NEW YORK STATE OF OPPORTUNITY. | Nathan S. Kline Institute

Nathan Kline Institute Science Day

Tuesday, September 24, 2019
Conference Room A-C
11:00 am – 3:00 pm
NKI Building 35

Brought to you by the Community Building Committee to bring together faculty, staff and trainees from all departments and raise awareness of the ongoing research activities at the Nathan Kline Institute.

NKI Science Day
September 24, 2019

11:00 - 11:10 am	Welcome and Introduction **Melissa Alldred, PhD** Research Scientist, Center for Dementia Research, Nathan Kline Institute
11:10 - 11:25 am	Resting-State Functional Connectivity Underlying Interoception in Obsessive-Compulsive Disorder **Goi Khia Eng, PhD** Postdoctoral Fellow, Clinical Research, Nathan Kline Institute
11:25 - 11:40 am	Perinatal interference with the serotonergic system affects VTA function in the adult via glutamate co-transmission **Catia M. Teixeira, PhD** Research Scientist, Emotional Brain Institute, Nathan Kline Institute
11:40 - 11:55 am	Trk inhibition in a new experimental model of seizures and spreading depolarization/spreading depression **Yi-Ling Lu, PhD** Postdoctoral Fellow, Center for Dementia Research, Nathan Kline Institute
11:55 - 12:10 pm	CB1R Mediated CDK5 and RAC1 Signaling Control Neurobehavioral Abnormalities in Postnatal Ethanol Exposed Mice **Basavaraj S. Balapal, PhD** Research Scientist, Analytical Psychopharmacology, Nathan Kline Institute
12:10 - 12:25 pm	Effects of neonatal ethanol on GABA neuron development through adolescence **John F. Smiley, PhD** Research Scientist, Neurochemistry, Nathan Kline Institute
12:25 - 12:30 pm	Closing Remarks **Alexandre Franco, PhD** Research Scientist, Center for Biomedical Imaging and Neuromodulation, Nathan Kline Institute
12:30 - 1:00 pm	Break with Refreshments/ Poster placement
1:00 - 3:00 pm	Poster Session

Poster Presentations:

1) A novel excitatory and epileptogenic effect of dentate gyrus mossy cells in a mouse model of epilepsy.
   Justin J Botterill, Yi-Ling Lu, John J LaFrancois, Hannah L Bernstein, David Alcantara-Gonzalez, Swati Jain, Paige Leary, Helen E Scharfman.

2) Enhanced Generation of Intraluminal Vesicles in Neuronal Late Endosomes in the Brain of a Down Syndrome Mouse Model with Endosomal Dysfunction.
   Pasquale D'Acunzo, Tal Hargash, Monika Pawlik, Chris N. Goulbourne, Rocío Pérez-González, Efrat Levy.

3) Extracellular Vesicles: Where the Amyloid Precursor Protein Carboxyl Terminal Fragments Accumulate and Amyloid β is Not Generated.
   Yohan Kim, Rocio Pérez González, Chelsea Miller, Monika Pawlik, Efrat Levy.

4) Quantitative analysis of early endosomal pathology within basal forebrain cholinergic neurons (BFCNs) of young and aged Ts65Dn mice following maternal choline supplementation (MCS).
   Megan K. Gautier, Melissa J. Alldred, Arthur Saltzman, Sang Han Lee, Stephen D. Ginsberg.

5) Long-Lasting Reduction in Somatostatin-Positive Cell Densities in the Cortex and, Hippocampus of Mice Exposed to Neonatal Ethanol.
   Mariko Saito, John F. Smiley, Maria Hui, Kurt Masiello, Mitsuo Saito, Donald A. Wilson.

6) RNA-sequencing (RNA-seq) of medial septal nucleus basal forebrain cholinergic neurons (BFCNs) within the Ts65Dn mouse model of Down syndrome (Ds) and Alzheimer's disease (AD) identifies dysregulated transcriptional pathways.
   Melissa J. Alldred, Sang Han Lee, Sai C. Penikalapati, Tenzin Lhakhang, Adriana Heguy, **Stephen D. Ginsberg**.

7) Reliability of dynamic network reconfiguration: impact of data length and cognitive states
   Zhen Yang, Qawi Telesford, Alexandre Franco, Shi Gu, Lei Ai, Ting Xu, Chaogan Yan, Stan Colcombe, Michael P. Milham.

8) Gene Expression Of Methylation Cycle And Related Genes In Lymphocytes Of Patients With Schizophrenia And Non-Psychotic Controls
   Henry Sershen, Robert C Smith, Jordan Meyers, James Auta, Jenny Drnevich Zadeh, Mary Youseff, Renwong Wu, Jingping Zhao, Hua Jin, Abel Lajtha, John M Davis, Alexandro Guidotti.

9) Effects of Transcranial Stimulation on Cognitive Function and Brain Functional Changes in Schizophrenia
   Robert C Smith, Wei Li, Stan Colcombe, Yiran Wang, Jiangling Jiang, Jijun Wang, John M. Davis, Chunbo Li.

10) Betahistine Effects on Weight-Related Measures in Patients Treated with Antipsychotic Medications: A Double-Blind Placebo Controlled Study
    Robert C. Smith, Lawrence Maayan, Renrong Wu, Mary Youseff Zhihui Jing, Henry Sershen, Victoria Szabo, Jordan Meyers, Hua Jinf, Jinping Zhao, John M Davis.

11) p38α MAP kinase inhibition blocks rab5 activation and rescues the neurodegenerative phenotype of the Ts2 Down Syndrome (DS) mouse model
Ying Jiang, Anna Pensalfini, Mohan Panaiyur, Philip Stavrides, Sandipkumar Darji, James Peddy, Dunsheng Yang, Cynthia Bleiwas, John Smiley, Ursula Germann, John Alam, Ralph A Nixon.

12) An Investigation Of Resting State Naa And Naag Fluctuations In Rodent Brain At 7 T And At 21.1 T
David N. Guilfoyle, Morris H Baslow.

13) A modified density-based method to separate brain-derived extracellular vesicles shines a light on their heterogeneity and neuropathological potential
Tal Hargash, Pasquale D'Acunzo, Rocío Pérez-González, Chris N. Goulbourne, Monika Pawlik, Efrat Levy.

14) Adult neurogenesis in the normal adult mouse protects against experimental seizures, excitotoxicity, and the development of epilepsy.
Swati Jain, John J. LaFrancois, Justin J. Botterill, David Alcantara-Gonzalez, Helen E. Scharfman.

15) Data-driven biophysically-detailed model of auditory thalamocortical system rhythms
Salvador Dura-Bernal, Erica Y Griffith, Annamaria Barczak, Noelle O'Connell, Tammy McGinnis, Peter Lakatos, William W Lytton, Samuel A Neymotin.

16) Endogenously oscillating excitatory motoneurons produce undulatory output in a connectome-based neuromechanical model of C. elegans without proprioception
Haroon Anwar, Soheil Saghafi, Lan Deng, Jack E. Denham, Thomas Ranner, Netta Cohen, Casey Diekman, Gal Haspel.

17) Social Versus Non-Social Reward Learning in Schizophrenia
Julia A. Ermel, Deanna M. Barch, Stephanie Histon, Matthew J. Hoptman, Tarek Sobeih, Jaana Yeaton, and Pamela D. Butler.

18) Estradiol administration modulates functional activation of the fear extinction network in women using oral contraceptives: an fMRI study
Mira Z Milad, Jagan J Jimmy, Shari Lieblich, Lily Brown, Anu Asnaani, Cobb Scott, Ruben Gurr, Edna Foa, **Mohammed R Milad**.

19) Dynamic extracellular space alters spatiotemporal distribution of chemical signals in brain: experiment and modeling.
Sabina Hrabetova, Jan Hrabe.

20) Cognitive and Neurophysiological Correlates of Visual Active Sensing Deficits in Schizophrenia
Elisa C. Dias, Abraham C. Van Voorhis, Filipe Braga, Julianne Todd, Javier Lopez-Calderon, Antigona Martinez, Daniel C Javitt.

21) A brainstem-central amygdala circuit underlies defensive responses to learned threats
Yiran Gu, Walter T. Piper, Lauren A. Branigan, Elena M. Vazey, Gary Aston-Jones, Longnian Lin, Joseph E. LeDoux, **Robert M. Sears**.

22) CB1R Mediated HDAC-EGR1 Pathway Causes Neurobehavioral Defects In Postnatal Ethanol Exposed Mice
Madhu Shivakumar, Vikram Joshi, Shivakumar Subbanna, Balapal Basavarajappa**.**

23) Caspase Inhibitor Prevents Postnatal Ethanol-Induced Loss of MeCP2 in Neonatal Mice and Synaptic, Learning and Memory Impairments in Adult Mice
Shivakumar Subbanna, Nagaraja Nagre, Madhu Shivakumar, Delphine Psychoyos, Balapal Basavarajappa.

24) Amygdala-olfactory cortical interactions in odor fear
Brett S. East, Donald A. Wilson.

25) Urgency Mediates the Relationship between Aggression and Right Frontal Pole Structure and Functional Connectivity in Schizophrenia
Matthew J. Hoptman, Daniel C. Javitt.

26) Tracking rhythmicity of neural oscillations in the auditory thalamocortical system
Samuel Neymotin, Annamaria Barczak, Noelle O'Connell, Tammy McGinnis, Noah Markowitz, Elizabeth Espinal, Erica Griffith, Salvador Dura-Bernal, William W Lytton, Stephanie Jones, Stephan Bickel, Peter Lakatos.

27) Sociodemographic Correlates of Childhood and Adolescent Depression
Danielle Rette, Erin McDonald, Matthew J. Hoptman, Kate Collins, Russell Tobe, Dan Iosifescu.

28) Region-Specific Effects Of Early-Life Status Epilepticus On The Adult Hippocampal CA3 – Medial Entorhinal Cortex Circuitry In Vitro: Focus On Interictal Spikes And Concurrent High-Frequency Oscillations
Christos Panagiotis Lisgaras, Caterina Psarropoulou.

29) Embarking on discovering the mechanisms of resilience: combining language use analysis with neuroscience.
German Todorov, Karthikeyan Mayilvahanan, **Catarina Cunha.**

30) The Psychometric Properties of the Self-Evaluation of Negative Symptoms Scale (SNS) in Treatment-Resistant Schizophrenia (TRS)
Abraham Goldring, Jean-Pierre Lindenmayer, Amanda Hefner, Sophia Borne, Anzalee Khan, Amod Thanju.

31) The Effects of Clozapine and Non-Clozapine Antipsychotics on Neurocognitive Functions in Chronic Schizophrenia
McKenzie Osborne, Abraham Goldring, Jean-Pierre Lindenmayer, Anzalee Khan, Susan McGurk.

32) Are Repeated Psychotic Relapses Associated with Cognitive Decline in Schizophrenia: A Naturalistic Longitudinal Study of Cognitive Deficits in Chronic Schizophrenia
Jean-Pierre Lindenmayer, Owen Jones, **Abraham Goldring**, Sophia Borne, Anzalee Khan, Lucia Roitma, Christina Lee, Amanda Hefner, Mohanika Gowda, Dominic Arjuna Ugarte.

33) Cognitive Training for Social Cognition in Impulsive Aggression in Schizophrenia
Jean-Pierre Lindenmayer, Anzalee Khan, Isidora Ljuri, Owen Jones, Joanne Yoon, Amanda Hefner, Marc Budgazad, Benedicto Parker, Mohan Parak, Harinder Gill, Lucia Roitman, Mila Kirstie-Kulsa, Matthew Hoptman, Anthony Ahmed, **Tiffani Padua.**

34) Association of ZNF804A rs1344706 genotype and impulsivity in patients with chronic schizophrenia
Amod Thanju, Jean-Pierre Lindenmayer, Anzalee Khan.

35) The retina as a window to early dysfunctions of Alzheimer's disease following studies with a 5xFAD mouse model
Chiara Criscuolo, Elisa Cerri, Carlotta Fabiani, Simona Capsoni, Antonino Cattaneo, Luciano Domenici.

36) Age-related changes in the generation and secretion of murine brain exosomes
Chelsea Miller, Yohan Kim, Monkia Pawlik, Efrat Levy.

37) Cocaine modulates the level and cargo of specific brain extracellular vesicles in a gender-dependent manner
Bryana Barreto, Audrey Hashim, Monika Pawlik, Stefanie Canals, Pasquale D'Acunzo, Mitsuo Saito, Henry Sershen, Mariko Saito, Efrat Levy.

38) Amygdalostriatal circuits mediating outcome-dependent vs. habitual avoidance
Robert Sears, Lindsay Laughlin, Erika Andrade, Erick Martinez, Danielle Moloney, **Christopher Cain.**

39**)** Evaluation of a Visual Remediation Intervention in Schizophrenia
Stephanie Histon, Anthony Ahmed, Emily Blanco, Audrey Carrillo, Julia Ermel, Morgan Gomez, Thomas Holvey, Leah Israel, Tiana Pistillo, Aaron Seitz, Steven M. Silverstein, Tarek Sobeih, Trevor Stavropoulos, Judy L. Thompson, Jaana Yeaton, Pamela D. Butler.

40) Assessing the role of the amygdala nuclei in goal-directed vs. habitual active avoidance
Danielle Moloney, Robert Sears, Christopher Cain.

41) Reducing shock imminence, but not certainty, greatly improves active avoidance conditioning
Lindsay Laughlin, Robert Sears, Christopher Cain.

42) Brain expression and processing of the amyloid precursor protein is unaffected by apolipoprotein E genotype
Mariah J Novy, **Samantha F Newbury**, Jose Morales-Corraliza, Melissa J Alldred, Stephen D Ginsberg, Paul M Mathews**.**

43) Eye movement-related contextual modulation of auditory cortical activity
Annamaria Barczak, Monica N. O'Connell, Tammy McGinnis, Samuel A. Neymotin, Charles E. Schroeder, Peter Lakatos.

44) Real-time fMRI Motion Tracking: should I stop and restart the scan?
Nathalia Esper, Maicon Much, Dario Azevedo, Augusto Buchweitz, Michael Milham, **Alexandre Franco.**

45) Clinical Insight as a Predictor of Time to Relapse in Schizophrenia: A Two-Year Follow-up Study
Anzalee Khan, Phil D. Harvey, Richard S.E. Keefe, Christian Yavorsky, Lora Liharska, Ryan Bowser, Jean-Pierre Lindenmayer, Mary Seddo, Lucia Roitman

46) Long-Term Stability of Ketamine and Metabolites in Human Plasma
Raymond F. Suckow, Vinod K. Yaragudri, Anna Jarosky, Thomas B. Cooper.

47) Integrating electronic patient reported outcomes (ePROs) in schizophrenia trials: Clinician and Patient Perceptions for scale refinement
Anzalee Khan, Jean-Pierre Lindenmayer, Christian Yavorsky, Isidora Ljuri, **Mary Seddo.**

48) Regulation of Binge-Like Alcohol Consumption By Antagonists of CB1 and NPY1 Receptors
Vinod K. Yaragudri, Andrea Balla, Bin Dong, Kiran Vemuri, Alexandros Makriyannis, Henry Sershen, Raymond F. Suckow, Subhash C. Pandey

49) Single amyloid-beta injection exacerbates acutely-induced seizures and changes the synaptic response in the hippocampus
David Alcantara-Gonzalez, Benjamin Villasana-Salazar, Fernando Peña-Ortega, Helen Scharfman.

50) Over-activating neuronal Rab5 in mice by itself causes AD-related endosomal, synaptic, cholinergic, and cognitive deficits and, in APP-models of AD, accelerates disease.
Anna Pensalfini, Seonil Kim, Shivakumar Subbanna S, Cynthia Bleiwas, Chris N. Goulbourne, Philip H. Stavrides, Ying Jiang, Monika Pawlik, Chunfeng Huo, Martin J. Berg, John F. Smiley, Balapal S. Basavarajappa, **Ralph A Nixon**.

51) APP-βCTF Regulates vATPase-mediated Lysosomal Acidification
Eunju Im, Ying Jiang, Ju-Hyun Lee, and Ralph A. Nixon.

52) Non-Equilibrium Phase Transitions in Biological Information Processing: Principles of Brain Connectivity
Victor V. Dyakin and Justin Lucas.

Slide Presentations:

1) **Goi Khia Eng**, Carina Brown, Molly Ludlow, Katherine Collins, Russell H. Tobe, Dan V. Iosifescu, Lazar Fleysher, Emily R. Stern.

Resting-State Functional Connectivity Underlying Interoception in Obsessive-Compulsive Disorder

Background: Obsessive-compulsive disorder (OCD) is a debilitating disorder. Past work has proposed that OCD may be associated with altered interoception – the process by which individuals detect, attend, and utilize information from the body - yet few studies have directly examined the neural mechanisms of interoception in the disorder. This study examined dimensions of interoception and associations with resting-state functional connectivity in a preliminary sample of adults with OCD.
Methods: 62 patients with OCD (44 males, 18 females) and 48 controls (30 males, 18 females) underwent an 8-minute resting-state scan with eyes opened in a 3T MRI scanner. Participants completed the Multidimensional Assessment of Interoceptive Awareness (MAIA), a self-report measure of interoceptive awareness consisting of 8 subscales. In addition to a subscale reflecting one's general awareness and sensitivity to body sensations ["noticing" subscale]; the other subscales broadly segregate into "adaptive" and "maladaptive" interoceptive tendencies. Adaptive subscales include the ability to control attention to sensations ("attentional control"); awareness of the link between the body and emotion ("emotional awareness"); ability to regulate emotion through attention to the body ("self-regulation"); listening to the body for insight into emotion ("listening"); and experiencing the body as safe and trustworthy ("trusting"). Maladaptive scales include the tendencies to distract from uncomfortable sensations ("distracting") and worry about uncomfortable sensations ("worrying"). Participants also completed the Beck Anxiety Inventory (BAI) and Yale-Brown Obsessive Compulsive Scale (Y-BOCS), a general measure of OCD symptom severity.
The factor structure of the MAIA in OCD was investigated using principal component analysis (PCA) with quartimax rotation. Correlations between resultant factor scores and global connectivity (i.e., connectivity between a given voxel and all other voxels in the brain) were conducted using the Conn toolbox, with gender as a covariate of no interest ($p < .005$ voxelwise uncorrected, and $k > 40$).
Results: Compared to controls, patients with OCD showed greater scores on the noticing, emotional awareness, distracting, and worrying subscales ($p < .05$, Bonferroni-corrected). Results from PCA showed a 2-factor solution in the OCD group. Dimensions loading onto Factor 1 were the "adaptive" scales of attentional control, emotional awareness, self-regulation, body listening, and trusting. By contrast, dimensions loading onto Factor 2 included noticing and the "maladaptive" scales of distracting and worrying. Greater global connectivity in the right medial occipital, thalamus, rolandic operculum extending into posterior insula, and the supramarginal gyrus was associated with increasing Factor 1 scores. Interestingly, increased global connectivity in the right thalamus and right medial occipital region was correlated with lower OCD symptom severity ($r = -.26$, $p = .04$), and state anxiety ($rs = -.35$, $p = .005$), respectively. By contrast, greater global connectivity in the right precentral, anterior-mid insula, and supplementary motor area was associated with increasing Factor 2 scores.
Conclusion: We identified a 2-factor solution of interoception in OCD that generally segregated into maladaptive vs. adaptive responses to body sensations and had different global connectivity patterns. The fact that some brain regions that were associated with "adaptive" factor 1 scores were also linked to reduced symptom severity reveals a potential neural basis of body processing that contributes to positive effects on mental health. The association of anterior

insula with “maladaptive” factor 2 scores is consistent with prior work linking anterior insula to negative emotion and anxiety. These preliminary neural and behavioral distinctions between factors of interoception have potential clinical implications and warrant further investigation.

2) Catarina Cunha, John F. Smiley, Nao Chuhma, Relish Shah, Francisco X. Castellanos, Mark S. Ansorge, **Catia M. Teixeira.**

Perinatal interference with the serotonergic system affects VTA function in the adult via glutamate co-transmission

Serotonin and dopamine are neurotransmitters associated with multiple psychiatric disorders. How they interact during development to affect subsequent behavior remains unknown. Knockout of the serotonin transporter or administration of selective-serotonin-reuptake inhibitors (SSRIs) during early-life lead to novelty-induced exploration deficits in adulthood. Here we show that Raphe nucleus serotonin neurons activate ventral tegmental area (VTA) dopamine neurons via glutamate cotransmission and that this cotransmission is impaired in postnatally SSRI treated animals. Moreover, we show that the SSRI-induced hypolocomotion is mimicked by blocking serotonin neuron glutamate cotransmission. Optogenetic activation of dopamine neurons rescued this hypolocomotor phenotype. Our data demonstrate that serotonin neurons modulate dopaminergic activity via glutamate cotransmission and that this pathway is developmentally malleable, with high serotonin levels during early life blunting this capacity, resulting in reduced novelty-induced exploration in adulthood. Moreover, we have preliminary evidence that early-life exposure to SSRIs leads to deficits in effort-related motivation, correlated with deficits in dopaminergic system. Finally, our preliminary data suggests that these deficits in motivation can be rescued, in the adult, by using antidepressants working on the dopaminergic system and worsened by antidepressants acting on the serotonergic system., The relevance of these observations for humans is based on the high prevalence of risk factors for increased serotonin levels during development, e.g., maternal inflammation and the substantial use of SSRIs (~ 10%) by women during pregnancy. Together our data provide translational insight into developmental mechanisms underlying endophenotypes of neuropsychiatric disorders. Such insight into how environmental factors can confer risk for disease will aid improving prevention, diagnosis and treatment approaches.

3) **Yi-Ling Lu**, Jeffrey S. Sprouse, Helen E. Scharfman.

Trk inhibition in a new experimental model of seizures and spreading depolarization/spreading depression

Spreading depolarization or depression (SD) is a large, often sudden depolarization of cortical neurons that has been proposed as an underlying mechanism for migraine and seizures. We hypothesized that there was an important role of the neurotrophin brain-derived neurotrophic factor (BDNF) acting at TrkB receptors and developed a new experimental model to test this hypothesis in rodent hippocampal slices. This experimental model provides the first opportunity to study SD as well as simulate epileptogenesis and do so in a slice chamber amenable to whole-cell recording. Slices were made using standard methods (350 μm-thick, horizontal plane, dissection in sucrose-based artificial cerebrospinal fluid (aCSF)) and put in a holding chamber in sucrose aCSF with temperature gradually increasing to 35°C and maintaining at 35°C for 45 min. Slices were kept in the holding chamber at room temperature in sucrose aCSF until being

transferred to the recording chamber with a high flow rate (6-7 mL/min) of 0 mM Mg2+/5 mM K+ NaCl-based aCSF flowing above and below the slice (Warner, RC-27LD). The recordings were acquired in area CA3. We observed ictal-like events in all rat slices (5 slices, 3 rats) and 50% of mouse slices (11/22 slices, 16 mice). SD events were only observed in mouse slices (18/22 slices), and the first SD or ictal-like event developed at 31.2 ± 1.9 min after 0 mM Mg2+/5 mM K+ aCSF exposure (range: 19.0-55.8 min; n = 22 slices, 16 mice). These events were delayed 10.5 ± 2.3 min by pre-treatment of K-252a for 15 min in the holding chamber and continuous K-252a exposure in the recording chamber when compared to vehicle (unpaired t-test, p = 0.0076; 500 nM K252a, 35.6 ± 2.5 min; 0.001% dimethyl sulfoxide, 25.1 ± 2.3 min; 8 slices from 7 mice for each group). We conclude that Trk inhibition delays but does not block SD and ictal-like events. These results suggest that this new ex vivo model could be beneficial to understand the mechanisms and roles of neurotrophins and Trk receptors underlying migraine and seizures.

4) **Balapal Basavarajappa**, Shivakumar Subbanna, Madhu Shivakumar, Vikram Joshi.

CB1R Mediated CDK5 and RAC1 Signaling Control Neurobehavioral Abnormalities in Postnatal Ethanol Exposed Mice

Alcohol drinking during pregnancy exposes the fetal brain to alcohol and impairs brain development, leading to persistent neurobehavioral problems, including cognitive impairments, which collectively is known as fetal alcohol spectrum disorder (FASD). However, the molecular mechanisms underlying these impairments are poorly defined. In our previous studies, we demonstrated that postnatal ethanol-induced CB1R-mediated activation of the extracellular-signal-regulated kinase (ERK) causes neurodegeneration followed by behavioral deficits. In this study, we report that the ethanol exposure of postnatal day 7 (P7) mice that induces neurodegeneration activates cyclin-dependent kinase 5 (CDK5), impairs cAMP response element binding protein (CREB) activation, and impairs the expression of RAC1and activity-regulated cytoskeleton-associated protein (ARC) in neonatal mice. Inhibition of CDK5 activity before ethanol exposure rescues deficits in RAC1, pCREB, and ARC expression followed by neurodegeneration in neonatal mice. Also, inhibition of CB1R rescued CDK5 activation and RAC1 deficits. Furthermore, the administration of a CDK5 inhibitor before ethanol treatment of P7 mice inhibited pCREB, ARC, long-term-potentiation (LTP), and spatial memory deficits in adult mice. Collectively, these results reveal that the ethanol activated CB1R activates CDK5, induces RAC1 deficits, causes neurodegeneration in the P7 mice brain, and causes long-lasting neurobehavioral impairments in adult mice. Acknowledgments: Funded by NIH/NIAAA grant AA019443.

5) **John F. Smiley**, Cynthia Bleiwasa, Kurt Masielloa, Eva Petkova, Judith Betz, Maria Huia, Donald A. Wilson, Mariko Saito.

Effects of neonatal ethanol on GABA neuron development through adolescence

For reasons that are poorly understood, GABA neurons in cerebral cortex are selectively sensitive to disruptions of early brain development. The mechanisms might include reduction of GABA neuron number or suppression of their GABAergic phenotype. To begin to distinguish these possibilities, we examined the development of GABA neuron number in mouse cortex following ethanol toxicity at postnatal day 7 (P7). Immediately after P7 ethanol treatment, we found apoptotic markers expressed in both pyramidal neurons and GABAergic interneurons. By

P14 both pyramidal neurons and GABA neurons were reduced nearly 20% in stereological cell counts. However, only the GABA neuron reduction persisted in subsequent ages, whereas pyramidal neuron number returned to near-normal levels by P20. We hypothesize that pyramidal neurons have the capacity to compensate for early cell loss by modulating normal programmed cell death that is ongoing in the first postnatal weeks. Programmed cell death in GABA neurons is thought to be regulated by a cell-autonomous mechanism that is distinct from that of pyramidal neurons, and this difference may explain their persisting loss. Our study indicates that GABA neuron loss following early developmental lesions can be explained at least partially by cell death that occurs around the time of the lesion.

Poster Presentations:

1) **Justin J Botterill**, Yi-Ling Lu, John J LaFrancois, Hannah L Bernstein, David Alcantara-Gonzalez, Swati Jain, Paige Leary, Helen E Scharfman.

A novel excitatory and epileptogenic effect of dentate gyrus mossy cells in a mouse model of epilepsy

The sparse activity of hippocampal dentate gyrus (DG) granule cells (GCs) is thought to be critical for cognition and behavior, whereas excessive DG activity is thought to contribute to disorders such as temporal lobe epilepsy (TLE). Glutamatergic mossy cells (MCs) of the DG are potentially critical to normal and pathological functions of the DG because they can regulate GC activity through direct innervation of GCs or indirectly through GABAergic neurons. Here we test the hypothesis that MC excitation of GCs is normally weak, but under pathological conditions, MC excitation of GCs is robust. Our results show that selectively inhibiting MCs during severe seizures reduced manifestations of those seizures, hippocampal injury, and chronic epilepsy. In contrast, selectively activating MCs was pro-convulsant. Mechanistic in vitro studies using optogenetics further demonstrated the underappreciated ability of MC axons to excite GCs under pathological conditions. These results demonstrate a novel, excitatory and epileptogenic effect of MCs in the DG.

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

Enhanced Generation of Intraluminal Vesicles in Neuronal Late Endosomes in the Brain of a Down Syndrome Mouse Model with Endosomal Dysfunction

Down syndrome (DS) is a human genetic disease caused by trisomy of chromosome 21 and characterized by early developmental brain abnormalities. Dysfunctional endosomal pathway in neurons is an early event of DS and Alzheimer's disease. Recently, we have demonstrated that exosome secretion is upregulated in human DS postmortem brains, in the brain of the trisomic mouse model Ts[Rb(12.1716)]2Cje (Ts2) and by DS fibroblasts as compared with disomic controls. High levels of the tetraspanin CD63, a regulator of exosome biogenesis, were observed in DS brains. Partially blocking exosome secretion by DS fibroblasts exacerbated a pre-existing early endosomal pathology. We thus hypothesized that enhanced CD63 expression induces generation of intraluminal vesicles (ILVs) in late endosomes/multivesicular bodies (MVBs), increasing exosome release as an endogenous mechanism to mitigate endosomal abnormalities in DS. Herein, we show a high-resolution electron microscopy analysis of MVBs in neurons of the frontal cortex of 12-month-old Ts2 mice and littermate diploid controls. Our quantitative analysis revealed that Ts2 MVBs are larger, more abundant, and contain a higher number of ILVs per neuron compared to controls. These findings were further corroborated biochemically by Western blot analysis of purified endosomal fractions showing higher levels of ILVs proteins in the same fractions containing endosomal markers in the brain of Ts2 mice compared to controls. These data suggest that upregulation of ILVs production may be a key homeostatic mechanism to alleviate endosomal dysregulation via the endosomal-exosomal pathway.

3) **Yohan Kim**, Rocio Pérez González, Chelsea Miller, Monika Pawlik, Efrat Levy.

Extracellular Vesicles: Where the Amyloid Precursor Protein Carboxyl Terminal Fragments Accumulate and Amyloid β is Not Generated

The amyloid β precursor protein (APP) is a single pass transmembrane protein whose proteolysis by α and β secretases generates α and β carboxyl terminal fragments (APP CTFs), respectively. γ secretase cleavage of APP CTFs generates amyloid β (Aβ), the major component of the amyloid deposits in the brain of Alzheimer's disease patients. The involvement of extracellular vesicles (EVs) in Aβ amyloidosis was proposed because full length APP, APP cleaving enzymes, APP CTFs, and a minute fraction of Aβ were identified in association with EVs. Here we undertook to determine whether in addition to Aβ binding to EVs in the extracellular space as was previously shown, EVs are a source of Aβ. We investigated the processing of APP in exosome enriched EVs isolated from the brain of wild type and APP overexpressing Tg2576 mice, aged 4 to 6 months. EVs were isolated from brain extracellular space using a method developed in our laboratory. The EVs were incubated in human CSF for different time periods at 37℃ and analyzed by Western blotting. We found that APP was enzymatically processed in isolated brain EVs following 24h incubation, generating APP CTFs. We not only confirmed the presence of the α and β secretases, ADAM10 and BACE1 in the EVs, but also found the presence of all the γ secretase subunits. Interestingly, treatment of EVs with the γ secretase inhibitor, L-685, did not affect the levels of APP CTFs, suggesting no further processing of APP CTFs in EVs. Lastly, we found a decrease in the level of the 4 kDa monomeric Aβ accompanied by an increase in the level of Aβ signals at 8-9kDa following 24h incubation. This indicates the recruitment of EV associated Aβ into dimers, which have been suggested as a building block of toxic assemblies. As a result, our data show that while exosomes are not a major source of Aβ generation, it seeds oligomeric Aβ.

4) **Megan K. Gautier**, Melissa J. Alldred, Arthur Saltzman, Sang Han Lee, Stephen D. Ginsberg.

Quantitative analysis of early endosomal pathology within basal forebrain cholinergic neurons (BFCNs) of young and aged Ts65Dn mice following maternal choline supplementation (MCS)

Down syndrome (DS) is a genetic disorder caused by triplication of chromosome 21. By middle-age DS individuals develop Alzheimer's disease (AD) neuropathology including amyloid-β plaques, neurofibrillary tangles, and early endosomal abnormalities. The trisomic Ts65Dn mouse model recapitulates several key aspects of DS/AD pathology, including cognitive dysfunction, basal forebrain cholinergic neuron (BFCN) degeneration, and dysregulation of the endosomal-lysosomal system. We hypothesize that BFCN degeneration stems from deficient neurotrophic support, a biproduct of aberrant septohippocampal endosomal transport. We have previously shown that maternal choline supplementation (MCS), a well-tolerated treatment modality, is able to improve neuronal size, shape, and density of septohippocampal neurons in Ts65Dn mice, as well as attenuate the overexpression of genes underlying endosomal defects. These data indicate MCS may improve the efficiency of endosomal transport. To determine whether MCS treatment can significantly improve endosomal defects in BFCNs, we conducted unbiased regional surveys of early endosomes in Ts65Dn mice and their normal disomic (2N) littermates at two time-points: 3-4 months of age and 10-12 months of age. BFCNs within the medial septal nucleus (MSN) were dual labeled with antibodies directed against choline acetyltransferase (ChAT) and rab5, a cholinergic marker and an early endosomal marker,

respectively. Quantitative analysis of vesicular attributes such as rab5-immunoractive endosomal area were performed via 3D z-stack reconstruction utilizing Imaris software (Bitplane). Comparison between young and aged cohorts indicates that the average number of rab5-immunoreactive endosomes per BFCN increases with age in both Ts65Dn and 2N littermates. However, the magnitude of this increase is heavily impacted by genotype. 11-month-old Ts65Dn mice have significantly increased numbers of rab5-positive endosomes per BFCN compared to 2N littermates when these offspring were fed a normal choline diet. MCS administered in utero decreased the average number of early endosomes per BFCN at 11 months regardless of genotype, suggesting that early-life MCS treatment may confer long-lasting neuroprotective benefits on vulnerable neuronal populations.

5) **Mariko Saito**, John F. Smiley, Maria Hui, Kurt Masiello, Mitsuo Saito, Donald A. Wilson.

Long-Lasting Reduction in Somatostatin-Positive Cell Densities in the Cortex and, Hippocampus of Mice Exposed to Neonatal Ethanol

While high rates of sleep disruption have been reported among children with fetal alcohol spectrum disorder (FASD), mechanisms behind the effects of prenatal alcohol on sleep structure/homeostasis have not been elucidated. Binge-like ethanol (EtOH) exposure in postnatal day 7 (P7) mice, used as the third trimester FASD model, induces acute apoptotic neurodegeneration as well as long-lasting anatomical and behavioral abnormalities, including reduction in parvalbumin (PV) cell numbers and impairment in cognitive functions and non-REM sleep. Because recent literature indicates important roles of somatostatin (SST) interneurons in spatial memory and non-REM sleep, the effects of P7 EtOH on the survival of SST neurons were examined. Results indicated that P7 EtOH significantly reduced SST cell numbers in the neocortex and hippocampus of adult mice. Fate mapping studies using Nkx2.1-Cre;Ai9 mice (in which a reporter tdTomato is mainly expressed in PV and SST neurons and their progenitors) suggested that P7 EtOH induced both cell loss and reduction in SST expression in surviving neurons. Based on these experiments, we have hypothesized that P7 EtOH-induced PV and SST cell deficits may lead to abnormalities in non-REM sleep and other physiological functions. To test this hypothesis, 1) the effects of optogenetic stimulation of surviving SST neurons on sleep, and 2) the effects of transplantation of embryonic medial ganglionic eminence (MGE) cells (which mainly give rise to PV and SST neurons) into the cortex of P7 EtOH-treated pups (P8-P13), were investigated. Preliminary results suggested that optogenetic stimulation of SST neurons enhanced slow wave sleep in both control and P7 EtOH mice, and MGE cell transplantation into the neocortex of P13 mice impacted neocortical physiology, partially reversing both P7 EtOH-induced waking cortical hyper-excitability and increased cortical E/I balance. Thus, developmental EtOH-induced damage in subgroups of GABAergic neurons may induce sleep disruption although further studies are needed.

6) Melissa J. Alldred, Sang Han Lee, Sai C. Penikalapati, Tenzin Lhakhang, Adriana Heguy, **Stephen D. Ginsberg**.

RNA-sequencing (RNA-seq) of medial septal nucleus basal forebrain cholinergic neurons (BFCNs) within the Ts65Dn mouse model of Down syndrome (Ds) and Alzheimer's disease (AD) identifies dysregulated transcriptional pathways.

Basal forebrain cholinergic neuron (BFCN) loss is a hallmark of individuals with Down syndrome (DS) and Alzheimer's disease (AD). DS subjects also experience hippocampal CA1 pyramidal

neuron degeneration and synaptic loss. Further, they develop AD pathology including neurofibrillary tangles and amyloid plaques by the third decade of life. The septohippocampal pathway, including BFCNs which project to CA1 pyramidal neurons exhibit selective vulnerability in both DS and AD patients during disease progression. Current therapeutics have been unsuccessful in slowing disease progression, likely due to the complex pathological interactions and dysregulated pathways that are still poorly understood. The Ts65Dn mouse model recapitulates both the cognitive and morphological deficits of DS and AD, including BFCN degeneration. We utilize this trisomic mouse model to further understand the mechanistic pathways that underlie BFCN degeneration. We performed high-throughput, single population RNA sequencing (RNA-seq) to assess expression level changes in BFCNs from the medial septal nucleus (MSN) in the Ts65Dn mouse and in normal disomic (2N) littermates. Expression profiles from MSN BFCNs were generated by laser capture microdissection (LCM) to isolate ~500 choline acetyltransferase-immunoreactive neurons in adult Ts65Dn and 2N littermates. This procedure enabled quantitative analysis of mRNAs and noncoding RNAs to help understand mechanism(s) underlying neurodegeneration, and link these expression level changes to established pathological hallmarks and cognitive decline for therapeutic development in human DS and AD. RNA-seq library preparation was performed on isolated RNA species to determine the viability RNA-seq from individual neuronal cell types for downstream transcriptional analysis. Results indicated unique transcriptomic profiles for MSN BFCNs from Ts65Dn and 2N littermates at ~6 months of age. We further analyzed the resulting differences utilizing Ingenuity Pathway Analysis to link the changes seen in gene expression profiles to canonical pathways, along with dysregulated disease networks and aberrant physiological functions. Preliminary results indicate pathological changes in specific genes within a multitude of pathways, including RNA expression and molecular transport. Validation strategies include qPCR from LCM-Nissl stained neurons and protein assays from regional tissue dissections. The resultant expression profiles are posited to provide key information leading to mechanistic understanding of selective vulnerability within the septohippocampal circuit in models of DS and AD for therapeutic intervention.

7) **Zhen Yang**, Qawi Telesford, Alexandre Franco, Shi Gu, Lei Ai, Ting Xu, Chaogan Yan, Stan Colcombe, Michael P. Milham.

Reliability of dynamic network reconfiguration: impact of data length and cognitive states

Introduction
Unlike traditional network approaches, multilayer networks model the temporal dependence between distributed neural circuits (Mucha et al. 2010). Following an initial demonstration of the potential utility (Bassett et al. 2011), application of these methods have provided novel insights into how network dynamics is central to cognitive functions (Braun et al. 2018). Although encouraging, their test-retest reliability, a prerequisite for studying individual differences, is yet to be established. Here, we evaluated reliability of three key multilayer network-derived dynamic statistics (flexibility, integration, recruitment) at various scan lengths. Given the growing popularity of naturalistic viewing as a more tolerable (Vanderwal et al. 2015) and reliable (Wang et al. 2017) alternative to resting state fMRI, we examined reliability during inscapes and movies as well to directly quantify the modulatory effect of mental states.

Methods
Ten subjects with minimal head motion from Healthy Brain Network's Serial Scanning dataset were used (ages 23–37; mean: 29.8; 50% male) (O'Connor et al. 2017). Each has 12 scanning

sessions collected using the same imaging protocol over 1~2 months period (fMRI: multiband factor 3, 1.45s TR). Each session has 3 task conditions (10 min/condition): resting state, inscapes, and movie. Images were preprocessed using C-PAC. After preprocessing, mean signals from 200 ROIs (Craddock et al. 2012) were extracted as nodes. Edges were estimated using wavelet coherence (0.01-0.1Hz) on sliding windowed-time series (length 60s, no overlap). For each task, 12 sessions were randomly split into 2 matched datasets and concatenated to form 10-, 20-, 30-, 40-, 50-, and 60-min scans. To increase the robustness of the results, 100 randomized samples were created.
For each sample, windows of a scan were coupled into a multilayer network. A dynamic community detection algorithm (Blondel et al., 2008) was applied to extract putative functional modules over time (Bassett, et al. 2011).The modular allegiance matrix is computed to summarize how consistent functionally-defined systems (Yeo et al. 2011) are assigned to their own communities over time. To characterize the features of this multi-slice community structure, we used flexibility to quantify the number of times a region changes its community membership and used recruitment and integration to measure a region's probability to co-occur with regions from the same vs. other communities, respectively. Test-retest reliability was evaluated using intraclass correlation coefficient (ICC). A 3- level hierarchical linear mixed model was applied to calculate between-conditions and between-sessions reliabilities.

Results
ICC increases with scan duration. This pattern is consistent across dynamic measures and task conditions. However, the test-retest reliability of flexibility and integration is low even at 60 min. Recruitment has high ICC when scan length is over 40 min (47.5% of ROIs with ICC>0.6). For recruitment, mean ICC across ROIs and scans increases when external stimuli become more enriched (movie>inscapes>resting, $p<0.001$). We found in higher level ICC model that the between-condition ICCs are significantly higher than between-session ICCs ($p< 0.001$).

Conclusions
Dynamic analyses results obtained using short scans (<30 min) need to be interpreted with caution. The requirement for scan duration to achieve good test-retest reliability depends on the measure and task. Natural viewing is a promising paradigm for probing the network dynamic reconfiguration. If long scans for a single task are unavailable, one potential solution is to combine data from different tasks collected during the same session, as the dynamic features are much more reliable between conditions than between sessions. It is critical for future work to test how robust our findings are to important methodological choices.

8) **Henry Sershen**, Robert C Smith, Jordan Meyers, James Auta, Jenny Drnevich Zadeh, Mary Youseff, Renwong Wu, Jingping Zhao, Hua Jin, Abel Lajtha, John M Davis, Alexandro Guidotti.

Gene Expression Of Methylation Cycle And Related Genes In Lymphocytes Of Patients With Schizophrenia And Non-Psychotic Controls

Introduction: some of the biochemical abnormalities underlying schizophrenia, studied in both brain and pericephalic blood, involve differences in methylation and methylating enzymes, as well as other genes uncovered by chip seq or RNA seq analysis. enzymes and some of the target genes. However, few of these studies have examined the effect of sex and drug treatment on the differences between chronic schizophrenics and controls. We present e results of a larger study at differences in mRNA in lymphocytes of chronic schizophrenics (CSZ)and non-psychotic controls (NPC) emphasizing the differential effect os sex and antipsychotic drug treatment on the different biochemical findings.

Methods: We studied mRNA in lymphocytes of 61 CSZ and 49 NPC subjects using qPCR assays with TaqMan probes for multiple genes to assess mRNA levels for DNMT, TET, GABAergic genes, Glucocorticoid receptor, BDNF, and several genes with high hits from RNA sequence analysis. Statistical analysis tested the effects of diagnostic status (CSZ vs. NPC) on these mRNA levels and investigated the effects of sex differences and differences in antipsychotic drug treatment on the mRNA levels in CSZ and NPC.
Results: DNMT1 and DNMT3A mRNAs were significantly higher only in male CSZ subjects, with the small sample of females showing no statistical difference between CSZ and NPC, but a trend in the opposite direct from the male CSZ vs NPC comparison. Several other mRNA's differences between CSZ and NPC showed a trend for a greater diagnostic difference in males than in females. The GAD1, glucocorticoid receptor (NR3C1) and CNTNPA2 mRNAs were significantly higher in CSZ than NPC. The FPRF3 mRNA was significantly lower in CSZ vs NPC, and the GAD67 mRNA showed a trend in the same direction for males. In CSZ currently treated with clozapine, GABAergic mRNAs (GAD1, GAD67, GAD25) mRNA were significantly higher than in patients not treated with clozapine. CSZ treated with clozapine had significantly lower TET1 mRNA. There was a trend (P<.10) for NR3C1-B mRNA to be higher in clozapine patients. When we did analysis of differences between CSZ and NPC subjects, incorporating the clozapine treatment variable, it was clear that for the GABAergic mRNAs (GAD1, GAD67, GAD25), and for NR3C1-B , CNTNPA2, and IMPA2 mRNAs, that clozapine treated CSZ were primarily responsible for the difference from NPC, whereas non-clozapine treated CSZ had mRNA values more similar to NPC controls.
Conclusions: It is important to consider sex and antipsychotic drug treatment in comparing mRNA levels in in schizophrenic patients to controls, since some of the differences are only present in male subjects and other may be explained by clozapine treatment rather than primarily diagnosis. Many previous studies of similar differences in post-mortem brain samples, and some studies of methylation differens using peripheral blood cells, have not examined sex and drug treatment effects, and these could be possible confounds in interpreting diagnostic differences in these biochemical effects.

9) **Robert C Smith**, Wei Li, Stan Colcombe, Yiran Wang, Jiangling Jiang, Jijun Wang, John M. Davis, Chunbo Li.

Effects of Transcranial Stimulation on Cognitive Function and Brain Functional Changes in Schizophrenia

Background:
Transcranial direct current stimulation (tDCS) has been reported to improve cognition and symptoms in schizophrenia. The brain mechanisms underlying these effects have not been systematically explored. We report a double-blind study which measured effects of tDCS on cognition, symptoms, and brain activation in schizophrenia.
Methods:
41 Chinese schizophrenics were randomized to receive 10 sessions of Active or Sham tDCS. Cognition was evaluated with the MATRICS(MCCB), Paced Auditory Serial Addition Task and CogState. Psychiatric symptoms were evaluated with PANSS. Brain function were evaluated with fMRI at baseline and after 10 tDCS sessions for resting state changes in brain activation.
Results:
There were no strong effects (P<.05) of Active vs Sham tDCS on cognition, but there were significant (P<.01) effects on differences in brain activation assessed by fMRI. Furthermore, on several measures patients treated with active tDCS showed improved on some cognitive measures at 2 weeks and 4 weeks after the last tDCS session. On MCCB, there were trends

(P=.06) for Active tDCS vs. Sham tDCS to improve Speed of Processing. There were no effects of active vs sham tDCS on psychiatric symptoms. There were significant differences between active vs sham tDCS on resting state activation in several brain areas including middle frontal gyrus, superior frontal gyrus and superior and inferior parietal gyrus; active tDCS increased and sham tDCS decreased activation. There were significant relationships between changes in several MCCB scores and changes in brain activation in specific areas.
Conclusions
tDCS had significant effects on resting state brain activation which were significantly related to changes in MCCB. However, in this sample 10 sessions of active vs sham tDCS did not show marked effects on overall cognitive function.

10) **Robert C. Smith**, Lawrence Maayan, Renrong Wu, Mary Youseff Zhihui Jing, Henry Sershen, Victoria Szabo, Jordan Meyers, Hua Jinf, Jinping Zhao, John M Davis.

Betahistine Effects on Weight-Related Measures in Patients Treated with Antipsychotic Medications: A Double-Blind Placebo Controlled Study

Rationale: Weight gain during treatment with antipsychotics is a prominent side-effect, especially with some second generation antipsychotics, such as olanzapine and clozapine, and pharmacological treatments which ameliorate this side-effect are important to investigate. Decreases in histaminergic transmission in the brain induced by antipsychotics may be one of the mechanisms contributing to weight gain. Since betahistine is a histaminergic agonist, it may potentially counteract the weight gain effects of antipsychotics.
Method: We conducted a double-blind placebo controlled study to evaluate the effects of 12 weeks of treatment with betahistine (N=29) or placebo (N=22) in adolescents and adults on anthropomorphically measured weight related parameters, appetite, and fasting glucose-lipid and leptin levels in 51 patients treated with first and/or second-generation antipsychotics who had gained weight during treatment or had high body-mass-index(BMI). Psychopathology and side-effects were also assessed with relevant scales.
Results: In a sub-group of patients being treated with olanzapine or clozapine (n=26), betahistine was significantly (P<.05) better than placebo in preventing increases in weight (3.1 kg less weight gain than placebo), BMI and waist circumference. Betahistine did not decrease weight or BMI in patients treated with other antipsychotics. There was also no effect of betahistine on preventing weight or BMI gain in the total combined sample of all subjects. Betahistine did not significantly improve appetite or glucose-lipid measures in either subgroup. There were no significant differences in side-effects or psychopathology changes in the betahistine vs. placebo treated patients.
Conclusions: These results suggest that betahistine may potentially be a useful adjunctive drug for decreasing weight gain in patients treated with antipsychotics that are potent histamine antagonists, such as olanzapine or clozapine, but may not be useful for this purpose in patients on other antipsychotic medications. The results justify larger placebo controlled studies to further confirm these effects before specific recommendations can be made for routine use.

11) **Ying Jiang**, Anna Pensalfini, Mohan Panaiyur, Philip Stavrides, Sandipkumar Darji, James Peddy, Dunsheng Yang, Cynthia Bleiwas, John Smiley, Ursula Germann, John Alam, Ralph A Nixon.

p38α MAP kinase inhibition blocks rab5 activation and rescues the neurodegenerative phenotype of the Ts2 Down Syndrome (DS) mouse model

Endosomal-lysosomal pathway deficits characterized by upregulated endocytosis, aberrant endosome trafficking and signaling, and progressive lysosomal dysfunction are a signature neuropathological pattern emerging at the earliest stages of Alzheimer's disease (AD). Notably, this pattern begins perinatally in Down syndrome (DS) (Cataldo, 1997), a disorder in which an early onset form of AD invariably develops due mainly to a third copy of APP present on trisomic chromosome 21. Beyond roles in sorting and recycling internalized cargoes and in cell signaling, endosomes actively process APP via BACE1 (beta site cleaving enzyme 1) generating beta-cleaved carboxy terminal fragment of APP (APP-βCTF), which mediates AD-related endosome dysfunction and diverse neuronal deficits (Nixon, 2017). Notably, BACE1 activity and APP-βCTF levels are elevated in AD brain in the absence of detectable APP elevation (Kim, 2016). Early neuronal accumulation of APP-βCTF in AD mouse models is linked to neuronal hyperactivity (Goutagny et al., 2013), Aβ-independent long-term potentiation deficits and cognitive impairment (Lauritzen, 2012; Mondragon-Rodriguez, 2014). Endocytic abnormalities, lysosomal dysfunction and basal forebrain cholinergic degeneration develop in the DS mouse model Ts2 (Jiang, 2016, 2019) as in AD models.

P38α MAP kinase is linked to synaptic dysfunction in AD (Colié, 2017; Benarroch, 2018), partially due to increased BACE1 expression resulting from p38α-mediated impairment of autophagy-lysosomal protein degradation (Schnöder, 2016). Neflamapimod (VX-745) is an orally-active p38α inhibitor that reverses spatial learning deficits in aged rats (Alam, 2015) and may improve episodic memory in patients with early AD (Scheltens, 2018) in preliminary trials. Neflamapimod is currently being evaluated in a proof-of-concept phase 2b clinical study (https://clinicaltrials.gov/ct2/show/NCT03402659).

Here, using a concentration and dosage well below its inhibitory effect on inflammation (Duffy, 2011), we showed that neflamapimod treatment normalized AD-related endosomopathy in both DS fibroblasts and Ts2 mice and ameliorated the Rab5 hyperactivation and cholinergic neuron degeneration in the medial septal nucleus of Ts2 mice (Jiang, 2010, 2016). Those findings provide the first evidence that p38α antagonism can attenuate the neurodegenerative process beyond reversing synaptic dysfunction as previously observed. Furthermore, the known regulatory effects of p38α on Rab5 activation via GDI (GDP Dissociation Inhibitor) (Cavalli, 2001), combined with the central role of Rab5 in APP-induced endosomal dysfunction (Nixon, 2017), suggests these effects of neflamapimod are mediated via reversal of Rab5 hyperactivation.

12) **David N. Guilfoyle**, Morris H Baslow.

An Investigation of Resting State Naa And Naag Fluctuations In Rodent Brain At 7 T And At 21.1 T

The exact cellular mechanisms involved in the signaling between neurons and the vascular system, known as neurovascular coupling (NVC) remains unclear. Based on several recent studies, there is now a consensus that NVC in brain is bimodal. There is a fast-phasic component associated with synaptic firing, resulting in an increase focal blood flow within 2-3 seconds. Second, there a slow tonic component that is not associated with synaptic firing and results in an increase in focal blood flow in 10's of seconds. In some of our recent publications, we have proposed and presented preliminary evidence that suggests the brain metabolite N-acetylaspartylglutamate (NAAG) plays a key role in the mechanism of slow tonic signaling. We currently have an active MR protocol at the National High Magnetic Field Laboratory (NHMFL)

in Tallahassee, Florida. In this presentation we will show our preliminary results of NAAG changes taken on our own 7T MRI scanner at NKI and on the 21.1 T scanner at the NHMFL, the world's strongest MRI machine.

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

A modified density-based method to separate brain-derived extracellular vesicles shines a light on their heterogeneity and neuropathological potential

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 were 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, cryogenic electron microscopy, and nanoparticle tracking analysis.
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 and bear mitochondrial markers. These results demonstrate that our improved separation method isolates distinct types of EVs from the adult murine brain and allows to further investigate the roles of each type of vesicle in cellular homeostasis. Furthermore, we were able to describe a new, previously unidentified, class of EVs that bear mitochondrial but not exosomal nor microvesicular proteins, that we name 'mitosome'. 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) **Swati Jain**, John J. LaFrancois, Justin J. Botterill, David Alcantara-Gonzalez, Helen E. Scharfman.

Adult neurogenesis in the normal adult mouse protects against experimental seizures, excitotoxicity, and the development of epilepsy.

We studied the role of adult-born neurons in the normal adult mouse brain with loss-of-function and gain-of-function approaches. We found that adult-born neurons protect against severe seizures induced by the convulsant pilocarpine. Further, adult-born neurons protect from the excitotoxicity following severe seizures and the long-term consequences, i.e. epilepsy.

15) **Salvador Dura-Bernal**, Erica Y Griffith, Annamaria Barczak, Noelle O'Connell, Tammy McGinnis, Peter Lakatos, William W Lytton, Samuel A Neymotin.

Data-driven biophysically-detailed model of auditory thalamocortical system rhythms

We developed a detailed biophysical computer model of the auditory thalamocortical system, using the NEURON simulator and the NetPyNE tool, constrained with in vivo electrophysiological data obtained from nonhuman primates. Our latest model of A1 includes 29 neural populations of multiple cell types (5 excitatory types, 4 interneuron types) distributed across the 6 cortical layers. The thalamic model includes the thalamic relay nucleus (MGB) and the thalamic reticular nucleus (TRN), and includes 3 populations (2 excitatory types: thalamocortical and bursting thalamocortical, 1 inhibitory type: reticular nucleus interneuron). Layer boundaries, neuronal densities and cell type distributions per layer were based primarily on macaque thalamocortical data.

Excitatory cell types included intratelencephalic (IT), pyramidal-tract (PT) and corticothalamic (CT). Following experimental data, IT cells were distributed across L2-L6; PT cells in L5A and L5B; and CT cells in L5B and L6. L4 IT cells were further subdivided into pyramidal and spiny stellate cell types. Inhibitory cell types included Layer 1 inhibitory cells were included somatostatin (SOM), parvalbumin (PV), vasoactive intestinal peptide (VIP) and neurogliaform (NGF), all of which have been shown to play an important role in thalamocortical oscillations. L1 only includes NGF neurons, whereas L2-L6 include all 4 interneuron types.
All model neurons are multicompartment, conductance-based and include multiple ion channels, with parameters optimized to reproduce physiological responses, to in vitro somatic current clamps.

Connectivity depended on pre- and post-synaptic cell type and layer and was derived from thalamocortical data from macaque and rodents. Information about connection probability and somatic unitary connection postsynaptic potential amplitudes (weights) were obtained from slice dual recordings and optogenetic laser-scanning photostimulation experiments. The A1 model was reciprocally connected to thalamic model to enable production of thalamocortical rhythms. MGB included core and matrix populations with distinct projection patterns to different layers of A1.

We are building the model to investigate mechanisms and function of distinct types of neuronal oscillatory patterns observed in the auditory system in linear electrode array electrophysiological data recorded simultaneously from nonhuman primate primary auditory cortex (A1) and the medial geniculate body (MGB) of the thalamus. Recordings are performed during resting state or while awake subjects are presented with different classes of auditory stimuli, including speech. We have analyzed a large database of these recordings, extracting the spatial and temporal signatures of the commonly observed physiological oscillation frequency bands (delta, theta, alpha, beta, gamma). We intend to use the model to explore the mechanistic origins of the spatiotemporal neuronal oscillatory patterns observed in vivo. Refinement of the model by including the results of our detailed data analyses from multisite recordings will also enable predictions on how other brain regions, including pulvinar, contribute to the oscillatory dynamics. To confirm model predictions, we plan to use targeted deep brain electrical microstimulation and pharmacological manipulations.

16) **Haroon Anwar**, Soheil Saghafi, Lan Deng, Jack E. Denham, Thomas Ranner, Netta Cohen, Casey Diekman, Gal Haspel.

Endogenously oscillating excitatory motoneurons produce undulatory output in a connectome-based neuromechanical model of C. elegans without proprioception

Neural circuits producing rhythmic behavior are often driven by pacemaker neurons. The endogenous pacemaker activity is often modulated by proprioceptive or descending signal. Although all the components of the compact locomotion circuit of Caenorhabditis elegans are identified and their connectivity has been deduced from electron micrographs, the neural mechanisms underlying rhythm generation and undulatory locomotion are still unknown. In C. elegans, undulation is produced by a propagation of alternating activation of 95 dorsal and ventral muscle cells along the animal body, opposite to the direction of movement. Past studies have mainly focused on two hypotheses: 1) Sensory feedback suffices to generate and propagate the rhythm: There are no pacemaker neurons and the neural circuit merely integrates over proprioceptive inputs to generate and propagate appropriate muscle activity (Boyle et al. 2012; Cohen and Sanders 2014). 2) Head oscillator model: A dorsoventral alternating pattern is generated in the neck by an oscillator, which drives the sensory feedback propagation along the animal (Niebur and Erdös 1993; Karbowski et al. 2008; Wen et al. 2012, Kunert et al. 2017). Haspel and colleagues (Gjorgjieva et al 2014) revisit a third hypothesis: Dorsoventral alternations are produced locally by oscillating pacemaker neurons and the orchestrations of appropriate phase relations are mediated by the finely tuned neuronal circuitry. In this study, we chose a computational approach to test the conditions for generation of locomotion patterns relying on pacemakers in the known connectivity in the absence of proprioceptive feedback.

We use our previously described neuromuscular network (Haspel and O'Donovan 2011) that spans the full length of an animal and includes seven classes of motoneurons, muscle cells, and synaptic connections, both chemical and electrical. Using two kinds of motoneuron classes and muscle cells: leaky (passive) and endogenously oscillating (pacemaker), we systematically screened all 2^7=128 configurations of passive and pacemaker motoneuron classes. For each configuration, we screened parameter space and used parameter optimization approach to search for synaptic weights that produce a propagating dorsoventral alternation of muscular activity in forward or backward directions. The opposing directions of locomotion were induced by adding a tonic current to forward or backward motoneurons, emulating the function of premotor interneurons. We scored the dorsoventral alternation phases to evaluate simulation outputs, and used the same scoring algorithm on biological animals to assess biologically realistic undulation patterns. In the second stage, to see how fictive patterns translate in an embodied scenario, successful neuromuscular outputs were fed into a neuromechanical model (Denham et al. 2018) to test for realistic forward and backward locomotion.

When motoneuron classes were either all passive or all endogenous oscillators, an undulatory pattern in both forward and backward directions was not generated. We found that several configurations in which some excitatory motoneurons were oscillators produced undulatory-like activity pattern in both forward and backward directions. Moreover, implementation of these motor programs in the neuromechanical model produced multiple trajectories with varying speed and waveform, and clear wave propagation during both forward and backward locomotion depending on descending drive.

17) **Julia A. Ermel**, Deanna M. Barch, Stephanie Histon, Matthew J. Hoptman, Tarek Sobeih, Jaana Yeaton, and Pamela D. Butler.

Social Versus Non-Social Reward Learning in Schizophrenia

Social cognitive deficits are a hallmark of schizophrenia and related to functional disability. Failure to learn from social feedback may critically impair learning of appropriate social interactions. Deficits in monetary reward learning are seen in schizophrenia and are related to decreased motivation and pleasure. However, little is known about social reward learning in schizophrenia. We assessed learning from positive or negative feedback in structurally identical social and monetary learning tasks. Results showed that controls achieved similar performance on the social and monetary tasks, and that patients were able to perform above chance. There was a significant Group X Reward interaction, with patients showing greater impairment on social than monetary reward learning versus controls. Patients and controls did not differ in ability to recognize emotions in the task or in preferences for faces. Patients showed significantly greater anhedonia on the Chapman Physical Anhedonia scale compared to controls, though better social reward learning was related to lower anhedonia in controls, but not patients. Results support previous studies showing reward learning deficits in schizophrenia and extend these findings to social reward learning. Patients appear more impaired at social than non-social reward learning. As such, social reward learning may be a novel intervention target.

18) Mira Z Milad, Jagan J Jimmy, Shari Lieblich, Lily Brown, Anu Asnaani, Cobb Scott, Ruben Gurr, Edna Foa, **Mohammed R Milad**.

Estradiol administration modulates functional activation of the fear extinction network in women using oral contraceptives: an fMRI study

Background: Fluctuations of estradiol (E2) in women influence fear extinction. High levels of E2 engage the ventromedial prefrontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC) and the amygdala. We explored the effect of E2 administration on the fear extinction network in healthy women on oral contraceptives using fMRI.

Methods: 48 participants were fear conditioned on day 1. On day 2, participants were randomized to take either E2 or placebo pill ~5 hours prior to extinction learning. Extinction memory recall was assessed on day 3. Outcome measure was BOLD signal. Blood samples were ascertained from all participants to measure estradiol. Variance in estradiol levels across all subjects was correlated with brain activations during extinction learning and during extinction recall.

Results: We observed a significant positive correlation between E2 levels and vmPFC ($t=4.16$, $pFWE<0.05$ [$r=0.51$ $p<0.001$]) activation during extinction learning and with dACC ($t=4.9$, $pFWE<0.05$ [$r=0.52$ $p<0.001$]) during recall. In an exploratory between group analyses (E2 vs. placebo groups), we found that women in the E2 group exhibited significantly less activation in the amygdala ($t=3.02$, $pFWE=0.05$) during renewal of fear. During extinction learning, we observed a trend towards significance within activations in the E2 group in the dACC and the amygdala ($t=3.55$, $pFWE=0.07$; $t=3.55$, $pFWE=0.07$, respectively).

Conclusions: Exogenous E2 engages regions involved in fear regulation, supporting the role of estradiol administration as enhancer of extinction-induced activations and reducing amygdala reactivity during renewal. We provide further support to the possibility of using estradiol as an adjunct to behavioral therapies aimed at fear and anxiety-based disorders.

19) **Sabina Hrabetova**, Jan Hrabe.

Dynamic extracellular space alters spatiotemporal distribution of chemical signals in brain: experiment and modeling.

Brain can be considered as a porous medium. The brain cells form a solid phase while the liquid-filled extracellular space (ECS) forms a porous phase that surrounds each individual cell. Brain ECS is of a fundamental importance for brain function [1]. It serves as a reservoir for ions and a channel for diffusion-mediated transport of biologically significant molecules and therapeutics. ECS volume is the main factor governing the extracellular concentrations of these substances. Any ECS volume change may lead to a change in concentration of ions and transported substances, and this has consequences for brain function. Volumes of extracellular and cellular phases undergo reciprocal changes during certain physiological and pathological events in brain. For example, transition from sleep to awake state is associated with a reduction in ECS volume [2,3] and expansion of one type of brain cells [3]. Here we introduce a new phenomenon, the Transient Volume Reductions (TVR) in the ECS that appear to play an important role in sustaining epileptic seizures. Epileptic seizures represent abnormal synchronous excitatory activity in neurons. While they are often thought of as mediated by cellular mechanisms, there are extracellular mechanisms too, such as a rise in extracellular potassium and ephaptic (field) interactions. When studying epileptic seizures in hippocampus, we found TVRs that occurred in concert with epileptiform potentials. We hypothesize that TVRs promote epileptiform activity and its propagation by enhancing the extracellular mechanisms, and ask how the TVRs propagate in space and time and influence local diffusion and concentration of different molecules. The MCell simulator [4] recently acquired capability to incorporate time-dependent geometry. This enabled us to explore how concentration waves in the ECS can be generated by localized TVRs, possibly acting as a novel engine driving the diffusion flux. Preliminary numerical experiments with MCell suggest that TVR can generate interesting and unexpected effects. If a TVR occurs only in one layer of hippocampus, this layer acts as a transient macroscopic diffusion source and generate concentration wave of molecules endogenous to the ECS that spreads to the surrounding layers. Numerical modeling is in agreement with the experiments in brain and helps us to understand the relationship between TVRs and epileptiform activity in brain.

20) **Elisa C. Dias**, Abraham C. Van Voorhis, Filipe Braga, Julianne Todd, Javier Lopez-Calderon, Antigona Martinez, Daniel C Javitt.

Cognitive and Neurophysiological Correlates of Visual Active Sensing Deficits in Schizophrenia

Normal visual search is achieved through a series of alternating saccades and fixations. At each fixation the phase of ongoing neuronal rhythmic oscillations is reset, a process termed “active sensing.” In the visual system, this phase-reset process is reflected in the generation of an early fixation-related potential (FRP, or "lambda" potential) that can be recorded over visual cortex. In this study, we evaluated behavioral and neurophysiological indexes of active sensing during a Guided Visual Search task in schizophrenia, and hypothesized that FRP generation would be significantly reduced, and that deficits would correlate with impaired search-related neurocognitive impairments. Subjects (24 patients, 25 controls) performed serial (conjunction search) and parallel (feature search) versions of a visual search task, while their eye movements and EEG were recorded. In each trial, a search field composed of 48 distractor

gabor patches was presented, and subjects pressed a button to indicate detection of a target, which was a vertically oriented, low contrast gabor patch. In the parallel version, all distractors were of the same contrast as the target, but oriented horizontal. In the serial version, half the distractors had the same orientation as the target, but were of higher contrast, and 24 were of the same contrast, but horizontal. Subjects performed 192 trials of each task. Eye-tracking was used to both evaluate determinants of impaired search time in schizophrenia and calculate fixation-related activity. Search times were significantly increased for patients vs. controls across all conditions, reflecting increased number of fixations. Interestingly, in patients there was an increase in the distance between the fixation before the final fixation on the target (pre-final fixation), and the center of the target, suggesting a reduction of the width of the visual "spotlight" at each fixation. Highly significant FRP deficits were also observed and correlated significantly with the reduced spotlight width, as well as impaired performance in visual domains (Speed of Processing, Attention/Vigilance) of the MATRICS Consensus Cognitive Battery. Fixation locations within search fields were similar across groups, suggesting similar search strategies. In addition to previously described deficits in sensory processing, these results indicate that schizophrenia patients have deficits in visual active sensing that undermine their ability to efficiently extract information from the environment. They also suggest that FRPs may be used along with other neurophysiological measures to explore neural mechanisms underlying early-stage visual information processing deficits in schizophrenia and their relation to neurocognitive impairments.

21) Yiran Gu, Walter T. Piper, Lauren A. Branigan, Elena M. Vazey, Gary Aston-Jones, Longnian Lin, Joseph E. LeDoux, **Robert M. Sears**.

A brainstem-central amygdala circuit underlies defensive responses to learned threats

Norepinephrine (NE) plays a central role in the acquisition of aversive learning via actions in the lateral nucleus of the amygdala (LA). However, the function of NE in expression of aversively-conditioned responses has not been established. Given the role of the central nucleus of the amygdala (CeA) in the expression of such behaviors, and the presence of NE axons projections in this brain nucleus6, we assessed the effects of NE activity in the CeA on behavioral expression using receptor-specific pharmacology and cell- and projection-specific chemogenetic manipulations. We found that inhibition and activation of locus coeruleus (LC) neurons decreases and increases freezing to aversively conditioned cues, respectively. We then show that locally inhibiting or activating LC terminals in CeA is sufficient to achieve this bidirectional modulation of defensive reactions. These findings support the hypothesis that LC projections to CeA are critical for the expression of defensive responses elicited by conditioned threats.

22) **Madhu Shivakumar**, Vikram Joshi, Shivakumar Subbanna, Balapal Basavarajappa**.**

CB1R Mediated HDAC-EGR1 Pathway Causes Neurobehavioral Defects In Postnatal Ethanol Exposed Mice

Alcohol abuse during pregnancy exposes the fetal brain to alcohol and impairs brain maturation, leading to persistent neurobehavioral abnormalities, including cognitive decline, which together is known as fetal alcohol spectrum disorder (FASD). However, the molecular mechanisms triggering these developmental deficits are poorly explained. In this study, we report that the binge-type ethanol exposure of P7 mice, which activates caspase-3, enhanced the histone deacetylase (HDAC) 1, HDAC2 and HDAC3 levels and reduced histone 3 (lysine 14, K14) and

histone 4 (lysine 8, K8) acetylation in mature neurons (neuron-specific nuclear (NeuN) positive). Ethanol exposure repressed early growth response 1 (Egr1) gene and protein expression. The repressed gene promoter region displayed differential HDACs, enhanced G9a, H3K14ac and histone 3 (lysine 9, K9) dimethylation enrichment. However, CREB-binding protein (CBP) enrichment was reduced at Egr1 promoter region. Inhibition of class 1 HDACs with trichostatin (TSA) before ethanol exposure, rescued H3K14ac and H4K8ac levels and prevented caspase-3 activation. Antagonism or null mutation of cannabinoid receptor type-1 (CB1R) before ethanol exposure, which inhibits caspase-3 activation, prevented H3K14ac and H4K8ac loss. TSA administration before ethanol exposure prevented ethanol-induced loss of Egr1 expression, restored epigenetic remodeling and neurobehavioral defects in adult mice. Together, these findings demonstrate that ethanol-activated CB1R regulates epigenetic/gene expression mechanisms causing persistent neurobehavioral defects. CB1R/HDAC-mediated epigenetic remodeling disrupts gene expression and is a critical step in cognitive decline development in FASD, which is reversed by restoring histone acetylation in the brain.

23) **Shivakumar Subbanna**, Nagaraja Nagre, Madhu Shivakumar, Delphine Psychoyos, Balapal Basavarajappa.

Caspase Inhibitor Prevents Postnatal Ethanol-Induced Loss of MeCP2 in Neonatal Mice and Synaptic, Learning and Memory Impairments in Adult Mice

Alcohol consumption during pregnancy exposes fetal brain to alcohol and impairs brain development, leading to long-lasting behavioral problems, including cognitive impairments, collectively called fetal alcohol spectrum disorder (FASD). However, the molecular mechanisms underlying these deficits are poorly understood. In our previous studies, we demonstrated that postnatal ethanol-induced activation of caspase-3 impairs DNA methylation. In this study, we report that the ethanol exposure of postnatal day 7 (P7) mice that activates caspase-3 in neonatal mice as well causes a reduction in methylated DNA binding protein (MeCP2) levels. The ethanol treatment of P7 mice enhanced MeCP2 mRNA levels but reduced protein levels. The administration of a broad-spectrum caspase inhibitor before ethanol treatment of P7 mice inhibited caspase-3 activation and reversed the loss of MeCP2 proteins as well as cAMP response element binding protein (CREB) activation and activity-regulated cytoskeleton-associated protein (Arc) expression. The inhibition of caspase-3 activity prior to ethanol administration prevents ethanol-induced CREB activation, Arc expression, long-term-potentiation (LTP) and spatial memory deficits in adult mice. Collectively, these results reveal that the ethanol activated caspase-3 degrades MeCP2 proteins in the P7 mice brain and causes long-lasting neurobehavioral deficits in adult mice.

24) **Brett S. East**, Donald A. Wilson.

Amygdala-olfactory cortical interactions in odor fear

Odor perception and hedonics are highly intermeshed at both the behavioral and neural circuit level in humans and non-human animals. This association may in part reflect the fact that the piriform cortex (PCX) is particularly tightly linked with the amygdala. The amygdala targets the posterior PCX (and to a lesser extent the anterior PCX), with the PCX sending reciprocal connections back to the amygdala. The basolateral amygdala (BLA) is required for odor fear learning, and work from our lab has shown that PCX odor responses are shaped by both fear learning and by BLA input. For example, discriminative odor fear conditioning involving both a

CS+ and CS- results in odor-specific learned fear responses, as well as narrowing of PCX single-unit odor receptive fields (i.e., enhanced PCX odor acuity). This modification of PCX odor coding may be due to input from the BLA since optogenetic activation of BLA fibers within the PCX can modify single-unit and single-unit ensemble odor responses in anesthetized rodents. However, how the BLA and PCX work in tandem to shape PCX odor coding and hedonics is unknown. In this work, rats received ibotenic acid lesions of the pPCX (or control) prior to being trained on a differential odor fear task followed by testing for learned freezing 24 hours later. In support of previous work, bilateral pPCX lesions significantly reduced learned, odor-evoked freezing compared to controls suggesting that the pPCX may not only encode odor information but also learned odor associations. Ongoing work is selectively manipulating BLA input to the pPCX during conditioning in order to explore the precise role of communication between PCX and BLA in odor perception and memory.

25) **Matthew J. Hoptman**, Daniel C. Javitt.

Urgency Mediates the Relationship between Aggression and Right Frontal Pole Structure and Functional Connectivity in Schizophrenia

People with schizophrenia show elevated levels of impulsive aggression compared to healthy populations. Previously, we (Hoptman et al., 2014) showed that impulsivity in the context of strong positive mood (positive urgency) and negative mood (negative urgency) are negatively associated with both right frontal pole cortical thickness and right frontal pole functional connectivity with rostral anterior cingulate cortex in 33 patients with schizophrenia. Moreover, we found that both positive and negative urgency correlated with self-rated aggression. Here we extend these findings by examining whether the brain correlates of urgency also correlate with aggression, and whether urgency mediates these relationships. First, we found that self-reported aggressive attitudes were negatively correlated both right frontal pole cortical thickness and with right frontal pole functional connectivity with rostral anterior cingulate cortex. Then we used Hayes' PROCESS Macro for SPSS, v. 3.0, and found that positive urgency completely mediated the relationship between right frontal pole functional connectivity with rostral anterior cingulate cortex (Sobel test = -2.54, p = .011), and that negative urgency fully mediated the relationship between aggression and right frontal pole cortical thickness (Sobel test = -2.35, p = .018). These results highlight the potential importance of urgency as an explanatory mechanism for aggression in schizophrenia and provide a plausible target that can be engaged to reduce impulsive aggression.

26) **Samuel Neymotin**, Annamaria Barczak, Noelle O'Connell, Tammy McGinnis, Noah Markowitz, Elizabeth Espinal, Erica Griffith, Salvador Dura-Bernal, William W Lytton, Stephanie Jones, Stephan Bickel, Peter Lakatos.

Tracking rhythmicity of neural oscillations in the auditory thalamocortical system

A central debate about neural oscillations focuses on whether they occur continuously with amplitude fluctuations, or primarily as brief pulse-like events (e.g. event-related potentials). In the latter case, some argue that the presence of high spectral power is not sufficient to use the term oscillation, but that the definition depends on the underlying neural generators, and whether they are rhythmic or stochastic, in which case high power reflects specific temporal domain features.

It is possible both hypotheses are correct, applying variously in different physiological frequency bands and depending on brain area or task. Quantification of specific signal features contributing to oscillations, such as number of cycles during high power activity, and measures of rhythmicity (coefficient of variation squared: CV2, Fano-Factor, lagged coherence) could help resolve these questions.
To approach these questions, we quantified rhythmicity in two resting state (order of minutes) invasively recorded electrophysiology datasets: 1) simultaneous laminar electrode array local field potentials in nonhuman primate primary auditory cortex and medial geniculate body; 2) electrocorticography from human superior temporal gyrus. We extracted moderate/high power spectral events using Morlet Wavelets (4X median cutoff), determining event duration, peak frequency, number cycles (peak frequency x duration), and unfiltered waveform shape.
All frequency bands had a wide/similar range of cycles/event, seen in unfiltered waveforms (1-24; median:3-4). We formed inter-event interval distributions and calculated CV2 (=1 is Poisson, < 1 is more rhythmic). CV2 increased with number of events in a time window, from longer windows of analysis, and for higher frequency oscillations, suggesting nonstationary inter-event interval distributions. To control for this, we varied window size for different frequencies (longer for slower frequencies) to produce similar number of events per window (N=16). All oscillations had a median CV2 (0.7 with end to start intervals, 0.5-0.6 with peak to peak intervals) and Fano-Factor (0.3-0.7 from delta to high gamma) consistent with rhythmicity. Lagged coherence, measuring phase continuity across epochs, was rhythmic across physiological oscillation frequencies (median 0.1-0.2). Narrow-band oscillations from 0.5-200Hz had higher lagged coherence (0.2-0.6, average 0.4).
Our analyses demonstrate that both event-like pulses and rhythmic oscillations are widespread in thalamocortical dynamics. Further work is needed to delineate circuit origins of the different processes and their behavioral/cognitive consequences.

27) **Danielle Rette**, Erin McDonald, Matthew J. Hoptman, Kate Collins, Russell Tobe, Dan Iosifescu.

Sociodemographic Correlates of Childhood and Adolescent Depression

Depression among children and adolescents is a significant health problem that causes marked distress, functional impairment and may even lead to suicide. However, the exact correlates of childhood and adolescent depression remain largely unknown. To investigate potentially relevant factors and identify at-risk groups, we analyzed demographic correlates of depressive symptoms in a community-ascertained sample of volunteers between ages 7 and 17 (N=358; 165 females) drawn from the Nathan Kline Institute-Rockland Sample. Depression severity was measured using the self-report Children's Depression Inventory 2 (CDI-2). Using multiple regression, we found a significant interaction of age x gender on depression severity (R^2change=.046, $F(1,352)=17.58$, $p<.001$). Specifically, in the 7-10 age group, boys reported significantly more depressive symptoms than girls (CDI-2 score= 11.5±8.6 vs. 7.2±5.8, p=.001). However, a shift occurs at age 11, coinciding approximately with the onset of puberty in girls. Girls reported significantly more depressive symptoms than boys in the 11-13 (8.1±7.5 vs. 4.5±3.7, p=.001) and 14-17 (9.6±6.9 vs. 7.2±5.7, p=.041) age groups. These findings suggest that clinicians may need to approach the risk of depression differentially in younger children, when boys may have a higher risk, compared to pre-teens, when the risk is higher in girls.

28) **Christos Panagiotis Lisgaras**, Caterina Psarropoulou.

Region-Specific Effects Of Early-Life Status Epilepticus On The Adult Hippocampal CA3 – Medial Entorhinal Cortex Circuitry In Vitro: Focus On Interictal Spikes And Concurrent High-Frequency Oscillations

The neuronal network linking the hippocampus proper and the medial entorhinal cortex (mEC) is implicated in physiological and pathophysiological functions. We have earlier shown that a Pentylenetetrazol (PTZ)-induced Status Epilepticus (SE) at postnatal day 20 impacts on the adult hippocampal interictal high-frequency oscillations (HFOs) modifying their cholinergic control (Mikroulis A et al. Neuroscience. 2018; 369: 386-398). Here, we investigated post-immature SE communication modalities in the adult hippocampal CA3-mEC loop by disrupting their functional connections and by measuring interictal epileptiform discharge (IED) frequency and concurrent HFOs.

Temporal hippocampal-mEC slices were prepared from adult rats, >40 days after a PTZ-induced-SE or from their normal littermates (N). 4-Aminopyridine-induced IEDs were recorded simultaneously from the CA3 pyramidal and mEC deep layers of intact slices followed by 2 successive incisions: 1st disrupting the CA3-CA1 path, 2nd the mEC-CA3 path. Waveforms were filtered at 80-200Hz (Ripples-R), 200-600Hz (Fast Ripples-FR) and HFOs were visually identified as local power maxima in the time-frequency domain.

Paired recordings from N and SE slices showed that mEC IED frequency was significantly lower than in CA3 (n=16N, p<0.0001; n=9SE, p=0.002); isolation of the 2 areas did not alter IED frequency or this relationship. CA3 IED frequency was similar in N & SE slices, however, mEC IED frequency was higher in SE vs N slices (n=16N, 9SE, p=0.014). Temporal raster plots indicated no specific pattern of coincidence between CA3 and mEC IEDs either in intact slices or after the successive cuts (N, SE). CA3 HFOs had 100-times higher power than those of mEC. Interestingly, the direction of post-SE power changes of Rs and FRs was a mirror image between CA3 & mEC and also between N & SE slices. In intact slices, FR/R ratio was lower in CA3 vs mEC (n=14N, p=0.032; n=8SE, p=0.009), a difference that disappeared post-isolation, because of CA3's FR/R ratio increase (N, p=0.0007; SE, p=0.005). Furthermore, CA3 FR/R ratio was increased in SE vs N sices both in the presence and in the absence of mEC in the network (p= 0.0008).

Findings from this in vitro 4-AP model suggest that (i) functional network connections between CA3-mEC exert an "inhibitory" role on hippocampal HFO output; moreover, their disruption affects HFOs not IED frequency supporting the notion that these represent surrogate indices of excitability. Also, (ii) an early-life SE may affect in the long-term neuronal synchronization properties (HFOs) in a region-dependent way (cortex vs hippocampus).

29) German Todorov, Karthikeyan Mayilvahanan, **Catarina Cunha.**

Embarking on discovering the mechanisms of resilience: combining language use analysis with neuroscience.

Novel treatments in mental health focus on one's ability to recover and develop resilience. Current concepts are based on The Adaptations Level Theory, which describes the ability of resilient individuals to accustom to new and even downgraded conditions as the new standard, find meaning in trauma, and adapt to new social settings. However, it is not known which treatments specifically help to build up resilience in patients and how to reliably screen for it. We hypothesize that resilience is associated with salient behavioral, physiological and

neurobiological characteristics (such as language use patterns and response dynamics of noradrenergic vs the inhibitory neural circuitry) that can be detected, analyzed and leveraged to improve resilience in individuals at risk of stress and trauma-related disorders. Recent studies demonstrated that distinct patterns of language use correlated with various mental health conditions. Utilizing text samples from Holocaust survivors, we compared language use in resilient individuals to people with PTSD and the general population. Holocaust survivors' language use was significantly different from PTSD sufferers, which suggests that we detected a possible resilience word use pattern. Next, we looked into the brain circuitry mechanisms that could be involved in resilience. We found that norepinephrine, the key neurotransmitter in stress response, modulated the activity of amygdala circuitry in a non-linear concentration-dependent manner. The shape and other characteristics of this dependency could be associated with the capacity for resilience.

30**) Abraham Goldring**, Jean-Pierre Lindenmayer, Amanda Hefner, Sophia Borne, Anzalee Khan, Amod Thanju.

The Psychometric Properties of the Self-Evaluation of Negative Symptoms Scale (SNS) in Treatment-Resistant Schizophrenia (TRS)

Background
Evidence suggests that clinically objective measures of negative symptoms differ from the patient's subjective evaluation of negative symptoms (Fleischacker et al., 2005). The subjective experience of deficits generally precedes clinically observable signs (Jaeger et al., 1990; Jaeger et al., 2004). Incorporating self-assessment of negative symptoms may afford early detection, and can increase the sensitivity of clinical assessments.
The Self-evaluation of Negative Symptoms (SNS), recently developed to assess the subjective experience of negative symptoms by patients, fulfills the five negative dimensions agreed upon by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) group. The SNS has been validated among high functioning patients with schizophrenia (Dollfus, Mach, & Morello, 2016). However, the feasibility of the SNS has yet to be examined in a low functioning sample of patients with schizophrenia. The present study sought (i) to evaluate the feasibility of the SNS in low functioning patients with chronic schizophrenia and (ii) to examine the concurrent validity of the SNS to a validated object measure of negative symptoms.
Methods
Stable adult patients with a DSM-5 diagnosis of schizophrenia or schizoaffective disorder and primary negative symptoms were recruited from an urban tertiary care psychiatric center. Primary negative symptoms were defined as the presence of negative symptoms with minimal EPS score on the SAS <12 and the absence of depression as measured by the CDSS. For inclusion in the study, it was required that participants be able to read and write—as confirmed by the WRAT. Patients were excluded from the study if they had a clinically diagnosed neurological disorder, a history of intellectual impairment pre-dating the onset of symptoms of psychosis, or if they exhibited active suicidal or violent behavior.
Results
Participants included 50 in-and-outpatients with a mean age of 43.71 years (SD = 11.03), 86% male, 64.81% African American, with a mean chlorpromazine equivalency dose of 869.22 (SD = 59.69). Mean premorbid IQ was 79.71 (SD = 17.51), and BACS Composite T Score mean was 33.56 (SD = 12.11). Cronbach's coefficient of the SNS ($\alpha = 0.69$), and the ICCs for the total scores of the 20 items between baseline and T1 and T2 (ICC = 0.690, 95% CI [0.450,0.825]) showed moderate internal consistency. There was a statistically significant difference between

the SNS total scores at Visit 1 (M = 17.33, SD = 8.97) and Visit 2 (M = 15.92, SD = 9.49), p < .001. There was no statistically significant correlation between the SNS items and the NSA-16 scores of Global Negative Symptoms or Global Level Of Functioning.

Discussion

The lack of correlation between the SNS and the NSA-16, suggests that objective measures of negative symptoms differ from the patients' subjective evaluation of internal experiences. The self-evaluation of negative symptoms on the SNS was inconsistent across time points, indicating poor test-retest reliability of the SNS among patients with chronic schizophrenia. The small sample size prevented us from conducting exploratory analysis to identify confounding variables (i.e. cognitive deficits). Future research should consider whether the expressions used in the SNS are culturally and linguistically appropriate for low functioning patients with chronic schizophrenia.

31) **McKenzie Osborne**, Abraham Goldring, Jean-Pierre Lindenmayer, Anzalee Khan, Susan McGurk.

The Effects of Clozapine and Non-Clozapine Antipsychotics on Neurocognitive Functions in Chronic Schizophrenia

Background

Cognitive impairments observed in patients with chronic schizophrenia are considered core features of the illness and are major determinants of social function and community adjustment (Goldberg et al., 1987; Shallice, Burgess & Frith, 1991). Antipsychotic medications provide limited benefit across cognitive domains (Mishara and Goldberg 2004) and often result in extrapyramidal side effects, requiring anticholinergic treatment which has been shown to influence cognitive performance (Strauss et al 1990; McGurk et al 2005). The present study assesses neurocognition in patients with chronic schizophrenia who are treated with clozapine or other antipsychotic medications (non-clozapine) in order to explore (1) the comparison of neurocognitive profiles between patients who are on clozapine and those on non-clozapine antipsychotics, and (2) demographic and clinical contributors to cognitive impairment.

Methods

A total of 171 subjects with DSM-IV/V diagnosis of schizophrenia (52%) or schizoaffective (48%) participated in at least one of two computerized cognitive training programs from 2014 to 2019 at Manhattan Psychiatric Center (inpatient (88.3%) and outpatient (11.7%)). At baseline, all subjects completed the MATRICS Consensus Cognitive Battery (MCCB), Positive and Negative Syndrome Scale (PANSS) and laboratory tests for various metabolic parameters. Independent samples t-test was used to assess MCCB domains and neurocognitive composite scores between individuals on clozapine compared to those not on clozapine.

Results

Of the 171 subjects (Clozapine (CL) n =63, non-Clozapine (NCL) n = 108) , 82% were male, 68.1% were African American, 57.3% had prior work history and 67.3% had a history of substance abuse (SA). The mean age was 39.94 years (SD = 12.316), mean chlorpromazine equivalency dose of the group was 685.64 (SD = 396.04). Additionally, 29.8% were receiving benzodiazepines, and 63.7% were receiving mood stabilizers. The mean PANSS total score was 73.49 (SD = 10.88). Demographic comparison showed significant differences between the groups for age (t = -3.537 p<.001 with non-clozapine patients being older), education (t = 2.205 p = .029 with non-clozapine having higher levels of education), chlorpromazine equivalence (t = 4.321 p<.001) with clozapine patients having 589.82 (sd=390.66) CPZ equivalency compared to non-clozapine patients (335.79 (sd=143.18)) and PANSS total score (t = 2.043 p=.043 with non-clozapine patients being more severe). There were no significant (p<.05) differences observed

between groups for MCCB domain scores. The cognitive domain scores included Speed of processing T-score (Cl M = 22.08 (SD = 12.888) vs. NCL M = 21.86 (SD = 13.979), Attention vigilance T-score (Cl M = 26.05 (SD = 12.419) vs. NCL M = 27.90 (SD = 12.643), Working memory T-score (Cl M = 21.78 (SD = 13.771) vs. NCL M = 25.41 (SD = 13.451), Verbal learning T-score (Cl M = 28.13 (SD = 5.470) vs. NCL M = 30.00 (SD = 6.385), Visual learning T-score (Cl M = 29.57 (SD = 14.749) vs. NCL M = 32.31 (SD = 15.336), Reasoning and problem solving T-score (Cl M = 36.17 (SD = 9.902) vs. NCL M = 36.70 (SD = 8.902), Social cognition T-score (Cl M = 30.54 (SD = 10.308) vs. NCL M = 29.92 (SD = 12.309), and Overall composite T-score (Cl M = 14.03 (SD = 12.629) vs. NCL M = 16.60 (SD = 13.216).

Discussion

We did not find any significant differences between clozapine and non-clozapine groups in terms of neurocognitive profiles, although we did find significant differences in clinical areas and lifestyle history between the groups. Our future research will look at the clear patterns of worse cognitive functioning in the clozapine group with the effects of metabolic parameters (ie metabolic syndrome), and the anticholinergic burden as covariates between clozapine and non-clozapine groups.

32) Jean-Pierre Lindenmayer, Owen Jones, **Abraham Goldring**, Sophia Borne, Anzalee Khan, Lucia Roitma, Christina Lee, Amanda Hefner, Mohanika Gowda, Dominic Arjuna Ugarte.

Are Repeated Psychotic Relapses Associated with Cognitive Decline in Schizophrenia: A Naturalistic Longitudinal Study of Cognitive Deficits in Chronic Schizophrenia

Cognitive functions have been shown to be significantly impacted in individuals with schizophrenia spectrum disorders and impairments are considered a core feature of the illness (Goldberg et al., 1987; Shallice, Burgess & Frith, 1991). There is increasing evidence that these impairments increase over time and may be even more impacted by repeated psychotic relapses. This study is a naturalistic, retrospective longitudinal assessment of global cognitive functions, measured by the MoCA (Montreal Cognitive Assessment) as an effect of repeated hospitalizations due to psychotic relapse in patients with chronic schizophrenia.

33) Jean-Pierre Lindenmayer, Anzalee Khan, Isidora Ljuri, Owen Jones, Joanne Yoon, Amanda Hefner, Marc Budgazad, Benedicto Parker, Mohan Parak, Harinder Gill, Lucia Roitman, Mila Kirstie-Kulsa, Matthew Hoptman, Anthony Ahmed, **Tiffani Padua.**

Cognitive Training for Social Cognition in Impulsive Aggression in Schizophrenia

The association between schizophrenia and violence is an important issue in psychiatry. The impact of several factors (social cognition, neurocognition, alexithymia, emotion regulation capacity, and the therapeutic milieu) on aggression in schizophrenia creates an opportunity for the development and evaluation of novel treatments for aggression. Previous studies show that cognitive remediation training (CRT) and social cognitive training (SCT) help to decrease hostility. The parent study examined whether cognitive training leads to improvements in cognition emotion regulation capacity, and impulse control in participants with a history of impulsive aggression. The current study examined the effectiveness of CRT alone versus a combination of CRT and SCT in terms of emotion recognition and cognitive improvement.

34) **Amod Thanju**, Jean-Pierre Lindenmayer, Anzalee Khan.

Association of ZNF804A rs1344706 genotype and impulsivity in patients with chronic schizophrenia

Background:
The single nucleotide polymorphism of allele A, rs1344706, located in intron 2 of the zinc-finger protein gene ZNF804A, continues to be the common variant most strongly associated with schizophrenia risk (P=1.1_10–13).
ZNF804A is highly expressed in adult brain and functional effects on both protein expression and altered DNA–protein interaction have been reported. We hypothesized that a single nucleotide polymorphism in ZNF804A could be associated with impulsivity. The aim of this study was to assess the association of a single nucleotide polymorphism rs1344706 with the PANSS excitement factor.

Methods:
Inpatients and outpatient subjects with DSM-IV-TR schizophrenia or schizoaffective disorder were consecutively enrolled from the parent study assessing the effectiveness of CRT (Lindenmayer et al., 2008) and were genotyped. All subjects were on stable antipsychotic medications during the 12 week duration of CRT. Inpatient subjects enrolled in the CRT program were in the sub-acute illness phase awaiting placement into a community residence. All subjects, inpatients and outpatients, were enrolled in rehabilitation programs which included treatment groups on understanding mental illness, coping skills, nutrition, and understanding medications and symptoms.

Inclusion criteria : (1) Age 18 – 55 years; (2) Inpatients or outpatients; (3) DSM-IV-TR schizophrenia or schizoaffective disorder, with an illness duration ≥5 years; (4) Auditory and visual acuity adequate to complete cognitive tests; (5) Stable dose of atypical antipsychotic medication for at least 4 weeks prior to enrollment; (6) Good physical health determined by physical examination and laboratory tests; (7) Capacity and willingness to give written informed consent; (8) at least an 8 grade Reading level as evidenced from psychological assessment during the chart review or the Wide-Range Achievement Test–Third Edition (WRAT-3).
Exclusion criteria: (1) Inability to read or speak English; (2) Documented disease of the central nervous system (CNS); (3) History of intellectual disability pre-dating onset of symptoms of psychosis; (4) Clinically significant or unstable cardiovascular, renal, hepatic, gastrointestinal, pulmonary or hematologic conditions; (5) HIV +; (6) Subjects diagnosed with substance dependence.

Genotyping and Analysis:
Saliva samples were collected in Oragene DNA collection kits (DNA Genotek) and batch processed. DNA was extracted using a PureGene DNA isolation kit (Gentra systems, Minneapolis, MN). The rs1344706 genotype was analyzed using a Taqman assay, which is based on the 5'-exonuclease activity of AmpliTaq Gold DNA Polymerase, according to the manufacturer's protocol (reviewed by De La Vega et al (De la Vega et al., 2005) (Life Technologies).
PCR reactions were carried out and analyzed in 384 well plates on an ABI Prism 7900HT Sequence Detection System. Three patterns of fluorescence are generated and captured by the instrument: homozygotes to both allele and heterozygotes. Genotype calls are made using the SNP auto-caller feature and the data are displayed in one of several convenient formats.
Scores on the PANSS excitement factor were compared between individuals who expressed allele A (group AA) and those who expressed allele C (individuals with the alleles AC and CC were grouped together). General Linear Model (GLM) was used to analyze the differences

between groups for the PANSS Excitement Factor (assessed by the summation of: excitement, hostility, uncooperativeness and poor impulse control).

Conclusion:
While the risk ‘A’ allele at rs1344706 has been associated poor outcome and a risk factor for psychosis, our results shows an association of the ‘C’ allele at rs1344706 with impulsivity in chronic schizophrenia patients. The difference of our findings as compared to previous reports may have to do with the differing ethnic distribution of our population, which is predominantly African-American. This finding could be of ...

35) **Chiara Criscuolo**, Elisa Cerri, Carlotta Fabiani, Simona Capsoni, Antonino Cattaneo, Luciano Domenici.

The retina as a window to early dysfunctions of Alzheimer’s disease following studies with a 5xFAD mouse model

Alzheimer’s disease (AD) is a progressive neurodegenerative disease leading to neuronal dysfunctions with cognitive impairment. In addition to progressive cognitive disorder, there is increasing evidence of visual involvement in this pathology. Indeed, AD can affect visual pathways and visual cortex and result in various visual changes and problems. A wide range of visual disturbances is reported in AD patients, including a decrease in visual acuity. As well, there is evidence of amyloid beta (Aβ) deposits and cell death in the retinas of AD patients and these, together with an Aβ deposition found in the lens fiber cells, may be responsible for some of the visual deficits seen in AD. Moreover, these visual deficits are strongly correlated with cognitive ability. Despite this knowledge, how early the visual dysfunctions occur in AD is still a matter of discussion. However, visual spatial impairment and thinning of the retinal ganglion fiber layer may be one of the earliest symptoms of AD-type neurodegenerative change. Given the fact that evaluating pathologic changes in the brain during life has always been an indirect process, the opportunity to study microscopic functional cellular changes in the eye non-invasively may be used as a window to facilitate early diagnosis of AD and monitor treatment efficacy. We used a familial AD mouse model, 5xFAD, characterized by severe progressive amyloid pathology and cognitive deficits. The 5XFAD transgenic mouse most closely approximates the human Aβ40 or Aβ42 peptide load in the retina, in the late stage of neurodegeneration, besides showing the highest concentration of Aβ peptides in the brain compared with other murine models. These characteristics make 5xFAD mouse a suitable in-vivo models for studying the mechanism of amyloidogenic neurodegeneration in the retina and the pathogenic signals that may progressively spread across the anteroposterior axis of the visual circuitry. In our work, visual function was monitored using Pattern Electroretinogram (P-ERG), whose source is in the inner retina at the level of retinal ganglion cells, and visual cortical evoked potential (VEP) together with a behavioral assessment of the visual acuity. Visual tests and recordings were conducted at different ages in 5xFAD mice, corresponding to different phases of neurodegeneration and beta amyloid accumulation. We showed that the visual system is impaired in 5xFAD mice. In particular, we found that the inner retina impairment precedes neuronal disorders in other brain areas and cognitive deficits. Thus, monitoring the visual function at earlier stages of neurodegeneration, we describe the time course of the visual dysfunction in relationship with the cognitive impairment. Our results suggest that noninvasive retinal electrophysiology can provide a support for assessing early visual dysfunctions in AD.

36) **Chelsea Miller**, Yohan Kim, Monkia Pawlik, Efrat Levy.

Age-related changes in the generation and secretion of murine brain exosomes

Extracellular vesicles (EVs) are a heterogeneous population of secreted vesicles that includes exosomes and microvesicles. EVs in the brain play a role in cellular homeostasis, including clearing intracellular waste, regulating cell-to-cell communication, and facilitating appropriate brain functions. Since aging is the greatest risk factor for neurodegeneration such as Alzheimer's disease (AD) where exosomes have been proposed to be involved in the disease pathogenesis, understanding how EVs act over age in a wild type genotype may help establish a baseline of what is normal and potentially protective. In order to understand the effect of aging on brain EVs, using a sucrose step gradient, we isolated brain EVs from 3, 6, 12, 18, and 24-month-old C57BL/6 mice (n=3) and compared their morphometric and biochemical properties. There were no significant changes in total EV protein levels nor in EV morphology or the number of EV particles determined by a protein assay, electron microscopy and nanoparticle tracking analysis, respectively. Using biochemical analyses, we found an increase in the exosomal markers relevant to both exosome biogenesis (Alix, TSG101 and CD63) and exosome release (Rab27a), suggesting an age-dependent increase in exosomal generation and secretion. For the AD-related proteins, we observed that the amyloid b precursor protein (APP) and APP-carboxyl-terminal fragments, which are enriched in exosomes, accumulate in brain EVs over age. Though we could not detect changes amongst neprilysin, one of the amyloid β degrading enzymes in the brain, it was the most prominent protein in annexin 2-positive fractions, suggesting its microvesicle enrichment. Over age, we see an increase in exosome generation and secretion levels needed to clear out intracellular waste that accumulates over time. This increase suggests that exosomes are necessary in the brain to maintain homeostasis thus, protective.

37) **Bryana Barreto**, Audrey Hashim, Monika Pawlik, Stefanie Canals, Pasquale D'Acunzo, Mitsuo Saito, Henry Sershen, Mariko Saito, Efrat Levy.

Cocaine modulates the level and cargo of specific brain extracellular vesicles in a gender-dependent manner

The manifestation of addictive behaviors and adverse physiological effects of cocaine abuse have been extensively studied; however, the underlying biological mechanisms that promote cocaine dependency are not entirely understood. Cocaine has been shown to cause alterations in the endosomal, autophagic, and lysosomal system. Formed by the membrane invagination of late endosomes, exosomes are a subpopulation of extracellular vesicles (EVs) that encapsulate cytoplasmic materials, and are secreted into the extracellular space, along with plasma-membrane-derived microvesicles. We hypothesized that cocaine reconfigures intra-extracellular mechanisms through modifications in exosomal biogenesis and formation of microvesicles. To test our hypothesis, we isolated EVs from the right hemibrain of three-month-old C57BL/6J mice, injected daily with saline or cocaine for 14 days, during which sensitization responses to cocaine-induced locomotor activity was observed. EV subpopulations were fractionated by an iodixanol-based density-gradient and EV levels and cargo composition were characterized. We found that cocaine impacts the level and cargo of distinct types of brain-derived EVs differently in males and females. Both male and female mice showed decreased levels of the exosomal markers TSG101 and Hsc70. While the level of the exosomal marker CD63 decreased in EVs of male mice, cocaine did not impact the level of CD63 in females. Interestingly, a significant difference between males and females was found in the level of Annexin II, a microvesicular marker, which decreased in the EVs of males, but increased in female mice after repeated

cocaine administration. These data demonstrate that cocaine has differential effects across genders for certain EV species, such as CD63 and Annexin II containing EVs; while the generation of other EV species, such as TSG101 and Hsc70 containing EVs are irresponsive to gender differences. A difference in addiction behavior was previously demonstrated between men and women, and our data suggest that EV release and/or content may have a role in the difference. Understanding the role that the endosomal-exosomal pathways play in cocaine addiction, may provide insight for novel targets in therapies for addiction.

38) Robert Sears, Lindsay Laughlin, Erika Andrade, Erick Martinez, Danielle Moloney, **Christopher Cain.**

Amygdalostriatal circuits mediating outcome-dependent vs. habitual avoidance

In the active avoidance paradigm, subjects learn to escape an aversive CS and prevent a painful US by emitting a specific avoidance response (AR; e.g. shuttling). I will discuss two lines of research investigating the outcome-dependence and amygdalostriatal-dependence of ARs in rats. Using a novel devaluation procedure, we found that counterconditioning of explicit response-produced safety signals impaired ARs after moderate training, but not after overtraining. This aligns with our lesion and c-Fos data suggesting that basolateral amygdala (BLA) is required for avoidance early in training but not after overtraining. It also aligns with our new data demonstrating that KORD-mediated suppression of dorsomedial striatum impairs moderately-trained avoidance whereas suppression of dorsolateral striatum only impairs ARs if safety signals are devalued before testing. This pattern of results suggest that avoidance brain circuits have more in common with appetitive instrumental conditioning circuits than Pavlovian fear circuits. Implications for learning theory and clinical resilience will also be discussed.

39**) Stephanie Histon**, Anthony Ahmed, Emily Blanco, Audrey Carrillo, Julia Ermel, Morgan Gomez, Thomas Holvey, Leah Israel, Tiana Pistillo, Aaron Seitz, Steven M. Silverstein, Tarek Sobeih, Trevor Stavropoulos, Judy L. Thompson, Jaana Yeaton, Pamela D. Butler.

Evaluation of a Visual Remediation Intervention in Schizophrenia

Schizophrenia is associated with impairments in multiple visual perceptual processes, including low-contrast stimulus detection and perceptual organization (i.e., processes that integrate visual features into perceptual “wholes”). These visual-processing deficits are significantly related to impairments in higher-level cognitive and social cognitive functions (e.g., visual working memory, facial emotion recognition), poorer treatment response and worse functional outcomes. However, very few studies have evaluated the potential of interventions that target specific visual processes. Thus, our primary aim in an ongoing R61/R33 randomized controlled trial (RCT) is to evaluate the efficacy of a visual perceptual training program. Two computerized training programs are used, designed to target two levels of visual processing: contrast sensitivity (CS) and perceptual organization (PO). A control treatment (“Happy Neuron”; HN) that targets executive function, memory, and speed of processing is also included. Participants are randomly assigned to one of four groups: CS+HN; PO+HN; CS+PO; and HN+HN. Participants complete 3-4 one-hour training sessions per week, for a total of 40 sessions. Targets for the first (R61) phase of the study are contrast sensitivity and contour integration. Targets for the second (R33) phase of the study also include cognitive and social function. In pilot work, participants with schizophrenia received 20 to 35 sessions of visual training (Butler et al., 2017; Thompson et al., 2019) and showed improvement in contrast sensitivity and contour

integration. Pilot study results also indicated feasibility and tolerability and suggest treatment-related gains in visual functions, which we aim to confirm with the ongoing well-powered multi-site RCT of these visual interventions. This research offers a novel approach to treatment that may improve perceptual processes and related higher-level cognitive and social cognitive functions in schizophrenia.

40) **Danielle Moloney**, Robert Sears, Christopher Cain.

Assessing the role of the amygdala nuclei in goal-directed vs. habitual active avoidance

In the active avoidance paradigm, rats learn to suppress Pavlovian reactions (e.g. freezing) and emit actions (e.g. shuttling) that escape threats and prevent pain. Avoidance responses (ARs) are believed to reflect instrumental learning, though it remains unclear how goal-directed (action-outcome) vs. habitual (stimulus-response) associations contribute to behavior. In appetitive paradigms, the basolateral amygdala (BLA) is critical for goal-directed responses early in training and the central amygdala (CeA) is critical for habitual responses after overtraining. The goal of this project is to test the effects of pre-training excitotoxic lesions of BLA or CeA on ARs after different amounts of training. A novel outcome-devaluation procedure will be used to differentiate between goal-directed and habitual ARs. Based on our published and unpublished data, we predict that BLA lesions will prevent AR learning regardless of the amount of training. We also predict that CeA lesions will not impair the development of goal-directed or habitual ARs. This would suggest that reward- and punishment-based instrumental tasks recruit overlapping but distinct neural circuits. Understanding the role of the BLA and CeA in avoidance will aid in the development of treatments for human disorders such as anxiety and addiction, in which ARs are believed to become maladaptive via interference with normal activities and an unusual persistence.

41**) Lindsay Laughlin**, Robert Sears, Christopher Cain.

Reducing shock imminence, but not certainty, greatly improves active avoidance conditioning

In the active avoidance paradigm, rats learn to suppress Pavlovian reactions (e.g. freezing) and emit actions (e.g. shuttling) that escape threats and prevent pain. Though most rats acquire the avoidance response (AR) within five sessions, approximately 25% of animals exhibit high freezing and never master the task (“poor avoiders”). This has led some researchers and theoreticians to suggest that avoidance could not have evolved as a major mechanism of defensive learning, since unsuccessful encounters with a predator lead to death. However, we hypothesize that instrumental AR learning is ideal for coping with anxiety-inducing threats that signal distant or uncertain harm, rather than fear-inducing threats that signal imminent or certain harm. To test this, we modified the standard avoidance protocol in which 15s tones signal footshocks on 100% of trials. In experiment 1 (Contingency), the 15s tone was used but on failed trials shocks were delivered on 100%, 50% or 25% of trials. In Experiment 2 (Imminence), tones always signaled footshock, but the tone duration was varied (15s, 60s, 120s or 240s). Reducing tone-shock contingency did not improve AR learning but reducing shock imminence led to perfect avoidance for all rats within 45 trials (240s condition). Subsequent analyses confirmed that low-imminence ARs are instrumental and emitted with latencies similar to high-imminence ARs in good avoiders. These results are consistent with the notion that AR learning mechanisms evolved to cope with anxiety-inducing, rather than fear-inducing, threats. They also

solve a longstanding problem for active avoidance research by offering a protocol that all subjects can solve.

42) **Mariah J Novy**, **Samantha F Newbury**, Jose Morales-Corraliza, Melissa J Alldred, Stephen D Ginsberg, Paul M Mathews**.**

Brain expression and processing of the amyloid precursor protein is unaffected by apolipoprotein E genotype

The three human apolipoprotein E gene (APOE) alleles have varying effects on an individual's risk of developing Alzheimer's disease (AD). Compared to the risk-neutral APOE ε3 allele (APOE3), the ε2 allele (APOE2) is protective against AD while the ε4 allele (APOE4) is associated with increased AD risk. APOE4 expression is linked to increased amyloid-β peptide (Aβ) deposition, an established pathology of AD. This is the result, in part, of decreased clearance of parenchymal Aβ when APOE4 is present. Additionally, there have been suggestions that APOE4 may modulate the expression or processing of the amyloid precursor protein (APP), increasing the generation of Aβ. While prior studies have examined APOE allele effects in APP overexpressing transgenic mice and in cell models, we examined the impact of APOE genotype on in vivo APP expression and processing by examining endogenous murine APP in the brains of humanized APOE mice homozygous for each allele. App gene expression and the levels of APP holoprotein were not affected by APOE genotype. Additionally, our analysis of APP metabolites showed that APOE genotype does not impact APP processing. The levels of both α- and β-cleaved soluble APP fragments (sAPPα and sAPPβ) were similar across genotypes, as were the levels of the cell-associated α- and β-cleaved C-terminal fragments (αCTFs and βCTFs). Expression of the three APOE alleles did not alter the levels of brain Aβ derived from the endogenous APP. Thus, while expression of APOE4 is known to impact Aβ clearance, seeding, and amyloid deposition, in a model without APP overexpression that displays endogenous levels of APOE expression, brain expression and processing of APP is independent of the expression of the three APOE alleles. In addition, these findings support our argument that the impact of APOE4 expression on endosomal-exosomal pathway function in neurons in vivo (see poster by Peng et al.) is unlikely to be mediated through changes in APP and Aβ levels.

43) **Annamaria Barczak**, Monica N. O'Connell, Tammy McGinnis, Samuel A. Neymotin, Charles E. Schroeder, Peter Lakatos.

Eye movement-related contextual modulation of auditory cortical activity

The auditory and visual sensory systems are both used by the brain to obtain and organize information from our external environment, yet there are fundamental differences between these two systems. For example, while actively searching a scene, information is acquired using systematic patterns of fixations and saccades, which are controlled by internal motor commands. In this condition, sensory input occurs in volleys, strictly tied to the timing of eye movements. The auditory system in contrast, does not use such an overt motor sampling routine so the relationship between sensory input timing and motor activity is less clear. Previous studies of primary visual cortex (V1) in nonhuman primates have shown that there is a cyclical modulation of excitability tied to the eye movement cycle. Eye movements modulate visual processing in V1 such that stimulus responses are larger when stimuli are presented just after fixation onset as opposed to later during the fixation. The analysis of neuronal oscillations

in V1 suggests that this eye movement-related modulation of excitability stems from phase reset in the theta-alpha frequency range. We hypothesized that if eye movements provide a supramodal temporal context for environmental information then we should also see eye movement-related modulation of oscillatory activity in primary auditory cortex (A1) as nonhuman primates shift their gaze around their surroundings. To examine this eye movement related activity in A1, we used linear-array multielectrodes to record cortical laminar neuroelectric activity profiles while subjects sat in a darkened silent chamber. Analysis of oscillatory activity in A1 suggests that, as in visual cortical regions, saccades are indeed capable of resetting neuronal oscillations in auditory cortex. When compared to the laminar-angular patterns of phase reset by auditory stimuli, a consistent difference was observed. Our results indicate that besides environmental multisensory inputs, motor sampling patterns like saccades can alter auditory cortical excitability despite the sampling of auditory inputs rarely being coherent with any motor action.

44) Nathalia Esper, Maicon Much, Dario Azevedo, Augusto Buchweitz, Michael Milham, **Alexandre Franco.**

Real-time fMRI Motion Tracking: should I stop and restart the scan?

Excessive head motion is the main reason for discarding fMRI data. As researchers, we regularly ask volunteers to stay inside the scanner for a long period of time and attempt to not move their head, which is especially difficult for children and some clinical populations. Preprocessing of functional neuroimaging data has been consistently improving [3], however, if the noise levels are too high due to head motion, there is only so much it can correct. Collecting good data surpasses any preprocessing strategy.
Typically, with a real-time fMRI software it is possible to monitor head motion through graphs (3-translation and 3-rotation or Framewise Displacement [FD] plots). Nonetheless, using this type of system is not straightforward on deciding if a run where a subject is moving their head should be interrupted or not. This decision is typically subjective. Considering that we would want to perform an fMRI session as quickly as possible and not have to repeat an entire run, can we predict within a short amount of time if an fMRI run will later be discarded? If so, for how long should we run the scan before we interrupt the run and remind the subject to not move their head?
Our group developed software that advises the researcher if a scan should be interrupted or not based on head motion. We quantified the utility of this tool on a large study with children

45) **Anzalee Khan**, Phil D. Harvey, Richard S.E. Keefe, Christian Yavorsky, Lora Liharska, Ryan Bowser, Jean-Pierre Lindenmayer, Mary Seddo, Lucia Roitman

Clinical Insight as a Predictor of Time to Relapse in Schizophrenia: A Two-Year Follow-up Study

OBJECTIVE:
A majority of people diagnosed with schizophrenia experience multiple relapses. The first two years after stabilization are thought to be key for long-term functional and clinical prognosis. This study aimed to identify the two-year post stabilization course of illness in individuals with schizophrenia, to determine whether demographic and clinical factors are associated with time to relapse.
METHODS:

A total of 138 participants diagnosed with schizophrenia or schizoaffective disorder were assessed with a comprehensive assessment at one year and two year following discharge from a long-term psychiatric facility. Regression models were used to determine factors predicting time to relapse and other elements of functioning.
RESULTS:
Relapse rates were 56.52% (n=78 of 138) by Year 1, and 69.56% (n=96 of 138) by end of Year 2. The estimated relapse-free period for all individuals at the end of the study was 8.78 months. The best predictive variables for relapse at each of the time points were lack of insight/judgment, average years of substance use, PANSS baseline score on Disorganization, and number of previous hospitalizations. Negative Symptom factor scores at baseline, and lack of insight/judgment were the best predictive variables of functioning at the Year 1 follow-up.
CONCLUSIONS:
Subjects were found to have a relatively short time to relapse during the first two years following discharge into the community. Lack of insight was a greater predictor of relapse than other demographic and clinical characteristics. Knowing potential triggers of relapse can help in developing resources for this population to reduce treatment failures and associated costs.

46) **Raymond F. Suckow**, Vinod K. Yaragudri, Anna Jarosky, Thomas B. Cooper.

Long-Term Stability of Ketamine and Metabolites in Human Plasma

The study of ketamine and its metabolites has recently become major research item in psychiatry. Ketamine, a derivative of phencyclidine (PCP), has been used as an anesthetic both in animal as well as humans. Because of its dissociative effects in humans, and its propensity for abuse, ketamine has become a controlled substance. However, recent reports have indicated that ketamine, and one or more of its metabolites, can rapidly reverse severe depression and suicidal ideation.

The Analytical Psychopharmacology Laboratory (APL) at NKI has been involved in measuring ketamine and its metabolites for numerous clinical studies for past 25 years. Recent interest in the various hydroxy metabolites of ketamine and norketamine contributing to, or being responsible for, the pharmacologic effect prompted re-analyses of samples from previous studies.

To validate the long-term stability of ketamine and its metabolites, we selected 51 previously analyzed human plasma samples from various studies during 2012 to 2016. All samples had been stored frozen at -20o C, with sufficient amount of plasma for re-analysis. The same validated liquid chromatographic method with UV detection, in use in our lab for ~20 years, was used to measure ketamine and its metabolites both originally, and again for re-analysis in 2018.

Statistical analyses indicated that there was no significant difference between ketamine or its two major metabolites, norketamine and dehydronorketamine, when measured originally vs. 2-6 years later. This study suggests that ketamine samples may not have to be analyzed immediately following collection of the sample and may be stored for future batch processing if kept frozen. Additionally, if the hydroxy metabolites of ketamine demonstrate similar stability, re-analyses of frozen ketamine samples for these metabolites would be of interest.

47) Anzalee Khan, Jean-Pierre Lindenmayer, Christian Yavorsky, Isidora Ljuri, **Mary Seddo.**

Integrating electronic patient reported outcomes (ePROs) in schizophrenia trials: Clinician and Patient Perceptions for scale refinement

The Methodological Question Being Addressed: Should use of patient and clinician perspectives be incorporated in the guidelines for development, refinement, feasibility and usability of ePROs in schizophrenia trials?

Introduction:
Patient-centered outcomes research (PCOR) improve care quality and patient outcomes by providing information that patients, clinicians, and family members need regarding treatment alternatives, emphasizing patient input to inform the research process and development of assessment tools. Although ePROs has been implemented successfully in many populations, there is insufficient evidence regarding the performance of ePROs in schizophrenia. Symptom exacerbations are not timed events. Knowing that patients are under no direct obligation to enter data on a real-time basis, and that they can wait days or even weeks and then try to recall their experience, ePRO can provide the necessary assurance that data was entered by the patient at the time the episode occurs. The aim of the present study was to provide patient and clinician perceptions of completing ePROs, expectations of ePRO devices for PCOR and on-site clinical visit to refine ePRO deployment in schizophrenia.

Methods:
35 individuals with schizophrenia were enrolled, and 12 clinicians were surveyed. Participants completed assessment of the ePRO (Awareness of Insight: AIS) disseminated as push messages weekly for 6 months, CGI-S, SF-36, PANSS, and Brief Assessment of Cognition (BACS). Compliance rates, feasibility and usage, user acceptability and reliability and validity estimates were assessed.

Results:
Compliance rates showed a consistent decrease in use of ePRO device from Week 1 to Week 24 (90% to 62%). 80% participants found the app easy to use, 58% indicated operational issues (app did not work, font size was too small, difficult to press buttons due to EPS), 58% indicated it was easier to answer the questions on an app than to a clinician, and 25% indicated they could not differentiate between options for each question (e.g., rarely and sometimes). Additionally, 54% indicated they did not like the frequency with which they had to answer the ePRO questions. 92% of clinicians indicated they liked the email notifications for participants flagged for aberrant changes in Insight as opposed to logging into a dashboard daily, and 83% indicated that they thought the app was helpful to get information on the participant outside of clinic visits. Clinicians also reported the quality of the phones resulted in delays in data uploads and data collection for 86.36% of subjects. Internal Consistency for the ePRO, AIS, was high ($\alpha = 0.81$), AIS correlated with PANSS G12 ($r = 0.50$, $p = .009$) and with the PANSS Disorganization factor ($r = 0.41$, $p = .011$). Test-retest reliability are moderate, ICCs = 0.70.

Conclusions:
Health-related smartphone apps are being widely considered for individuals with schizophrenia for self-monitoring and follow-up. Many clinicians believe that ePROs may improve patient outcomes compared with traditional methods of monitoring change, which usually does not occur until a clinic visit which can be weeks or months apart. Importantly, the issues encountered in this population are likely to differ according to the type of electronic device, study design (eg, frequency of assessments), and the content of the instruments used. User

Acceptability, feasibility, comparison with standard validated measures and accessibility are important factors to consider for validation of ePROs beyond the psychometric analysis.

48) **Vinod K. Yaragudri**, Andrea Balla, Bin Dong, Kiran Vemuri, Alexandros Makriyannis, Henry Sershen, Raymond F. Suckow, Subhash C. Pandey

Regulation of Binge-Like Alcohol Consumption By Antagonists of CB1 and NPY1 Receptors

Previous studies have shown importance of both endocannabinoid and neuropeptide Y (NPY) systems in alcohol drinking behaviors. However, the molecular mechanisms are not clearly understood at present. In this study, we examined the effect of novel cannabinoid-1 receptor (CB1 receptor) neutral antagonist AM4113 and NPY1 antagonist on binge-like alcohol consumption in C57BL/6J mouse model using a drinking-in-dark (DID) paradigm. AM4113 (1 and 3 mg/kg body weight, i.p.) suppressed alcohol consumption without significant alterations in the body weight, ambulatory activity, preference for tastants and alcohol metabolism. AM4113 pretreatment attenuated acute alcohol-induced (1.5 g/kg, i.p.) increase in dopamine release and phosphorylation of dopamine- and cAMP-regulated phosphoprotein-32 at threonine 34 (DARPP-32 Thr34) in nucleus accumbens. The deletion of CB1 receptors increased the expression of NPY in nucleus accumbens and amygdala, and reduced alcohol consumption compared to CB1 receptor wild-type mice. The systemic administration of brain permeable antagonist of NPY1 receptor, BMS-193885 (10 mg/kg, i.p.) increased alcohol consumption subtly in CB1 knock out mice. These studies suggest an important role of CB1 receptor-mediated regulation of binge-like alcohol consumption through modulation of dopaminergic and NYP signaling, and further points to the potential utility of CB1 neutral antagonists for the treatment of binge alcohol drinking.

49) **David Alcantara-Gonzalez**, Benjamin Villasana-Salazar, Fernando Peña-Ortega, Helen Scharfman.

Single amyloid-beta injection exacerbates acutely-induced seizures and changes the synaptic response in the hippocampus

Accumulation of amyloid-beta (Aβ) in temporal lobe structures, including the hippocampus, is related to a variety of Alzheimer's disease symptoms and seems to be involved in the induction of neural network hyperexcitability and even seizures. Still, a direct evaluation of the pro-epileptogenic effects of Aβ and of the underlying mechanisms, is missing. Thus, we tested whether the intracisternal injection of Aβ modulates 4-aminopyridine (4AP)-induced epileptiform activity, hippocampal network function, and whether it affected the synaptic response. When tested 3 weeks after its administration, Aβ reduced the latency for 4AP-induced seizures, increased the number of generalized seizures, exacerbated the time to fully recover from seizures, and favored seizure-induced death. These pro-epileptogenic effects of Aβ correlate with a reduction in the power of the spontaneous hippocampal network activity, involving all frequency bands in vivo and only the theta band (4–10 Hz) in vitro. The pro-epileptogenic effects of Aβ also correlated with altered synaptic responses in vitro, which was exacerbated by the sequential bath application of 4-AP and Aβ. In summary, Aβ produces long-lasting pro-epileptic effects that may be due to alterations in the hippocampal circuit, impacting its coordinated network activity and its synaptic efficiency. It is likely that normalizing synaptic integration and/or coordinated neural network activity (i.e., theta activity) may contribute not only

to improve cognitive function in Alzheimer's disease but also to avoid hyperexcitability in conditions of amyloidosis.

50) Anna Pensalfini, Seonil Kim, Shivakumar Subbanna S, Cynthia Bleiwas, Chris N. Goulbourne, Philip H. Stavrides, Ying Jiang, Monika Pawlik, Chunfeng Huo, Martin J. Berg, John F. Smiley, Balapal S. Basavarajappa, **Ralph A Nixon**.

Over-activating neuronal Rab5 in mice by itself causes AD-related endosomal, synaptic, cholinergic, and cognitive deficits and, in APP-models of AD, accelerates disease.

Abnormalities of endocytosis in AD are linked to APP, APOE4 and multiple GWAS-identified genes associated with increased AD risk. Rab5-positive early endosome enlargement, reflecting aberrantly upregulated endocytosis, is the earliest known neuronal pathology specific to AD. Rab5 hyperactivation by APP-β-secretase-cleaved-C-terminal fragment (APP-βCTF) mediates endocytic dysfunction in Down Syndrome and likely in AD.
To investigate the role of Rab5 over-activation in AD pathogenesis independently of its triggering by APP-βCTF, we generated mice overexpressing myc-tagged human Rab5 selectively in neurons via a Thy-1 promoter. Increased Rab5 expression significantly elevated levels of activated Rab5 (Rab5-GTP) on endosomes as measured by anti-Rab5-GTP antibody labeling *in situ* and GTP-agarose bead pull down. Regional brain levels of APP metabolites were unaltered by Rab5 upregulation. By 6 months, Rab5 Tg mice displayed the signature AD-endosome phenotype, with enlarged endosomes seen ultrastructurally accumulating in dendrites, synaptic terminals and axons in cortex and hippocampus. Consistent with known regulatory actions of Rab5 at synapses, long-term depression (LTD) was defective in hippocampal CA1 synapses, accompanied by AMPAR dephosphorylation at sites known to mediate receptor internalization from the postsynaptic surface. A significant deficit in novel object recognition memory accompanied reduced dendritic spine density and long-term potentiation (LTP) deficits. Neurodegenerative changes and loss of basal forebrain cholinergic neurons (BFCN) increased with age. When Rab5Tg mice were crossed with mouse models of late-onset AD, intracellular APP-βCTF and Aβ immunoreactivity accumulated more rapidly and BFCN degeneration was accelerated.
The Rab5 Tg mouse represents a new and unique model of AD pathogenesis revealing the earliest disease stages prior to amyloid deposition leading to degeneration of the most vulnerable cholinergic neuron population linked to memory decline. Our results indicate that Rab5 over-activation by itself is a key driver of AD pathobiology and accelerates neuronal Aβ accumulation and β-amyloidogenesis in the context of APP overexpression/mutation.

51) **Eunju Im**, Ying Jiang, Ju-Hyun Lee, and Ralph A. Nixon.

APP-βCTF Regulates vATPase-mediated Lysosomal Acidification

Object: 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. Presenilin 1 (PSEN1) mutations impair lysosomal acidification via the vATPase complex. Here, we investigated how amyloid precursor protein (APP) influences lysosomal function. *Methods:* Having found that elevated levels of beta-secretase C-terminal fragment of APP (APP-βCTF) reversibly impair lysosomal acidification in Down Syndrome (DS) patient fibroblasts and neurons of TS2 DS mice (3N APP), we investigated the underlying mechanism(s) in lysosomes from DS fibroblasts and hAPP-over-

expressing N2a neuroblastoma cells, where APP-βCTF levels were additionally manipulated by β- and ɣ-secretase inhibition or siAPP. *Results:* In N2a cells or 2N fibroblasts, APP-βCTF traffics to lysosomes where it interacts selectively with specific subunits of the lysosomal vATPase complex controlling association of the V0/V1 sectors of the complex which regulates activity and acidification. At elevated levels, APP-βCTF competes with these subunits for complex assembly, lowering their levels on lysosomes and promoting dissociation of the V0/V1 sectors, which results in pH elevation. Lowering APP-βCTF levels fully restores lysosome acidity and pH in DS fibroblasts and, in 2N fibroblasts a further lowering induces modest additional acidification and V1/V0 association, suggesting a degree of tonic regulation of vATPase activity by APP-βCTF. *Conclusions:* Multiple distinct effects of aberrant APP-βCTF signaling on endosomal-lysosomal function are likely primary contributors to AD pathogenesis, underscoring the close relationship between the major AD-related genes and early endosomal-lysosomal pathway dysfunction. Funding: NIA: 5P01AG017617

52) **Victor V. Dyakin** and Justin Lucas.

Non-Equilibrium Phase Transitions in Biological Information Processing: Principles of Brain Connectivity

Our attention to the molecular chirality and non-equilibrium phase transitions (PhTs ^{NE}) associated with protein folding is navigated by our dominant regard to the nature of the higher cognitive function. We will move from the intra-molecular, inter-molecular, intra-cellular, and inter-cellular interactions to the spatial distribution of neuronal networks activity. We want to trace the association between the architecture of the neuronal signaling with the perception and transformation of sensory information. We will consider the biological spatiotemporal self-organization, evident from the molecular to organism levels, from the prism of nonequilibrium phase transitions (PhTs ^{NE}). The experimental and theoretical works support the validity of the Norther's theorem (1918) regarding the fundamental role of symmetry (intimately related to the conservation laws) in the non-equilibrium thermodynamic systems non-biological and biological nature. The latte one is a matter of our consideration concerning protein folding, phospholipids-protein interaction, cytoplasmic protein condensation, dynamic nature of membrane-less organelles (MLOs), and biological information processing. Nonequilibrium thermodynamics utilizing the notions of energy, entropy, and symmetry is the ground of all information theories, including related to the biological information processing. The ATP/ADP energy and chirality transformations in the biological system is a driving force of the PhTs ^{NE}. Phase transitions (PhTs) are utilized for the spatial and temporal organization of the intracellular MLOs and information flow. The chirality code of protein synthesis, underlying the transfer of chiral information through molecular structures differential complexity, and cell-cell communications are well-known facts. In the living organisms, representing the inherently nonequilibrium systems, molecular complexes of DNA, RNA, proteins, and lipids are «adapted» to recording, reading, and transfer of chiral information. The adaptation employs molecular biochirality. The evolution of biochirality in living organisms is evident from bacteria to mammals. Bacteria exhibit the greatest capacity to the synthesis of a wide variety of D-amino acids (D-AAs), while eukaryotes (as known so far) are synthesizing only two kinds of D-AAs: D-serine and D-aspartate. Despite the enormous progress in understanding the role of biochirality, the spectrum of underlying mechanisms remains to be studied. Within the broad subject of biological nonequilibrium phenomena, we will be focused primarily on the molecular and cellular phase transitions. Among molecular one we are paying attention predominantly to protein folding. Protein PhTs ^{NE} considered in association with the biological information processing, Shannon's information theory, and maximum entropy principles (MEP). This view allows appreciating the

complementary contribution of nonequilibrium thermodynamics, and nonequilibrium statistics, to the molecular biochirality, cell physiology, and cognitive neuroscience. The subject of our analysis is the role of the spatial symmetry determinants in the biologic PhTs ^{NE}, intrinsically disordered proteins (IDPs) and MLOs. The trinity of PhTs ^{NE}, IDPs, and MLOs are considered in the light of prevalent bio-chirality, stereochemistry of protein folding, biological information processing, and laterality of cognitive brain functions.