of the 9 participants at the MPC site, 6 were enrolled, 2 completed the study, 3 screen failed, and 3 are currently active as of 04APR2023. Adverse effects included sialorrhea, constipation, weight gain, HTN, low B12, increased appetite, medication overdose, sedation, and dryness of hand. Data inconsistency checks found 39% of PANSS, CGI and MCVI visits had scoring inconsistencies in the first 6 months, leading to a refresher training for all raters, which reduced inconsistencies to 13% at 12 months. The largest inconsistencies were related to PANSS-EC mapping to corresponding scores on the CGI for Aggression.

Conclusions: The study's preliminary data shows that participant recruitment is progressing well with minimal medication-related adverse events and good medication adherence. However, data quality by raters has been a concern, and a recertification process for all blinded raters was conducted to address this issue, as it can affect signal detection. The inclusion and exclusion criteria seem appropriate for maintaining participant recruitment.

40. NKI-Rockland Sample 2 Multimodal Data Collection

Christa Ouellette*, Anna MacKay-Brandt, and Stan Colcombe

NKI- Rockland Sample II is a large-scale study aiming to characterize a normative community population in Rockland and surrounding counties. As in Rockland Sample I, the study uses multi-modal data collection for its MRI protocols, but uniquely employs multi-modal data collection for its Mobile Brain and Body Imaging (MoBI) protocol. Data types collected in this protocol range from brain images (EEG) to physiological data (ECG, EDA, respiration), to eye tracking. We provide an overview of this protocol and

emphasize the importance of multi-modal data collection methods to better understand how the body responds to a variety of tasks, including watching videos, drawing, resting, and cognitive performance tasks. We also focus on eye tracking as a particularly insightful measurement, by first reviewing what it can tell us in the context of the Rockland Sample II study, and then in other contexts, such as informing about cognitive processes like decision-making, or about behavioral differences like Autism Spectrum Disorder.

41. *Mesoscale Neural Effects of Transcranial Magnetic Stimulation*

Arnaud Yves Falchier*, Alexander Opitz, Nipun Perrera, Kurt Masiello, Brent Butler, Gary Linn, Brian Russ, and Charles Shroeder

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation method that is rapidly growing in popularity for studying causal brain-behavior relationships. However, its dose-dependent direct neural mechanisms and indirect sensory co-stimulation effects remain hotly debated. Understanding how TMS modulates neural activity at different scales and how stimulation parameters affect brain responses is vital for the rational design of TMS protocols. Studying these mechanisms in humans is challenging due to the limited spatiotemporal resolution of available non-invasive neuroimaging methods. In the experiments we are running at NKI, we leverage invasive recordings of local field potentials in nonhuman primates and show that mesoscale early TMS-evoked potentials are dose and location dependent. Further, we employ several control conditions to dissociate direct neural responses from auditory and somatosensory co-activation. These experiments provide crucial evidence regarding TMS neural effects at the brain circuit level. Our findings are highly relevant for interpreting human TMS studies and biomarker developments for TMS target engagement in clinical applications.

42. *Lysosomal Dysfunction in Down Syndrome and Alzheimer Mouse Models is Caused by Selective V-Atpase Inhibition by Tyr682 Phosphorylated APP* β*CTF*

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Early appearing, progressive lysosomal dysfunction is a prominent pathophysiological feature in Alzheimer's disease (AD), linked to major causative and risk genes for AD and diverse aspects of AD pathology, including neurodegeneration. In Down syndrome (DS), a model of early onset AD, elevation of beta-secretase C-terminal fragment of amyloid precursor protein (APP-βCTF) disrupts lysosomal acidification (Jiang et al., J Neurosci, 2019), depressing hydrolytic activities and turnover of autophagic and endocytic substrates, which is vital to neuronal survival. Notably, in AD mouse models, lysosomal acidification declines in neurons well before extracellular amyloid deposition and is associated with early-appearing deficiencies of lysosomal v-ATPase activity and APP-βCTF and Aβ accumulate selectively in enlarged poorly acidified autolysosomes leading to massive autophagic stress and intraneuronal membrane-limited fibrillar β-amyloid, and cell death yielding senile plaques (Lee et al., Nat Neurosci, 2022). Herein, we investigated how APP-βCTF influences lysosomal function. Having found that elevated levels of APP-βCTF reversibly impair lysosomal acidification in DS patient fibroblasts and neurons of Ts2 DS mice (3N APP), we investigated the underlying mechanism in lysosomes from DS and DS models. In fibroblasts from DS individuals or Ts2 DS model mice, APP-βCTF, especially the tyrosine phosphorylated form of βCTF, accumulates in lysosomes where it interacts selectively with the V0a1 subunit of the lysosomal v-ATPase complex, the proton pump regulating lysosomal pH. By binding V0a1, βCTF with V1 subunits controlling association of the V1 sector with the V0 sector of the complex, thereby promoting V0/V1 dissociation that results in lowered v-ATPase activity and increased pH. Similar deficits are seen in Ts2 DS model mice. Lowering APP-βCTF Tyr682 phosphorylation almost fully restores lysosome acidity and pH in DS fibroblasts and in vivo in brains of DS model mice. Notably, lowering APP-βCTF Tyr682 phosphorylation below normal constitutive levels induces modest additional V1/V0 association, suggesting a degree of tonic regulation of v-ATPase activity by tyrosine phosphorylation of APP-βCTF. Elevated APP-βCTF Tyr682 phosphorylation in two mouse AD models similarly disrupts v-ATPase function. These findings offer new insight into the

pathogenic mechanism underlying faulty lysosomes in all forms of AD. The multiple adverse effects of APP-βCTF on endosomal-lysosomal function underscore a partnership between AD-related genes and early endo-lysosomal pathway dysfunction in the etiology of AD.

43. Hippocampal-Network-Targeted Stimulation Influences Multiple Signatures of Memory Encoding

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Non-invasive transcranial magnetic stimulation (TMS) is a powerful tool for modulating brain function in basic research and clinical applications. While TMS can be readily applied to superficial target sites, connectivity-based targeting approaches are increasingly used to target networks that include deeper brain structures. A growing body of work suggests that hippocampal-network-targeted TMS applied to inferior parietal cortex (IPC) influences neural and behavioral markers of hippocampal function, which may hold promise for modulating memory in clinical applications. However, the mechanisms by which TMS influences memory, and specific mnemonic processes influenced by stimulation, are not well understood. Here, we tested the influence of continuous theta-burst TMS to IPC (versus an active control site) on fMRI-based activation during object-location memory encoding and rest. Replicating prior work, hippocampal-targeted TMS enhanced associative (object-location) memory relative to control TMS. Hippocampal-targeted TMS enhanced resting state perfusion in the hippocampus, providing evidence for a downstream influence on hippocampal function. During memory encoding, hippocampal-targeted TMS did not influence levels of hippocampal activation, but instead decreased activation during successful memory encoding in interconnected sites (medial parietal and prefrontal cortices). Moreover, hippocampal-targeted TMS increased hippocampal pattern differentiation (dissimilarity of activation patterns) across trials with objects in nearby locations. These findings suggest that hippocampal-targeted TMS improves associative memory, in part, by down-regulating activity in some brain regions and enhancing the separation of overlapping experiences during encoding. Future work using related network-targeted approaches to strategically modulate memory will be discussed.

44. Electrophysiological Mapping of Interoception in the Macaque Monkey Insular Cortex

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The central integration of multi-sensory information facilitates communication between brain, body and environment. One specialized brain region integrating interoceptive (bodily) with exteroceptive (world) afferents is the insular cortex (IC). The granular dorsal fundus of the posterior IC receives thalamocortical projections encoding interoceptive states from all the organs and tissues of the body (e.g., viscероception and cutaneous thermoreception). Here, we studied how the IC processes interoceptive information from thalamocortical afferents along its dorsal sector, an insular area that projects to the ventral anterior agranular IC (AIC) through its poly-modal dysgranular areas. The AIC harbors the atypical large spindle-shaped von Economo neuron and has been functionally connected to a network of higher-order cognitive functions and salience processing. Taken together, the transmission of information along this neural pathway appears to be crucial in supporting cortical evaluation of the body's homeostatic state. To topographically map functional representations of dynamic bodily processes within the anatomically distinct sub-regions of the IC, we performed electrophysiological recording of underlying neuronal responses to several distinct interoceptive stimuli or endogenous bodily activities. Multi-unit activity revealed neuronal populations tuned to skin temperature change, pinch, vestibular stimulation, and cardiac cycle. Electrophysiological recording throughout the dorsal IC revealed a topographical arrangement of population responses, reflecting an interoceptive body map with foot-to-head orienting along the posteroanterior trajectory. As such, thermal stimulation of the limbs (hand and foot) consistently activated a region located posterior to a middle face and dense oral cavity region. In addition, we identified insular sub-populations with neuronal response locking to ongoing physiological activities, specifically cardiac cycle events. These recordings of primary interoceptive cortex activity provide the first fine-grained mapping of

interoceptive modalities in the primate IC. Our findings and future elaborations of this map are of paramount importance for our appreciation of the neurobiological substrates underlying interoceptive processing and its relationship with psychosomatic phenomena.

45. *The Role of Insula in Perceptual Decision Making and Performance Monitoring*

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Human neuroimaging has previously implicated the anterior insular cortex (AIC) in accumulating abstract sensory evidence during perceptual decision making. Concurrently, neuroimaging and iEEG work implicates the AIC in performance monitoring processes (i.e., selective responses to negative feedback and/or self-detected errors). It is currently unclear whether the same or distinct areas of the AIC might be involved in these separate processes, and if so, what spatiotemporal dynamics support their role in these functions.

Our work capitalized on the high spatiotemporal precision of invasive intracranial EEG recordings in humans to investigate the neural dynamics of the anterior insula (AIC) during perceptual decision making. We recorded data from presurgical epilepsy patients while they made speeded perceptual categorizations. In two separate tasks, subjects judged either the direction (up vs. down) of random-dot stimuli (N=17), or the pitch (high vs. low) of tone cloud stimuli (N=9), and reported their choice with a button press. Feedback on the accuracy of the responses was provided after each trial. We analyzed high frequency activity (70-170Hz) in the insular cortex, time-locked to the presentation of sensory evidence, choice commitment, and performance feedback. Neural responses to sensory evidence were found across both anterior and posterior regions of the insula. However, we observed distinct activity profiles between these two regions.

The posterior insula exhibited activity consistent with sensorimotor-related processes, peaking at or after motor response in an effector-selective manner (i.e., showing effector-dependent hemispheric lateralization), and showed no response to task feedback. In contrast, activity in the AIC during evidence presentation resembled a possible abstract evidence accumulation signal, showing a gradual ramping response which scaled positively with the strength of sensory evidence, increased at a rate that predicted reaction time, was independent of motor effector, and peaked just before commitment to choice. Intriguingly, at the time of feedback, the same sites showed stronger responses to error than correct choices (i.e., negative vs. positive feedback), consistent with the known role of the AIC in feedback monitoring. A preferential response to error trials was also observed earlier, immediately after commitment to choice (and before feedback was provided). Our preliminary results are in line with the known anterior-posterior dichotomy of functions in the insular cortex, and suggest a common substrate for abstract evidence accumulation and performance monitoring processes in the anterior insula.