McKNIGHT BRAIN
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POSTER RECEPTION

In conjunction with
The Society for Neuroscience

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Capitol Ballroom
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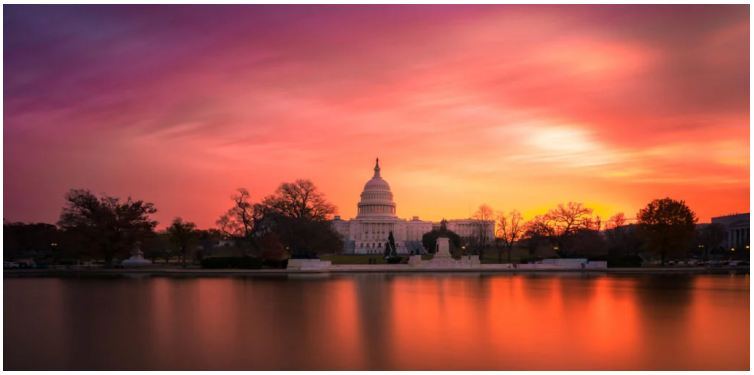
WASHINGTON, DC 20001



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First Author: Acevedo-Triana, Cesar

Abstract Title: **Male Mecp2 knockout mice do not form stable social hierarchies: a consequence of impaired social memory due to lack of neuronal synchrony in the mPFC?**

McKnight Institute:
Evelyn F. McKnight Brain Institute at UAB

Lab: Pozzo-Miller Lab

ABSTRACT

The activity of mouse mPFC neurons is correlated with the interaction with conspecifics and is thought to encode social memories used to establish hierarchical social rankings. Atypical social behaviors are prevalent in neurodevelopmental disorders, and a mouse model of Rett syndrome shows impaired social memory caused by heightened activity of the monosynaptic projection from the ventral hippocampus to the mPFC. We performed the classical 'tube' test over 6 consecutive days to establish the social hierarchy within groups of 3 age-matched male mice of the same genotype. This assay revealed that *Mecp2* KO mice failed to form stable social ranks, displaying fewer dominant behaviors inside the tube than WT mice. We followed the 'tube' test with a novel 'warm' spot test, where the same 3 age-matched mice of each genotype compete to stand on a single warm spot in a cage with a cooled floor. As expected, the 'dominant' WT mouse occupied the 'warm' spot far longer than the other 2 mice ('intermediate' and 'submissive'), while *Mecp2* KO mice equally shared the 'warm' spot regardless of their social rank, showing fewer dominant behaviors than WT mice. *In vivo* Ca2+ imaging with head-mounted miniscopes to follow neuronal activity in unrestricted mice poses a significant challenge to study *Mecp2* KO mice because they begin to have neurological impairments around P50. To overcome this, we performed a single surgery to inject AAVs expressing CaMKII-driven GCaMP6 and implant a GRIN lens in the mPFC of WT mice at P25. After 2 weeks, WT mice displayed stable social ranks in the 'tube' and 'warm spot' tests, indicating that GRIN lens implantation in one hemisphere's mPFC did not affect this social behavior. *In vivo* Ca2+ imaging from pyramidal neurons in the prelimbic mPFC confirmed the presence of social-ON and social-OFF cells, i.e., neurons that increase and decrease activity during social interactions, respectively. mPFC pyramidal neurons in *Mecp2* KO mice showed fewer and smaller Ca2+ transients during baseline, as well as during social interactions in the 'warm spot' test. The activity of social-ON and social-OFF neurons in *Mecp2* KO mice seems to be less synchronous than in WT mice. To further reduce the number of surgeries and their duration, we tested pre-coating the GRIN lenses with a mixture of jGCaMP-encoding AAV and silk fibroin. Preliminary results in WT mice show that the silk-coating yield comparable numbers of jGCaMP-expressing neurons without affecting the optical performance of GRIN lenses, assessed by raw jGCaMP intensity and the amplitude and kinetics of its Ca2+-dependent dF/F transients.

First Author: Alexandre, Fapianey	Presenter (if someone other than First Author):
Abstract Title: Metabolism and Memory: Exogenous Ketone Supplementation to Offset Age-Associated Cognitive Decline	
McKnight Institute: McKnight Brain Institute at the University of Florida	Lab: Burke Laboratory for Brain Organization and Aging

ABSTRACT

Glucose is a sugar molecule metabolized by the body as the main energy source of the brain. As our brains age, their ability to utilize glucose decreases, resulting in cognitive deficits. Ketone metabolism, however, remains the same across the lifespan, and the brain will break down ketones for energy in the absence of glucose. Inducing ketosis (a non-pathological increase of ketone levels in the bloodstream) helps mitigate the neuronal stress that is associated with normal aging by providing the brain with an alternative energy source to glucose. Ketosis is typically achieved by a high-fat, low carbohydrate ketogenic or “keto” diet. Since older populations face difficulty maintaining a strict ketogenic diet, our study investigates whether, with an otherwise normal diet, exogenous ketone supplementation will induce ketosis and whether this ketosis will mitigate age-related cognitive decline. We propose a dietary supplement consisting of two ketosis-inducing compounds widely available to the public: medium-chain triglyceride (MCT) oil, a fatty acid converted to ketone bodies in the liver, and beta-hydroxybutyrate (BHB), a ketone body synthesized in the liver. Aged rats, a preclinical model extensively used to investigate mechanisms of cognitive decline, experience the same neural impairments associated with age as elderly humans. We hypothesize that animals, particularly aged animals, receiving the supplement will perform better than their control counterparts on behavioral-cognitive assessments. Four groups of Fischer-344 brown Norway hybrid rats (young females, young males, aged females, and aged males) were given BHB and MCT oil, and BHB levels were recorded at 0, 2, 4, and 24 hours postprandial after 1, 4 and 7 days on the supplement. Supplementation was found to elevate BHB in all groups, achieving ketosis levels comparable to those derived from a keto diet. Animals then underwent assessments of spatial learning, memory, and visual discrimination via mnemonic description and navigation tasks. In a pilot cohort of animals, statistical comparison of supplemented animals to controls showed improvements across all groups receiving the supplement, leading us to speculate that cognitive performance is enhanced in old age as a result of an exogenous ketone supplement to a normal diet. Behavioral assessments of a second and third cohort of rats are under way to determine whether firm statistical conclusions can be drawn of the supplement’s efficacy in aged animals.

First Author (Last name, first name): Bahabry, Rudhab	Presenter (if someone other than First Author):
Abstract Title: **Alterations in 5-hmC DNA Methylation Patterns in the Hippocampus of an Experimental Model of Refractory Temporal Lobe Epilepsy**	
McKnight Institute: **UAB**	Lab: **Farah Lubin Lab**

ABSTRACT

Epigenetic DNA methylation (DNAme) mechanisms have been shown to play a critical role in regulating gene expression changes in the epileptic hippocampus. While research has largely focused on the role of the 5-methylcytosine (5-mC) form of DNAme in temporal lobe epilepsy (TLE), the involvement of 5-hydroxymethylcytosine (5-hmC) modification, catalyzed by the ten-eleven translocation (TET) enzymes, remains unexplored. Here, we investigated the role of TET-mediated 5-hmC in TLE.

Human samples used for mass spectrometry analysis (MS) were obtained from patients with epilepsy, and controls were obtained from non-epileptic post-mortem samples. Seizures were induced in Male Sprague Dawley rats by administering Kainic Acid (KA) intraperitoneally. Eight weeks following status epilepticus (SE), hippocampal tissue was isolated and processed for MS and 5-hmC DNA immunoprecipitation followed by sequencing (hMeDIP-seq). To examine the effect of Tet1 on seizures, Tet1 small interfering RNA (siRNA) was used to knockdown Tet1 expression, and Tet1 was overexpressed via lentivirus. Behavioral seizure severity was assessed using the Racine scale. Post-SE, hippocampal 5- mC/5-hmC levels were measured via enzyme-linked immunosorbent assay (ELISA).

We found that bulk hippocampal 5-hmC levels were significantly reduced in both patients with TLE and in the kainate rat model of TLE. We found no significant changes in bulk 5-mC levels in the epileptic hippocampus. hmeDIP-seq analysis showed 5-hmC loss within intergenic regions and significant changes in gene bodies and promoters in the epileptic hippocampus. Gene Ontology analysis suggests that 5-hmC enrichment at critical gene pathways such as GABA signaling and ion transport. Reducing Tet1 expression in the hippocampus resulted in reduced 5-hmC levels and was associated with a decreased seizure threshold, suggesting that blocking Tet1 is sufficient to increase seizure susceptibility. In contrast, Tet1 overexpression in the hippocampus increased 5-hmC levels, leading to a delayed onset of SE and improved seizure resiliency.

Together, these findings indicate that TET1/5-hmC changes play a crucial role in the epigenetic regulation of gene processes in TLE. Future studies will assess the effect of manipulating TET1/5-hmC on epileptic seizures and determine the cell type-specific changes in Tet1 expression contributing to abnormal gene transcription programs in TLE.

First Author (Last name, first name): Bassett, Zoe	Presenter (if someone other than First Author):
Abstract Title: Estrogen receptor-beta agonist treatment confers ischemic protection via altered brain metabolism in aged female rats	
McKnight Institute: Miami	Lab: Raval lab at Peritz Scheinberg Cerebral Vascular Disease Research Laboratory

ABSTRACT

One-fifth of postmenopausal women suffer stroke in the United States. Menopause is characterized by decline in endogenous estradiol-17β (E2), which is normally neuroprotective against ischemia. Despite safety concerns of E2 treatment, women appear to be naturally protected against ischemic neuronal damage during pre-menopausal life, suggesting an estrogen-influenced neuroprotective mechanism. In a published study, we demonstrated that pretreatment with a specific E2 receptor subtype-beta (ER-β) agonist reduces ischemic brain damage in reproductively senescent (RS) female rats. Here we hypothesize that ER-β agonist treatment induces metabolic changes in the brain of RS female rats resulting in neuroprotection. We randomly assigned female Sprague-Dawley retired breeder rats (9-10 months; n=6/group) to two cohorts. The first was exposed to either vehicle (DMSO) or ER-β agonist every 48 hours for a month then brains were analyzed for global metabolomic (Metabolon Inc) changes. The second cohort was exposed to transient middle cerebral artery occlusion (tMCAO; 90 min) or sham surgery. At 4.5h after tMCAO, they were treated with either DMSO or ER-β agonist, and then treated every 48 hours for one month. One-month post-surgery, we measured percent freeze-time in a hippocampal-dependent contextual fear conditioning model then perfused and collected brains for infarction quantification. We observed significantly ($p<0.05$) reduced infarct volume in ER-β agonist-treated rats as compared to DMSO, as well as significantly increased freezing, suggesting cognitive improvement. Metabolomics data demonstrated significantly altered ($p<0.05$) levels of intermediates of histidine, glutathione, and purine metabolism, as well as intermediates in the gamma-glutamyl cycle. These observed metabolic changes may be targets for protecting the brain from oxidative damage in RS rats.

First Author (Last name, first name): Cleere, Angela	Presenter (if someone other than First Author):
Abstract Title:Acute morphine and glucocorticoid signaling regulate FKBP5 expression in astrocytes	
McKnight Institute:UAB	Lab: Day Lab

ABSTRACT

Author List: Angela C Cleere, Jennifer J Tuscher, Nathaniel J Robinson, Robert A Philips III, Lara Ianov, Robert Sorge, Jeremy J Day

Acute morphine and pain have been shown to induce transcriptional changes in the ventral tegmental area (VTA), a brain structure important in drug-seeking behavior, both in vivo and in vitro. We recently used single-nucleus RNA sequencing (snRNA-seq) in the VTA of adult rats to identify cell-type specific changes in gene expression after acute morphine experience in a chronic pain model. Surprisingly, we found that glial cell populations, which are non-neuronal cells that help support neuron function, had more changes in gene expression than neuronal cell populations. Astrocytes, a type of glial cell, were particularly transcriptionally responsive to acute morphine and showed strong induction of Fkbp5, regardless of pain state. Previous literature has implicated glucocorticoid receptors (GR) in pain responses and transcriptional changes of FKBP5. Here, we employed a human-derived astrocyte cell culture system to investigate the mechanisms behind opioid and glucocorticoid-induced changes in gene expression. We differentiated neural progenitor cells into astrocytes and delivered pharmacological treatments at DIV14. We determined that treatment with the endogenous glucocorticoid cortisol, and the GR agonist dexamethasone, were both sufficient to drive FKBP5 expression in astrocytes. Pretreatment with the GR antagonist mifepristone blocked dexamethasone-induced transcriptional changes. These findings suggest GR activation is both sufficient and necessary to induce FKBP5 expression in astrocytes. Future experiments will use a CRISPRi tool for selective repression of NR3C1, which encodes for GRs, in astrocytes to further investigate how GR signaling mediates opioid-induced transcriptional responses.

First Author (Last name, first name): Coachman, Audrey	Presenter (if someone other than First Author): Coachman, Audrey
Abstract Title: With our Powers Combined: A Collaboration between UAB CNC and McWane Science Center to Create Impactful Brain Awareness Week Experiences	
McKnight Institute: University of AL at Birmingham	Lab: Visscher

ABSTRACT

UAB CNC and McWane Science Center have partnered to provide outreach experiences for Brain Awareness Week (BAW) in the Birmingham community for over a decade. This partnership and our public engagement efforts have developed over the years with our 2023 BAW programs reaching over 2000 participants interested in learning more about the brain and neuroscience. This abstract outlines the conceptual framework that led to the development of better methods for engaging and educating participants during BAW.

The success of BAW can be attributed to the combination of in-depth knowledge and passion for neuroscience at UAB and the community engagement expertise of a science center. By incorporating key elements of impactful STEM experiences, the BAW team created experiences that were social, connected, inclusive, engaging, needed, conversational, and evidence-based. These elements were intentionally included in each BAW activity alongside opportunities to connect with experts in the field. We will discuss some best practices, found by trial and error.

One of the main challenges was communicating complex neuroscience concepts in an accessible and engaging manner. To address this challenge, an organized website was created to help BAW volunteers and community members understand the goals and objectives of BAW. This website, www.brainawarenessuab.com, provides a platform for promoting the event, sharing resources, and facilitating communication between organizers and participants.

Overall, the success of BAW can be attributed to the thoughtful planning and execution of a comprehensive outreach strategy. By focusing on accessibility, engagement, and meaningful learning experiences, BAW has become a valuable resource for promoting public awareness and understanding of neuroscience.

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First Author (Last name, first name): Cook, Anna	Presenter (if someone other than First Author):
Abstract Title: Progranulin insufficiency and TDP-43 overexpression interact to worsen phenotypes in a mouse model of Frontotemporal Dementia	
McKnight Institute: UAB	Lab: Andrew Arrant

ABSTRACT

Heterozygous, loss-of-function mutations in progranulin (GRN), most of which result in progranulin haploinsufficiency, are a major cause of Frontotemporal Dementia (FTD). FTD-GRN patients commonly present with behavioral changes such as social withdrawal, apathy, disinhibition, and compulsivity. These patients also develop TDP-43 pathology, characterized by nuclear clearing of TDP-43, TDP-43 mislocalization to the cytoplasm, and formation of TDP-43 inclusions. Grn+/– mice are a genetic model of FTD-GRN and model the behavioral symptoms of FTD, exhibiting age dependent deficits in social dominance, fear conditioning, and sociability. However, Grn+/– mice do not develop TDP-43 pathology. Grn–/– mice develop some TDP-43 inclusions at advanced ages, but model the complete loss of progranulin that causes Neuronal Ceroid Lipofuscinosis. To better model FTD-GRN, we crossed Grn+/– mice with a human TDP-43 transgenic mouse line (TAR4 line). Homozygous human TDP-43 transgenic mice (hTDP++) develop TDP-43 mislocalization and inclusions, resulting in severe motor deficits that are fatal by 30 days of age. Hemizygous human TDP-43 transgenic mice (hTDP+) have a mild phenotype and normal lifespan, developing subtle motor deficits and gliosis by 12 months of age. To determine if progranulin insufficiency exacerbates development of TDP-43 pathology, we crossed Grn+/– mice with hTDP++ mice. We found that the Grn+/–:hTDP++ mice had significantly more CD68 and GFAP immunoreactivity than Grn+/+:hTDP++ mice. Ongoing studies are investigating if TDP-43 mislocalization and aggregation is also worse in the Grn+/–:hTDP++ mice. Behavioral changes are a key feature of FTD-GRN, so we investigated behavior in the Grn:hTDP mice. Due to the early mortality of hTDP++ mice, we utilized hTDP+ mice to generate the cross. Grn+/–:hTDP+ mice had more severe social dominance deficits that either Grn+/–:hTDP– mice or Grn+/+:hTDP+ mice in the tube test, an assay dependent on the medial prefrontal cortex (mPFC). This low social dominance phenotype occurred without worsened TDP-43 pathology or signs of lysosomal dysfunction and inflammation. To elucidate the mechanisms of behavior abnormalities, we utilized mRNA sequencing of the mPFC and analyzed dendritic branching and dendritic spine morphology of mPFC neurons.

First Author (Last name, first name): Cooper, Mary Bullock	Presenter: Cooper, Mary Bullock
Abstract Title: Alzheimer's Disease Clock Gene Expression Alterations in Parvalbumin Interneurons	
McKnight Institute: University of Alabama at Birmingham	**Lab:** Erik D. Roberson

ABSTRACT

Alzheimer's disease (AD) features subclinical epileptiform activity predominantly during the inactive circadian phase. Parvalbumin (PV) interneurons are the most abundant interneuron type in the hippocampus and cortex, and therefore, could likely contribute to the imbalance in excitation and inhibition. Because epileptiform activity in AD follows a circadian rhythm of expression, we hypothesized that clock gene dysfunction in PV interneurons of the hippocampus and cortex contributes to AD-related hyperexcitability. To begin testing this hypothesis, we asked if there are alterations in the transcription of core clock genes in PV interneurons in the hippocampus and cortex of the hAPPJ20 mouse model of AD. Mice were entrained using controlled lighting and brains were collected after 2 days of constant darkness across 6 circadian timepoints. RNAscope was then used to measure the gene expression of the chosen clock genes within the PV cells in our respective regions of interest. Our results aim to confirm the existence of clock gene alterations within PV cells to elucidate the connection between circadian dysfunction and epileptiform activity in AD. Future studies include the analysis of additional clock genes and regions of interest.

First Author (Last name, first name): Cox, Kenedy	Presenter (if someone other than First Author):
Abstract Title: Live Cell Imaging Single mRNAs Using an MS2-MCP System	
McKnight Institute: Neuroscience	Lab: Dr. Abisambra

ABSTRACT

Studying regulation of gene expression through live imaging of single mRNAs in their native environment may provide valuable insights into the dynamic processes and intricate mechanisms governing gene expression. The MS2-MCP system enables specific tagging of mRNAs with 24 repetitive MS2 stem loops incorporated into the target 3'UTR. These MS2 loops have high affinity for MCP protein and allow visualization of puncta MCP-GFP interacting with the RNA. To achieve this, three plasmids,Suntag MS2V5, MCP-GFP, and MS2V7,were acquired from Addgene. Due to the improved performance for live mammalian cell imaging, the MS2V5 sequence in the Suntag plasmid was replaced with the MS2V7. The Suntag plasmid was digested with enzymatic restriction enzymes for removing the MS2V5 sequence and purified on agarose gel. Two PCRs were required to reconstitute the Suntag plasmid with the new MS2V7 sequence. The cloning was performed through a Gibson assembly and the product of assembly was transformed into E.Coli. Single clones resistant to ampicillin were amplified and plasmids were purified by miniprep. The intergrity of the plasmid was verified by enzymatic digestion. We obtained several successful clones which were sent for DNA sequencing. The plasmids containing the desired sequences were amplified through a midi prep for further transfection experiments. HeLa cells were co-transfected with the modified Suntag-MS2V7 and MCP-GFP plasmids using the lipofectamine 3000 transfection reagent. Wide-field fluorescence microscopy was then utilized to track the dynamic transport and stability of individual mRNA molecules within the transfected HeLa cells. The successful cloning and transfection of the modified plasmids, coupled with the application of wide-field fluorescence microscopy, have the potential to reveal valuable insights into mRNA dynamics and localization within the cellular context.

First Author: Cutts, Elam	Presenter: (If other than first author)
Abstract Title: Quantifying retinal functional health in patients with varying scotoma patterns by accounting for cortical magnification factor	
McKnight Institute: UAB	Lab: Dr. Kristina Visscher

Quantifying retinal functional health in patients with varying scotoma patterns by accounting for cortical magnification factor Currently the leading cause of vision loss in older adults, macular degeneration is an eye disease that leads to death of photoreceptors in localized portions of the retina. This results in variable scotoma patterns from patient to patient. Complex visual tasks such as reading or navigation require both visual input as well as high-level visual processing. Patients differ wildly in their performance on complex visual tasks, even in patients with similar retinal damage. This suggests that high level visual processing differs between participants, but this difference has been challenging to quantify. As a step toward accurate quantification of high level processing, we developed a metric describing functional retinal health. It is not appropriate to define retinal functional health using typical performance measures such as acuity or contrast sensitivity because participants with extensive scotomas just outside the fovea can have excellent scores. On the other hand, methods like Macular Integrity Assessment (MAIA) give a more comprehensive view, as they examine perceptual thresholds at many locations across the retina. However, it has been unclear how to quantify MAIA images in order to compare visual performance between patients, whose patterns of scotoma can vary widely. We sought a measure of retinal functional health which appropriately weights spared central vision more strongly than spared peripheral visual locations. Cortical areas V1, V2, and V3 are retinotopically mapped, meaning that different portions of cortex correspond to different portions of vision. Less cortical area is devoted to portions of the retina responsible for peripheral vision than central vision; this means that central vision has a higher cortical magnification factor than does peripheral vision. By weighting the scores obtained on the MAIA by the cortical magnification factor of that part of vision, we account for the relative ‘importance’ of different portions of the visual field for performing a range of visual tasks. This retinal functional health measure predicts how an individual’s scotoma pattern influences performance on visual tasks. Here we describe validation of the technique, and argue that our measure gives a reliable value of retina functional health that can be used to better understand individual differences in performance for participants with low vision. This framework allows us to estimate the components of a participant’s performance on complex visual tasks that can be explained by retinal functional health. In turn, this allows estimation of the degree to which a participant’s performance relies on high-level visual processing.

First Author (Last name, first name): **Damani, Saher**	Presenter (if someone other than First Author):
Abstract Title: **Adolescent Substance Use and Neural Reactivity to Stress**	
McKnight Institute: **UAB**	Lab: **Dr. David Knight**

ABSTRACT (Arial 11, One page limit)

Adolescence is a maturational period during which recreational substance use often begins and emotional processes undergo important development. Adolescent substance use may have long-term ramifications on the brain function that underlies emotional processes, like stress reactivity. The present study investigated the relationship between adolescent substance use (i.e., alcohol, tobacco, and cannabis) and neural reactivity to acute psychosocial stress in young adulthood. Stress reactivity is mediated by a neural network that consists of the prefrontal cortex (PFC), inferior parietal lobule, hippocampus, and amygdala. We hypothesized that stress-induced activity within these brain regions would vary with substance use. Substance use was assessed, and latent growth curve modeling (LGCM) was used to estimate trajectories of substance use across ages 11, 13, 16, & 19 years in participants (N = 1594) from the Healthy Passages study. A subset of these participants (n = 301; 20 years of age) completed a psychosocial stress task (Montreal Imaging Stress Task) during functional magnetic resonance imaging. Linear mixed-effects models compared stress-evoked brain activity and behavioral stress reactivity to cumulative substance use during adolescence. Tobacco use varied negatively with stress rating and skin conductance response (SCR), and cannabis use varied negatively with SCR. No relationship was observed between alcohol use and behavioral measures. Dorsomedial PFC, hippocampal, and amygdala reactivity to stress varied negatively with cumulative alcohol use. PFC (ventromedial and dorsolateral) and hippocampal activity varied negatively with cumulative tobacco and cannabis use. Separate analyses used multivariate modeling to compare stress-evoked brain activity to each participant's trajectory of use based on the LGCM (early use, change, and acceleration) for each substance. Early alcohol use was associated with stress-related ventromedial PFC activity and change in alcohol use was associated with dorsolateral and ventromedial PFC activity. Early tobacco use was associated with PFC (dorsolateral, ventrolateral, and dorsomedial) and hippocampal activity, while acceleration of tobacco use was associated with dorsolateral PFC activity. Early cannabis use was associated with PFC (dorsolateral, ventrolateral, and dorsomedial) activity and acceleration of cannabis use was associated with dorsolateral and dorsomedial PFC activity. These findings demonstrate that stress-related PFC, hippocampal, and amygdala activity varies with adolescent substance use and may have long-term ramifications upon emotional function.

First Author (Last name, first name): Davis, Natalie	Presenter (if someone other than First Author):
Abstract Title: Loss of Alzheimer's disease risk factor BIN1 from inhibitory neurons induces network hyperexcitability	
McKnight Institute: University of Alabama at Birimingham	Lab: Erik Roberson

ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative disease, affecting more than 6 million Americans. Despite its prevalence, much is still not understood about the disease. To better understand the disease, genome-wide association studies have been conducted to identify genetic risk factors. One risk factor, a single nucleotide polymorphism in the *bridging integrator 1 (BIN1)* gene, is present in approximately 40% of the population and has the largest effect size of the common AD genetic risk factors. While the association between *BIN1* and AD has been established, the function of the protein and its contribution to AD remains understudied. We previously showed that increasing *BIN1* expression in primary hippocampal neurons increases neuronal excitability (Voskobiynyk & Roth et al., 2020). However, primary hippocampal neurons are predominantly composed of excitatory neurons, so the contribution of BIN1 from inhibitory neurons remains unknown. This is particularly important as inhibitory dysfunction contributes to AD, affecting cognitive function and epileptiform activity. Additionally, expression of the primary neuronal isoform of BIN1 is lower in AD patients compared to healthy age-matched controls. We thus hypothesized that a loss of Bin1 from all neurons will lead to increased network hyperexcitability, with differing effects with a loss of Bin1 from excitatory or inhibitory neurons. Using conditional knockout mice, we selectively reduced murine Bin1 from all neurons (*Nestin*-Cre-driven), excitatory neurons (*CaMKIIα*-Cre-driven), or inhibitory neurons (*Viaat*-Cre-driven). We examined network hyperexcitability through a pentetrazol-induced seizure susceptibility assay and found that a pan-neuronal loss of Bin1 increased seizure susceptibility in a gene-dose dependent manner. Bin1 loss from excitatory neurons decreased seizure susceptibility, while Bin1 loss from inhibitory neurons increased seizure susceptibility, suggesting that it is the loss of Bin1 from inhibitory neurons driving the overall effect. We then generated a mouse line to selectively reduce Bin1 in parvalbumin (PV) interneurons to further define cell-type specificity. While PV interneurons contribute to inhibitory dysfunction in AD, we saw no change in seizure susceptibility from controls. This suggests that a different interneuron subpopulation may be responsible for the changes in seen in the total inhibitory knockout of Bin1, or that loss of Bin1 from PV interneurons alone is not sufficient to drive this overall effect. Overall, this study contributes to our understanding of how BIN1 regulates network hyperexcitability at a cell-type specific level.

First Author (Last name, first name): Demirayak, Pinar	Presenter (if someone other than First Author):
Abstract Title: Functional connections of discrete cortical regions defined based on individuals' experiences are plastic and individual-specific	
McKnight Institute: UAB	Lab: Visscher Lab

ABSTRACT

While the functional connectivity patterns in the adult brain have been well investigated, quantitative study of individual-specific plasticity in functional connectivity have been more limited. We examine this in people with late stage Macular Degeneration (MD). These patients lose the sensory receptors for central vision and often use locations in peripheral vision for daily tasks requiring vision. Because of the retinotopic organization of early visual areas, different parts of the cortex experience sensory deprivation and increased usage. Two participants with similar sensory loss may develop individual-specific neural strategies for adaptation to vision loss. Our aim is to examine experience-dependent plasticity in functional connections for the deprived area of cortex (lesion projection zone, LPZ), an area of increased use (the preferred retinal locus (PRL), and a control region (unpreferred retinal locus, URL) corresponding to areas in V1 in individuals with MD. We performed seed-to-voxel analyses (fingerprints) from the cortical correspondence of LPZ, PRL, and URL in 21 MD and 23 control participants. This allowed us to examine how 'typical' the whole-brain functional connection pattern is for each participant, that is, how similar the pattern is to that of a typical healthy vision control. Given that LPZ and PRL experienced different usage in MD participants, we hypothesized that their cortical representations would have less typical fingerprints in MD participants than in controls. Our approach also allowed a within-subject control, as we expect no difference for the URL. Our results indicated that both LPZ and PRL fingerprints are less typical in MD than control. Further, within the MD participants, LPZ and PRL fingerprints are less typical than URL fingerprints, showing within-subject effects. We also assessed LPZ and PRL fingerprint similarities to compare increased vs decreased usage of the retinal regions. In MD patients, the PRL fingerprints were less typical than the LPZ fingerprints, whereas this difference was less pronounced within the control group. These findings support the idea that functional connections from V1 maintain the capacity to adapt in the adult brain and that these adaptations may be idiosyncratic to the individual's experiences.

First Author (Last name, first name): Dieckhaus, Laurel	Presenter (if someone other than First Author):
Abstract Title: Age-related changes in Ex Vivo Female Bonnet Macaque Brains: Insights from Multi-parametric MRI Analysis	
McKnight Institute: University of Arizona	Lab: Dr. Elizabeth Hutchinson

ABSTRACT

To better understand disease progression in neurodegenerative disorders such as Alzheimer's disease, it is important to first characterize changes in brain structure that occur during normal aging and how these changes link to cognitive performance. Non-invasive imaging techniques, such as magnetic resonance imaging (MRI), play a critical role in this characterization. For example, Diffusion Tensor Imaging (DTI) offers a more accurate representation of regional macro-structural size changes and micro-structural changes related to axon integrity and orientation. As such, DTI may be a better method for assessing regional brain size changes compared to non-DTI MRI metrics.
Fractional Anisotropy (FA), a type of DTI map, measures brain white matter axonal orientation, which may indicate neural restructuring. Trace is tissue-specific and can measure cell loss in grey matter while myelination levels in white matter. Additionally, R2* maps, a non-DTI derived metric, can indicate the presence of iron, which is elevated in certain brain regions in Alzheimer's disease. We conducted high-resolution versions of these MRI scans on post-mortem female bonnet macaque whole brains ranging from 10 to 25 years in age. We found no differences in whole brain ($p=0.076$) and normalized hippocampal ($p=0.15$) volumes based on a classification of adult (n=6, age range=9.83-11.16 years) or aged (n=5, age range=20.66-25 years). As opposed to traditional MRI metrics, DTI-derived average subtraction maps of brain size showed a reduction in cortical volume in the aged population, but no change hippocampal volume. This indicates that atrophy is not uniform across the brain. Beyond volumetric changes, trace increased in the neocortical regions other than the hippocampus, indicating a potential increase in cell loss compared to the rest of the brain. Fractional Anisotropy showed localized clusters of decreases in white matter in the aged population, indicating age-associated white matter loss. Finally, we correlated MRI metrics with cognitive performance, but no correlations were observed across any individual metric, despite this cohort of animals exhibiting age-associated changes in behavior.

Because single MRI metrics did not accurately capture the behavioral observations, we hypothesized that multi-parameter approach would better identify age-related changes in brain structure. To do this, we trained a support vector machine to classify each voxel as adult or aged, using all DTI metrics. By mapping the accuracy across the whole brain, we can then identify brain regions that best delineate between the adult and aged classification, potentially better predicting behavior-associated outcomes. Once it is established that multi-variate classification better predicts age, we will assess the contribution of each metric to the model by leaving out a single MRI map type for each run of the support vector machine.

Our study demonstrates the power of advanced MRI techniques, particularly DTI, in elucidating age-related brain structural changes. While conventional measures may not reveal significant differences in brain volume within our cohort, distinct patterns observed in our DTI-derived maps emphasize the complexity of the aging process in the brain alongside cortical atrophy observations. By considering a multi-parametric approach, which incorporates various MRI metrics, we will enhance our ability to understand and predict age-related changes in brain structure.

First Author: Faraji, Mojdeh	**Presenter:** Faraji, Mojdeh
Abstract Title: Optogenetic inactivation reveals temporally-distinct contributions of ventral hippocampus to risky decision making in rats	
McKnight Institute: University of Florida	**Lab:** Bizon-Setlow

Optogenetic inactivation reveals temporally-distinct contributions of ventral hippocampus to risky decision making in rats

Mojdeh Faraji[2,3], Omar A. Viera[1], Lily Cao[1], Barry Setlow[2,3], Jennifer L. Bizon[1,3]

Departments of [1]Neuroscience, [2]Psychiatry, and [3]McKnight Brain Institute, University of Florida, Gainesville Florida

The hippocampus has been extremely well studied in contexts related to memory and learning. In contrast, the contributions of this structure to cost-benefit decision making are less well understood. While the dorsal hippocampus is known to be more involved in cognitive processes, the ventral hippocampus (vHPC) is more closely tied to affect and motivated behavior. In this work, we employed an optogenetic approach to dissect the contributions of vHPC to temporally distinct phases of a task that assesses decision making under risk of punishment, and that engages multiple elements of emotional and motivated behavior. Young adult (6 mo.) male and female Fischer 344 x Brown Norway F1 hybrid rats were surgically implanted with guide cannulae targeting the vHPC (AP: -5, ML: ±5, DV: -6), through which pAAV-CaMKIIa-eNpHR3.0-mCherry (halorhodopsin) was injected and optic fibers were implanted. After recovery, rats were trained in standard operant chambers on a risky decision-making task, in which they made discrete choices between a small, “safe” food reward and a large “risky” food reward that was accompanied by varying probabilities of footshock punishment. Upon reaching stable task performance, a within-subjects design was used to evaluate the effects of optogenetic vHPC inactivation during discrete phases of the task. The results show that vHPC inactivation during receipt of the large reward on trials when it was punished caused rats to reduce their preference for the large, risky reward, whereas vHPC inactivation during receipt of the large reward on trials when it was unpunished did not affect choice behavior. These findings suggest that vHPC is critical for using information about the punishment to evaluate the subjective value of the large reward, such that deficits in integrating that information into the decision structure leads to overestimation of the risk associated with the large reward, and ultimately attenuated choice of this option (i.e., risk aversion). In addition, inactivation during the intertrial interval caused a similar decrease in choice of the large, risky reward, suggesting a role for vHPC in maintaining/consolidating memory for previous choices and outcomes that is necessary for assessment of the subjective value of the risky choice in future trials. Future work is needed to elucidate the circuitry through which vHPC is involved in mediating risky decision-making.

First Author (Last name, first name): Farmer, Anna	Presenter (if someone other than First Author):
Abstract Title: Functional connectivity alterations associated with restricted repetitive behavior and its attenuation by environmental enrichment	
McKnight Institute: L2-100C	Lab: Mark H. Lewis (former)/ Brandon Zielinski (current)

ABSTRACT

Restricted repetitive behaviors (RRB) encompass a variety of inflexible motor and cognitive behaviors diagnostic for autism spectrum disorder and common in neurodevelopmental disorders. As yet, no effective biomedical treatments exist for RRB, and treatment development has been limited by poor understanding of RRB neurocircuitry. Studies using animal models, however, show environmental enrichment (EE) reduces RRB, although few investigations have addressed the underlying mechanisms of this attenuation. Identifying underlying mechanisms of EE effects could yield potential intervention targets.

We used functional magnetic resonance imaging (fMRI) to identify functional connectivity differences associated with RRB and its attenuation by EE in male and female C58 mice, an animal model of RRB, and C57BL/6 controls lacking RRB. Mice were randomly assigned to standard or EE housing at weaning. At 6 weeks postweaning, we assessed repetitive motor behavior and acquired anatomical and resting state fMRI scans using a Magnex Scientific 11.1 T scanner. These same methods were also performed in a younger cohort of male and female C58 mice at 3 weeks postweaning to examine EE effects during RRB development. fMRI data were preprocessed using software tools in Analysis of Functional NeuroImages (AFNI), FMRIB Software Library (FSL) and Advanced Normalization Tools (ANTs), which entailed skull-stripping, susceptibility correction, despiking, motion and linear drift removal, highpass filter of 0.0009 Hz, independent component analysis (ICA) noise reduction, a low-pass filter >0.12Hz, spatial smoothing (0.4mm FWHM), correction for field inhomogeneities, and registration to the Allen mouse brain atlas. Separate ICAs were conducted for each age cohort in FSL MELODIC to identify 20 independent components representing resting state networks (RSN). Analyses were conducted in FSL dual regression using 5000 permutations and threshold-free cluster enhancement. Mouse strain and housing differences were examined with t-tests, and RRB scores were correlated with connectivity in each RSN.

Mouse strain differences were found in 10 of the 20 RSNs suggesting widespread functional connectivity differences between C58 and C57BL/6mice. RRB was associated with functional connectivity alterations in multiple sensory pathways. In the older cohort, RRB was positively correlated with connectivity between the right somatosensory network and right thalamic nuclei involved in pain and somatosensory perception. RRB in the older cohort was also positively correlated with connectivity between a caudal striatum network with the right medial and posterior amygdalar nuclei suggesting alterations in chemosensory processing and threat perception. RRB in the younger cohort was associated with reduced connectivity between the right visual network and right ventrolateral striatum. EE significantly reduced RRB in female C58 mice and altered somatosensory and visual networks. In the older cohort, EE increased connectivity between the left somatosensory network and the right hippocampus and anterior pretectal nucleus, a region important in antinociception. In the younger cohort, EE reduced connectivity between the left visual network and right area prostriata, an area involved in reflexive responses to visual threats. Our results suggest RRB in C58 mice is associated with aberrant sensory, pain, and threat processing. EE may reduce RRB by altering connectivity in pain and visual pathways.

First Author (Last name, first name):
Fitzgerald, N. Dalton Presenter (if someone other than First Author):
Abstract Title:
Neuronal activation by cocaine varies across molecularly-defined subpopulations of VTA dopamine neurons
McKnight Institute: UAB Lab: Day Lab

ABSTRACT

Co-Authors: Lydia Slocum, Emma Andraka, Robert A. Phillips III, Jennifer J. Tuscher, Jeremy J. Day

Substance use disorder is a complex neurobiological disease characterized by a loss of control over drug-taking and drug-seeking behaviors. Drugs of abuse increase dopamine (DA) transmission from ventral tegmental area (VTA) dopamine neurons that densely innervate the nucleus accumbens (NAc). While the presence of tyrosine hydroxylase (Th) has long been used to identify DA neurons in this pathway, more recent studies have revealed remarkable heterogeneity among VTA DA neurons, with some neurons co-expressing markers for both dopamine and glutamate transmission. Using single nucleus RNA sequencing to comprehensively profile the VTA, we identified unique markers for these two subpopulations of DA neurons. Slc26a7, a gene that encodes an anion transporter, serves as a selective marker for combinatorial neurons that harbor expression of genes implicated in both glutamate and DA neurotransmission. Likewise, the GTP cyclohydrolase Gch1 was identified as a marker for DA-only neurons. Here, we used multiplexed fluorescence in situ hybridization to examine whether distinct DA neuron subpopulations respond differently to drugs of abuse. We identified unique induction of the neuronal activity marker Fos in Slc26a7+ cells in the VTA 1 hour following cocaine experience. The same response was not observed in Gch1+ cells, suggesting a difference in response to cocaine between these DA neuron populations. Notably, fentanyl administration (or co-administration of fentanyl and cocaine) elevated Fos mRNA in both DA subpopulations. These results suggest that two subpopulations of DAergic cells in the VTA respond to cocaine in unique ways and may in turn drive distinct downstream effects and behavioral responses to cocaine.

First Author (Last name, first name): Fox, Stephanie	Presenter (if someone other than First Author):
Abstract Title: AAV-progranulin gene therapy increases interstitial progranulin and reduces neurodegeneration biomarker in a mouse model of Frontotemporal Dementia	
McKnight Institute: UAB	Lab: Erik Roberson

ABSTRACT

Frontotemporal dementia (FTD) is a common form of early-onset dementia and is characterized by neuronal dysfunction in the frontal and temporal lobes leading to progressive language and behavioral impairment. Mutations in the progranulin gene (*GRN)*, a lysosomal glycoprotein, can cause FTD. Of the 70 pathogenic mutations in *GRN* identified, the majority are loss-of-function, making AAV-progranulin gene therapy to boost protein levels an attractive approach for FTD. Previous work from my lab has demonstrated the effectiveness of neurotrophic AAV-mouse progranulin (AAV-m*Grn*) gene therapy in progranulin deficient mice. Neurotrophic AAV-m*Grn* therapy can reverse lysosomal deficits, lipofuscinosis, and microgliosis observed in mice with complete loss of progranulin (*Grn*$^{-/-}$). When *Grn*$^{-/-}$ mice were injected with AAV-m*Grn* we found a boost in parenchymal levels of AAV-derived progranulin with immunohistochemistry. To further explore this, microdialysis was used as a tool to measure the levels of progranulin protein in the interstitial space (ISF) in the prefrontal cortex. To do this, mice were injected with either AAV-m*Grn* or AAV-*Gfp* as a control and ISF was collected using the zero-flow microdialysis technique. We found an increase in the total amount of progranulin protein in the ISF in mice injected with AAV-m*Grn.* Young and aged *Grn*$^{-/-}$ mice have an increase in biomarkers associated with neurodegeneration in both the plasma and cerebrospinal fluid compared to littermate controls. To understand the connection between the increase in interstitial progranulin and neurodegeneration, biomarkers were measured in plasma from aged *Grn*$^{-/-}$ mice injected with AAV-m*Grn*. A reduction in neurodegeneration biomarkers was found, suggesting an increase in ISF progranulin is protective against neurodegeneration associated with aged *Grn*$^{-/-}$ mice. These data demonstrate the importance of boosting progranulin as a potential therapeutic for FTD.

First Author (Last name, first name): Gazarov, Emely	Presenter (if someone other than First Author):
Abstract Title: Effects of chronic cannabis smoke exposure on inflammatory markers and tau pathology in mice	
McKnight Institute: University of Florida	Lab: Dr. Barry Setlow/Dr. Jennifer Bizon

ABSTRACT

With the rise in cannabis use among older adults, as well as increasing cases of Alzheimer's disease (AD), there is a need to understand how cannabis impacts the aging brain and AD pathology. Aging is associated with an increase in chronic low-grade inflammation, which plays a role in the pathogenesis of Alzheimer's disease. Cannabinoids can reduce inflammatory markers, protect against oxidative stress, and reduce plaque burden in mouse models of AD-like pathology; however, studies of cannabinoids on aging and AD-like pathology have primarily used methods of cannabinoid administration that do not effectively model human use, and have focused on models of amyloidosis rather than tauopathy. To address these points, we are evaluating the effects of chronic cannabis smoke exposure on inflammatory markers in young adult and aged mice, and tau pathology in rTg4510 mutant tau transgenic mice.

To determine the effects of cannabis smoke on peripheral and brain markers of inflammation, we exposed young adult (4 months old) and aged (22 months old) C57BL/6J mice (n = 40, half female) to smoke from burning either cannabis (5.9% THC) or placebo (0% THC) cigarettes daily for 30 days. Serum and brain lysate were analyzed for 40 cytokines using Quantibody cytokine arrays (RayBiotech, Peachtree Corners, Georgia). Additionally, rTg4510 tau-overexpressing transgenic mice (n = 23, 4 months old) were exposed to cannabis or placebo smoke daily for 6 weeks. Immunohistochemical analyses for pathological tau using MC1, antibodies to a number of tau phosphoepitopes, as well as Iba1 and GFAP to measure gliosis will be conducted. Soluble and sarkosyl-insoluble tau levels and phosphorylation state will also be assessed.

Results from the inflammation study revealed that aged mice had significantly higher IL-12p40 levels and significantly lower levels of galectin-3 in serum compared to young-adult mice. Additionally, aged female mice exposed to cannabis smoke had significantly higher levels of RANTES in serum compared to young adult female mice and aged female mice exposed to placebo smoke, which was not evident in aged male mice and suggests sex-specific effects of cannabis on aging in this model. Analyses of brain inflammatory markers and effects of cannabis on rTg4510 tau pathology are ongoing.

First Author: Gonzalez, Katherine	**Presenter (if someone other than First Author):**
Abstract Title: Sex differences in the effects of age on prefrontal cortex-mediated cognition in Fischer 344 x Brown Norway F1 hybrid rats	
McKnight Institute: University of Florida	**Lab:** Jennifer L. Bizon and Barry Setlow

ABSTRACT

Prefrontal cortex (PFC)-mediated executive functions have been shown to change with age and have successfully been modeled in rats; however, the majority of this work has been conducted exclusively in males. With the recent availability of aged females, we began initial evaluations of young adult (6 mo.) and aged (22 mo.) Fischer 344 x Brown Norway F1 hybrid rats of both sexes in intertemporal choice, working memory, probabilistic reversal learning, and progressive ratio tasks, on all of which young adult and aged males have been shown previously to differ. In the intertemporal choice task, rats selected between a small, immediately available food reward and a large, delayed food reward delivered after a variable delay period (0-60s). Males (but not females) exhibited an age difference, with aged males preferring the large, delayed reward to a greater extent than young males. In the working memory task, rats had to recall the location of a lever following a variable delay period (0-24s). Once again, males demonstrated an age difference, with aged males performing less accurately than young males (especially at long delays) but no age difference in females. In the probabilistic reversal learning task that assessed cognitive flexibility, rats had to learn to discriminate between two levers that were reinforced at different probabilities, which were then switched multiple times per test session. Females of both ages performed more reversals than males, but there were no age differences. In the progressive ratio task that assessed food motivation, the number of lever presses required to earn a food reward increased with each successive reward earned. Aged males earned fewer food pellets than young males and females of both ages. Collectively, these data suggest that aging has both qualitatively and quantitatively different effects on executive functions in males and females, with aged females exhibiting few if any differences from their young counterparts. We are currently testing a cohort of aged ovariectomized and sham females on the same tasks, to evaluate the effects of estropause on executive functions in female aging.

First Author (Last name, first name): Graziano,Bianca	Presenter (if someone other than First Author):
Abstract Title: Investigating the role of glial KCNQ K+ channels in neuronal function in C. elegans	
McKnight Institute: Miami	Lab: Laura Bianchi

ABSTRACT

Abstract: KCNQ channels are voltage-gated K+ channels that are expressed in the nervous system where their function is to reduce cellular excitability. Genetic mutations in KCNQ channels are associated with epilepsy and autism spectrum disorder (ASD) in children. KCNQ channels are expressed both in neurons and in glia, but their role in glia is still unknown. We used the model organism C. elegans to elucidate the function of KCNQ channels in glia and their influence on neuronal function. First, we tested neuronal function by performing octanol avoidance assays, which test the sensitivity of the nematode to the repulsive odor octanol. We found that both global knockout of the KCNQ nematode homolog kqt-2 and its glial specific knockdown delayed the response to octanol [KO: t= 4.3 +/- 0.23; n=142; RNAi: t= 4.4 +/- 0.55; n=40] as compared to the wild type [t=1.8 +/- 1.05; n=144] [Anova; p<0.0001]. Expression of kqt-2 in glia rescued the defective avoidance response [t=1.5 +/- 0.12;n=42] [Anova; p<0.0001]. Taken together, these data support a role for glial KCNQ channels in regulating neuronal function. Rescue of kqt-2 knockout phenotype was also achieved by expression of the human KCNQ2 and KCNQ3 channels in glia [KCNQ2: t= 2.09 +/- 0.19; n=100; KCNQ3: t= 2.1 +/- 0.12; n=175]. This result supports the homology of function of KCNQ channels across species. To investigate the role of kqt-2 in glial and neuronal activity, we performed Ca2+ imaging experiments in vivo using the genetically encoded calcium sensor GCaMP6s. We found that kqt-2 knockout decreases Ca2+ transients in glia in response to octanol [mean=31.2 +/- 7.65; n=11], while it increases Ca2+ transients in the neurons [mean=251.1 =/- 29.83; n=10] as compared to the wild type [glia: mean=181.6 +/- 36.12, n=13; neurons: mean=97.3 +/- 11.78, n=10]. Both glial and neuronal Ca2+ changes were rescued by expression of the nematode and human KCNQ channels in glia. The increase in neuronal Ca2+ transients in kqt-2 knockout is a sign of neuronal hyperexcitability, suggesting reduction of inhibition or increase in excitation in this mutant. Thus, we tested whether glial KCNQs might be involved in glial GABA release. To do this, we performed imaging and behavioral assays in which we enhanced GABA signaling in kqt-2 knockout, or reduced GABA signaling in wild type using genetic, optogenetic, and pharmacological approaches. Results that we will present support the novel idea that glial KCNQs regulate GABA release from glia thereby reducing neuronal activity. To conclude, our data point to the contribution of glial KCNQs to the expression of epilepsy and ASD phenotypes via reduction of GABA release from glia.

First Author (Last name, first name): **Grey, Devon**	Presenter (if someone other than First Author):
Abstract Title: **Neural reactivity to stress varies with trajectories of adolescent discrimination exposure**	
McKnight Institute: **UAB**	Lab: **Dr. David Knight**

ABSTRACT

Discrimination is a long-term stressor linked to the disruption of stress reactivity processes associated with emotional distress (e.g., depression, anxiety, posttraumatic stress). Discrimination exposure may be particularly detrimental during adolescence, an important period of both neural and emotional development. Specifically, emotional processes (e.g., stress reactivity) are mediated by a neural network that includes the prefrontal cortex (PFC), inferior parietal lobule (IPL), hippocampus, and amygdala. Adolescent exposure to discrimination is associated with emotional distress. Further, dorsolateral PFC, IPL, and hippocampal reactivity to stress varies with discrimination exposure. However, it remains unclear whether distinct trajectories of adolescent discrimination exposure have a differential impact on stress-related brain function. Thus, this project investigated the relationship between trajectories of adolescent discrimination exposure and stress-elicited brain activity. Latent growth curve modeling (LGCM) estimated trajectories of adolescent discrimination exposure at ages ~11, 13, 16, and 19 years in participants (N = 1594) from the Birmingham cohort of the Healthy Passages study. A subset of these participants (n = 301) then completed the Montreal Imaging Stress Task during functional magnetic resonance imaging to assess neural reactivity to stress in young adulthood (Age 20 years). LGCMs estimated trajectories representing early exposure to discrimination, progression of adolescent discrimination exposure, and acceleration of adolescent discrimination exposure. Multivariate modeling then compared stress-elicited brain activity to the trajectories of discrimination exposure. Early discrimination exposure was positively associated with dorsolateral PFC and IPL activity and negatively associated with dorsomedial PFC, ventromedial PFC, and hippocampal activity. Further, the progression of discrimination exposure was positively associated with dorsolateral PFC and dorsomedial PFC activity, while the acceleration of discrimination exposure was positively associated with hippocampal activity. The present results suggest that the trajectory of adolescent discrimination exposure (early exposure, progression, and acceleration) might alter the neural response to future stressors within brain regions that support emotional function. These findings might have important implications for understanding the interrelationships among discrimination exposure, adolescent neural and emotional development, and mental health outcomes.

First Author (Last name, first name): Gryshyna, Anastasiia	Presenter (if someone other than First Author):
Abstract Title: The role of Heme and Hemopexin in Urologic Chronic Pelvic Pain Syndrome in Mice.	
McKnight Institute: Behavioral Neuroscience	Lab: Dr. Jennifer DeBerry

ABSTRACT

Introduction: Urologic chronic pelvic pain syndrome (UCPPS) is a chronic pain condition characterized by pelvic hypersensitivity, often presenting with increased urinary frequency and urgency. Currently, the etiology of UCPPS is unclear and likely multifaceted which makes it difficult to develop effective therapeutics. Epidemiological data suggest stress is an important factor in pain associated with UCPPS in a sex-dependent fashion. Metabolism of heme, an organic porphyrin molecule, has been linked with both stress and regulation of nociceptive processes. However, a role for heme in pain associated with UCPPS has not been explored. Hemopexin (HPX) is a heme scavenging protein that transports free heme to the liver for degradation. The aim of the current study was to explore the relationship between stress, heme scavenging, and pelvic/visceral nociception in HPX-deficient mice.

Methods: Adult male and female HPX knockout (KO) mice and wild type (WT) littermate controls were included in all experiments. Sensory testing was performed to assess hindpaw, pelvic floor, and urinary bladder sensitivity at baseline and following exposure to acute water avoidance stress (WAS). A simplified up-down method with von Frey monofilaments was used to assess mechanical sensitivity of the pelvic region and hindpaw. The void spot assay VSA) was used to quantify spontaneous urine voiding. In female mice, visceromotor responses (VMRs) to bladder distension were subsequently quantified to assess bladder nociception. All of the experiments were approved by the Institutional Animal Care and Use Committee (IACUC) at University of Alabama at Birmingham.

Results: The results demonstrate that, overall, HPX KO mice had significantly greater mechanical sensitivity in the pelvic region ($p<.001$) but not in the hindpaw. A significant sex difference in number of voids and total area of voids during VSA was observed ($p<.001$). Following WAS exposure, female HPX KO mice had significantly greater VMRs compared to WT ($p<0.05$, one-tailed).

Conclusions: These findings indicate that although hemolysis may be a systemic phenomenon, some tissues or organs, like bladder, are more susceptible to hemolytic effects.

First Author (Last name, first name): Guswiler, Olivia	Presenter (if someone other than First Author):
Abstract Title: Possible strain differences of the Fischer 344 rat in a temporal order object recognition task	
McKnight Institute: University of Arizona	Lab: Carol Barnes

ABSTRACT

Object recognition tasks are commonly used to assess learning and memory processes in rodents. Such tasks are extremely useful as they can be used to investigate the function of targeted brain regions without the need for extensive training protocols. The temporal order memory (TOR) task is a simple and efficient test used to assess recognition memory, specifically, the ability to recall when an object or event was committed to memory (Ennaceur & Delacour, Behav. Brain. Res., 1988, 31:47). In this task, animals are allowed to freely explore two different pairs of identical objects across two sample phases, and then, during a test phase one copy of each familiar object is simultaneously presented. Greater exploration of the temporally more remote familiar object over the temporally more recent familiar object has been observed in several rodent species/strains, and it has been shown that lesions to the medial prefrontal cortex significantly disrupt performance on this task in young rats (Mitchell & Laiacona, Behav. Brain Res., 1998, 97:107; Belblidia et al., Behav. Brain Res., 2023, 437:114151; Barker et al., J. Neurosci., 2007, 27:2948; Barker & Warburton, J. Neurosci., 2011, 31:10721). In humans, prefrontal cortex-dependent memory exhibits some of the most dramatic and early changes relative to other brain functions with normative aging (Park et al., Psychology and Aging, 2002, 17:299). Although the TOR task has been utilized in a number of studies of early development, there has been little research on the impact on performance in animals of older ages. The purpose of this study was to investigate whether this task could be used to detect age-related performance changes in a rodent model of healthy aging. We tested male Fischer 344 (F344) rats of three separate age groups, young (4-6mo), adult (8-9mo), and old (23-27mo), using both published protocols, and modified protocols to increase exploratory behaviors. In spite of improvement of overall engagement and exploration with the modified procedures, we were unable to replicate results consistent with what has been reported by others employing the TOR task. A number of reasons for this might be offered, such as strain differences (Ennaceur et al., Behav. Brain Res., 2005, 159:247; van Goethem et al., Behav. Brain Res., 2012, 232:323), and the ages of the animals tested, as ours were clearly mature or old, and most other studies utilized animals of younger or much younger ages. We report this here to contribute to a growing literature concerning rodent strain related differences in behavioral performance.

First Author (Last name, first name): Hernandez, Abbi	Presenter (if someone other than First Author):
Abstract Title: **Exploring metabolism as an intermediary in the gut-brain-axis using the TgF334 rat model of Alzheimer's disease**	
McKnight Institute: UAB	Lab: Hernandez lab (my lab)

ABSTRACT

While nearly 6 million Americans are currently living with the debilitating effects of Alzheimer's disease (AD), the lack of treatment options and impoverished understanding of the underlying causes of cognitive decline, metabolic impairment, impaired gut function and other symptoms leads to severe impairments in quality of life. In addition to cognitive impairment, AD is associated with neuropathology, impaired metabolic function and gut microbiome dysbiosis. However, the relationships between gut health (including the gut microbiome), metabolism and cognitive decline remains largely unknown, despite strong evidence that the gut-brain-axis is an important intermediary in neurodegenerative disease. Moreover, normal aging also influences both gut microbiome composition and peripheral metabolic health, demonstrating the importance of including geroscience as a factor. Gut dysbiosis can result in impaired insulin resistance as well as obesity, both of which increase the risk of developing AD. Therefore, this work aims to elucidate how altered gut microbiome composition can influence cognitive outcomes in an aged rat model of AD to identify potential targets for therapeutic intervention. In particular, this work investigates whether the gut is able to exert its influence over cognition through metabolic intermediates, as the gut microbiome directly influences metabolite production and energy homeostasis. Our data indicate that aged female TgF344-AD rats have impaired cognitive performance, glucose metabolism, short chain fatty acid excretion and lifespan. Moreover, significant differences in gut microbiome composition across genotypes are regionally dependent along the length of the intestinal tract and fecal samples. Several differential analysis methods revealed distinct amplicon sequence variants (ASVs) within each intestinal region at multiple taxonomic levels. PICRUSt2 (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States) was utilized to predict functional abundances based these sequences, which revealed several Enzyme Classifications that significantly differed based on genotype, helping to discern the functional relevance of changes in gut microbiome populations. Collectively, these data further strengthen the gut-brain-axis's role in AD and can be utilized to generate potential therapeutics targeting the gut for the amelioration of age and AD related cognitive and neurobiological impairments.

First Author (Last name, first name): Presenter (if someone other than First Author): Langman, Julia
Abstract Title: **Conditional Knockout of Gnal in Cerebellum Produces Dystonia-Like Motor Symptoms**
McKnight Institute: University of Florida Lab: Mark Moehle

ABSTRACT

Conditional Knockout of Gnal in Cerebellum Produces Dystonia-Like Motor Symptoms

Julia Langman[1, 3], Nicole Chambers[1], Dominic Hall[1], Tiffany Curry[1], Morgan Kaplan[1], Lauren Sanchez[1], James Clikas[1], Michael Millett[2], Mark Moehle[2]

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[3] UF McKnight Brain Institute and Dept of Neuroscience Summer Neuroscience Internship Program

GNAL-linked dystonia is an adult onset disorder which is characterized by abnormal muscle clenching and twisting of the limbs. GNAL is a gene which encodes the alpha subunit of the heterotrimeric G protein, Galpha olf . Within the brain, GNAL is expressed abundantly in the cerebellum, but cerebellum-specific contributions to this form of dystonia are unknown. Therefore, in the current study we stereotaxically injected the cerebellum of Gnal floxed/floxed mice with adeno-associated viruses to express Cre recombinase or fluorophore control to remove expression of Gnal in adult mice. Using this viral mediated adult knockout model, we investigated how loss of Gnal in the cerebellum leads to dystonia symptoms and circuit dysfunction using electrophysiological and behavioral techniques. Cerebellar Gnal conditional knockout animals showed slowed fine motor movements in the Erasmus ladder and pole test, difficulty balancing on the ledge test, and dystonia like movements. To further narrow down the contribution of specific cerebellar neurons to these symptoms, we crossed an L7 cre mouse line to our Gnal floxed mice, thus producing embryonic conditional knockout of Gnal which is selective for Purkinje neurons. Overall, we found that these mice had behavioral deficits which were comparable to those of adult cerebellar knockout mice. This suggests that Purkinje neurons contribute to GNAL-linked dystonia symptoms. Finally, we found alterations in Purkinje neuron firing patterns via ex vivo electrophysiology. Overall, the results of this study show that the cerebellum may be involved in the pathology of GNAL-linked dystonia.

This work was funded and supported by the UF Mcknight Brain Institute and Department of Summer Neuroscience Internship Program and the following grants: NIH R25AG076396 and NIH/NINDS R00NS110878

First Author: Leem, Seowung	Presenter: Leem, Seowung
Abstract Title: Deep neural network for differential aversive & appetitive conditioning	
McKnight Institute:	Lab: SMILE Lab (P.I: Dr.Ruogu Fang)

Introduction:

A computational model for the brain has helped neuroscientists to better understand in a variety of directions. Especially, the convolutional neural network (CNN) is now known as one of the excellent models of the ventral visual stream of the human brain. However, in cognitive neuroscience, despite the conventional computational model's lack of biological background, dependency on specific parameter choices, and poor performance, the capabilities of neural networks as successful goal-driven models are not well supported. In this study, we aim to utilize the modeling power and flexibility of convolutional neural networks to explain the very first neural network model for affective processing mechanisms via conditioning. We first developed a computational model decoding hedonic valence from the natural scenes. Then, we performed associative learning to evaluate the level of explainability of our model at behavioral and representational levels.

Materials & Methods:

Our convolutional neural network is built based on a VGG-16, well-established CNN model for object recognition. Then we augmented the model with additional modules inspired by the affective processing of the brain. (1) The shortcut pathway was inspired by the connection between the human ventral visual stream and the amygdala, built for the processing of sensory information related to threats for fast fear response. (2) The concatenation layer and (3) fully connected layers after concatenation were added to play the role of the amygdala and other subcortical regions which efficiently map the computed features from the sensory area to evoke the affective response. The model was first trained with a videoframe dataset from Cowen and Keltner’s study. Then it was fine-tuned on the International Affective Picture System (IAPS). The fine-tuned model was used throughout the associative learning process. Associative learning was performed by associating conditional stimulus (CS+) with unconditional stimulus (US). We used 2 orientations orthogonal to each other in the form of a Gabor patch for CS+ and we used aversive and appetitive images from the IAPS dataset for US. We introduced the CS+ and US to the model by placing them in the same input in the different quadrants. Then, we only presented CS+ and other orientations for evaluation.

Results:

Our model was successful in 3 tasks. First, the model successively associated the valence from natural scenes to the CS+ which was neutral before association. Second, the associated valence was generalized to the orientations that were not seen during the training process. Lastly, the association occurred in deeper layers of the model, indicating that associative learning is a high-order cognitive process.

Conclusion:

Our results show that brain-inspired artificial neural networks can be successful in modeling output behavior and mechanisms of high-order cognitive tasks. In future studies, we aim to validate the hypothesis of the role of sensory cortices in affective processing with the model and use the results to design a new experimental paradigm for empirical studies to come up with a new hypothesis.

First Author (Last name, first name): Li, Chang	Presenter (if someone other than First Author):
Abstract Title: Cerebellar Astrocytes Encode and Regulate Reward-Associated Behavior	
McKnight Institute: University of Alabama at Birmingham	Lab: Dr. Wei Li & Dr. Lucas Pozzo-Miller

ABSTRACT

The cerebellum, a brain structure renowned for its involvement in motor coordination and balance, has recently emerged as a key player in cognitive and emotional processing. Astrocytes, a type of glial cell, have been shown to actively contribute to higher-order brain functions by regulating the extracellular environment, providing metabolic support to neurons, and modulating synaptic transmission. Despite these advancements, the implications of cerebellar astrocytes in cognitive processes remain unknown. In this study, we employed fiber photometry to capture astrocytic population activities in mice expressing the glial Ca2+ sensor GCaMP6f during a reward task. The task involved a 30-minute period during which mice had to enter the trigger zone to initiate a trial, followed by the reward zone to trigger water ejection and receive a sucrose water reward. Our preliminary data revealed that Ca2+ dynamics in cerebellar cortex astrocytes were correlated with reward and exhibited three distinct patterns in different astrocytic domains, referred to as type I, type II, and type III astrocytes. Type I astrocytes displayed rapid activation of Ca2+ signals when trained mice left the trigger zone or entered the reward zone. In contrast, type II astrocytes exhibited a gradual and robust rise in Ca2+ as the animals approached the reward. This Ca2+ enhancement was followed by a marked decrease when the animals licked water. Type III astrocytes showed rapid Ca2+ signals when trained mice entered the trigger zone with a cued tone and slowly increased signals when the mice licked water. To modulate astrocyte activities, we selectively activated the Gi or Gq pathways of astrocytes in specific regions using chemogenetic tools, targeting the entire cerebellar cortex. Activation of both Gq and Gi pathways resulted in decreased Ca2+ transients, leading to observable changes in reward behaviors, including fewer activated trials during the 30-minute period and reduced licking time. Overall, our study provides compelling evidence that cerebellar astrocytes actively encode and regulate reward behaviors, shedding light on their crucial role in the reward circuitry.

First Author (Last name, first name): Liu, Peiwei	Presenter (if someone other than First Author):
Abstract Title: Effects of acute and chronic administration of intranasal oxytocin on large-scale brain networks in older adults	
McKnight Institute: Department of Psychology	Lab: Natalie Ebner

ABSTRACT

Title: Effects of acute and chronic administration of intranasal oxytocin on large-scale brain networks in older adults

Authors: Peiwei Liu[1], Tian Lin[1], Rebecca J. Polk[1], Hakan Fischer[2], David Feifel[3], & Natalie C. Ebner[1,4,5,6]

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Abstract:
Intranasal oxytocin (IN-OT) is a key modulator of social-cognitive capacities such as emotion identification (*Horta et al., 2019)*, social memory (*Tse et al., 2018),* animacy perception (*Valdes-Hernandez et al, 2021).* IN-OT has also been shown to modulate resting-state functional connectivity (rs-FC) between key nodes of the salience network (e.g., insula and amygdala; *Ebner et al., 2016; Brodmann et al., 2017*), known to gate attention (*Uddin, L. Q., 2016).* However, not well understood yet are IN-OT's effects on large-scale brain networks: (i) among older adults, despite robust evidence of age-related differences in brain network function and increasing evidence of age-differential effect of IN-OT on both brain and socioemotional behavior (*Ebner et al., 2013; Horta et al., 2020);* (ii) for chronic (i.e., repeated) in addition to acute (i.e., single-dose) administration regimens, to determine OT's therapeutic potential (*Horta et al., 2020)*. Given that, the research aim in the present study is to determine the extent to which IN-OT (relative to placebo) modulates rs-FC between the salience network and its key nodes in the aging brain both after acute (*Study 1*) and chronic (*Study 2*) IN-OT. The results were shown that (i) acute IN-OT decreased rs-FC of right insula with the salience network in both young and older adults; (ii) chronic IN-OT decreased rs-FC of right insula with the salience network in older adults; (iii) OT reduced rs-FC of the right insula with the salience network was more pronounced after chronic than acute IN-OT.

First Author: Lovett, Sarah	Presenter: Lovett, Sarah
Abstract Title: Comparative analysis of rodent hippocampal LFP and cortical EEG: Implications for translational cognitive aging research	
McKnight Institute: University of Florida	Lab: Brain Organization and Aging Lab Dr. Sara Burke and Dr. Andrew Maurer

Comparative analysis of rodent hippocampal LFP and cortical EEG: Implications for translational cognitive aging research

Sarah D. Lovett*, Nicholas M. DiCola, Mark S. Lovett, Jack P. Kennedy, Armen Brotgandel, Kimberly L. Robertson, Sara N. Burke, Andrew P. Maurer

Neurophysiological approaches for understanding brain-behavior relationships in rodents commonly use invasive intracranial electrodes to measure the local field potentials (LFP). Human neurophysiological monitoring, on the other hand, is often measured using non-invasive scalp EEG recordings. While EEG recordings can also come from rodents, there is a dearth of approaches that relate scalp EEG to the intracortical LFP. Our experimental goal is to derive a relationship between these approaches by demonstrating how EEG recorded through stainless steel screws placed on the skull surface can correlate with the hippocampal LFP obtained from intracranial silicon probes. After training five male Fisher Brown Norway hybrid rats to appetitively run on a circular track for a food reward, they were implanted with an intracranial silicon probe in the CA1 region of the dorsal hippocampus (AP: -3.2 ML: 1.5 DV: 4.0), and three screw electrodes were adhered to the skull surface, without fully penetrating the bone: One screw over the contralateral prefrontal cortex (AP: 3.3 ML: -0.7), one over the ipsilateral prefrontal cortex (AP: 2.7 ML: 0.7), and one over the ipsilateral parietal cortex (AP: -4.5 ML: 4.0). After a recovery period, the rats were reintroduced to the circular track, and data were then collected from each site. We observed that signals from the CA1 pyramidal layer, the CA1 stratum lacunosum moleculare (LM) layer, the prefrontal cortices, and the parietal region were modulated by running speed. Theta power increased as a function of velocity across all regions, and power-power correlations showed a strong coupling between theta frequencies and their harmonics. Interestingly, there was little variability between the cortical recordings, despite their spatial distance from each other, suggesting a correlation between hippocampal LFP and cortical EEG. As hippocampal theta is widely reported as being slower in advanced age, we believe that further exploration of these findings may advance diagnostic inferences of hippocampal integrity (e.g., aging deficits) using scalp EEG.

First Author (Last name, first name): Lucke-Wold, Brandon	Presenter (if someone other than First Author):
Abstract Title: How do children fare compared with adults? Comparing relative outcomes after thrombectomy for acute ischemic stroke due to large-vessel occlusion	
McKnight Institute: Neurosurgery	Lab: Brian Hoh

ABSTRACT

Objective: Safety and efficacy data for endovascular thrombectomy for acute ischemic stroke secondary to large-vessel occlusion in children are lacking compared with those for adults. We undertook an updated systematic review and meta-analysis of endovascular thrombectomy in children and compared their outcomes with adult data.

Methods: We searched PubMed, Medline, and EMBASE databases to identify prospective and retrospective studies describing patients <18 years treated with endovascular thrombectomy for acute ischemic stroke due to large-vessel occlusion.

Results: Eight pediatric studies were included (n = 192). Most patients were male (53.1 %), experienced anterior circulation large-vessel occlusion (81.8
%), and underwent endovascular thrombectomy by stent retreiver (70.7 %). The primary outcome was change in National Institutes of Health Stroke Scale score from presentation to 24 h after thrombectomy. Secondary outcomes included modified Rankin scale score improvement and 90-day score, recanalization rates, procedural complications, and mortality rates. After treatment, 88.5% of children had successful recanalization; the mean National Institutes of Health Stroke Scale score reduction was 7.37 (95 % CI 5.11-9.63, $p < 0.01$). The mean reduction of 6.87 (95 %CI 5.00-8.73, $p < 0.01$) for adults in 5 clinical trials (n = 634) was similar ($Qb = 0.11$; $p = 0.74$). Children experienced higher rates of good neurological outcome (76.1 % vs. 46.0 %, p
< 0.01) and revascularization (88.5 % vs. 72.3 %, $p < 0.01$), fewer major periprocedural complications (3.6 % vs. 30.4 %, $p < 0.01$), and lower mortality (1.0 % vs. 12.9 %, $p < 0.01$).

Conclusions: Endovascular thrombectomy may be safe and effective treatment for acute ischemic stroke due to large-vessel occlusion in children. The aggregated data demonstrated high rates of revascularization, favorable long-term neurological outcomes, and low complication rates.

Keywords: Acute ischemic stroke; Endovascular; Mechanical thrombectomy; Meta-analysis; Pediatric.

First Author (Last name, first name): Mallepalli, Suresh	Presenter (if someone other than First author):
Abstract Title: Recurrent hypoglycemia exacerbates cerebral ischemic damage in ITD rats by promoting mitochondrial dysfunction.	
McKnight Institute: University of Miami	Lab: Dr. Kunjan R. Dave Laboratory

ABSTRACT

Recurrent hypoglycemia exacerbates cerebral ischemic damage in ITD rats by promoting mitochondrial dysfunction.

Suresh Mallepalli[1-2], Lea Dalco[1-2], Ashish K. Rehni[1-2], Sunjoo Cho[1-2], Kunjan R. Dave[1-3]

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Diabetes is a risk factor for stroke. Recurrent hypoglycemia (RH) exposure is common in treated diabetes patients. Repeated RH exposure in diabetic rats worsens outcomes post-cerebral ischemia. However, the underlying mechanism is not well understood. Mitochondrial autophagy and dynamics play an important role in cerebral ischemic damage. In the present study, we examined markers of autophagy (HSP60, Beclin1, and LC3-II) and mitochondrial dynamics (OPA1, mitofusin1, and Fis1) in hippocampus (the most vulnerable area to ischemic damage). We used non-synaptic (NSM) and synaptic mitochondria (SM) of RH-exposed diabetic rats subjected to global cerebral ischemia (GCI) or sham surgery overnight after the last hypoglycemia exposure. Male insulin-treated streptozotocin diabetic rats (insulin-treated diabetes, ITD) were exposed to RH (hyperinsulinemic hypoglycemia) or ITD+RH+glucose (hyperinsulinemic euglycemia) (controls). After ~24 h post-surgery, mitochondria were harvested, and protein levels were assayed using western blots. Data from sham groups were pooled as no intergroup difference was observed, and results were expressed as % of the pooled sham group. The levels of HSP60 in NSM were higher by 255% (355±30, n=6, $p<0.001$) and 146% (246±15, n=5, $p<0.01$) in the RH+glucose+GCI and RH+GCI groups, respectively, when compared to the sham group (100±22, n=9). HSP60 levels in the RH+glucose+GCI group were higher by 44 % ($p<0.05$) as compared to the RH+GCI group in NSM. We observed a 173% increase in HSP60 levels in SM in the RH+glucose+GCI (273±18, n=6, $p<0.01$) group as compared to the sham group (100±32, n=11). In NSM, levels of LC3-II were higher by 145% in the RH+GCI (245±28, n=5, $p<0.01$) group when compared to the sham group (100±22, n=10). LC3-II in the RH+GCI group was significantly higher by 98% ($p<0.05$) as compared to RH+glucose+GCI (123±19, n=6) in NSM. Levels of OPA1 in NSM were higher by 144% (244±29, n=5, $p<0.01$) and 172% (272±43, n=6, $p<0.001$) in the RH+glucose+GCI and RH+GCI groups, respectively, when compared to the sham group (100±18, n=10). In NSM, the levels of mitofusin1 were higher by 87% (187±12, n=5 $p<0.01$) in the RH+GCI group as compared to the sham group (100±11, n=8). However, the RH+GCI group showed a significantly increased expression by 45% as compared to the RH+glucose+GCI group (129±19, n=6 $p<0.05$) in NSM. We observed no significant difference between groups in levels of Fis1 and Beclin1 in NSM and Beclin1, LC3-II, OPA1, mitofusin1, and Fis1 from SM. Our results demonstrate that RH exposure to ITD rats impacts mitochondrial dynamics and mitophagy markers more in NSM than SM.

Acknowledgement: AHA grant 20TPA35490411 and NIH grant NS122808.

First Author (Last name, first name): McCuiston, Macy	Presenter (if someone other than First Author):
Abstract Title: Neuroinflammatory protein networks associate with altered decision making, and impaired executive functions in the TgF344 Alzheimer's Disease rat model	
McKnight Institute: University of Alabama at Birmingham	Lab: Caesar M. Hernandez

ABSTRACT

Macy A. McCuiston1, Kristian Davis1, Nateka L. Jackson2, Lori L. McMahon2, Lynn E. Dobrunz3, Caesar M. Hernandez1

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The relative weight that individuals give to rewards and "costs" (such as delay to reward delivery) in making decisions varies significantly across the population and disease states. One aspect of decision making involves weighing the relative benefits and costs associated with immediate versus delayed outcomes. This aspect of decision making is often referred to as temporal discounting (or intertemporal choice) and can be assessed on tasks in which subjects are required to choose between small, immediate rewards and larger rewards delivered after varying delays. Furthermore, intact executive functioning and motivation are foundational to the decision-making process. Recent literature shows there is a great deal of variability in the temporal discounting phenotype between individuals with mild cognitive impairment, frontal temporal dementia, and Alzheimer's Disease (AD), with some showing no differences relative to healthy controls and others showing altered rates of temporal discounting. Even beyond these disorders, individual differences in choice behavior (either maladaptive or normative) in young adults predict a variety of life outcomes, including educational success and socioeconomic status. The current study used a behavioral and molecular approach to determine the effect of genotype on phenotypic differences in temporal discounting, motivation, and executive function and neuroinflammation in the TgF344AD (TgAD) rat model of AD.

Young adult (6-7 mo) wild-type (WT; n=6) and TgAD (n=6) were trained on a several operant tasks including temporal discounting (decision making), progressive ratio (motivation), set shifting (cognitive flexibility), and delayed response (working memory) tasks. Basolateral amygdala (BLA), Prelimbic Cortex, and Nucleus Accumbens tissue was then isolated and processed for use in a multiplex ELISA to assess markers of inflammation. Results suggest TgAD rats showed a greater preference for the large, delayed reward relative to WT, however, this preference did not translate to a greater number of total rewards earned. Additionally, TgAD rats were less motivated to obtain the larger reward, were less cognitively flexible, and showed impaired working memory relative to WT controls. Additionally, AD-associated markers of inflammation were higher in the BLA of TgAD rats relative to WT. Interestingly, young TgAD rats show a similar decision-making and cognitive phenotype as old rats, and these data suggest AD pathology may manifest as maladaptive decision making in addition to impaired executive functions early in life.

Support: Interdisciplinary Training in Pathobiology and Rehabilitation Medicine NIH/NICHD 2T32HD071866-06, 1K99AG078400, and R00AG078400 to CMH and R01 AG066489 to LLM.

First Author (Last name, first name): McDermott, Kelsey	Presenter (if someone other than First Author):
Abstract Title: Immunohistochemical analysis of Locus Coeruleus neuronal projections and of α1, α2, and β noradrenergic receptors in the hippocampus of cognitively assessed aged and adult rhesus macaques	
McKnight Institute: Tucson	Lab: Barnes

ABSTRACT

Kelsey McDermott1, Irina Sinakevitch1, Carol A. Barnes1,2

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The Locus Coeruleus (LC) is a noradrenaline (NA)-producing brainstem nucleus with wide projections throughout the cortex. NA acts via 3 classes of receptors (α1, α2, β) and this signaling is critical for optimization of cognitive performance. Some histological studies have suggested age-related decreases in NA fiber and varicosity density in the cortex, and autoradiographic studies have shown age- and disease-related decreases in α1 and α2 receptor densities. NA fiber density has not been investigated with density of all 3 NA receptor types or with respect to cognitive performance. We have previously developed a novel protocol for histological analysis of the NA system in rhesus macaques (McDermott et al, Program No. 574.04, 2022 Society for Neuroscience). Here, we utilize coronal brainstem sections from a colony of 30 adult and aged rhesus macaques ranging in age from 8-32 years (24 to 96 human years). All monkeys underwent tests of spatial short-term memory (delayed response), object recognition memory (delayed nonmatching-to-sample), and object discrimination. We used immunofluorescence techniques to identify three NA receptors (α1, α2a, β1) and NA fibers, as well as supporting cell types known to interact with the NA system: vasculature, microglia, and astrocytes. Images from both the dentate gyrus (DG) and CA3 region of the hippocampus from each immunolabeled section were taken at 40X on a high-resolution confocal microscope. NA receptor, NA fiber, glial cell and vascular densities were determined using unbiased stereological techniques. These data were then assessed with respect to the age and cognitive status of the monkeys. Preliminary results from a subset of the 30 animals reveal trends towards higher densities of β1 NA receptors in both DG and CA3 regions of the hippocampus, and higher NA fiber densities in CA3 in the aged macaques relative to the adults. Further data collection will reveal whether these results hold, and if there are age-related alterations in the noradrenergic system that relate to the cognitive impairments observed in the aged macaques.

Funding: R01 AG003376, McKnight Brain Research Foundation, CNPRC Center Grant RR000169

First Author (Last name, first name): Medeiros, Destynie	Presenter (if someone other than First Author):
Abstract Title: Hippocampal-prefrontal neuronal dynamics contributing to social memory deficits in a mouse model for Rett syndrome	
McKnight Institute: University of Alabama at Birmingham	Lab: Lucas Pozzo-Miller

ABSTRACT

Rett syndrome (RTT) is a neurodevelopmental disorder caused by loss-of-function mutations in the X-linked MECP2 gene, affecting mostly females with a prevalence of 1:10,000 births. Social memory impairments and underlying circuit-level deficits have been demonstrated in the monosynaptic projection from the ventral hippocampus (vHIP) to the medial prefrontal cortex (mPFC) of male *Mecp2* knockout (KO) mice, an established mouse model for RTT. This projection is also dysfunctional in neuropsychiatric disorders such as non-syndromic autism and schizophrenia. The hippocampal network is hyperactive in RTT mice, and such atypically heightened neuronal activity propagates to the mPFC through this monosynaptic projection, resulting in altered mPFC network activity and social memory deficits. However, the underlying mechanism of cellular dysfunction within this projection between vHIP pyramidal neurons (PYR) and mPFC PYRs and parvalbumin interneurons (PV-IN) resulting in social memory impairments in *Mecp2* KO mice has yet to be elucidated. We confirmed social memory deficits in *Mecp2* KO mice and wildtype (WT) controls using a novel 4-chamber social memory assay, where the test mouse is placed in the center chamber surrounded by 3 chambers separated by perforated plexiglass partitions. This novel arena is customized to reduce the impact of the optical fiber tethering required for *in vivo* neuronal recordings simultaneously with behavioral monitoring by reducing the distance that the test mouse needs to cover to interact with the surrounding chambers compared to the classical linear 3-chamber arena. We performed fiber photometry of the Ca^{2+} sensor GCaMP8m expressed in mPFC excitatory PYR (*CamkII* promoter) and the Ca2+ sensor FLEX-GCaMP8f expressed in mPFC of PV-Cre mice to characterize their respective activity during social interactions with novel and familiar mice. In addition, we performed structural analyses of vHIP synaptic inputs onto mPFC PYRs and PV-INs using near super- resolution confocal microscopy in *Mecp2* KO mice and WT controls. This work aims to elucidate underlying mPFC cellular populations that are targets of vHIP innervation, providing insight and potential therapeutic targets for psychiatric disorders associated with vHIP-mPFC dysfunction.

First Author (Last name, first name): N/A	Presenter (if someone other than First Author): Medina, Terrymar
Abstract Title: Functional Spatial Triple-omics Reveals Regional Specific Metabolic Shifts of Ketogenic Diet	
McKnight Institute: Gainesville, FL	Lab: Dr. Ramon Sun – Sun Lab

ABSTRACT

The integration of metabolomics, lipidomics, and glycomics provides a comprehensive view into the metabolic landscape underlying biological processes. Traditional pooled omics analyses often lack spatial resolution and integrated analyses of multiomics datasets, thus limiting our understanding of the spatial heterogeneity and pathway coverage of metabolic landscapes. To overcome these challenges, we have developed the Spatial Augmented Multiomics Interface (SAMI), a novel experimental and computational workflow for the simultaneous analysis of spatial metabolomics, lipidomics, and glycomics datasets using matrix-assisted laser desorption/ionization (MALDI) mass spectrometry imaging (MSI). SAMI provides a platform to perform spatial triple-omics, high-dimensional data integration, dimensionality reduction, spatial clustering, annotation, and pathway analysis. SAMI significantly increases rigor and reproducibility by minimizing sample preparation and handling, all which can be completed within 72 hours with 50μm spatial resolution. Utilizing a mouse brain for proof of concept, SAMI revealed distinct metabolic classifiers within brain regions and elucidated pathways contributing to metabolic heterogeneity of functional and anatomical regions. Finally, SAMI was applied to study the metabolic effects of ketogenic diets on both young and aged rats. The results indicated profound changes in lipid metabolism in multiple regions of the rat brain, specifically in aged rats. These data highlight SAMI's potential for advanced biological data analyses and biomedical discoveries. The development of SAMI represents a major advancement in the field, promising to reshape our understanding of spatial metabolic organization and providing a new avenue for hypothesis-driven research in complex biological systems.

First Author (Last name, first name): Mickle, Alyssa	Presenter (if someone other than First Author):
Abstract Title: Distribution of cervical spinal c-Fos expression after epidural stimulation in rats with cervical spinal cord injury	
McKnight Institute: BREATHE Center	Lab: Erica Dale lab

ABSTRACT

While treatments to restore breathing after cSCI are lacking, epidural stimulation has shown great promise in recovering volitional control of many functions. We have previously shown that closed-loop epidural stimulation (CL-ES) reinstates ipsilesional diaphragm EMG activity in C2-hemisected (C2HS) rats [Mickle et al., 2023]. With longer stimulation periods, CL-ES further elicits lasting increases in the excitability of the respiratory motor network [Malone et al. 2022]; together, these results show great promise for the use of CL-ES to restore independent breathing. Modeling studies have explored epidural stimulation current spread, but the neuronal pathways responsible for CL-ES restoration of diaphragm EMG output after C2HS are unknown. Here, we investigate the neural populations activated by inspiratory-triggered electrical stimulation. Rats were isoflurane anesthetized and implanted with diaphragm EMG and C4 stimulating electrodes before C2-HS. Inspiratory triggered spinal motor evoked potentials of the diaphragm (sMEPs) were recorded to determine motor threshold. Rats were exposed to either 20 minutes of biphasic CL-ES at 75% threshold (n = 3) or a sham waiting period (n = 3). A third group of time-matched controls (n = 3) remained electrically naïve with no sMEPs measurements. An hour after the start of CL-ES, animals were perfused with 4% PFA, spinal cords flash frozen, and the C4 segment serially sectioned. An initial screening of c-Fos protein expression every 240-300 μM was utilized to identify the location of highest expression at which point c-Fos, ChAT, and somatostatin spatial mRNA expression was determined via RNAscope. Total c-Fos expression did not reach significant differences between groups (cell count: 242 +/- 95 naïve, 301 +/- 36 sham, 400 +/- 64 stim). However, c-Fos localization was highly lateralized in electrically naïve animals, while animals receiving electrical stimulation had a more even distribution (lower side % of total: 21 +/- 5 naïve, 44 +/- 5 stim, $p < 0.05$). Stimulation did not alter colocalization with ChAT as ~15% of ChAT neurons were c-Fos positive across groups, and only marginally increased colocalization of c-Fos with somatostatin (% somatostatin c-Fos positive: 1.5 +/- 1.5 naïve, 2.8 +/- 0.9 sham, 5.8 +/- 0.8 stim). Work to identify c-Fos expression in CtB labeled phrenic motor neurons, inhibitory/excitatory neurons, interneurons, and glia is ongoing. While a definitive neural population activated by CL-ES remains elusive, this work begins to uncover the neural underpinnings of CL-ES's increase in motor output, which will be key to tailoring this therapy for maximal benefit in the clinic.

First Author (Last name, first name): **Cassandra Modrak**	Presenter (if someone other than First Author):
Abstract Title: **Investigation of sex-specific anxiety-like and meth-seeking behaviors in rats with a history of predator scent stress.**	
McKnight Institute: **University of Florida**	Lab: **Dr. Marek Schwendt**

ABSTRACT

Modrak, C. G., Wilkinson, C. S., Knackstedt, L., Schwendt, M.

Only a subset of trauma-exposed individuals go on to experience long-lasting behavioral impairments and receive a diagnosis of post-traumatic stress disorder (PTSD). Developing effective treatments for PTSD is complicated due to the heterogeneity of stress responses and comorbidity with other psychiatric disorders such as substance use disorder. As such, individual and sex-specific differences in stress responses have been observed in comorbid (and non-comorbid) populations, with females at a greater risk to develop PTSD after trauma exposure, and engaging in differential anxiety and fear-reactive behavior than males. Overall, PTSD patients are twice as likely to use methamphetamine (meth), and preclinical research shows that both early life stress and acute stress in adulthood augment meth-seeking, with females twice as likely to use meth with shorter abstinence periods. Unfortunately, animal research to date inadequately addresses the individual and sex-specific heterogeneity of stress responses. Thus, the present study sought to investigate the consequences of a trauma-like stressor on subsequent anxiety-like behavior and meth-seeking in male and female rats. Rats (n=40) were briefly exposed to either trimethylthiazoline (TMT) or a control scent (n=24) during the predator scent stress (PSS) task and evaluated for anxiety-like behavior one week later in the elevated plus maze (EPM) and acoustic startle response (ASR). Following re-exposure to the TMT context to assess conditioned fear response, rats underwent 21 days of meth self-administration, extinction training, and cue-primed reinstatement. Rats were perfused and evaluated for cFos expression throughout the prefrontal cortex, as prefrontal activation is linked to enhanced meth-seeking behavior. TMT-exposed rats exhibited elevated anxiety and fear behaviors as shown by increased freezing during re-exposure, hypolocomotion in EPM, and less time in the open arms during EPM compared to controls. This same group subsequently exhibited greater meth intake and significantly reinstated to meth-paired cues following extinction, suggesting elevated meth-seeking behaviors in response to stress. While there was no link between drug-seeking and cortical activity, there was a negative correlation between locomotion and time spent in the TMT quadrant during exposures and the prelimbic and infralimbic cortices, suggesting the possibility for a role of these regions in PSS-induced fear. Future directions are to use AI approaches to identify additional fear-reactive behaviors following PSS exposure.

First Author: NGWU-HYACINTH, OGECHUKWU	
Abstract Title: A comparison of the brain response to tactile stimulation with or without ultrasonic stimulation.	
McKnight Institute: McKnight Brain Institute	**Lab**: Dr. Mark Bolding

BACKGROUND

Brain stimulation techniques are vital tools for neurotherapeutics and allow for functional investigation of the brain. Ultrasound (USS) has emerged as a promising modality to diagnose and treat nervous system disorders noninvasively. However, the impact of direct peripheral nerve excitation with USS remains controversial, with varying research findings. It has been shown that USS reliably inhibits nerve activity, and its effects are influenced by nerve temperature (Lele,1963; Guo et al., 2022). Additionally, low-intensity USS could activate non-nerve tissue (e.g., skin or muscle) without directly exciting peripheral nerves (Guo et al., 2022). Thus, this study sought to clarify these inconsistencies and determine the correct parameters for ultrasonic neuromodulation.

OBJECTIVES

Hypothesis: The activation of the somatosensory cortex in response to tactile stimulation (nerve response to touch) will decrease when USS is applied to the corresponding digital nerve.

Aims: -To illustrate the effect of USS on the brain regions impacted by noninvasive tactile (touch) stimulation of the palmar digital branch of the median nerve.
-To investigate whether USS alone could directly modulate tactile-type response.

METHODS

One male volunteer participated in this study. A 500 kHz focused USS transducer was used to stimulate the palmar digital branch of the median nerve in the middle finger of the left hand. Functional MRI (fMRI) was employed to demonstrate neuronal activation in the brain in response to stimulus timing. Each fMRI run was 8 minutes, and stimuli were presented using a blocked paradigm with 30-second block durations and four block types: baseline blocks with no tactile or USS stimulation, tactile stimulation only blocks, USS stimulation only blocks, and tactile stimulation with USS blocks, presented in that order and repeated for the duration of the run. fMRI data were analyzed using FEAT 6.0 (FSL, FSL - FslWiki (ox.ac.uk)).

RESULTS

Tactile stimulation with or without USS produced significant bilateral activation in the primary (S1) and secondary (S2) somatosensory cortices. USS stimulation with or without tactile stimulation produced significant activation in S2 contralateral to the stimulus only. However, differential contrasts revealed that USS stimulation led to additional activation in the contralateral superior colliculus and thalamus, which was not observed during tactile stimulation alone.

DISCUSSION

To illustrate the brain mechanisms underlying the response to peripheral nerve stimulation, we have integrated peripheral nerve stimulation with the measurement of changes in brain activity using fMRI. Our study explored the effects of USS stimulation on the brain as a prelude to its potential application in neuromodulation. It found that tactile stimulation, in addition to USS stimulation, activated more brain regions than tactile stimulation alone. A possible reason for this discrepancy is that the noninvasive USS activates other non-nerve tissue (skin or muscle), which manifests as a heightened brain response to the USS stimulation. Additionally, USS alone could not directly modulate tactile-type response, as it showed no effect on S1, which was observed with tactile stimulation.

CONCLUSION

Further research with a larger sample size is recommended to standardize brain regions activated during ultrasonic stimulation of peripheral nerves. This could potentially facilitate the US diagnosis of functional neurological abnormalities.

First Author (Last name, first name): Panikkaveettil Ashraf, Harshad	Presenter (if someone other than First Author):
Abstract Title: Adult born neurons excel at temporal pattern separation.	
McKnight Institute: The University of Alabama at Birmingham (UAB)	Lab: Wadiche Labs, Department of Neurobiology| Heersink School of Medicine UAB | The University of Alabama at Birmingham, Birmingham, AL, USA.

ABSTRACT

Harshad P.A., Antoine D. Madar, Justin Ryu, Kapil Nathan, Matt V. Jones, Jacques I. Wadiche, and Linda Overstreet-Wadiche.

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The hippocampal circuit stores and recalls neuronal activity patterns to encode experiences and form episodic memories. Discriminating between similar memories requires pattern separation, which transforms similar patterns of incoming neural activity into divergent output patterns. The dentate gyrus, a hippocampal region with continuous adult neurogenesis, mediates pattern separation to increase memory capacity and prevent overlap of pattern recall in downstream CA3. Selective manipulation of neurogenesis suggests that young, adult-born granule cells (abGCs) play a crucial role in dentate pattern separation. However, a paradoxical feature of abGCs is high excitability, which predicts that abGCs may degrade pattern separation. A real-time assessment of pattern decorrelation of input spike trains by young abGCs is lacking, hence obscuring their computational capacity relative to mature GCs. In this study, we used simultaneous whole-cell recording of abGCs and mature granule cells (mGCs) to assess real-time changes in output spike patterns by optogenetically driving predefined input spike trains with different degrees of similarity. Our results indicate that abGCs perform a more substantial pattern decorrelation than mGCs, resolving an apparent paradox of how highly excitable cells can promote pattern separation. Additional experiments show that low excitatory drive correlates with pattern decorrelation, suggesting that reduced perforant path innervation contributes to this computational advantage of abGCs. Together, these results suggest that limited innervation of abGCs by cortical axons enhances pattern decorrelation of input spike trains, potentially contributing to the role of adult neurogenesis in memory resolution.

First Author: Perez, Gina
Abstract Title: Electronic cigarette vaping exacerbates cortical contusion after traumatic brain injury in female rats.
McKnight Institute: Miami
Lab: Raval lab at Peritz Scheinberg Cerebral Vascular Disease Research Laboratory

Electronic cigarette vaping exacerbates cortical contusion after traumatic brain injury in female rats.

Gina Perez[1,2], Hari Pradhyumnan[1,2], Shahil Patel[1,2], Ofelia Furones-Alonso[2-5], Helen Bramlett[2-5]and Ami P. Raval[1,2-4,5*]

[1]Peritz Scheinberg Cerebral Vascular Disease Research Laboratories,[2]Department of Neurology,[3]Department of Neurological Surgery,[4]Neuroscience Program, Leonard M. Miller School of Medicine, University of Miami, and [5]Bruce W. Carter Department of Veterans Affairs Medical Center, Miami, Florida, USA

Electronic cigarette (EC) nicotine delivery devices have become increasingly popular in recent years. Our understanding of the effects of EC vaping on the brain is incomplete and the effects of vaping on traumatic brain injury (TBI) has not been studied. We hypothesize that EC exposure will worsen contusion volume after TBI in female rats. Adult female Sprague-Dawley rats were exposed to EC (5% nicotine Juul pods) or air for 16 days. Per day, rats were exposed to 16 episodes of EC vapor. Each episode was comprised of 2 seconds of EC Juul puffs followed by 8 seconds of air rest over 8 minutes. Exposed rats underwent moderate fluid percussion injury or sham surgery. In brief, animals were anesthetized (3% isoflurane for induction, 0.5–2% isoflurane for maintenance with 70% N_2O, 30% O_2), and received a 4.8 mm craniotomy over the right parietal cortex (−3.8 mm bregma, 2.5 mm lateral), where a beveled 18-gauge syringe hub was secured to the craniotomy site. Animals recovered for 12–16 hours while fasting with water ad libitum and were re-anesthetized and mechanically ventilated. A fluid-percussion pulse (18 ms duration) of moderate (1.8-2.2 atm) pressure was delivered. Sham animals experienced all surgical procedures but were not subjected to the fluid percussion pulse. Rats were perfused seven days after TBI, and tissue was fixed for histopathology. To determine contusion volume, areas of tissue necrosis in coronal sections spanning the entire antero-posterior extent of the injury were traced using Neurolucida. Data of contusion volume quantification demonstrated that EC exposure significantly increased mTBI contusion volume as compared to the air control group, suggesting the toxic effects of EC vaping on TBI pathology in rats. We observed that there is an increased contusion and selective neuronal loss in the brain of the animal that is exposed to electronic cigarettes. We also observed that cotinine which is the primary metabolite of nicotine in the body is increased in women because of chronic EC vaping. Electronic cigarette (EC) vaping is a recent phenomenon and there have been no comprehensive studies evaluating the potential effects of EC vaping on the brain, neurological diseases, or cognitive declines.

First Author (Last name, first name): Phelps, Hannah	Presenter (if someone other than First Author):
Abstract Title: Stereological Quantification of the Impact of Aging on Dopaminergic and Cholinergic Neurons	
McKnight Institute: University of Florida	Lab: Dr. Matthew Burns

ABSTRACT

Parkinson's disease (PD), Dementia with Lewy Body (DLB) and Multiple System Atrophy (MSA) are common and rapidly growing neurodegenerative disorders, with age being the major risk factor. As a result, aged animal models have become increasingly valuable as representative models of disease. Loss of dopaminergic and cholinergic neurons in the substantia nigra and basal forebrain, respectively, are pathological hallmarks of PD, DLB, and MSA, but have also been associated with normal aging, making the use of aged animals for quantification of cell loss associated with disease potentially problematic. Comparing dopaminergic and cholinergic neurons in the young and aged rat brain using unbiased stereological quantification has not been well studied. We aimed to quantify the dopaminergic and cholinergic neurons in the substantia nigra and basal forebrain, respectively, in young and aged rats. As a result, we hope to elucidate differences among aged animals and any sex differences that exist. Using 5 month and 23-month-old Fischer 344 x Brown Norway F1 hybrid rats of both sexes, we investigated the number of dopaminergic neurons in the substantia nigra and ventral tegmental area and the number of cholinergic neurons in the basal forebrain. The rats were euthanized and underwent a transcranial perfusion with 4% paraformaldehyde. 50 µm sections were collected using a vibratome. After completion of free-floating immunofluorescence to stain for tyrosine hydroxylase (TH) and choline acetyltransferase (ChAT), dopaminergic and cholinergic cell bodies were quantified using the Optical Fractionator probe within Microbrightfield's StereoInvestigator software. TH+ and ChAT+ neurons were counted by distributing a series of counting frames (100 µm x 100 µm) within a systematic random sampling grid (300 µm x 300 µm) over the substantia nigra, ventral tegmental area, and basal forebrain. Objects were counted with a 40x oil immersion lens. Estimations of the total population were taken from the optical fractionator calculations and variability was determined using the Gunderson coefficient of error (< 0.1). Images were acquired at 5x using the slide scanning workflow within StereoInvestigator. Preliminary data suggest that the number of dopaminergic cells in the substantia nigra and ventral tegmental area decrease with age, indicating the aging process in rats is similar to that in humans. In addition, female rats possessed more dopaminergic cells than male rats. Preliminary data suggest differences in dopaminergic between young and aged rats. These results inform future stereological studies in age-related disease models. Although cell loss has been used in animal models as a marker of neurodegenerative disease, this data suggests that there may be age and sex-dependent cell loss to consider in animal models of disease.

First Author (Last name, first name): Pradhyumnan, Hari	Presenter (if someone other than First Author): Pradhyumnan, Hari
Abstract Title: Post-stroke cognition is worsened by electronic cigarette exposure in male and female rats	
McKnight Institute: Miami	Lab: Raval Lab at Peritz Scheinberg Cerebral Vascular Disease Research Laboratory

ABSTRACT

Smoking is a preventable risk factor for stroke and battery-operated nicotine delivery systems known as electronic cigarettes (EC) have gained popularity in the past two decades. EC heat and aerosolize a solution of nicotine and chemicals forming harmful toxicants such as formaldehyde hemiacetal in the process. Understanding about the effects of EC vaping on stroke outcome is limited. This study investigated the effects of a 16-day EC exposure on stroke outcome and neurotransmitter metabolism in male and female rats. Sprague-Dawley rats (2-3 months old) of both sexes were randomly assigned either to air or EC (5% nicotine Juul pods) exposure using the EcigAero-TM Aerosol Exposure Apparatus. Rats were exposed for 16 nights. Per night, rats were exposed to 16 episodes of EC. Each episode consisted of 2 seconds of EC puffs followed by 8 seconds of air over the period of 8 minutes. After 16 days, the rats were divided into two cohorts. The first cohort of rats underwent brain collection for unbiased metabolomic (Metabolon Inc.) and cotinine level analyses (USDTL) after exposure. The second cohort of rats were subjected to transient middle cerebral artery occlusion (tMCAO; 90 min) or sham surgery and survived for 21 days. Beginning on day 14 post- surgery, rats were tested for learning and memory capacity using the Morris water maze followed by perfusion-fixation and brain collection for histopathological analysis. EC exposure significantly increased infarct volume in female, but not male animals. Water maze data indicated worsened post-stroke cognition in EC groups compared to air groups in rats of both sexes. The worsened cognition due to EC was more prominent in female than male animals. Metabolomic analysis indicated that EC exposure resulted in significant increases ($p \leq 0.05$) in phenylalanine, tryptophan, and glutamate metabolites, and both increases ($p \leq 0.05$) and decreases ($p \leq 0.05$) in histamine and tyrosine metabolites in the brains of female and male rats. EC vape exposure, even for as short as two weeks, impacts the metabolism of neurotransmitters, induces cognitive deficits, and worsens stroke outcomes in a sex dependent manner. Future studies investigating the impact of long-term EC usage are required to understand the chronic effects of vaping on the brain.

First Author (Last name, first name): Puzzo, Christian	Presenter (if someone other than First Author): Puzzo, Christian
Abstract Title:Distinct corticothalamic integration by primary and higher-order inhibitory cells of the thalamus	
McKnight Institute:	Lab: Cruikshank

ABSTRACT

* Most sensory information undergoes processing and modulation in the thalamus before being transmitted to the neocortex. Interestingly, the neocortex itself exerts a top-down influence on this modulation via extensive descending projections to the thalamus. Central to these bidirectional interactions is the GABAergic thalamic reticular nucleus (TRN). The corticothalamic (CT) projections that descend from the neocortex excite TRN, leading to disynaptic inhibition of thalamic relay cells, gating the flow of thalamocortical signals.
* Recent evidence has shown that cells in sensory sectors of TRN are organized into primary and higher-order (HO) subpopulations, named according to their reciprocal connections with either primary or HO thalamic relay neurons. In addition to having distinct connections, these TRN cell subtypes have distinct physiological properties, resulting in pathway-specific variation in the way they process their thalamic inputs. Nevertheless, our understanding of functional roles of primary and HO TRN cells, and even basic knowledge about the organization and impact of CT systems on these distinct subpopulations, remains limited.
* Here, we investigate the integration of CT inputs in primary and HO cells of somatosensory TRN. Our findings indicate that layer 6 of somatosensory cortex (S1) drives distinct spiking patterns in the two classes of TRN cells, due to variations in both synaptic and intrinsic properties. Primary TRN cell spiking is strong and depressing; this results from robust synaptic input summating with powerful but transient T-type calcium currents that undergo inactivation during repetitive stimulation. On the other hand, HO TRN spiking is modest and facilitating, owing to weak but facilitating synaptic input and minimal T-type current. We also find that HO cells, but not primary cells, integrate convergent novel inputs from S1 layer 5 and motor cortex (M1). The synaptic currents evoked by layer 5 inputs are strong and depressing - hallmarks of layer 5 CT inputs to other nuclei. In contrast synaptic currents evoked by Ml inputs are initially weak but facilitate with repetitive activation, consistent with layer 6 CT pathways.
* Thus, in contrast to primary cells, which predominantly receive input from the canonical layer 6 sensory CT pathway, HO TRN cells integrate a mix of inputs from multiple CT pathways, mirroring the input patterns of HO thalamic relay neurons. The stark differences in organizational and integrative properties between TRN cell subtypes are likely to have important implications for CT disynaptic inhibition and top-down regulation of primary and HO thalamic subnetworks.

First Author (Last name, first name): Pyon, Wonn	Presenter (if someone other than First Author): Pyon, Wonn
Abstract Title: Investigating the functional role of ventral tegmental area dopamine neurons in decision making under risk of punishment	
McKnight Institute: University of Florida	Lab: Jen Bizon & Barry Setlow

ABSTRACT

A prevailing theory regarding the role of dopamine in reward-motivated behaviors is that dopaminergic neurons of the ventral tegmental area (VTA) signal discrepancies between predicted and actual outcomes of a particular event. This theory of reward prediction error signaling further implies that VTA dopamine neurons also play a role in cost-benefit decision-making in which outcomes can include reward alongside the potential for punishment. To elucidate the functional role of VTA dopamine neurons in decision making under risk of punishment, male and female tyrosine hydroxylase (TH)-Cre transgenic rats were injected with Cre-dependent GCaMP and trained on a risky decision making task in which they made discrete choices between a small, “safe” food reward and a larger food reward accompanied by ascending risk of mild footshock (0%, 25%, 75%). *In vivo* fiber photometric recording of VTA dopamine neurons revealed an increase in neuron activity during receipt of the large reward in the absence of probabilistic punishment, and this increase was greater in blocks of trials in which there was some chance of punishment (25% and 75%) vs. no chance of punishment (0%). In contrast, VTA dopamine neuron activity was suppressed during receipt of the large reward when it was accompanied by punishment.

To confirm that this change in VTA dopamine neuron activity was causal to risky decision making, Cre-dependent halorhodopsin was expressed in dopamine neurons of TH-Cre rats. After stable behavior was established, these neurons were then selectively inhibited during delivery of the large reward. Relative to baseline sessions, inhibition of VTA dopamine neurons during receipt of the large reward when it was unpunished reduced preference for the large reward. In contrast, inhibition of VTA dopamine neurons during receipt of the large reward when it was punished had no significant effect on behavior. These findings support a causal link between VTA dopamine neuron activity and decision making under risk of punishment through signaling errors in outcome predictions. These results also provide evidence for a “negative prediction error floor”, whereby further inhibition of VTA dopamine neurons during an already suppressive event does not result in further shifts in choice preference.

First Author (Last name, first name): **Raciti, Federica Maddalena**	Presenter (if someone other than First Author):
Abstract Title: **Transient Changes in Sound-Evoked Vestibular Myogenic Potentials in a Preclinical Model of Noise Overexposure**	
McKnight Institute: **Miami**	Lab: **Suhrud Rajguru**

ABSTRACT

The vestibular system, located in the inner ear, plays a crucial role in providing critical input for balance and posture by encoding changes in head rotation, translation, and gravity. Similar to the cochlea, the vestibular end organs also respond to loud acoustic stimuli, with the saccule and utricle being particularly susceptible to damage caused by hazardous noise or blast exposures. Over the years, extensive pre-clinical work has characterized the noise-induced changes in the morphological and functional features of the otolith organs using a combination of imaging techniques and the study of vestibular short-latency evoked potentials (VsEPs). However, due to challenges in recording VsEPs in humans, the clinical assessment of vestibular function in noise-exposed subjects rather relies on the analysis of vestibular evoked myogenic potentials (VEMPs). Although prior work has elucidated the neural basis of VEMPs, their use in preclinical studies to characterize the pathophysiology of vestibular dysfunctions has been limited, primarily due to the low level of reproducibility and high variability of the responses elicited in animal models so far. In this study, we employed a standardized preclinical cVEMP setup and test protocol developed by our group that closely mimics clinical methodologies. We provide a detailed characterization of cVEMPs evoked in noise-exposed rodents. Male Brown Norway rats (14-18 weeks) with normal hearing and vestibular function were screened using a Smart EP evoked potentials system (Intelligent Hearing Systems, USA). The animals were then exposed to broadband noise (4-16 kHz) at 110 dB SPL for 1 hour. Changes in thresholds, amplitude, and latency of auditory brainstem responses (ABRs) and cervical vestibular myogenic potentials (cVEMPs) evoked by pure tone bursts at 1 and 8 kHz were compared to baseline (pre-trauma) at multiple time-points up to 84 days post-noise. Within the cohort studied, measurements of auditory function showed a permanent threshold shift (PTS) following noise trauma. In contrast, cVEMP assessments at both frequencies tested revealed noise-induced temporary threshold shifts that recovered by Day 7. We also observed transient reductions in amplitude and increases in latency of vestibular responses to 90 dB SPL stimuli at 1 and 8 kHz, with full recovery by Day 28 and Day 14 respectively. The results of this study suggest that cVEMPs represent a reliable non-invasive diagnostic test in a preclinical setting, with significant implications for understanding early and long-term changes and potentially identifying the neural basis of vestibular disorders, including noise-induced vestibular deficits.

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First Author (Last name, first name): Rehni, Ashish K.	Presenter (if someone other than First author): Mallepalli, Suresh
Abstract Title: A single episode of hypoglycemia increases stroke risk in insulin-treated diabetic rats.	
McKnight Institute: Department of Neurology, University of Miami Miller School of Medicine, Miami, Florida - 33136, USA	Lab: Dr. Kunjan R. Dave Laboratory

ABSTRACT

A single episode of hypoglycemia increases stroke risk in insulin-treated diabetic rats.

Ashish K. Rehni[1-2], Sunjoo Cho[1-2], Ami P Raval[1-3], Kunjan R. Dave[1-3]

[1]Peritz Scheinberg Cerebral Vascular Disease Research Laboratories, [2]Department of Neurology and [3]Neuroscience Program, University of Miami Miller School of Medicine, 1600 NW 10th Ave, RMSB / 7050, Miami, Florida - 33136, USA

Diabetes is a widespread disease responsible for a major part of global healthcare expenditure and mortality and morbidity worldwide. Diabetes is one of the prominent risk factors for cardiovascular disease. Intensive antidiabetic therapy increases the risk of hypoglycemia in subjects with diabetes. Exposure to hypoglycemia increases stroke risk in subjects with diabetes[1]. Acute hypoglycemia (AH) exposure produces a prothrombotic effect[2]. We have previously shown that recurrent hypoglycemia (RH) exposure (one episode / day for 5 days) increases stroke risk in insulin-treated diabetic (ITD) rats. Next, we studied the effect of a single episode of hypoglycemia on stroke risk. Thus, in the present study, we determined how long the effect of AH on stroke risk lasts in young ITD rats of both sexes. Rats rendered diabetic using streptozotocin were treated with insulin 2-3 weeks after diabetes induction. ITD rats were randomly assigned to either ITD + AH + Glucose (hyperinsulinemic euglycemia: control) or ITD + AH groups (hyperinsulinemic hypoglycemia). Chi square test confirmed that the AH-exposed female group and the control group were balanced in terms of the proportion of rats at different stages of the estrous cycle. Stroke risk was evaluated using an in vivo model of thrombosis. Either 1 or 3 days after AH (for 3h), the jugular vein was connected to the carotid artery by a shunt containing a suture, and blood was allowed to flow for 15 minutes. The suture was then withdrawn and weighed to quantify thrombosis. The clot weights in the ITD + AH + Glucose and ITD + AH male groups quantified 1 day after hypoglycemia were 14 ± 1 mg (n = 7) and 20 ± 3 mg (n = 9), respectively. The clot weight in the male ITD + AH group was 48% greater ($p<0.05$) than in the control group. The clot weights in the ITD + AH male rats quantified 3 days after hypoglycemia (18 ± 1 mg, n=6) were not significantly different from the control group (16 ± 1 mg, n=7). Next, we confirmed if AH exposure also increases stroke risk 1 day after hypoglycemia in females. Clot weights in the ITD + AH
+ Glucose and ITD + AH female rats quantified 1 day after hypoglycemia were 15 ± 1 mg (n = 8) and 22 ± 2 mg (n = 9), respectively. The clot weight in the female ITD + AH group was 47% greater ($p<0.05$) than in the control group. Our data shows that AH increases stroke risk in ITD rats of either sex on day 1 post-exposure. In the future, we plan to identify the mechanism by which RH exposure increases stroke risk in diabetic rats. References: 1) Ann.N.Y.Acad.Sci. 2018;1431(1):25-34.; 2) Diabetes Care. 2018;41(12):2625-2633. Acknowledgement: NIH (NS122808).

First Author (Ross,Aleyna):	Presenter (if someone other than First Author):
Abstract Title: Validation of an Operant-Based Touchscreen Test of Mnemonic Similarity for Rodent Models of Cognitive Aging Ross, A, Logan,C, Gatton ,T, Eusanio ,E, Bizon,J, Maurer, A, Johnson, S, Burke, S	
McKnight Institute: Department of Neuroscience	Lab: Dr. Sara N Burke

ABSTRACT

The neurobiological basis of cognitive aging and brain resilience are currently unknown due to an incomplete understanding of the neural circuits responsible for cognitive decline. In human study participants, the Mnemonic Similarity task (MST; e.g., Stark et al., 2013) has been foundational for linking anatomical (e.g., Yassa et al., 2011; Bennet et al., 2016) and functional changes in the medial temporal lobe (Yassa et al., 2011; Reagh et al., 2018) to reduced accuracy in the ability to discriminate between stimuli that share features. Similar deficits are observed in aged rats (Johnson et al., 2017) and monkeys (Burke et al., 2011), but the testing conditions in animal models have traditionally used real world objects that may not be comparable to computer-based testing that is commonly used in clinical settings. In effort to bridge the translation gap between pre-clinical experiments with animals and clinical intervention research in human study participants, we have adapted the computer-based human mnemonic similarity task (MST) (e.g., Stark et al., 2013) for rodents. Using a variant of the object-cued spatial choice task developed by Ahn and Lee (2015), young (4 months) and aged (21 months) Fischer344 Hybrid x Brown Norway male and female rats were tested on the rodent MST in a touchscreen operant chamber. This task requires rats to discriminate between morphed stimuli that share varying levels of overlapping visual features across trials. Results show that aged rats were less accurate at performing this task than young animals. To further understand the neurobiology of this impairment, we are currently manipulating neural activity via the utilization of Designer Receptor Exclusively Activated by Designer Drugs (DREADDs). Adeno-associated viral vectors will be used to selectively express an inhibitory DREADD to inhibit signaling between the prelimbic cortex (PrL) and the perirhinal cortex (PER), which are two brain regions that are vulnerable in old age and critical for MST performance. Together these experiments may provide insight into how coordinated neural activity supports behavior and is disrupted in advanced age.

First Author: Jacob Salminen	**Presenter:** Jacob Salminen
Abstract Title: Older Adults' Electrocortical Dynamics Vary with Treadmill Walking Speed and Terrain Unevenness	
McKnight Institute: University of Florida	**Lab:** Human Neuromechanics Lab

Introduction. Falls are the leading cause of fatal and nonfatal injuries among persons aged ≥65 years (Bergen G, 2016). Preserving walking ability with advancing age is central to maintaining mobility and reducing fall risk. A review article in Frontiers in Human Neuroscience theorizes that older adults must devote more executive resources to walking compared to younger adults (Clark, 2015); therefore, challenging older adults during walking and measuring their brain activity may provide a valuable biomarker for assessing fall risk (Carolina Vila-Cha, 2022). Here, **we present** the changes in electrocortical dynamics and kinematics of older adults walking on a treadmill at different speeds and terrains. **We found** that brain areas associated with sensory integration and control of gait are majorly affected by the terrain conditions and minorly affected by the speed conditions, and that older adults adjust their kinematics to the increasing terrain difficulty.

Methods. We had 54 older adults wear a high-density electroencephalography (EEG) system to measure their brain activity. To measure kinematic changes of uneven terrain walking, we had participants wear an inertial measurement unit located on their pelvis, and force sensors inserted into the sole of their shoes (i.e., load soles). We analyzed the EEG and kinematic data using custom software built in MATLAB (Mathworks, 2020b). Empirically validated algorithms cleaned the EEG data of eye, muscle, and movement artifacts (Colton B Gonsisko, 2023) (Chang Liu, 2023). We made custom finite element head models extracted from subject specific MRIs, and then localized EEG data to regions within the brain using the head model and adaptive mixtures independent component analysis. K-means clustering grouped subjects' localized independent components into specific brain regions. Changes in mean spectral power for each brain region were calculated for the theta (4-8Hz), alpha (8-13Hz), and beta (13-30Hz) bands, and we present the changes in time-frequency power time-locked to the gait cycle in the form of event related spectral perturbations (ERSPs). We calculated kinematic changes across terrains and speeds in step duration (s), step duration coefficient of variation (CoV, %), anteroposterior excursion CoV, and mediolateral excursion CoV. We used generalized linear models to determine significant changes for EEG outcome measures, and a generalized linear mixed effects model (an added covariate of subject's terrain speed) to assess kinematic changes. Significance level was set to alpha < 0.05.

Results. For kinematic outcomes, we found significant increases in subjects' anteroposterior excursion CoV ($p<0.001$) and mediolateral excursion CoV ($p<0.001$) as terrain difficulty increased. Interestingly, we found significant decreases in step duration across speeds ($F=26.9$, $p<0.001$), but a weaker change across terrains ($F=4.54$, $p=0.004$). Additionally, there was a significant change of step duration CoV across terrains ($F=5.66$, $p<0.001$). For power spectrum changes, left and right **sensorimotor** areas significantly decrease alpha and beta power across terrains ($p<0.001$) as terrain difficulty increased. We found similar decreases in alpha and beta power ($p<0.001$) in the left and right **posterior parietal** areas across terrains. Interestingly, these changes are absent in the speed conditions, excluding the right **posterior parietal**. We also found significant decreases in theta, alpha, and beta power ($p<0.001$) in the **Cuneus**, but only a significant decrease in the alpha power ($p<0.001$) across speeds. Additionally, the **precuneus** had changes in the alpha and beta power ($p<0.001$) across terrains, but no such significant changes were found in the speed conditions. ERSPs revealed time-locked power changes with the gait cycle for each of the previously stated brain areas.

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doi:https://doi.org/10.3390/s23020928

First Author (Last name, first name): **Sanders, Caleb**	Presenter (if someone other than First Author):
Abstract Title: **White matter microstructure in posttraumatic stress disorder**	
McKnight Institute: **UAB**	Lab: **Knight Neuroimaging Laboratory**

ABSTRACT

Posttraumatic Stress Disorder (PTSD) is associated with the dysfunction of emotion expression and regulation processes. These emotional processes are associated with a neural network that includes the prefrontal cortex, inferior parietal lobule, hippocampus, amygdala, and hypothalamus. These brain regions are connected by white matter tracts that include the superior longitudinal fasciculus, cingulum bundle, uncinate fasciculus, and stria terminalis/fornix. Therefore, determining the relationship between posttraumatic stress and the microstructure of these white matter tracts may offer new insight into the neurobiological processes that underlie PTSD. The present confirmatory study examined the relationship between white matter microstructure and posttraumatic stress. Forty five participants (PTSD = 15; Controls = 30; M_{age} = 26.7 years; SD = 11.8) were recruited for this study. Participants completed the Life Events Checklist and Clinician-Administered PTSD Scale for DSM-5. Diffusion-weighted magnetic resonance imaging (TR = 3230 ms, TE = 89.2 ms, FOV = 210 mm^2, matrix size = 140 x 140, 1.5 mm isotropic resolution) was acquired in 98 directions (b = 0, 3000 s/mm^2). Voxel- wise cross-subject analysis of white matter fractional anisotropy (FA) data was completed using
Tract-Based Spatial Statistics. We hypothesized that FA would be greater within the stria terminalis/fornix, but lower in the superior longitudinal fasciculus, cingulum bundle, and uncinate fasciculus in participants with PTSD compared to healthy controls. We also hypothesized that FA would vary with PTSD symptom severity (positively: stria terminalis/fornix; negatively: superior longitudinal fasciculus, cingulum bundle, and uncinate fasciculus). Results showed greater FA in the uncinate fasciculus and stria terminalis/fornix in participants with PTSD compared to healthy controls. In addition, PTSD symptom severity was positively related to stria terminalis/fornix FA and negatively related to cingulum bundle FA. These results suggest that differences in the white matter of the cingulum bundle, uncinate fasciculus, and stria terminalis/fornix may underlie symptom expression in PTSD.

First Author (Last name, first name): **Schreiber Anna Maria**	Presenter (if someone other than First Author):
Abstract title: **The O-GlcNAc Transferase is associated with the Ten-Eleven Translocation Enzyme to control DNA hydroxymethylation in the epileptic hippocampus**.	
McKnight Institute: **University of Alabama at Birmingham**	Lab: **Farah Lubin Lab**

Background: Temporal lobe epilepsy (TLE) is one of the most common types of epilepsy, with seizures originating from the hippocampus and is associated with aberrant DNA hydroxymethylation and glucose hypometabolism. Approximately 5% of glucose feeds into the Hexosamine Biosynthetic Pathway (HBP), which is a precursor to the glycosylation pathway, generating the sugar nucleotide UDP-N-acetyl-glucosamine (UDP-GlcNAc) substrate. The O-GlcNAc Transferase (OGT) and O-GlcNAcase (OGA) catalyzes the addition and removal of the O-GlcNAc moiety at serine and threonine residues, respectively. In the present study, we investigated whether OGT recruits Ten-Eleven Translocation (TET) proteins, like TET1, to facilitate the conversion of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC) at gene regions associated with chronic epilepsy. We hypothesize that altered TLE associated glucose metabolism contributes to abnormal O-GlcNAc signaling to TET1 DNA hydroxymethylation mechanisms in the epileptic hippocampus. Methods: Male Sprague Dawley rats were injected with saline or 10mg/kg of kainic acid (KA) to induce Status Epilepticus (SE). Six weeks following SE induction, the hippocampus was sub-dissected out and tissue processed for TET1 and OGT interactions in nuclear protein extraction. TET1, OGT and O-GlcNAc levels were detected by western blotting. The physical interaction of TET1-OGT was assessed by co-immunoprecipitation (co-IP). O-GlcNAcylation of TET1 was determined by succinylated wheat germ agglutinin (sWGA) assay. Results: Co-immunoprecipitation analysis revealed that endogenous TET1 complexed with OGT in the hippocampus. Specifically, we found a significant increase in the ratio of OGT binding to TET1 in the epileptic hippocampus compared to non-epileptic controls. Furthermore, we observed a reduction in TET1 O-GlcNAcylation levels. Conclusions: Together, these findings indicate an increased association between OGT and TET1 proteins in the hippocampus of epileptic rats compared to non-epileptic controls. To our knowledge, this study is the first to demonstrate an endogenous interaction of OGT-TET1 in the epileptic hippocampus suggesting a possible dysregulation in the following: 1) glucose metabolism, 2) expression/activity of OGT/OGA, 3) cellular stress response or 4) other epigenetic mechanism influencing the expression of genes involved in HBP. Our future work will focus on elucidating the observed alterations in TET1-OGT interaction and TET1 O-GlcNAcylation gene regions in the epileptic hippocampus.

First Author (Last name, first name): Seedansingh, Johleen	Presenter (if someone other than First Author):
Abstract Title: Effects of chronic vagus nerve stimulation on cognitive performance in aging	
McKnight Institute: University of Florida	Lab: Bizon-Setlow

ABSTRACT:

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Disruptions in both excitatory and inhibitory signaling within the prefrontal cortex (PFC) contribute to age-related impairments in executive functions. These disturbances in neuronal excitability associated with cognitive decline may interact with or worsen due to dysregulated inflammatory signaling, which is itself associated with cognitive impairments in aging. Electrical vagus nerve stimulation (VNS) is an approved treatment for intractable epilepsy and certain neuropsychiatric disorders, and some individuals receiving VNS therapy have reported improvements in cognitive function as a side effect. The current study has two Aims: 1) to investigate the effects of chronic VNS on working memory in aging and 2) to investigate the effects of chronic VNS on inflammatory markers that are dysregulated with age and linked to cognitive dysfunction.

Aged male and female FBN rats (24 mo.) were surgically implanted with a cuff electrode around the left vagus nerve. For Aim 1, rats underwent daily testing on a delayed response working memory task in operant chambers, in which they had to learn and remember the left/right position of a response lever over short delays. Rats were tested on the task in the mornings and received sessions of VNS in the afternoons, using parameters shown previously to enhance cortical plasticity and other forms of PFC-dependent learning (100 stimulus trains/session at 30Hz, 700 μA, 120 μs biphasic pulse width, 0.8 s train duration). For Aim 2, rats underwent the same VNS parameters for 30 days, and blood and brain samples were collected at the endpoint and analyzed for inflammatory markers using ELISA. Control groups for both Aims consisted of rats implanted with sham cuffs that underwent identical procedures in the absence of VNS.

Data collected to date indicate that after 6 weeks of stimulation, rats that received VNS showed improved working memory compared to controls. Furthermore, after 30 days of VNS there were significant shifts in circulating levels of peripheral inflammatory markers in comparison to controls. These findings suggest that chronic VNS has the potential to remediate age-related impairments in working memory, possibly via remediation of dysregulated inflammatory signaling that occurs in aging.

Supported by: The McKnight Brain Research Foundation, NIH RF1AG067429

Sharma, Sabrina	
Title: Oral contraceptive treatments increase cerebral sphingolipid and ceramide metabolites in female rats	
McKnight Institute: Miami	Lab: Raval lab at Peritz Scheinberg Cerebral Vascular Disease Research Laboratory

Abstract:

The Centers for Disease Control and Prevention estimates that 64.9% of women between 15 and 49 years of age use some form of contraception. In the United States, combined estrogen and progesterone oral contraceptive (OC) pills are the most commonly used form of contraception, and hence was the focus of the current study. [1]. Studies show that OC is associated with an increased risk of stroke, especially during the first year of use, potentially due deviation from hemostatic balance. Importantly, this study provides new insights that the pronounced effects of OC usage are seen in the beginning of treatment apart from long-term OC usage, which is an independent risk for myocardial infarction, venous thromboembolism, stroke, and more, most prevalently in smokers [2, 3]. OC exposure makes females more susceptible to stress hormone effects on episodic memory, fear conditioning, and cognitive emotion regulation [4]. Our understanding regarding the contribution of short-term OC exposure on the severity and consequence of stroke injury is sparse, and hence is one of the goals of the current study. Adolescent and adult Sprague-Dawley female rats were randomly (n = 8/group) exposed to either placebo or OC for 16-21 days. At the end of the treatment, brain tissue was harvested to obtain an unbiased global metabolomic profile (performed by Metabolon Inc.) The metabolomic study was complemented with western blot analysis and enzyme activity measurements of key altered pathways. Metabolomics data using pathway enrichment analysis showed significant changes in sphingolipid metabolism. Sphingosine 1-phosphate (S1P) significantly ($p<0.05$) increased in the OC exposed brains as compared to placebo groups. The changes were more pronounced in adolescent rats as compared to adult. A growing body of literature implicates S1P as “a double-edged sword” in the pathogenesis of brain-related disorders [5]. Furthermore, S1P plays a key role in synaptic transmission, neuronal autophagy, and neuroinflammation [5]. Preliminary results indicate that there are four main metabolites that are potentially affected by OC: Sphingosine Kinase 1 (SphK1), Sphingosine Kinase 2 (SphK2), S1P Receptor (S1PR1), and S1P Lyase (S1PL). Discerning the exact effects of OC on overall brain metabolism, and S1P metabolism, at different ages and for both long term and short-term periods of time will help us understand stroke risks in OC users.

First Author (Last name, first name): Zachary Simon	Presenter (if someone other than First Author):
Abstract Title: Age and sex differences in behavior and functional connectomic measures in the human ApoE4 transgenic mouse model	
McKnight Institute: UF MBI	Lab: Febo Lab

Homozygosity of the Apolipoprotein-ε4 (ApoE4) gene in humans is the strongest genetic risk factor for Alzheimer's Disease (AD). The protein variant encoded by this gene has been linked to aberrant microglial activation, blood-brain barrier breakdown, decreased protein clearance, and increased protein aggregation. These outcomes of the ApoE4 genotype suggest that it may also affect functional network activity in brain regions involved in cognitive and affective behaviors. Here we tested the hypothesis that age alters functional network topology, particularly markers of network integration, in ApoE4 homozygous mice. Given that the effects of ApoE4 vary with age and there is a strong sex difference in AD risk, we imaged two age groups of male and female ApoE4 mice.

Male and female mice aged 1.5-2 months and 8.5-11 months, homozygous for the human ApoE4 transgene, were scanned on an 11.1 Tesla scanner under combined dexmedetomidine/isoflurane sedation using the following parameters: single shot echo planar images with echo time of 15 ms and repetition time of 1.5 seconds (600 total repetitions; 0.3mm^2 in plane resolution, 0.7 mm slice thickness n 17 slices). Images were processed and analyzed using nodes created via independent component analysis on the common coordinate framework mouse atlas (version 3) and graph theory algorithms in brain connectivity toolbox. Following fMRI scans, mice were run through a contextual fear conditioning (CFC) protocol over three consecutive days. One day 1, mice received CFC training for 17 minutes using a series of 4 trials in the presence of a foot shock (0.90mA, 1 second) applied at equal intervals over the timeframe. On day 2, mice were placed in the same chamber for the same time period without the presence of a foot shock in a 'recall' session and on a 3rd day the recall session was repeated with visual and tactile contextual cues modified.

Compared to young ApoE4 mice, adult transgenic mice showed trends toward decreased measures of network integration; specifically, assortativity and transitivity/clustering were decreased. Additionally, compared to age-matched males, female mice showed trends toward decreased small world coefficient and characteristic path length, but increased clustering/transitivity and network strength. During CFC, all mice developed robust freezing behavior during conditioning, with adult ApoE4 mice showing more robust fear conditioning than their young counterparts. Adult ApoE4 mice also showed greater freezing response during both recall sessions and less of a decrease in freezing behavior during modified context recall. In terms of sex-differences females exhibited a trend toward greater freezing during the same-context recall session. The results suggest that reduced network integration in adult ApoE4 mice is linked to increased fear behaviors and a decreased ability to recognize contextual changes. This suggests a link between network integration and contextual memory stability. Additionally, the data suggests that male and female mice of both age groups have differential responses to the ApoE4 genotype.

First Author (Last name, first name): Sinakevitch, Irina	Presenter (if someone other than First Author):
Abstract Title: Detailed examination of the locus coeruleus subnucleus - LC compact - in rhesus macaques	
McKnight Institute: Tucson	Lab: Barnes

ABSTRACT

The Locus Coeruleus (LC) is a brainstem nucleus with the largest group of noradrenaline producing neurons. Dysregulation of LC systems contributes to cognitive dysfunctions observed in aging and Alzheimer's disease. We previously reported our results from a study that examined 30 micrometer coronal brainstem sections along the rostral-caudal axis of the LC from a colony of 30 cognitively assessed rhesus macaques ranging in age from 7 to 32 years (human equivalent ~21-96 years). We used AMIRA software to reconstruct the LC from tyrosine hydroxylase (TH)-immunofluorescence and Nissl-stained serial sections aligned with previously collected MRI data. Using this method, we established the 3D structure of the LC nucleus and its subnuclei: LC lateral, LC medial, and LC compact (Sinakevitch et al. Program No. 574.08. 2022 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2022.) Here we present further analysis and description of one of the LC subnuclei: LC compact. The LC compact is the area of the LC with the highest neuronal density. It is located within the LC medial nucleus, which is comprised of both a densely packed region and a more scattered region of TH-positive cell bodies within periaqueductal gray (PAG), which surrounds the 4th ventricle. Analysis from a subset of the macaques (n=8) reveals that the rostro-caudal extent of the whole LC is between 2.10-2.55 mm. LC compact extends rostro-caudally from 1.44-1.95 mm within LC medial and it has TH-positive neurons with similar structure and cell diameters ranging from 29-43 micrometers. In rhesus macaques the LC compact has three subregions: rostral, middle, and caudal. The rostral LC compact begins with a small area of cells with high density near the enlarged mesencephalic nerve (me5) in the PAG. The middle LC compact extends through almost all the LC medial along the dorso-ventral axis, and the caudal LC compact is a small area with the highest density of cells. The volume of the LC compact varied from 0.62-0.92 mm3 (on each side) and comprises up to 69% of the total TH-positive cells in the LC. The fact that the LC compact closely follows the me5 tract raises the question of whether this structure may interact with the me5 tract. These detailed characterizations of LC compact might be used to further examine the specificity of the impact of age on this LC subnucleus.

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First Author (Last name, first name): Smith, Ethan	Presenter (if someone other than First Author):
Abstract Title: Human tauopathy strains defined by phosphorylation in repeat domains of tau	
McKnight Institute: University of Florida	Lab: Dr. Paramita Chakrabarty

ABSTRACT

Recent proteomic studies have identified a set of post-translational modifications (PTM) on tau protein located in the Proline-Rich Region (PRR), Microtubule Binding Region (MTBR), and C-terminal region that are found specifically in fibrillized tau isolated from Alzheimer's disease (AD) patients. In this study, our overarching aim was to determine whether selective phosphorylation on these PTM sites will impact tau seed-induced misfolding and aggregation of tau protein. Using host tau protein that is modified on these select phosphorylation residues, we show that presence of phosphorylation mimicking substitutions in the repeat domains(S262/T263/S289/S305) substantially reduce seeding efficiency of insoluble AD-tau seeds derived from Alzheimer's disease (AD). The resultant detergent-insoluble seeded tau shows deficient phosphorylation on AT8, AT270, AT100, AT180 and PHF1 epitopes compared to parent tau carrying no phospho-mutations indicating cooperativity between phosphorylation sites located across the different structural domains of tau during the seeding process. On the other hand, PSP-tau (derived from Progressive supranuclear palsy donors) seeding efficiency is not modulated by these phospho-mimicking mutations in the repeat domains, suggesting strain-specific differences between
AD-tau and PSP-tau seeds. Phospho-deficient substitutions in these selective sites do not alter seeding activity of either AD-tau or PSP-tau in our cellular assay. Finally, we identify S305 as a major determinant of the seeding efficiency of AD-tau, which suggests that modification(s) at this site could serve as a protective mechanism against templated seeding in the context of AD-tau seeds. Collectively, our data confirms the functional role of specific tau phosphorylation epitopes in determining the prion-like templated seeding properties of tau in AD and PSP.

First Author: Smith, Samantha	Presenter: Smith, Samantha
Abstract Title: Hippocampal-striatal interactions and response-driven behavior across the lifespan.	
McKnight Institute: University of Florida	Lab: Dr. Sara Burke

Samantha M. Smith[1,2], Sarah Lovett[1,2], Anna Montelongo[1,2], Daniela Zambrano[1,2], Kimberly Nguyen[1,2], Caroline Davidson[1,2], Sara N. Burke[1,2]

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Improving cognitive health in older adults requires understanding the neurobiology of age-related cognitive decline and the mechanisms underlying preserved cognition in old age. While the
hippocampus (HPC) is vulnerable to age-related functional decline, the dorsal striatum (DS) has been hypothesized to be resilient to age-related impairments. In spatial navigation contexts, there is a shift from HPC to DS-dependent learning with age. Furthermore, inactivation of the DS in aged rodents has recently been reported to rescue HPC-dependent spatial learning on a T-maze paradigm. To test the hypothesis that inactivation of the DS can rescue age-related cognitive decline outside of spatial navigation, we bilaterally inactivated the DS of young (n=8) and aged (n=7) rats during paired associates learning (PAL). We have previously shown that this task is sensitive to age-related cognitive decline in male rats and that old animals are more likely to use a DS-dependent response-based strategy. Inactivation of the DS did not alter PAL performance in young or aged rats ($T(7)=1.258$, $p = 0.249$; aged: $T(6) = 0.098$, $p = 0.925$), but did alter a control, DS-dependent spatial navigation task ($F(59,184) = 11.67$, $p < 0.0001$). The lack of an effect of DS inactivation on the PAL task could be due to the higher 'cognitive load' required for PAL performance compared to spatial learning in a T-maze. Thus, to investigate why inactivation of the DS may improve aged animals' performance on HPC-dependent navigation tasks but not other HPC-dependent tasks, current experiments are investigating the extent to which age-related increases to response-driven behavior are conserved across cognitive modalities. Preliminary results of a behavioral characterization between object-place associative learning and spatial learning in a water-based plus maze will be presented.

This research was supported by the McKnight Brain Research Foundation, University of Florida Center for Cognitive Aging and Memory, NIH/NIA R01 AG049722, and the American Federation for Aging Research.

First Author (Last name, first name): Srivathsa, Sahana	Presenter (if someone other than First Author):
Abstract Title: Investigating age-related changes of mPFC neural responses to ventral hippocampus stimulation	
McKnight Institute: Tucson	Lab: Barnes

ABSTRACT

Sahana V. Srivathsa1,3, Abhilasha Vishwanath1,2, Stephen L. Cowen1,2, Carol A. Barnes1,2

1Evelyn F. McKnight Brain Institute,2Department of Psychology, 3Department of Neuroscience, University of Arizona, Tucson, AZ

Neural ensembles in the hippocampus (HC) and medial prefrontal cortex (mPFC) play a crucial role in spatial working memory, a process susceptible to decline during aging in mammals. These regions are connected via a monosynaptic, unidirectional projection from the CA1 layer of intermediate (iHC) and ventral (vHC) hippocampus to the mPFC (Jay and Witter, 1991, J. Com. Neurol. 313:574). Damage or inhibition to this connection leads to impairments in spatial working memory tasks. Performance on spatial working memory tasks is known to correlate with increased synchrony of hippocampal theta (8-12 Hz) rhythms to mPFC neural activity. The temporal offset of mPFC neurons phase-locked to hippocampal theta corresponds to the conduction delay between HC and mPFC neurons, suggesting that the HC-mPFC synchronization is a direct result of this projection. Little is understood about how monosynaptic iHC and vHC inputs engage mPFC neural activity along the dorso-ventral axis of the mPFC or how these change with age.

To investigate these questions, we delivered a single biphasic electrical pulse (pulse width: 0.5 ms) of varied intensities (100-600uA) with a 30s interval between pulses to the CA1 layer in iHC and vHC of anesthetized male F344 young (9 months, n = 1) and old (27 months, n = 1) rats. We simultaneously recorded evoked neural activity along the dorsoventral length of the mPFC using Neuropixels probes. Recordings were obtained from neurons spanning 3.84 mm along the mPFC, including the prelimbic and infralimbic regions (areas 24b and 25). As iHC and vHC projections vary across the different layers of the mPFC, we also compare evoked neural responses across different layers of mPFC in response to HC stimulation – by recording first from layer II/III and then from layer V in mPFC. Stimulating both the iHC and vHC, we observed responses in the mPFC at only very specific depths across all stimulation magnitudes for a given rat.

The magnitude of LFP, however, was higher with vHC compared to iHC stimulation at the same stimulus intensity. Furthermore, the slope of the maximum LFP response increased and the response time decreased with increasing magnitude of stimulus Our preliminary findings allow for a comparison of the effect of hippocampal axonal input, monosynaptic or otherwise, along the dorsoventral length of the mPFC and connectivity changes with respect to age.

The increased LFP response time from stimulus in aging suggests a differential effect of anesthesia with age on the HC to mPFC synaptic connectivity. Our future analysis will further investigate layer and regional differences within the mPFC on LFP and single-unit activity with respect to HC stimulation.

First Author (Last name, first name): Staley, Hannah	Presenter (if someone other than First Author):
Abstract Title: Assessing changes in peripheral immune cell function caused by the PLCG2 P522R genetic variant	
McKnight Institute: University of Florida	Lab: Malú Tansey

ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative disease affecting our aging population, and it is characterized by the presence of beta-amyloid plaques extracellularly, and the formation of tau tangles within neurons. Current research focuses on the extent and manner in which these two pathological hallmarks compromise neuronal health. However, further evidence has implicated the immune system as another contributing factor to neurodegenerative disease progression. The brain itself contains various immune cells, of particular note are microglia, which function to maintain homeostasis within the brain as well as contribute to neuronal health. Genetic variants expressed primarily in microglia have been shown to have both negative and positive effects on risk for developing AD, further emphasizing the importance of this subset of cells on neuronal health. Specifically, a protective genetic variant in the phospholipase C gamma 2 (PLCG2) gene of microglia was recently discovered in a small cohort of AD cases. This genetic mutation, P522R, affords protection from AD-related cognitive decline even in the presence of beta-amyloid plaques. Recent evidence has shown that microglia with this mutation show an increase in both phagocytosis and inflammatory cytokine secretion. Although PLCG2 is highly expressed in brain-resident microglia, it is also expressed at lower levels in peripheral immune cells, including monocytes, B-cells, and natural killer cells. However, whether the mutation has any effect on these cell types has been largely overlooked. For this reason, we investigated whether peripheral immune cells carrying this mutation may also show functional differences. We performed a whole blood stimulation assay to determine the inflammatory phenotype of blood resident immune cells, as well as flow cytometry on splenocytes, plate blood mononuclear cells, and the brains of P522R variant carrier mice. We determined that mice that carry the P522R mutation have a different peripheral inflammatory phenotype upon stimulation, as well as changes in peripheral cell populations. Based on this we concluded that peripheral immune cells that carry the P522R mutation do have altered function compared to wild type peripheral immune cells.

First Author (Last name, first name): Tuckey, Ryan	Presenter (if someone other than First Author):
Abstract Title: Comparison of risk-modifying, Alzheimer's disease–associated APOE isoforms in lipid-bound state provides insight into structural differences	
McKnight Institute: McKnight Brain Research Foundation (MBRF)	Lab: Roberson Lab

ABSTRACT

Genetic variants in *APOE*, encoding the lipid carrier protein apolipoprotein E, are strongly associated with altering risk of developing Alzheimer's disease (AD), the leading cause of dementia worldwide. The common variants *APOE2* and *APOE4,* are associated with decreased and increased risk of developing AD, respectively, relative to the most common *APOE* variant, *APOE3*. The rare *APOE* variants *APOE3-R136S* (Christchurch), *APOE3-V236E* (Jacksonville), and *APOE4-R251G* have been found to protect against AD. Previously, we examined how these variants altered APOE structure in its lipid-free state. These models are limited as APOE is mostly in a lipid-bound state *in vivo*. Our current study uses molecular dynamics (MD) simulations to examine how common and rare variants in *APOE* alter its interaction with lipids while also comparing lipid-free and lipid-bound structures. Our starting APOE structure, provided by Prakashchand *et al.*, was generated from coarse-grained MD simulations of a mutant APOE structure (PDBID: 2L7B) in the presence of DPPC lipid molecules. We then took the lipid-bound APOE mutant and converted it to APOE3. Subsequent simulations were used to generate a representative structure APOE3 before mutating it to the other APOE isoforms.

These were made using APOE3 as it can be converted to all other variants via a single amino acid substitution using PyMOL, except for APOE4-R251G which was made using APOE4. MD simulations for each APOE variant were performed in triplicate beginning with separate starting APOE3 molecules. The last 300 ns of equilibrated simulations for each simulated system were used for analysis. Simulations of the APOE-lipid complex allowed for analysis of each isoform in relation to their lipid interactions, conformational stability, secondary structure occupancy, dynamic cross-correlated motion, and solvent accessible surface area. Findings from this study identify features that distinguish rare isoforms from common isoforms and show effects of lipidation on each APOE isoform. Comparison of isoforms by their lipid interactions, conformational stability, secondary structure occupancy, dynamic cross-correlated motion, and solvent accessible surface area highlight the impact variants have on APOE-lipid interactions. Alterations in structure and lipid binding ability of rare isoforms could potentially change downstream function, thereby contributing to their protection against developing AD. This work was supported by the NIH R01AG068395 and Alzheimer's Drug Discovery Foundation.

First Author (Last name, first name): Varholick, Justin	Presenter (if someone other than First Author):
Abstract Title: Patterning defects and nerve atrophy in aged spiny mice: Implications for regenerative therapies	
McKnight Institute: University of Florida	Lab: Burke

ABSTRACT

The African spiny mouse (*Acomys cahirinus*) is a novel animal model capable of regenerating a fully transected spinal cord and peripheral nerves with targeted reinnervation and no scarring. While this holds significant promise for regenerative therapies in humans, some evidence suggests their regenerative capacity declines with age, likely due to changes in the regenerative niche. Understanding aging in *Acomys* regeneration may improve the application of regenerative therapies in older populations. We used a 4mm ear-pinna biopsy to model tissue regeneration in 4-month-old (mo), 6mo, 9mo, and 22mo *Acomys*. We found that 9mo and 22mo *Acomys* had significantly slower regeneration (i.e., within 110 days) than 4mo *Acomys* (i.e., within 40 days). Age also affected cartilage and adipocyte regeneration, leading to shorter condensations, increased gaps, and fewer adipocytes in older *Acomys*. These delays and patterning defects were correlated with the atrophy of peripheral nerves, which are known to influence the growth and patterning of tissue regeneration in Axolotls and zebrafish via partial denervation. This research has implications for regulating regeneration following a regenerative therapy in aged populations and represents the first investigation into patterning defects and peripheral nerve atrophy in aged *Acomys*.

First Author (Last name, first name):	Presenter (if someone other than First Author):
VIERA, OMAR	
Abstract Title: Effects of systemic administration of oxytocin and oxytocin antagonist on risky decision making in female and male rats	
McKnight Institute: University of Florida	Lab: Bizon/Setlow

ABSTRACT

Oxytocin (OT) is a neuropeptide primarily known for its role in parturition, lactation, and pair-bonding, and can act via both peripheral and central nervous system mechanisms. Recent studies indicate that exogenous OT can attenuate addiction-related behaviors such as drug self-administration in preclinical models. OT signaling is, however, understudied in the context of cost-benefit decision-making, which is frequently altered in the context of drugs of abuse. Here, we investigate the role of this hormone in modulating decision-making under risk of punishment. Female (n=16) and male (n=8) Long-Evans rats were trained on a risky decision-making task (RDT), in whcih they made discrete choices between a large "risky" food reward accompanied by a probabilistic footshock (0%, 25%, 50%, 75%, 100% chance of punishment), and a small "safe" food reward without punishment. Drug administration began when stable performance in the RDT emerged. Rats were initially tested on the RDT following receipt of acute intraperitoneal injections (1.0ml/kg, 15 minutes before testing) of OT (0.0, 0.3, 1.0, 3.0 mg/kg) following a randomized, within-subject design, with at least a 48h washout period between successive injections. Upon completion of OT administration, rats continued testing on the RDT until stable performance reemerged. Next, rats received intraperitoneal injections (1.0 ml/kg, 40 minutes before testing) of the OT receptor antagonist L-368,899 hydrochloride (OT-A, 0.0, 1.0, 3.0 mg/kg) under a similar randomized, within-subject design.

In males, neither OR nor OT-A administration had statistically significant effects on choice of the large, risky reward. In females however, both OT and OT-A administration led to a significant reduction in preference for the large, risky reward. In addition, evaluation of shock reactivity thresholds in females showed no difference in reactivity between vehicle and OT or OT-A conditions. Together these results are indicative of sex differences in OT signaling mediating risk decision-making in the RDT. Ongoing experiments are investigating the mechanisms that regulate these effects.

First Author (Last name, first name): Kristina Visscher	Presenter (if someone other than First Author):
Abstract Title: Macular Degeneration and Plasticity: a newly shared dataset available as part of the NIH Connectomes in Human Diseases project.	
McKnight Institute: UAB	Lab: Visscher

ABSTRACT

We present a shared functional and structural MRI dataset that can be used to advance our understanding of plasticity in the human visual system. Macular degeneration refers to a group of diseases of the retina that result in their late stages in loss of photoreceptors in the macula, the part of the retina responsible for central vision. After central vision loss, patients' visual experiences are profoundly altered. Central vision can no longer serve its typical functions: e.g., reading, examining attended objects, etc. To the degree that patients use vision in daily life, they must learn to use peripheral vision. This represents a massive change in attentive use of the brain circuits that support peripheral vision.

The Macular Degeneration and Plasticity project is part of the Human Connectome Project, Connectomes in Human Diseases. We collected data from patients with macular degeneration, and age, gender, and education-matched controls, allowing group-level comparisons examining the effect of MD. Use of participants with MD also supports a within-subject approach to examining brain plasticity. Participants with macular degeneration have portions of the visual field which lose sensation (scotoma), portions where input stays the same (spared peripheral visual fields), and many participants have a portion of the visual field that is regularly used for attention-demanding tasks (preferred retinal locus). Because many brain areas are retinotopically mapped, these different portions of the visual field are represented in distinct regions of the cortex. Thus, this dataset allows examination of the impact of both increased and decreased usage in the same participant.

These data will be available for examining plasticity in a macular degeneration model. We include partial datasets in the repository to increase the utility of the dataset for a range of uses; there are 38 participants with macular degeneration and 30 controls.

Briefly, datasets, collected over 6 extensive sessions include: MRI measures, retinal health, behavior, neuropsychology, and demographics.

This dataset has produced a number of interim publications, and will be available to the public on the NIMH Data Archive and the Connectome Coordination Facility. We look forward to the innovative analyses that the neuroimaging community will perform on this singular dataset, which has potential to help the field understand the scope of neural plasticity in the visual system.

First Author (Last name, first name): Watson, Cory	Presenter (if someone other than First Author):
Abstract Title: Ketogenic diet effects on Morris Watermaze Performance in APOE4 Knock-in Rats	
McKnight Institute: University of Florida	Lab: Sara Burke

ABSTRACT

Age-related cognitive dysfunction, exacerbated by pathologies comorbid with aging such as Alzheimer's Disease, greatly impacts quality of life and the ability of older adults to live independently. One of the strongest risk factors for the development of Alzheimer's Disease is the presence of an allele of the apolipoprotein E gene, APOE4. There are 3 common alleles of the APOE gene, with ε3 being the most common, ε2 providing some level of protection against Alzheimer's Disease, and ε4 being associated with a highly increased risk of developing Alzheimer's Disease. APOE is a protein produced by astrocytes that assists in transporting cholesterol, and researchers have found that cells with the APOE4 allele have disruptions in lipid metabolism. Recent studies suggest that a ketogenic diet might mitigate biochemical alterations affiliated with advanced aging and improve performance on learning and memory tasks in a rat model of cognitive aging. A ketogenic diet is high in fat and very low in carbohydrates, which causes the body to enter a metabolic state of ketosis, where fats are used as the primary energy source instead of carbohydrates. Using a rat model with a homozygous replacement of the Rat APOE gene with the Human APOE4 gene, this project tests the extent to which a ketogenic diet can mitigate cognitive decline associated with the APOE4 allele compared to a standard rat feed diet. The Morris Water Maze is a commonly used behavioral task that tests special learning and memory abilities and can be used to assess age related cognitive decline such as that caused by Alzheimer's Disease. We hypothesize that APOE4 knockin rats fed a ketogenic diet will perform better when tested on the Morris Water Maze than those fed a standard rat diet high in carbohydrates.

First Author (Last name, first name): Xia, Qiangqiang	Presenter (if someone other than First Author):
Abstract Title:	**Effects of Deletion of Autism-related Gene *Gigyf2* in Mice**
McKnight Brain Institute at UAB	Lab: Craig Powell Lab

Effects of Deletion of Autism-related Gene *Gigyf2* in Mice

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Autism Spectrum Disorders (ASD) are neurodevelopmental disorders in which children display differences in social interaction/communication and repetitive stereotyped behaviors along with variable associated features.

GIGYF2 (Grb10 Interacting GYF (glycine-tyrosine-phenylalanine) Protein 2) is a protein-coding gene associated with neurodevelopmental disorders. GIGYF2 interacts with the Grb10 (growth factor receptor bound protein 10), which is an adaptor protein that known to interact with insulin or insulin-like growth-factor receptors and signaling molecules. This interaction suggests that *GIGYF2* is involved in signal transduction pathways and cellular signaling processes. The exact function of *GIGYF2* is not fully understood, but several sequencing studies have implicated its involvement in ASD. Previous studies suggest that *GIGYF2* mutations disrupt 4EHP function to increase protein translation.

Although complete knockout of *Gigyf2* is early post-natal lethal, our *Gigyf2* conditional knockout heterozygous (HET) mice are still viable and have a 40% reduction in *Gigyf2* expression and demonstrate modest behavioral differences including decreased locomotor activity in open field, increased repetitive grooming behavior, decreased rearing behavior, normal sociability (social preference) but impaired social novelty preference (social novelty) in 3-chamber test of sociability.

Both frequency and amplitude of mEPSC and mIPSC are unchanged in *Gigyf2* HET mice hippocampus. Heterozygous deletion of *Gigyf2* also did not affect baseline synaptic transmission, presynaptic transmission, or LTP in hippocampus except a slight increase in Paired Pulse Ratio (PPR) in hippocampus. AAV-Cre infection reduced Gigyf2 protein by 30% and 78% expression in HET and homozygous (HOM) neurons in culture, respectively. Both CaMKII-Cre mediated heterozygous deletion of *Gigyf2 in vivo* and AAV-Cre mediated homozygous deletion of *Gigyf2 in vitro* did not significantly impair the phosphorylation of AKT, ERK and S6K in mouse cortical neurons. Frequency and amplitude of mEPSC recordings were comparable between AAV-Cre infected *Gigyf2* WT, HET and HOM neurons in culture.

Taken together, these findings indicate that *Gigyf2* regulates some behaviors without significantly affecting synaptic transmission in hippocampus or cortical neurons in culture.

First Author (Last name, first name): Zempare, Marc	Presenter (if someone other than First Author):
Abstract Title: Determining the age of onset of cognitive impairment in male and female TgF344-AD rats	
McKnight Institute: Tucson	Lab: Barnes

ABSTRACT

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Alzheimer's Disease (AD) is characterized by age-dependent cognitive decline and neurodegeneration and is the most common form of dementia in the 65+ aging population in the United States. The pathological hallmarks of AD include the formation and aggregation of amyloid beta plaques and hyperphosphorylated tau proteins leading to failure of critical brain circuit function. Increasing evidence shows that the dorsal hippocampus and medial prefrontal cortex (mPFC) are among the brain regions that are most susceptible to AD pathology. These regions are crucial for learning, memory and spatial navigation and show significant impairment during progression of AD. A novel model of AD was developed by Cohen et al. in 2013 in Fischer 344 rats that express the familial AD human mutant genes: Swedish amyloid cursor protein (APPsw) and presenilin-1 delta E9 (PS1ΔE9). The TgF344-AD model results in a comprehensive set of AD-like phenotypes including: 1) progressive amyloid plaque aggregation and formation, 2) endogenous rather than engineered tauopathy leading to the formation of neurofibrillary tangles (NFTs), 3) cognitive decline and 4) gliosis and neuronal loss. While there has been some characterization of the behavioral status of the TgF344-AD rats, the onset of the behavioral deficit has been roughly determined to be around 9 months in both cross sectional (Cohen et al 2013) and in longitudinal (Berkowitz et al 2018) studies. A more fine- grained month by month analysis of when the behavior begins to change in the TgF344-AD male and female rats has yet to be determined. The purpose of this study was to identify this transition across several behavioral domains including the hippocampus-dependent spatial version of the Morris watermaze task, the medial prefrontal cortex (mPFC)-hippocampus-dependent temporal order recognition (TOR) memory task, and the amygdala-midbrain-dependent elevated zero (EZ) maze task. Six groups (n=65) of male and female TgF344-AD and wildtype (WT) rats at ages 4 months, 5 months, 6 months, 8 months, 9 months, and 10 months of age were tested on the tasks discussed above. Both male and female TgF344-AD rats were comparable in performance to their age-matched WT controls at 4 months, 5 months, 6 months of age on the spatial version of the Morris watermaze, the TOR task and on the EZ maze task. Ongoing testing of male and female TgF344-AD rats at 8 months, 9 months, and 10 months will determine the precise age-of- onset of impairment due to AD pathology across the listed behavioral domains of this study.

Keywords: Aging, Cognition, Alzheimer’s Disease

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First Author (Last name, first name): Zequeira, Sabrina	Presenter (if someone other than First Author):
Abstract Title: Effects of cannabis on cognition in young and aged rats	
McKnight Institute: University of Florida	Lab: Dr. Bizon and Dr. Setlow

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Cannabis use is growing rapidly among older adults. As the number of older adults in the US is expected to reach 90 million by 2050, it is imperative to understand the potential cognitive impacts of cannabis use in this population. This is especially true given that cannabis use in young adults can impair cognition, and that many aged individuals already exhibit such deficits, particularly in forms of cognition supported by prefrontal cortex (PFC) and hippocampus. We evaluated the effects of chronic oral administration of delta-9-tetrahydrocannabinol (THC; the major psychoactive component of cannabis) on a delayed response task that assessed PFC-dependent working memory and a water maze task that assessed hippocampal-dependent spatial memory in young adult (5 months) and aged (23 months) Fischer 344 x Brown Norway F1 hybrid rats of both sexes. Rats were initially trained on the delayed response task until reaching stable performance. In agreement with prior findings, aged rats were impaired compared to young adults, particularly at longer delays. Rats of both ages then consumed either plain gelatin or gelatin containing 1 mg/kg THC daily in their home cage. Drug was administered following daily behavioral testing to dissociate chronic from acute effects. Working memory was assessed after three weeks of daily consumption. No effects of THC were observed on working memory performance in young adult rats; however, aged rats consuming THC performed reliably better than aged rats consuming control gelatin. Rats were then trained on the water maze while continuing to consume gelatin following daily training. While aged rat performance in water maze was worse than young, no reliable effects of THC were observed at either age. In a second set of experiments, acute effect of cannabis smoke exposure were assessed and in a prefrontal cortex-dependent delayed response task, acute exposure to cannabis smoke enhanced working memory accuracy in aged males but impaired accuracy in aged females, while having no effects in young adults of either sex. In contrast, acute cannabis smoke impaired performance on a hippocampus-dependent trial-unique non-matching to location task, irrespective of age or sex. These findings suggest that chronic THC does not impair, and can provide benefit to, cognition in older subjects. Pharmacokinetics of Δ9THC and its metabolites were assessed using blood samples following both oral and smoke routes of administration, which revealed no significant differences between young and aged rats. Using Matrix-assisted laser desorption/ionization mass spectrometry (MALDI Imaging) brains will be analyzed to quantify changes in brain metabolism following chronic THC exposure in young and aged rats.