MCKNIGHT BRAIN RESEARCH FOUNDATION POSTER RECEPTION

SUNDAY, October 6, 2024
5:00 - 7:00 P.M.

Hilton Chicago
Williford ABC 3rd Floor
720 S Michigan Avenue Chicago, IL 60605

Questions:
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McKnight Brain Research Foundation
Poster Reception
Chicago, IL
October 6, 2024

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First Author (Last name, first name): Adamson, Ashley	Presenter (if someone other than First Author):
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Abstract Title: The role for cell cycle regulators in trichloroethylene-induced Parkinson's dementia

McKnight Institute (Arizona, Gainesville, Miami, UAB): UAB	PI Lab: De Miranda

ABSTRACT

Parkinson's disease (PD) is a neurodegenerative movement disorder in which up to 80% of patients develop cognitive impairments. There is significant heterogeneity between cognitive phenotypes in PD, yet there are no mechanisms to explain this, and genetic risk factors cannot account for most phenotypic differences. Environmental contaminants, such as pesticides and solvents, are epidemiologically linked to PD risk. Trichloroethylene (TCE) is an organic solvent and degreasing agent that contaminates the air, water, and soil in much of the United States. TCE is linked to elevated PD risk (OR 1.70, 95% CI: 1.39–2.07), induces dopaminergic neurodegeneration, and has been correlated to poor long-term cognitive performance (OR 1.51, 95% CI: 1.24-1.84); thus it represents a toxicant that could influence PD dementia; however, the mechanisms underlying this are not clear. Recently published research from our lab showed that twelve weeks of TCE exposure (100 ppm) via inhalation in adult mice induces parkinsonian pathologies (i.e., dopaminergic neurodegeneration in the substantia nigra, accumulation of phosphorylated αSyn, and neuroinflammation) as well as cognitive impairment. In addition, we observed a significant increase in senescent cell populations alongside an increase in the activation of cell cycle regulatory protein CDK5 within TCE-exposed animals, suggesting that accelerated cell cycle dysregulation may be a potential driver of TCE-induced neurodegeneration and cognitive dysfunction. Populations of neural stem cells (NSCs) in the brain that persistently replicate throughout adulthood reveal a unique influence of the cell cycle on a specific neuronal population, and loss of the adult-born neurons from NSCs leads to impairments in spatial memory cognitive functioning. Similarly, the overactivation of CDK5 has been shown to phosphorylate Tau at residues that are hyperphosphorylated in Parkinson's disease dementia. Therefore, we hypothesized that TCE exposure induces cell cycle dysregulation as a mechanism that induces senescence in neural stem cell populations alongside aberrantly activating CDK5 thereby influencing a PD phenotype with more prominent cognitive impairment.

To investigate this relationship, we exposed 12-month-old male and female C57BL/6 mice to 100 ppm TCE inhalation or control (filtered room air) over 12 weeks in a whole-body passive exposure inhalation chamber. Mice exposed to TCE showed significant loss of pyramidal neurons in the CA3 of the hippocampus ($p=0.0002$). Concurrently, we observed a significant increase in the senescent proteins p16 and p35 in neurons of the subgranular zone of the dentate gyrus – one of two regions where adult neurogenesis occurs and influences cognition ($p=0.0043$). In line with this, we saw a significant reduction in the number of immature neurons in this region ($p=0.0282$). Additionally, we observed an increase in the activation state of CDK5 within pyramidal neurons of the hippocampus ($p = 0.0208$) alongside an increase of hyperphosphorylated Tau at two separate residues implicated in PDD (Ser404 and Thr181). We then interrogated CDK5 inhibition as a therapeutic target for reducing senescence and preventing pTau accumulation in vitro and found that treating cells exposed to TCE with a CDK5 inhibitor reduced p16 expression ($p = 0.0408$) and accumulation of phosphorylated tau ($p = 0.0250$). Together, these data show that inhaled TCE exposure caused hippocampal neurodegeneration, impaired neurogenesis, pTau accumulation, and cognitive impairments, highlighting the potential role of environmental exposures in influencing the heterogeneity of cognitive impairment in PD. In addition, our data indicates that environmental toxicant-induced senescence and over-activated CDK5 could be fundamental new mechanisms that drive cognitive impairment in PD.

First Author (Last name, first name): Balsamo, Barbara	Presenter (if someone other than First Author):
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Abstract Title: Alpha-Synuclein Aggregation Impairs Executive Function in Aging: Insights from a Prefrontal Cortex Mouse Model Study	
McKnight Institute: Gainesville	**PI Lab:** Mark Moehle

ABSTRACT

Healthy aging is often accompanied by subtle cognitive changes, particularly in executive functions like cognitive flexibility, which is the ability to adapt to changes in the environment. Understanding the mechanisms behind these changes is critical for developing strategies to support cognitive health during aging. Emerging evidence suggests that the pathological accumulation of α-synuclein (α-syn), a protein linked to neurodegenerative disorders, may also contribute to cognitive decline during normal aging. α-syn forms intracellular aggregates known as Lewy bodies and Lewy neurites that spread throughout the brain, leading to psychiatric, physical, and cognitive impairments by disrupting brain circuits essential for cognitive functions.

The exact mechanisms linking α-syn to executive function deficits are not fully understood. Therefore, we aimed to explore changes in brain circuitry and α-syn's role in executive function impairments using a preformed fibril (PFF) mouse model. Mice were injected with either α-syn PFFs or α-syn monomers and underwent behavioral tests at six weeks and three months post-injection. We utilized a pairwise visual discrimination task to assess cognitive flexibility through two phases: acquisition and reversal. In the acquisition phase, mice learned to distinguish between two images, while in the reversal phase, the previously learned associations were reversed.

While no significant differences were observed at six weeks post-injection (2-Way ANOVA, $p=0.1099$), significant deficits in the acquisition phase (Log-rank test, $p=0.0050$) as well as the last day of the reversal phase were evident at three months post-injection (2-Way ANOVA, $p=0.0764$). These results correlate with electrophysiological findings suggesting that pathological α-syn induces neuronal hypoexcitability in the PL-mPFC, a region critical for executive function. This links α-syn aggregation with deficits in cognitive flexibility as the brain ages. Our findings suggest that α-syn aggregation may contribute to cognitive decline in neurodegenerative conditions and the healthy aging brain. Understanding these mechanisms could provide insights into preserving cognitive health and developing targeted interventions for cognitive impairments in aging populations.

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Abstract Title:Targeting AD-pathology by increasing Angiotensin (1-7) via genetically modified probiotic in TgF344-AD rats	
McKnight Institute (Arizona, Gainesville, Miami, UAB): UAB	PI Lab: Hernandez Lab

ABSTRACT

Targeting AD-pathology by increasing Angiotensin (1-7) via genetically modified probiotic in TgF344- AD rats.

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To date, proven treatments for preventing age- and AD mediated cognitive decline are lacking, thus research on potentially efficacious interventions is desperately needed. This work approaches the treatment of ADrelated neuropathological, synaptic, and cognitive decline through increased angiotensin (Ang) 1-7. Ang (1,7) binds Mas receptors expressed in multiple cell types within the brain, which can decrease inflammation and AD pathology. While previous attempts at sustaining increased levels of Ang1,7 have proven difficult, as traditionally this requires repeated injections or continuous infusions, the work presented herein utilizes a genetically modified probiotic (Lactobacillus paracasei secreting Ang (1,7); LP-A) that can be delivered orally to chronically increase Ang (1,7). LP-A colonizes in the gut microbiome, increases circulating Ang (1,7) and decreases cytokines in the brain of rats. Moreover, it improves cognitive performance in a drosophila model of AD. Therefore, we utilized LP-A to assess the capability of a sustained increase in Ang (1,7) to ameliorate cognitive and pathological deficits in a transgenic rat model of AD, the TgF344-AD rat. Behavioral performance was assessed on a variety of behavioral tasks, including measures of associative learning, spatial navigation, object recognitive memory, fear conditioning and anxiety-like behavior in TgF344-AD rats given Lactobacillus paracasei or the genetically modified LP-A, relative to TgF344-AD and wildtype rats given saline. Brain slice electrophysiology in the dentate gyrus was used to assess strength of basal transmission and long-term plasticity. LP-A administration significantly altered gut microbiome composition and can modify behavioral performance. Thus, utilizing this approach may be an appropriate avenue for the treatment of AD-related symptomology in future clinical trials.

First Author (Last name, first name): Barnes, Carol	Presenter (if someone other than First Author):
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Abstract Title: Relationships between cognition, MRI-based regional gray matter volume and amyloid and tau histopathology across the lifespan of male and female rhesus macaques	
McKnight Institute(Arizona, Gainesville, Miami, UAB): Arizona	PI Lab: Barnes

ABSTRACT

Relationships between cognition, MRI-based regional gray matter volume and amyloid and tau histopathology across the lifespan of male and female rhesus macaques.
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Primary histopathological correlates of Alzheimer's disease (AD) include A plaques, abnormally phosphorylated tau (ptau), neuron death and synapse loss, which in its severe form is accompanied by dementia. All of these features are represented in the NIA-AA Research Framework (ATN) designed for diagnosing AD in living people using imaging and biofluid biomarkers for amyloid (A), tau (T), and neurodegeneration/neural injury (N) (Jack et al., 2018). Another common feature of the brains of AD patients involves cerebral amyloid angiopathy (CAA). There have been no experiments that have examined potential relationships between cognition, regional brain distribution of amyloid plaques, cerebral amyloid angiopathy, ptau and MRI-determined gray matter volumes in the same group of behaviorally characterized nonhuman primates. Furthermore, ATN classification has not been conducted in nonhuman primates. Here, all of these variables were examined in a group of 32 male and female rhesus macaques ranging in age from 7 to 33 years. Amyloid plaques or cerebral amyloid angiopathy (CAA) was found in at least one brain region in 13 of 17 monkeys over 22 years of age, and ptau was found in at least one brain region in 6 of 17 monkeys over 22 years of age, indicative of "pretangles" but no actual neurofibrillary tangles were observed in any monkey. There was a sex difference in of the pattern of neuropathological findings in the brains of monkeys over 22 years, with males having more ptau than females, and females having more plaques and CAA than males. When ATN staging was conducted, those monkeys with "triple positive" ATN status had significantly slower learning and poorer DNMS retention scores than monkeys who were "triple negative, but no monkey had amyloid or ptau levels or distributions severe enough to indicate a diagnosis of AD, nor were any of the cognitive impairments severe enough to be consistent with dementia. As has been observed previously, monkeys over 22 years of age had lower grey matter volumes than did young, and the most striking behavioral correlates of the lower gray matter volumes in older monkeys was found in both acquisition and retention of an Object Discrimination task. Together these data suggest that not all primates are susceptible to AD.

First Author (Last name, first name): Baumgartner, Nina	Presenter (if someone other than First Author):
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Abstract Title: The rostral lateral septum drives estrous cycle state-dependent suppression of cued threat memory	
McKnight Institute (Arizona, Gainesville, Miami, UAB): UAB	PI Lab: Elizabeth Lucas

ABSTRACT

The rostral lateral septum drives estrous cycle state-dependent suppression of cued threat memory Nina E. Baumgartner, Kristen H. Adcock Binion, Neysa S. Dechachutinan, Gaven C. Bell, , Amuktha S.

Dasari, Audrey M. Dahlen, Dara S. Russell, Gavin C. Newberry, Timothy H. Rumbell, Jeremy M. Simon, & Elizabeth K. Lucas

Women are twice as likely as men to experience post-traumatic stress disorder (PTSD) and, among people diagnosed, women report more severe and longer-lasting symptoms. These differences are partially explained by cycling ovarian hormones across the menstrual cycle, as low levels of ovarian hormones are associated with worsened PTSD symptoms including dysregulated emotional memory. Here, we tested the hypothesis that ovarian hormone fluctuations across the reproductive cycle contribute to state-dependent learning, a phenomenon in which memory encoding and recall occur most efficiently in the same physiological state. Using cued threat conditioning, the most well-established model of emotional memory, we compared male mice to female mice that underwent training and recall under the same or opposite ovarian hormone state. We targeted high (proestrus, P) and low (diestrus, D) hormone states for a total of 5 experimental groups: male, P>P, P>D, D>D, D>P. Cued memory recall was indistinguishable between males and P>P females. Remarkably, all other groups exhibited increased recall. Next, we investigated brain regions involved in these behavior effects using c-fos expression as a neural activity marker following threat conditioning in males and females in P or D. Analysis of 114 brain regions revealed hormone state-dependent activation in a limited number of regions. The most prominent differences were observed in robust engagement of the rostral lateral septum (LS) in P females. Remarkably, when we quantified c-fos reactivation in the LS following cued memory recall, we found enhanced state-dependent reengagement in P>P females compared to all other groups. Next, using pan-neuronal chemogenetic activation of the LS, we found that LS activation during either threat conditioning or recall in D is sufficient to suppress expression of threat memory in females. We then sought to identify cellular populations within the LS involved in this P-specific neuronal ensemble for behavioral suppression of cued threat memory.

We performed single nucleus sequencing of the LS in naïve and trained P females and identified 52 transcriptionally distinct cellular clusters. Of these, only two neuronal clusters exhibited immediate early gene activation following threat conditioning: one population expressing both somatostatin and neurotensin (SST-NTS), and the other expressing corticotropin- releasing hormone receptor 2 (Crhr2). Fluorescent in situ hybridization revealed enhanced engagement of LS SST-NTS, but not Crhr2 neurons, following threat conditioning in P females. Ongoing work is measuring the calcium activity of LS SST- NTS neurons during threat memory processing across hormone states and investigating the downstream and upstream neural circuitry of this population. Together, we report strong estrous cycle state-dependent modulation of emotional memory via novel female-specific brain circuitry centered in the LS.

First Author (Last name, first name): Bolaram, Anudeep	Presenter (if someone other than First Author):
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Abstract Title: Neural Mechanisms of Adolescent Sustained Attention	
McKnight Institute(Arizona, Gainesville, Miami, UAB): UAB	PI Lab: David Knight, PhD

ABSTRACT

Attention is a fundamental process that modulates the performance of daily activities. Attention supports the identification of task-relevant information and rejection of task-irrelevant information to effectively execute goal-directed behaviors. Sustaining attention is important for goal-oriented behaviors (e.g., reading, listening to lecture, completing homework). Brain maturation during adolescence may be important for the ongoing development of sustained attention processes. However, investigations of the efficiency of sustained attention processes during adolescence are relatively scarce. Therefore, neuroimaging research into individual differences in sustained attention in adolescence may provide a better understanding of neurodevelopmental processes that underlie attention. The current study was designed to identify adolescent brain activity that underlies sustained attention and varies with performance during a sustained attention task. Forty participants [20 female, age = 15 ± 0.80 years (Mean ± SD)] completed the paced visual serial addition test (PVSAT) during functional magnetic resonance imaging (fMRI). Participants viewed single digit numbers (3 s duration) on a screen during sustained attention and control conditions of the PVSAT. Participants either reported the sum of the two most recent numbers (i.e., sustained attention) or reported the number on the screen without adding (i.e., control). The task was presented during two fMRI scans that contained 4 blocks of control trials that alternated with 3 blocks of sustained attention trials (10 trials/block; 1 s inter-trial interval). Task instructions were presented (6 s duration) prior to each block of trials. The percentage of correct responses across sustained attention vs control conditions served as a measure of performance accuracy. Neuroimaging data were acquired on a 3T Siemens Prisma scanner. Data were analyzed with a linear mixed effects model with performance accuracy as a covariate. Results revealed a main effect of PVSAT (i.e., sustained attention vs control). Greater dorsolateral prefrontal cortex (PFC), cingulate gyrus, anterior insula, and inferior parietal lobule activity was observed during the sustained attention than control condition. Results also revealed a significant interaction between PVSAT and performance accuracy. Performance accuracy during the PVSAT was related to activity within the superior parietal lobe and subcallosal gyrus. These findings suggest that superior parietal lobe and subcallosal gyrus activity may underlie individual differences in sustained attention during adolescence.

First Author (Last name, first name): Bonfitto, Anna	Presenter (if someone other than First Author):
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Abstract Title: Identification of Alzheimer's disease- and normative age-related transcriptional changes in human middle temporal gyrus.	
McKnight Institute(Arizona, Gainesville, Miami, UAB): Arizona	PI Lab: Huentelman

ABSTRACT

Identification of Alzheimer's disease- and normative age-related transcriptional changes in human middle temporal gyrus.

Anna Bonfitto, Ignazio Piras, Serena Song, Francis Taguinod, Juan Troncoso, Changiz Geula, Emily Rogalski, Claudia Kawas, Maria Corrada-Bravo, Thomas Beach, Geidy Serrano, Paul Worley, Carol Barnes, and Matt Huentelman

Alzheimer's disease (AD) and normal aging have demonstrable effects on the human temporal lobe. To better understand the transcriptional changes happening in the temporal lobe in the context of aging and dementia we collected a study cohort consisting of fresh frozen human brain samples from the middle temporal gyrus (n=622). In total it included 281 non-demented controls (ND), 210 with Alzheimer's disease dementia (AD), and 131 individuals with MCI or CIND (Cognitive Impairment with no Dementia) wherein each donor was cognitively characterized while living and neuropathologically assessed following death. Each brain specimen was molecularly characterized using bulk RNA sequencing and analyzed using differential expression, gene and cell set enrichment, coexpression, key driver, and pseudotime analytical approaches. The normative aging analysis included all ND donors and identified three genes significantly down-regulated (adj-p < 0.05) in the individuals who were 65 and older: GPR26, HSPA6, and TRPC3. Additionally, we identified 472 genes that were significantly differentially expressed in the total ND cohort. Gene Set Enrichment Analysis (GSEA) demonstrated a significant decrease in genes involved in angiogenesis with increasing age (adj-p < 2.3E-09) and Cell Set Enrichment Analysis (CSEA) showed a significant upregulation of oligodendrocyte genes and a significant downregulation of endothelial cell genes with increasing age. Finally, we observed a downregulation of inhibitory neuron genes but no changes in excitatory neuron genes in the total cohort, while genes specific to both cell types were downregulated in the ND cohort who were 65 and older. The AD-specific analysis included all ND and AD samples. We identified 4,414 significantly differentially-expressed genes including NPNT, GFAP, ADAMTS2, and KANK2 which were increased in expression in the AD samples. GSEA revealed known patterns of downregulated synapse-related functions in AD while CSEA demonstrated downregulation of excitatory neuron genes and upregulation of astrocyte, endothelial cell, microglial, and pericyte genes. Coexpression identified 76 differentially-expressed modules including upregulation of the regulation of vasculature development process (top key driver gene = COL1A2) and downregulation of the regulation of postsynaptic membrane potential process (top key driver gene = EGR2). Together this cohort-based analysis empowers the comparison of AD and normative aging transcriptional effects in the middle temporal gyrus of the human brain.

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Key Words: aging | Alzheimer's disease | genomics | SNP | transcription

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Abstract Title: **Examination of Motility and Neuronal Morphology in Variants Associated with *MAPK8iP3-related* Disorders**

McKnight Institute (Arizona, Gainesville, Miami, UAB): UAB	PI Lab: Dr. Camerron Crowder

ABSTRACT

MAPK8IP3-related disorders are rare, genetically diagnosed, neurodevelopmental disorder that results in intellectual disability, global developmental delay, and movement abnormalities in children. These disorders are caused by *de-novo* mutations in the *MAPK8IP3* gene, which codes for JNK-interacting protein 3 (JIP3). Majority of variants are missense and the impact of individual amino acid substitutions on JIP3 function remains unclear. This study aims to investigate genotype-phenotype correlations by overexpressing mRNA containing patient variants in zebrafish lacking JIP3 protein. JIP3 KO zebrafish display decreased motility, compared to wild-type fish. Patient variant mRNA, from 5 individual variants, was microinjected into zebrafish larvae at the single cell stage, and then larvae were assessed for movement phenotypes and neuronal morphology abnormalities. One variants, p.R1146C, rescued decreased locomotor activity in JIP3 KO fish, while 3 other variants, p.R521H, p.M543del, p.R578C, located in or in close proximity to the Rab-interacting protein domain, did not rescue and potentially worsened the motility phenotype, compared to wild type clutch mates. This suggests altered pathophysiological mechanisms at play across individual variants, with more severe outcomes in variants located in the Rab-interacting domain, compared to other protein domains.

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Abstract Ttle: Identification of novel activity-related transcripts using laser capture microdissection and RNA sequencing	
McKnight Institute(Arizona, Gainesville, Miami, UAB): Arizona	PI Lab: Barnes

ABSTRACT

Identification of novel activity-related transcripts using laser capture microdissection and RNA sequencing

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4TGen, Phoenix, AZ 5Neurogenomics

Abstract:
Activity-regulated genes (ARGs) are genetic regions that respond to neuronal cell activity changes. ARGs are important in neuronal health and disease, and play a central role in memory formation and plasticity. Arc (activity regulated cytoskeleton associated protein) is a prototypical ARG wherein neuronal depolarization results in increased transcription as well as a time-related differential compartmentalization of Arc RNA from the neuronal soma into the dendrites. To identify novel ARGs we laser capture microdissected four hippocampus cell compartments in the CA1, CA3b, CA2, and dentate gyrus regions including their soma and dendritic fields individually. The experimental cohort was comprised of six-month-old F-344 rats at multiple time points (10, 30 min, 1, 2, 4, and 24 hours; n=6 per time point) following maximal electroconvulsive shock (MECS). We used RNA sequencing and performed differential expression analysis to identify transcripts that were altered by MECS both in quantity and by compartment (soma vs. neuropil). We found eight novel activity-regulated genes that exhibited Arc-like transcriptional response profiles characterized by the following aspects; transcripts were (1) not differentially compartmentalized at rest, (2) significantly increased in expression in the soma compartment before the neuropil, and (3) not previously reported as an ARG. We validated one of these novel ARGs, Trib 1 (Tribbles Pseudokinase 1), using chromogenic in situ hybridization (RNAScope; ACD Bio). Trib1 expression was quantitated by pixel intensity analysis of images captured by the Aperio ImageScope in the same soma and neuropil regions of the hippocampus. The RNAScope results confirmed our RNA-sequencing findings and demonstrated that Trib1 exhibits both a transcriptional and compartmentalization response similar to Arc, positioning Trib 1 as a novel activity-regulated transcript. Trib1 is a pseudokinase that plays a role as a molecular scaffold to initiate degradation of its substrates via the ubiquitin proteasome system. One such substrate is C/EBPalpha; a member of a family of proteins with known roles in cognitive function. Trib1 has also been found to interact with and regulate various MAP kinase family members. Based on our observations, we propose that Trib1 is a new activity-regulated transcript and encourage future evaluations of Trib1 and the role it may play in activity-regulated neural cell physiology.

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Abstract Title: Arc mRNA expression pattern in the CA1 subregion of rat hippocampus following spatial behavior.	
McKnight Institute(Arizona, Gainesville, Miami, UAB): Arizona	PI Lab: Barnes

ABSTRACT

Arc mRNA expression pattern in the CA1 subregion of rat hippocampus following spatial behavior.

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Aging poses significant challenges to cognitive function, particularly in the domain of episodic memory, which relies on the integrity of the hippocampus CA1. Previous studies (Henriksen et al., 2010; Hartzell et al., 2013; Beer et al., 2018; Soltesz and Losonczy, 2018) have addressed functional specialization along the transversal axis of CA1, corresponding to input from the entorhinal cortex. Specifically, the distal CA1 receives projections from the lateral entorhinal cortex (LEC), the proximal CA1 receives projections from the medial entorhinal cortex (MEC), and the medial CA1 receives projections from a combination of LEC and MEC. These projections play a crucial role in processing distinct components of memory along the transversal axis of CA1, resulting in intricate neural representations and diverse behavioral performance. To enhance our understanding of chronological changes within the hippocampus neural network and the impact on cognitive competence, we conducted a comprehensive study investigating the cellular distribution of Arc mRNA in the distal, middle, and proximal subregions of the hippocampus CA1 in three distinct age groups (6 months, 15 months, and 23 months) of male Fisher-344 rats. Additionally, within each age group, rats were categorized into three different cognitive performance levels based on their behavior in the spatial version of the Morris watermaze. Our hypothesis was that an effect of aging and level of cognition within age groups would be evident in the cellular distribution of Arc mRNA within CA1 subregions. Behaviorally induced Arc mRNA expression was investigated by allowing the rats to explore the same environment twice for 5 minutes each, separated by a 20-minute rest period in their home cage. To test whether Arc mRNA distribution was consistent with network stability, we first conducted our data analysis in the middle CA1 region. No difference in network stability was noted in young rats with low, average, and high cognitive ability. Old rats, however, exhibited more network stability in the high-performing group compared with the others. The middle-aged rats exhibited a complex network relationship that we are still exploring. Going forward we will examine the data within distal and proximal regions with respect to aging and cognitive status.

First Author (Last name, first name): Claar, Robert	Presenter (if someone other than First Author):
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Abstract Title: Fronto-limbic activity and functional connectivity in post-traumatic stress disorder and mild traumatic brain injury	
McKnight Institute: Gainesville	PI Lab: Damon Lamb

ABSTRACT

Post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) are complex, heterogeneous, and disruptive medical conditions that afflict millions yearly. mTBI often co-occurs or precedes PTSD, particularly in military contexts. PTSD and mTBI share many symptom domains, most pertinent to this work being emotional dysregulation and executive dysfunction. These shared symptoms create diagnostic and treatment ambiguity for clinicians. Investigations into the neurobiology of PTSD and mTBI could help distinguish the two conditions or prove a common pathway for their shared symptoms, thereby improving diagnostic clarity and creating personalized treatments. Current first-line treatments for PTSD do not reduce symptoms in a significant portion of patients, and much is still not understood about what underlies PTSD and mTBI symptoms, making the potential impact of this work significant. We enrolled 428 right-handed aged 18-45 years old combat-Veterans, 119 of which fully qualified after medical record review and completed our study. Participants' health and available service records were reviewed to confirm diagnoses and identify any potential confounding factors. Participants were administered a large battery of neuropsychological, cognitive, and emotional assessments along with structural magnetic resonance imaging (MRI) and task-based functional MRI. Five individuals had incomplete and/or poor data quality, leaving 114 individuals split across four groups: healthy controls (HCs), PTSD and no history of TBI, history of mTBI but no history of PTSD, both PTSD and history of mTBI. Analyses were conducted to assess group differences in functional connectivity between frontal and limbic regions. Relationships were also explored between functional connectivity and assessment scores. We found significant group differences in functional connectivity between key limbic and frontal brain regions including key regions implicated in the etiology of emotional dysregulation such as the insula and lateral prefrontal cortex. We also observed a significant group by symptom interaction in functional connectivity measures and symptoms of emotional dysregulation. These results help advance our models of how executive dysfunction and emotional dysregulation may be related share common underlying neurobiological characteristics in both PTSD and mTBI. In addition, this evidence implicates potential biomarkers of disease which could help improve diagnostic accuracy for individuals with PTSD or mTBI.

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

ABSTRACT

Frontotemporal dementia (FTD) is a common form of dementia and patients typically present with language or behavioral impairments such as social withdrawal, disinhibition, or word finding difficulties. Heterozygous loss-of-function mutations in the progranulin (*GRN*) gene, resulting in haploinsufficiency of the protein, are a major cause of FTD with TDP-43 pathology. TDP-43 pathology is characterized by TDP-43's mislocalization from the nucleus to the cytoplasm and the formation of TDP-43 aggregates. $Grn^{+/-}$ mice are the genetic model of FTD due to progranulin mutations, but do not develop TDP-43 pathology. However $Grn^{-/-}$ mice, the genetic model of Neuronal Ceroid Lipofuscinosis type 11 (CNL11), an adolescent onset lysosomal storage disorder, develop mild thalamic TDP-43 aggregates at advanced ages. To investigate how progranulin insufficiency exacerbates development of FTD-relevant phenotypes, we crossed $Grn^{+/-}$ mice with transgenic mice expressing wild-type human TDP-43 under the Thy1 promoter (Jackson Lab #012836). We analyzed homozygous transgenic mice (hTDP++) for TDP-43 pathology and neuroinflammation, and hemizygous transgenic mice (hTDP+) for FTDrelated social deficits and pathology. Analysis of homozygous hTDP++ mice showed that $Grn^{+/-}$:hTDP++ mice had more cortical immunoreactivity for markers of reactive glia than $Grn^{+/+}$:hTDP++, but a Nanostring neuroinflammation panel showed little difference between the two groups. In contrast, $Grn^{-/-}$:hTDP++ mice had dramatic transcriptional changes consistent with greater inflammation. Analysis of hemizygous hTDP+ mice revealed more severe social dominance deficits in $Grn^{+/-}$:hTDP+ mice than either $Grn^{+/-}$:hTDP- or $Grn^{+/+}$:hTDP+ mice. This occurred in the absence of detectable TDP-43 pathology or inflammation. Dendritic spine analysis revealed that $Grn^{+/-}$:hTDP+ mice had lower mushroom spine density on basal dendrites of layer II/III pyramidal neurons in the medial prefrontal cortex, neurons involved in social dominance behavior. These data show that progranulin insufficiency and human TDP-43 overexpression interact to worsen inflammatory and social phenotypes, without worsening TDP43 pathology. $Grn^{+/-}$:hTDP+ mice have fewer mushroom spines, a potential cause of low social dominance behavior.

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): Davis, Natalie	Presenter (if someone other than First Author):
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Abstract Title: Loss of Alzheimer's disease risk factor *BIN1* in inhibitory neurons induces network hyperexcitability and behavioral abnormalities

McKnight Institute (Arizona, Gainesville, Miami, UAB):	PI Lab:
UAB	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 AD, 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. Given evidence of a reduction of the neuronal isoform of *BIN1* in AD patients, we generated cell-type specific conditional knockout mice to study the effects of loss of Bin1 from various neuronal cell types. We found that a loss of Bin1 from all neurons (*Nestin*-Cre-driven) increased pentylenetetrazol (PTZ)-induced seizure susceptibility in a gene-dose dependent manner. Examining cell-type specificity, we found that a loss of Bin1 from excitatory neurons (*CaMKIIα*-Cre-driven) decreased seizure susceptibility, while a loss of Bin1 from inhibitory neurons (*Viaat*-Cre-driven) increased seizure susceptibility much like the pan-neuronal loss of Bin1. These data suggest that it is a loss of Bin1 from inhibitory neurons that drives network hyperexcitability, but does not address what type of interneurons. Parvalbumin (PV) expressing interneurons are altered in AD, contributing to inhibitory dysfunction, oscillatory network activity, and cognitive functioning. Therefore, we hypothesized that loss of Bin1 from PV interneurons contributes to network hyperexcitability and cognitive dysfunction. While Bin1 loss from PV interneurons (Bin1-pvKO) had no effect in the PTZ-induced seizure susceptibility assay, electroencephalogram (EEG) recordings showed differences in sub-epileptiform activity in the Bin1-pvKO mice compared to controls. Additionally, Bin1-pvKO mice showed very few differences from controls in traditional behavioral assays, but utilizing machine-learning based behavioral analysis, we found differences in kinematics and pose dynamics between groups. Overall, our findings show that Bin1 alters network hyperexcitability and cognitive functioning in a cell type–specific manner, but complete inhibitory loss is needed to induce widespread changes.

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Abstract Title: Demographic, health, medical, and lifestyle factors associated with longitudinal verbal memory performance across the lifespan.	
McKnight Institute(Arizona, Gainesville, Miami, UAB): Arizona	PI Lab: Huentelman

ABSTRACT

Demographic, health, medical, and lifestyle factors associated with longitudinal verbal memory performance across the lifespan.

Matt De Both, Megan Johnson, Harshini Venkatachalam, Marcus Naymik, Meredith Hay, Roberta Brinton, Carol Barnes, Lee Ryan, and Matt Huentelman

There is significant interest in identifying factors associated with changes in cognitive performance across the human lifespan. This information may help identify protective and risk factors that could be leveraged to improve age-related cognitive changes as well as ameliorate disease susceptibility. A major challenge is that most research studies tend to focus on a narrow age range which hinders an ability to extend recommendations across the human lifespan. To address this, we utilized our internet-based MindCrowd study which currently includes over 3,418 longitudinal participants that span ages from 18-97 years of age. Each of these participants include at least two longitudinal data points for verbal memory that were spaced apart by at least 365 days. The verbal memory task demonstrates upward sloping results (improvement in performance across time) for participants aged 20s-40s, relatively flattened slopes for 50s and 60s, and downward sloping results for the 70s, 80s, and 90s+. These data suggest that in the participants under 50 there are demonstrable practice effects even with at least a year interval between test sessions which then wane in the 50s and 60s and disappear entirely in those 70 and older. Using a model that included time and demographic variables to model change in performance as the outcome, we identified the following factors that were significantly predictive: age (pval 1.41e-5; beta -0.055 per year), seizures (pval 0.03; beta 2.02), and time since last test (pval 2.58e-8; beta -4.27e-6 per year). Participants that reported taking MindCrowd previously performed on average 2.1 word pairs better than those individuals who were repeat participants but did not indicate as such (pval 4.42E-12). In summary, we utilized longitudinal participants from our internet-based cognitive aging study, MindCrowd, and identified factors that were associated with longitudinal verbal memory performance across the aging spectrum under a single study design.

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Key Words: longitudinal | cognition | memory | normal aging | internet testing

First Author (Last name, first name): Demirayak, Pinar	Presenter (if someone other than First Author):
Abstract Title: Cortical Thickness Differs Between Central and Peripheral Vision Processing Areas in Autistic Individuals	
McKnight Institute: UAB	Lab:Visscher Lab

ABSTRACT

In the human primary visual cortex (V1), central and peripheral vision are specialized for different functions. The central vision, which corresponds to the fovea, is associated with high acuity and detailed processing, making it useful for reading and object recognition. Peripheral vision encompasses a larger portion of the visual scene but with reduced spatial resolution. Altered fixation behavior and eye movements were reported in autism Spectrum disorder (ASD). Specifically, off-center fixations (Pelphrey et al., 2002) and higher variability in saccadic amplitude (Takarae et al., 2004) in the ASD population suggest that precision of eye movements is less reliable in ASD, which might affect the development of visuospatial maps. Due to altered processing in central and peripheral vision, a better understanding of the extent of neuroanatomical alterations in ASD will help to enlighten neurodevelopmental changes in autistic individuals. We investigated the cortical thickness differences in V1 both between autistic and neurotypical (NT) individuals as well as between autistic children and adults. The sample consisted of T1-weighted MRI data from: 27 (age range:18-40 yo) ASD adults, 27 (age range:8-17 yo) ASD children, 33 (age range:18-36 yo) NT adults and 23 (age range:8-16 yo) NT children. Multivariate ANOVA analyses on cortical thickness from Desikan Killiany Atlas areas were performed to assess group differences. This was followed by linear model mixed-effect ANOVA analyses on anatomical ROIs corresponding the 0.5-1.5, 1.5-3, 3-5, 5-8, 8-12, 12-18, 18-28, 28-500 eccentricities along dorsal and ventral V1 bilaterally according to Benson atlas (Benson et al., 2014). Given the lack of consistency and accuracy of the eye movement measures in ASD individuals, we hypothesized that cortical thickness would be altered in autistic children and adults in central and far peripheral eccentricities. We found group main effect in whole brain analysis mainly in bilateral parieto-temporal areas. In addition, in V1, we found thinner cortex in the central vision processing section (0.5-1.50) in autistic children compared to autistic adults in the left hemisphere. We also found thicker cortex in far peripheral vision processing sections (28-500) of V1 in autistic children compared to autistic adults in both hemispheres. Group differences between autistic and NT individuals were not statistically significant. Overall, these findings support the idea that peculiarities in gaze and stereotyped visual behaviors have the potential to alter cortical thickness in different directions in central vs peripheral vision processing sections of V1 during neural development.

First Author (Last name, first name): Cabeda Diaz, Indy	Presenter (if someone other than First Author):
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Abstract Title: Estrogen receptor-beta activation reduces cognitive deficits after stroke in middle-aged female rats.	
McKnight Institute: Miami	PI Lab: Raval

ABSTRACT

Estrogen receptor-beta activation reduces cognitive deficits after stroke in middle-aged female rats.

Indy Cabeda Diaz[1], Zoe Quinn Bassett[1], Kunjan R. Dave[1], Miguel A. Perez-Pinzon[1], and Ami P. Raval[1, 2]

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Chronic 17β-estradiol (E_2) treatment has been shown to be neuroprotective in animal brain injury models. However, the failure to reproduce its beneficial effects in the clinic raised concerns regarding its safety. Our previous study demonstrated that a single bolus of E_2 pretreatment reduces ischemic brain damage in the ovariectomized rats via activation of estrogen receptor subtype beta (ER-β). Subsequently we demonstrated that either pre- or post-treatments with ER-β agonist reduced ischemic brain damage and cognitive deficits. As a logical continuation after our findings, the goal of the current study is to investigate the underlying mechanism responsible for the ER-β agonist-mediated neuroprotection. Given the role of E_2 in brain metabolism, we aim to investigate the effects of ER-β agonist pretreatment on the global metabolic changes in the brain of reproductively senescent (RS) female rats. Retired breeder (9–10 months) Sprague–Dawley female rats were considered RS after remaining in constant diestrus phase for more than a month. The RS rats were treated with either ER-β agonist (beta 2, 3-bis(4-hydroxyphenyl) propionitrile; DPN; 1 mg/kg; s.c.) or DMSO vehicle at 48 hr intervals for 10 injections. Forty-eight hours after last injection, brains were collected for unbiased global metabolomic analysis. The data analysis showed significant alterations in the metabolites of glycolysis and other carbohydrate pathways, amino acid metabolism, nucleotide metabolism, and lipid metabolism in the brains of ER-β agonist treated RS rats as compared to vehicle treated. Many of the observed metabolic changes after ER-β agonist treatment can boost brain energy production and support the brain under stress conditions such as ischemia. For example, ER-β agonist significantly decreased Glucose 6-phosphate (G6P) in the brain of RS female rats. A decrease in G6P levels might reduce the flux through the glycolytic pathway, potentially lowering oxidative stress and promoting cellular resilience. Reduced G6P levels could trigger stress response pathways such as the AMPactivated protein kinase (AMPK) pathway or the sirtuin pathway, which are involved in cellular adaptation to metabolic stress and may confer neuroprotective effects. Activation of these pathways due to ER-β agonist treatment may enhance cellular antioxidant defenses, improve mitochondrial function, and promote cellular repair mechanisms, thus protecting the brain from ischemic damage in RS female rats.

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Abstract Title: Violence Exposure, Psychosocial Stress, and Prefrontal Cortex Reactivity	
McKnight Institute (Arizona, Gainesville, Miami, UAB): UAB	PI Lab: Dr. David Knight

ABSTRACT

Adolescent violence exposure (VE) is a chronic stressor that has detrimental effects on emotional well-being, leading to higher rates of mental illness in adulthood. Adolescence is a period in life during which the brain, specifically the prefrontal cortex (PFC), undergoes extensive maturation. Chronic stressors, such as VE, experienced during adolescence may affect the development of the PFC. Thus, PFC activity may underlie the effects of adolescent VE on emotional processes. The present study examined the interrelationships between adolescent VE, stress-elicited young adult brain activity, and depression in young adults. Participants (n = 301; mean age = 20.03 ± 1.51 years), who were previously assessed for adolescent VE, completed the Major Depression Subscale of the Diagnostic Interview Schedule for Children. Participants then completed the Montreal Imaging Stress Task (MIST) during functional magnetic resonance imaging (fMRI). Pearson's correlation indicated that greater adolescent VE was linked to greater depression symptoms in young adulthood ($r = 0.12$, $p < 0.05$). Additionally, stress reactivity varied with VE. Specifically, greater VE was linked to lower stress ratings during the MIST ($r = -0.26$, $p < 0.01$). Further, linear mixed effects analyses of fMRI data revealed a three-way interaction between MIST condition (Stress vs. Control), VE, and depression symptoms. Specifically, stress-elicited dorsoolateral (1323 mm^3; 921 mm^3) PFC activity varied with VE and depression symptoms, with greater stress-elicited dorsolateral PFC activity in those exposed to high levels of VE who reported high levels of depression than those exposed to high levels of VE who reported low levels of depression ($p < 0.05$FWEcorrected). Additionally, participants with low VE who reported low levels of depression showed more stress-elicited dorsolateral PFC activity than participants with low VE who reported high levels of depression. These findings suggest that depression modulates the link between adolescent VE and stress-elicited PFC activity. These results suggest that PFC function may underlie the relationship between adolescent VE and stress reactivity, but this relationship is further impacted by depression symptoms. The present findings provide insight into the neural substrates that underlie the interrelationship between adolescent violence exposure and stress reactivity, which may have important implications for future mental health.

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Abstract Title: Age associated changes in brain phospholipids are mitigated by vagus nerve stimulation	
McKnight Institute (Arizona, Gainesville, Miami, UAB): Gainesville	PI Lab: Bizon-Setlow

ABSTRACT

Age associated changes in brain phospholipids are mitigated by vagus nerve stimulation

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Phospholipids play a crucial role in brain functions, including neuronal communication and synaptic plasticity. Brain phospholipid composition changes in aging and neurodegenerative diseases and has been implicated in cognitive decline. The goals of this study were to characterize exactly how aging alters the spatially-resolved brain lipidome and to determine the degree to which such age changes are modifiable with chronic vagus nerve stimulation (VNS) in different brain regions. Brains from young (4 months) and aged (24 months) Fischer 344 x Brown Norway F1 hybrid rats were processed for spatial lipidomics by matrix-assisted laser desorption/ionization mass spectrometry (MALDI-IMS) imaging. Relative to young, aged rats had increased long chain highly saturated phospholipid species which are typically associated with inflammation and oxidative stress. In contrast, aged rats had reduced long chain unsaturated phospholipid species which are generally neuroprotective. We next determined the extent to which these age-related changes were modifiable by VNS. A separate cohort of aged (24 months) Fischer 344 x Brown Norway F1 hybrid rats were surgically implanted with a 4-channel VNS cuff electrode around the left vagus nerve. After recovery, rats received 30 days of VNS using stimulation parameters (100 stimulus trains over 1 hr; 30Hz, 120 μS pulse width, 700 μA, 0.8 s train duration) previously shown to enhance cortical plasticity. MALDI-IMS imaging compared the lipidome between VNS and aged rats receiving sham stimulation. Overall, VNS mitigated many of the age-associated changes in phospholipid composition, indicating both that lipid composition is highly modifiable even in the aged brain and that VNS has potential to rewire age-related changes in brain lipid metabolism. Additional spatial analysis is ongoing to characterize regionally specific effects of aging and VNS on brain lipidome.

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Abstract Title: Block of Sortilin Binding in Progranulin Gene Therapy Increases Progranulin Levels and Corrects Lipid Abnormalities, Behavioral Phenotypes, and Neurodegeneration Biomarkers in Progranulin Deficient Mice	
McKnight Institute (Arizona, Gainesville, Miami, UAB): UAB	PI Lab: Erik Roberson

ABSTRACT

Progranulin is a secreted protein that is transported to the lysosome through receptors including sortilin. Within the lysosome, progranulin serves as a chaperone for lysosomal enzymes to facilitate the degradation of proteins and lipids. Homozygous loss-of-function mutations in progranulin lead to neuronal ceroid lipofuscinosis (NCL), while heterozygous loss-of-function mutations cause frontotemporal dementia (FTD). The loss of progranulin protein leading to neurodegeneration points to a potential therapy where progranulin protein can be restored using AAV-gene therapeutics. Previous studies have demonstrated the effectiveness of AAV-progranulin tagged at the carboxy-terminus, disrupting its interaction with sortilin. This led us to hypothesize that transduction of progranulin lacking its carboxy-terminal sortilin-binding domain might be a more effective alternative to progranulin with intact sortilin binding. We compared treating progranulin knockout mice with carboxy-terminally blocked progranulin, progranulin with intact sortilin binding, or GFP control. We used multiple outcome measures including immunohistochemistry, microdialysis, lipidomics, machine learning behavioral assays, and biomarker analysis to assess the impact of carboxy-terminal blockade. Progranulin with a blocked carboxy-terminal increased progranulin levels at the injection site through immunohistochemistry and microdialysis. Additionally, both progranulin with and without its sortilin binding corrected BMP deficiency and ganglioside accumulation, with the carboxy-terminal blocked progranulin more effective in cerebellar BMP deficiency and cortical and thalamic ganglioside accumulation. Interestingly, only the carboxy-terminal blocked progranulin reduced plasma NfL, a neurodegeneration biomarker, in progranulin knockout mice. Machine learning behavioral analysis revealed that mice treated with carboxy-terminally blocked progranulin resembled wild-type mice, while those with intact sortilin binding resembled progranulin knockout mice. These findings indicate that blocking the carboxy-terminus of progranulin enhances the effectiveness of progranulin gene therapy.

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

ABSTRACT

With the rise in cannabis use among older adults, alongside 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 AD pathogenesis. While cannabinoids demonstrate potential in reducing inflammation, protecting against oxidative stress, and lessening plaque burden in AD-like pathology in mouse models, studies often fail to mimic human usage and focus on amyloidosis rather than tauopathy. To address these points, we are evaluating the effects of chronic cannabis smoke exposure on inflammatory markers in young and aged mice, and tau pathology in rTg4510 mutant tau transgenic mice.

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 lysates were analyzed using Quantibody cytokine arrays (RayBiotech). 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 AT8 and AT100 antibodies, as well as Iba1 and GFAP to measure gliosis were conducted.

The results revealed that aged mice had significantly higher IL-12p40 serum levels. Aged female mice exposed to cannabis smoke also had higher RANTES serum levels compared to young and aged female mice exposed to placebo smoke, suggesting sex-specific effects of cannabis on aging. Additionally, aged mice had significantly higher levels of P-Selectin, TNF RI, PF4, OPN, Galectin-3, and bFGF in hippocampus and prefrontal cortex compared to young mice (Main effects of Age using 3-way ANOVAs [Sex, Age, Drug]). Male mice experienced more changes in brain inflammatory markers following cannabis smoke exposure compared to female mice. These findings suggest that cannabis smoke affects inflammatory markers differently based on sex, age, and brain region, which could help explain potential effects of cannabis on gliosis and tau pathology progression in rTg4510 mice. Chronic cannabis smoke exposure in rTg4510 mice produced a trend toward decreased GFAP immunostaining in frontal cortex, but not posterior cortex or hippocampus. Further quantification of other immunolabels as well as Western blot analysis of soluble and sarkosyl-insoluble tau levels are ongoing.

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Abstract Title: Adolescent neural reactivity to stress varies with dietary nutrients	
McKnight Institute (Arizona, Gainesville, Miami, UAB): UAB	PI Lab: David Knight, PhD

ABSTRACT

The nutrients people consume in their diet are important factors that underlie healthy emotional function. The role diet plays in emotional functioning is particularly important to study in adolescence, when substantial neural and emotional development occurs. For example, diet may affect emotional function through its role in stress reactivity (e.g., hypothalamic-pituitary-adrenal (HPA) axis). For example, deficient levels of magnesium, zinc, and iron are associated with greater stress via HPA axis dysregulation, while vitamin B6 and B12 supplementation are associated with reduced stress. Stress reactivity, and related emotional processes, are mediated by a neural network that includes the prefrontal cortex (PFC), inferior parietal lobule (IPL), hippocampus, and amygdala. However, the relationships between specific nutrients and stress-elicited activity within these brain regions are unclear. Therefore, this project investigated the relationship between adolescent dietary nutrient intake and stress-elicited brain activity. We hypothesized that greater intake of magnesium, zinc, iron, and vitamins B6 and B12 would be negatively associated with stress reactivity in brain regions that support emotional function (e.g., PFC, IPL, hippocampus, amygdala). Neural reactivity to stress was assessed in 35 adolescents using the Montreal Imaging Stress Task during functional magnetic resonance imaging. Adolescent diet was measured using a 24-hour dietary recall, and the intake of specific nutrients was calculated using Nutritionist Pro. Linear mixed-effects models predicted stress-elicited brain activity from dietary nutrient intake (i.e., magnesium, zinc, iron, vitamins B6 and B12). Covariates included race, sex, and socioeconomic status. Dietary zinc, iron, and vitamin B6 and B12 intake was negatively associated with stress-elicited dorsolateral PFC, dorsomedial PFC, and hippocampal activity. Zinc was also positively associated with IPL activity. Similarly, dietary magnesium levels were positively associated with dorsolateral PFC activity. The present results suggest that dietary nutrient intake may alter the neural response to stress within brain regions that support emotional function (e.g., PFC, IPL, hippocampus). These findings may have important implications for understanding the interrelationships among adolescent diet, neural function, and emotional processes.

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Abstract Title: Exploring the Impact of Reward Objects on Mnemonic Discrimination and Aging: Insights from Rodent Model	
McKnight Institute (Arizona, Gainesville, Miami, UAB): Gainesville	PI Lab: Dr. Sara Burke

ABSTRACT

Aging is linked to mnemonic discrimination impairments, specifically when performing tasks that call for distinguishing between similar stimuli. According to earlier studies, this mechanism is largely driven by the perirhinal cortex and the hippocampus. It also involves the prefrontal cortex (PFC), which is crucial for coordinating communication between the PFC and the hippocampus (Johnson et al., 2022). This study will employ a Lego Object-Based Mnemonic Similarity task, modified from human studies, to examine the effect of a reward object on mnemonic discrimination using rodent models. Using the DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) technology in combination with this behavioral assessment, we will selectively block neuronal activity between the prelimbic cortex and the perirhinal cortex. Our research aims to further understand the distinct roles of these brain regions in age-related cognitive decline and identify possible targets for therapeutic intervention by combining behavioral assessment with focused manipulation of neural circuits.

Johnson, S. A., Zequeira, S., Turner, S. M., Maurer, A. P., Bizon, J. L., & Burke, S. N. (2021). Rodent mnemonic similarity task performance requires the prefrontal cortex. *Hippocampus*, *31*(7), 701–716. https://doi.org/10.1002/hipo.23316

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Abstract Title: Cognitive effects of intra-striatal injection of α-synuclein preformed fibrils in young versus aged rats

McKnight Brain Institute: Gainesville

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ABSTRACT

Alpha-synuclein is a protein that has commonly been implicated in Parkinson's disease (PD) and synuclein-associated dementias. This protein aggregates into preformed fibrils (PFFs) and thus contributes to the progression of Parkinson's disease. As a result, many researchers have adopted intra-striatal injections of α-synuclein PFFs in rats to model cognitive and motor symptoms of Parkinson's disease. Despite age being the most significant risk factor contributing to synuclein-associated dementias, aged animal models are rarely used. The focus of our research is to evaluate the cognitive effects of injecting α-synuclein PFFs into young versus aged rats. Sixty-three male Fischer 344 x Brown Norway F1 hybrid rats, either young (6 months) or aged (20 months), underwent surgery to inject either α-synuclein PFFs (experimental group) or α-synuclein monomers (control group) into the bilateral striatum. Two months post-surgery, rats were food restricted and tested on a delayed response working memory task followed by a probabilistic reversal learning task. Our initial hypothesis was that in comparison to the monomer control group, working memory and cognitive flexibility would deteriorate more rapidly in aged compared to young rats injected with PFFs. Data to date show that aged rats injected with PFF perform numerically worse on the working memory task in comparison to the other groups, especially at long retention delays. Results from the reversal learning task were consistent with the working memory data, and show that aged but not young rats injected with PFFs completed fewer reversals than monomer-injected controls (three-factor, repeated measures ANOVA, group X age interaction, $F(1,16)=8.49$, $p=.01$). Prior work with the PFF model shows that α-synuclein levels peak 2-4 months after injection and decline thereafter, and thus we will evaluate cognition in these rats at these later timepoints, as well as conduct neuroimaging and immunohistochemistry to assess PFF effects on brain structure. The initial results suggest that this aged rat model can replicate the progression of PD and its resulting cognitive deficits.

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Abstract Title:A large normative aging dataset for the characterization of verbal memory performance across the lifespan.	
McKnight Institute: Arizona	PI Lab: Huentelman

ABSTRACT

A large normative aging dataset for the characterization of verbal memory performance across the lifespan.

Megan Johnson, Matt De Both, Harshini Venkatachalam, Marcus Naymik, Meredith Hay, Roberta Brinton, Carol Barnes, Lee Ryan, and Matt Huentelman

Numerous studies have established that young adults typically perform better on episodic memory tests than older adults. However, detailed insights into how memory functions within specific age groups, and the variations in memory performance across different ages, remain limited. Additionally, there is a scarcity of research with large enough participant groups to thoroughly explore these aspects. To adequately address this, researchers need extensive datasets spanning the adult lifespan, which include diverse populations in terms of sex, educational backgrounds, race/ethnicity, and various health and lifestyle factors. Furthermore, the chosen cognitive tasks must be finely tuned to detect age-related performance shifts, avoiding any significant biases towards top or bottom scores, and should have proven sensitivity to known influential factors. Utilizing an online testing platform that we developed called MindCrowd (available at https://mindcrowd.org/), we gathered high-quality data from 143,197 adults ranging in age from 18 to 100. This data collection, which started in 2013, focused on a verbal paired associates learning task (MC-PAL). The MC-PAL task is believed to measure associative learning, a cognitive process particularly vulnerable to aging. Given its reliance on the functioning of the medial temporal lobe, various forms of this test have been used in clinical contexts to distinguish between normal age-related cognitive decline, mild cognitive impairment, and Alzheimer's disease. Using this cohort we (1) create a free portal for exploration of the data and facilitate its use to readily obtain quality norms for any given individual, considering variables that might otherwise not be available, including age, sex, education, race/ethnicity, and location (urban or rural zip code), and (2) we report on new findings from the use of MindCrowd data; including race/ethnicity specific MC-PAL predictor variables and health, medical, and lifestyle factor influences on MC-PAL performance in well-powered cohorts. MindCrowd has demonstrated the power of an internet-based approach to participant recruitment and research, particularly in the area of cognitive aging. This normative dataset represents one of the largest cognitive cohort studies to date and should serve to provide diverse comparative data for researchers interested in predicting individual differences in agerelated memory performance. This study is a collaboration with the Precision Aging Network research team.

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Abstract Title: The Ketogenic diet modifies O-GlcNAc transferase expression in neurons and astrocytes within the aged hippocampus	
McKnight Institute : UAB	PI Lab: Farah D. Lubin, PhD

ABSTRACT

Age-related memory loss is associated with normal aging but can be addressed with healthy intervention. O-linked N-acetylglucosamine (O-GlcNAc) is a glucose-dependent posttranslational modification that controls gene transcription and is associated with healthy longterm memory (LTM) formation. The aging hippocampus, the brain region for LTM formation, is characterized by reduced levels of the O-GlcNAc transferase (OGT) enzyme which is associated with memory impairments. This suggests that modifying O-GlcNAc signaling is a potential intervention for restoring memory. The ketogenic diet (KD), a high-fat low carbohydrate diet, uses ketone bodies as an alternative energy source when glucose levels are low. Given that the KD has shown promise for LTM restoration, we sought to investigate if the KD-mediated LTM improvements involve the modification of O-GlcNAc signaling within hippocampal neurons and astrocytes of aged mice. Male and female C57Bl/6J mice aged 18+ months and 3-5 months were fed a commercially available KD for 2 months and weights were recorded daily. Following euthanasia, brains were processed for OGT-immunohistochemistry in neurons and astrocytes. Aged mice on KD gained weight compared to aged control (41±0.59 vs 34±0.21) while young mice on KD lost weight compared to young controls (28±0.25 vs 29±.21). IHC analysis shows changes in OGT expression within hippocampal subfields as well as age-specific changes in OGT expression within astrocytes found in the CA2. These data suggest both age and subfieldspecific changes in OGT in a cell-type-specific manner.

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Abstract Title: Accuracy of BrainAGE Estimates Produced by Machine Learning Algorithms	
McKnight Institute (Arizona, Gainesville, Miami, UAB): Gainesville	PI Lab: Dr. Eric Porges

Title: Accuracy of BrainAGE Estimates Produced by Machine Learning Algorithms

Authors: Joshua Juhasz, Mark K. Britton, Emily Carter, Kathleen Hupfeld, Richard A.E. Edden, Eric C. Porges

Background: BrainAGE is a novel biomarker of cognitive aging. Machine learning algorithms are trained on lifespan structural neuroimaging datasets to estimate the chronological age of a structural MRI, or its estimated "brain age." The difference between BrainAGE and chronological age is known as brain-predicted age difference (brain-PAD). Larger Brain-PAD has been reported in clinical populations (e.g., HIV, psychiatric disorders, obesity), reflecting brains that are predicted to be older. Additionally, larger Brain-PAD has been associated with increased risk of dementia and mortality. This study evaluates the accuracy and inter-method reliability of current BrainAGE algorithms by generating estimates from three algorithms in a dataset of healthy, normal-aging adults.

Methods: T1-weighted structural MRI data were collected from healthy adults (N = 73; age range: 18-75, mean = 44.3, SD = 16.4; 52% female). Brain-predicted ages and brain-PAD were generated using pyBrainAge, ENIGMA, and BrainageR algorithms. Inter-algorithm similarity in brain-predicted ages and correspondence to chronological age were tested with Spearman correlations. Descriptive statistics, ANOVA, and pairwise t-tests were conducted to assess distribution.

Results: Chronological age correlated strongly with brain-predicted ages from the ENIGMA model ($\rho=0.87$, $p<0.0001$) and the BrainageR model ($\rho=0.91$, $p<0.0001$), and more weakly with the pyBrainAge model ($\rho=0.24$, $p=0.038$). There was a statistically significant effect of algorithm on brain-predicted age difference (brain-PAD), ($F(1.46,104.88)=182.04$). The pairwise t-tests comparing the ENIGMA, BrainageR, and pyBrainAge algorithms showed no significant difference in brain-PAD between BrainageR (mean=−2.60±6.26) and ENIGMA
(mean=−3.95±8.32; $t(72)=1.51$, $p=0.136$). However, significant differences were found between BrainageR and pyBrainAge (mean=−24.30±14.80; $t(72)=13.7$, $p<0.0001$), and between ENIGMA and pyBrainAge ($t(72)=16.3$, $p<0.0001$).

Conclusions: The high correlation between BrainageR and ENIGMA with chronological age provides evidence of the convergent validity of these algorithms in healthy adults. However, the weak correlation with pyBrainAge indicates the need for further evaluation of specific BrainAGE algorithms before widespread use or clinical implementation. The validity in clinical populations may also differ from validity in the healthy, highly educated participants used in this study. Further research may be conducted to gain further insight into BrainAGE and its research and clinical applications. This includes longitudinal studies assessing BrainageR and ENIGMA algorithm performance, best practices for BrainAGE algorithm development, and assessing BrainAGE as a predictor of age effects in other imaging modalities (e.g., MRS).

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Abstract Title: Characterizing the Genetic Expression Profile of an Alzheimer's Disease risk gene TREM2 Variant in a Co-Culture Model of Organoids and Microglia

McKnight Institute: Arizona	PI Lab: Matt Huentelman

ABSTRACT

Microglia cells play a primary role in maintaining homeostasis in human brain by clearing the debris and waste through phagocytosis. In Alzheimer's disease (AD), however, microglia is a double-edged sword which can lead to deleterious outcome contributing to neuronal damage and neuroinflammation, mainly in the disease's later stages. This harmful transition is partly influenced by the microglia receptor, Triggering Receptor Expressed on Myeloid Cells 2 (TREM2). Mutations in TREM2, such as common variant R47H, are associated with an increased risk of AD. In this work, we utilize iPSC-derived forebrain organoids and microglia to investigate the inflammatory mechanisms and neurodegeneration linked to this mutation. We grew these organoids for up to day 150 and co-cultured with microglia. We performed both bulk RNA and single-cell RNA sequencing to analyze the transcriptomic profiles using DESeq and Seurat on R. We observed increased phosphoTau(Thr-231)/total Tau protein expression in older organoids, confirmed by immunoassay (MSD) and immunostaining, which also verified successful microglia integration. While data collection and analysis for these experiments are still in progress, preliminary results suggest that co-culturing microglia with brain organoids harboring a patient-derived mutation facilitates the identification of genetic transcriptional shifts and molecular pathway activities. Collectively, these findings provide insights into the molecular dynamics of the TREM2 variant in a controlled, physiologically relevant microenvironment, eliminating the need for animal models. This approach opens new avenues for applying mutation-specific research to enhance our understanding of AD and develop precision medicine strategies and better therapeutic options.

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Abstract Title: Assessing The Impact of the GLP-1 Receptor Agonist Exendin-4 On Reward-Mediated Behaviors.

McKnight Institute: Gainesville	PI Lab: Bizon, Setlow

ABSTRACT

Balancing perceptions of expected reward versus expected costs of behaviors is instrumental in several types of behaviors, including risk-taking behaviors. Extreme preference for one over the other is a feature of multiple neuropsychiatric conditions such as substance use disorder (risk tolerance) and anorexia nervosa (risk avoidance). Dopamine signaling in mesostriatal neural circuits is thought to play a fundamental role in mediating perceptions of both expected and experienced behavioral costs and rewards, making them compelling targets for therapeutic modulation of in the treatment of predominantly risk-taking behaviors. Fortunately, pre-clinical evidence has suggested that the GLP-1 receptor agonist family of medications modulate mesostriatal dopamine signaling with greater specificity that several other classes of dopaminemodulating drugs, and initial clinical studies indicate that they may reduce frequency of behaviors ranging from gambling to alcohol consumption. Therefore, to determine if GLP-1 receptor agonism could influence risk-taking behaviors, we injected 7-month-old male and female (n=8 male, 7 female) Sprague-Dawley rats with escalating doses of the intermediateacting GLP-1 receptor Exendin-4 (0.1-3.0 µg/kg, dose order was randomized) 1 hour prior to performance on our lab's validated risky decision-making task. On this task, animals are presented with levels that corresponding to either a small reward (1 food pellet) with no risk of punishment or a large reward (2 food pellets) with a risk of a mild footshock at increasing risk frequencies across task blocks (ranging from 0-100%). Preliminary evidence shows that male rats reduce risky choice-making in a dose-dependent manner (two-way ANOVA, dose x risk, main effect of dose, $F_{(4,24)}=15.66$, $p<.001$). Even when excluding the highest dose (3.0 µg/kg), which is the only dose of those chosen that is reportedly sufficient to suppress food intake, this finding remained significant ($p=0.004$). Importantly, no difference was observed when there was no risk of punishment. Validation of outcomes in females is ongoing. Should these observations hold in females, we will replicate these experiments in the presence of a dopamine β-hydroxylase inhibitor, nepicastat, to confirm that these results are specific to dopamine and not norepinephrine signaling. Furthermore, we will use in vivo photometry to measure dopamine signaling in the Nucleus Accumbens core in rats performing our risky decision-making following treatment with a range of Exendin-4 doses. Collectively, these outcomes will inform the mechanism by which the incretin family of medications influence reward-driven behaviors. Risk versus reward behaviors have been well characterized to be altered over the course of normal neurocognitive aging, highlighting a fundamental question as to whether dopamine-modulating pharmacology can influence such behaviors in a manner than mirrors younger age demographics. Alongside evidence that this drug class may reduce neuropathological accumulation and neurodegenerative progression as well as support neuroplasticity in aged individuals, begging to characterize behavioral consequences of the incretin drug class will be foundational is characterizing their clinical utility in aging cohorts.

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Abstract Title: Sex-specific multisystem alterations in metabolome in aged TgF344-AD rats	
McKnight Institute: UAB	PI Lab: Abbi Hernandez

ABSTRACT

Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by cognitive decline and neuronal dysfunction, as well as increased risk of metabolic impairment and disruption of gut microbiota composition. Moreover, we recently demonstrated systemic metabolic dysfunction may be driven by these alterations in gut microbiome composition. However, how specific metabolite production and utilization is altered with AD, and whether this is tissue specific, remains unknown. Therefore, the primary objective of this study is to assess metabolic perturbation within both the central nervous system and intestine through untargeted metabolomic investigation using an aged transgenic rat model of AD (TgF344-AD). These rats exhibit AD-like neuropathology, metabolic impairment, and cognitive decline that progressively worsen with age, making it a suitable model for our studies. Small and large intestinal content, along with hippocampal and frontal cortical samples, were taken from 19-month-old TgF344-AD and WT rats. Samples were analyzed using liquid chromatography/mass spectrometry

(LC/MS). Data normalization and multivariate partial least squares discriminate (PLS-DA) analyses, including Variable importance in projection (VIP) and Principal Component (PCA) analyses, were performed using

MetaboAnalyst 6.0. PCA analysis revealed a statistically significant separation of metabolite profiles between TgF344-AD and WT groups in intestinal and brain tissues, demonstrating regional specificity of metabolic-related alterations in AD. Several individual metabolites contributed to the differential metabolite profiles between TgF344AD and WT groups, including several neurotransmitters and essential amino acids that were up or down regulated uniquely across tissues. Notably, glutamate was upregulated within the hippocampus, but downregulated within frontal cortex. These data align with regional differences in excitatory signaling that occur with aging and AD. Moreover, there were significant differences in metabolome across sex as well as interactions between sex and genotype, such that metabolite profiles differed across genotype differently in male and female subjects. These data demonstrate AD-related impairments in the metabolome of aged subjects include a broad range of metabolites and are sex- and region-specific. Moreover, this work further highlights targeting the gut for therapeutic interventions aimed at alleviating AD-related dysfunction.

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Abstract Title: Dynamics of Default Mode Network Activity Linked to Processing Speed in Cognitively Healthy Oldest-Old	
McKnight Institute: UAB	PI Lab: Kristina Visscher

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Background: Cognition in cognitively intact “oldest-old” individuals can differ significantly, including in executive functions, memory, and processing speed. Dynamic brain activity can be clustered on the individual time-point level to produce group-averaged “brain states,” termed “co-activation patterns” (CAPs). These can offer high resolution temporal information regarding brain activity. This study marks the first attempt to explore the correlation between brain dynamics and cognition within the oldest-old demographic.
Methods: In a study conducted across four sites—University of Alabama at Birmingham, University of Florida, University of Miami, and University of Arizona—146 cognitively healthy participants aged 85-99, without cognitive impairment, underwent an 8-minute, 2.4-second TR, 3T resting-state functional magnetic resonance imaging session (rs-fMRI). Additionally, the participants completed neurocognitive assessments as part of the McKnight Brain Aging Registry collaboration. Co-activation patterns (CAPs) were calculated using a k-means clustering algorithm. Dynamics were defined based on Fraction of occurrence (percentage of time spent in a specific state), persistence (consecutive time spent in a specific state), and transitions (movements from one state to another state).

Results: The CAP displaying the highest stability across models (mean r = 0.92) has highly active default mode network (DMN) (z = 2.2), relatively high activation of the ventral attention network (VAN, z = 1.0) and low activation of every other network (z < -0.6). We examined the dynamics of the predominant CAP to five aggregated cognitive performance measures. These dynamics were strongly correlated only with processing speed, where better processing speed was associated with greater transition entropy, longer persistence, and greater fraction of occurrence.

Conclusions: The default mode network was identified as a stable, common group-wide measure in the oldest-old cohort, regardless of model. Better processing speed was correlated to dominant and persistent default mode network activity. CAPs add a nuanced, dynamic dimension to fMRI and hold promise as a potential biomarker for cognitive intervention in future studies.

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Abstract Title: Unveiling the dynamics of hippocampal theta wave propagation in freely moving rats

McKnight Institute (Arizona, Gainesville, Miami, UAB): Gainesville , Florida	PI Lab: Dr. Andrew Maurer

ABSTRACT

Understanding the mechanisms by which theta waves propagate across the hippocampus is of utmost importance in understanding various aspects of cognition in rodent models. A current hypothesis in the field is that hippocampal rhythms are synchronous throughout the medial temporal lobe. However, recent studies have concluded that theta oscillations travel as nonsynchronous waves along the septotemporal axis of the hippocampus. Our experimental goal was to derive a relationship between theta oscillations in the anterior and posterior regions of the hippocampus by examining local field potential in freely moving rats. We trained a mixedsex cohort of five Fisher Brown Norway hybrid rats to run on a circular track for a food reward and implanted them with an intracranial silicon probe in the CA1 region of the anterior dorsal hippocampus (AP: -2.85 ML: 1.5 DV: 4.0) and the CA1 region of the posterior parietal hippocampus (AP: -5.6 ML: 4.2 DV: 4.5). After a recovery period, the rats were reintroduced to the circular track where data was collected from each site. We found that theta power increased as a function of velocity in the dorsal and ventral regions of the hippocampus. Additionally, a phase offset was observed between the raw LFP of the dorsal and ventral hippocampus, and the magnitude of this offset decreased as running speed increased. These findings suggest that theta may propagate across the hippocampus of rats in a traveling, non-synchronous manner with a phase offset dependent on running velocity.

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Abstract Title:

Aging Like A Pro: Do educational lectures promote positive behavioral changes among older adults?

McKnight Brain Institute - Miami	PI Lab:

Introduction: Since 2000, there has been a 25% increase in the number of people aged 65 and older with Alzheimer's and other dementias in Florida, according to the Alzheimer's Association. Today in the U.S., the NIH estimates about 40% of people aged 65 or older have age associated memory impairment. That number is expected to more than double by 2060. The Alzheimer's Association's 2017 Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial is the first randomized controlled trial (RCT) showing that it is possible to prevent cognitive decline using a multidomain lifestyle intervention among older at-risk individuals. Furthermore, AHA research also has shown that cognitive risk factors can be impacted by various lifestyle factors, with 40% of dementia cases and 70% of stroke cases attributable to modifiable risk factors. Therefore, we designed the "Aging Like A Pro" community lecture series to show the e[ectiveness of educational lectures in promoting positive behavioral changes among older adults to improve their brain health and to age better.

Methods: A total of 304 participants attended more than 15 lectures addressing sleep hygiene, mindfulness practices, and nutritional guidelines, with the objective of enhancing their overall well-being and brain health as they age. To evaluate the impact of these interventions, participants completed an eleven-question survey. Information included, gender, age, education level, occupation, retirement status, and ethnicity. Effectiveness of the lectures was demonstrated by the questions that asked learning from lecture, willingness to make changes in his/her life, and recommend the lecture to a friend. Additionally, willingness to participate in research showed continued interest to topic.

Results: The preliminary results revealed high levels of satisfaction, with an average score of 4.5/5 indicating that participants felt they learned valuable information. Additionally, a score of 4.2/5 demonstrated that many attendees would implement changes in their daily lives based on the content of the lectures. Furthermore, a recommendation score of 4.7/5 suggests that the majority found the information useful enough to share with others.

Conclusions: These findings suggest that educational interventions focusing on key aspects of health-such as sleep, mindfulness, and nutrition-are effective in promoting health literacy and encouraging positive lifestyle changes among aging populations.

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Abstract Title: Role of cofilin in recurrent hypoglycemia exposure-linked stroke risk in insulintreated diabetic rats.	
McKnight Institute: University of Miami	PI Lab: Dr. Kunjan R. Dave

ABSTRACT

Suresh Mallepalli[1,2,4], Sunjoo Cho[1,2,4], Ashish K. Rehni[1,2,4], Kunjan R. Dave[1-4]

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Diabetes is one of the most significant risk factors for stroke. Stroke is one of the major causes of death and permanent disability. People with diabetes have a 1.5-2 times higher stroke risk. Correlational clinical observations indicate that hypoglycemia exposure is linked to an increased risk of stroke and worsened post-stroke outcomes in diabetes patients. Antidiabetic therapies increase the risk of hypoglycemia in diabetes patients. Acute hypoglycemia, ischemic stroke, and cardiac arrest increase platelet activation. In earlier studies, we observed that the ITD (insulintreated diabetic) rats exposed to mild/moderate recurrent hypoglycemia (RH) had a 20% shorter clotting time than the ITD+RH+Glucose control rats. Additionally, in the in vivo thrombosis model, the clot weight in the ITD+RH rats was 46% higher than the control rats. Furthermore, the rate of ADP and collagen-induced platelet aggregation was higher in the ITD+RH rats when compared to the control rats. Moreover, cofilin is known to regulate platelet activation by regulating actin dynamics, which is vital for adhesion, spreading, aggregation during hemostasis, and thrombosis. Since the role of cofilin in RH exposure-induced increased platelet sensitivity is not known, we examined the effect of RH exposure on platelet cofilin (both phospho and total) levels. Young male rats were made diabetic using streptozotocin and insulin pellets were implanted to correct hyperglycemia. Insulin and insulin+glucose was given once a day for 5 consecutive days to induce RH (or euglycemia) in ITD+RH and ITD+RH+Glucose rats, respectively. One day after the last hypoglycemia/euglycemia exposure, blood was drawn from the rat, and platelets were isolated. The p-cofilin and total cofilin protein levels in platelets were then determined using western blotting, and p-cofilin levels were normalized with total cofilin levels. Levels of p-cofilin were significantly higher by 80% (180±20, n=12, $p<0.05$) in the ITD+RH rats as compared to the ITD+RH+Glucose rats (100±24, n=7). Our findings, so far, suggest that cofilin hyperphosphorylation in RH-exposed ITD rats may be responsible for platelet activation and increased stroke risk. Next, we are planning to determine how RH exposure affects platelet function and stroke risk by increasing cofilin phosphorylation. Acknowledgement: AHA 24POST1198296, NIH NS122808, and Evelyn F. McKnight Brain Institute at the University of Miami.

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Abstract Title: Effects of ketone diester supplementation on fear extinction impairments in the TgF344AD rat model of Alzheimer's disease across the lifespan

McKnight Institute(Arizona, Gainesville, Miami, UAB): UAB	PI Lab: Caesar M. Hernandez

ABSTRACT

Fear extinction impairments appear in normative aging in conjunction with impaired executive functions. There is a greater prevalence of fear-based disorders in older populations and in those with Alzheimer's disease (AD). The basal lateral amygdala (BLA) is a part of central medial lobe structures that is involved in fear-based circuitry. We have previously shown extinction impairments in TgF344AD (AD) rats across the lifespan that are associated with BLA hyperexcitability and inflammation. Ketogenic diets have been shown to reduce epileptiform activity and inflammation. To determine if the extinction memory impairments can be ameliorated by leveraging a supplement that mimics the anti-epileptiform and anti-inflammatory properties of a ketogenic diet, we supplemented young and aged WT and TgAD rats with a subchronic dose of a ketone diester (or saline) prior to fear memory acquisition and extinction. We hypothesize that a daily dose of ketone diesters can rescue fear extinction deficits through targeting mechanisms related to hyperexcitability and/or neuroinflammation in AD rats.

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Abstract Title: Changes in noradrenergic receptor density in hippocampus across the lifespan of the rhesus macaque	
McKnight Institute (Arizona, Gainesville, Miami, UAB): Arizona	PI Lab: Barnes

ABSTRACT

Changes in noradrenergic receptor density in hippocampus across the lifespan of the rhesus macaque
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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. Two of these receptor classes (α1 and β) lead to increased likelihood of cell excitability, and the third (α2a) tends to diminish cell responsiveness. Some 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 protocol for histological analysis of the NA system in rhesus macaques (McDermott et al, Program No. 574.04, Society for Neuroscience 2022). Here, we utilize coronal brainstem sections from 30 adult and aged rhesus macaques ranging in age from 7-32 years (21 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 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. No difference was seen in the density of NA fibers in the DG or CA3. Preliminary results reveal higher α2a and microglia density in the DG and higher density of all three NA receptor subtypes as well as astrocyte and microglia density in CA3 of aged animals. Because glial density is increased in both CA3 and DG in aging, the selective increases in density of all three NA receptor types in CA3 is not likely to be solely explained by glia but rather by increased expression in neuronal elements as well. Thus far, only retention of the object discrimination task was found to be related to NA receptor density- specifically, higher density of the excitatory β1 receptor density in CA3 in aged macaques was associated with worse retention on the object discrimination task. This suggests that optimal concentrations of the β1 NA receptor in CA3, which is critical for synaptic plasticity, may modulate interactions between fronto-parietal, temporal and occipital cortices that are necessary for performance on the object discrimination task.

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Abstract Title: Effects of Alzheimer's disease risk factor BIN1 on L-type voltage-gated calcium channel surface localization in neurons

McKnight Institute: UAB	PI Lab: Dr. Erik Roberson

ABSTRACT

Alzheimer's disease (AD) is the leading cause of dementia, afflicting over 32 million individuals. Promisingly, genome-wide association studies identified bridging integrator 1 (BIN1) as the second leading AD genetic risk factor. Yet, BIN1's contribution to AD is poorly understood. In cardiac myocytes, BIN1 transports L-type voltage-gated calcium channels (LVGCCs) to the cell surface, increasing calcium influx. In neurons, increased calcium influx drives neuronal hyperexcitability – a hallmark of AD. Interestingly, BIN1 overexpression in neurons increases firing (PMID 32657270), but the mechanism is unknown. We hypothesized that BIN1 may mediate LVGCC surface localization in neurons, as in cardiac myocytes, to increase calcium influx and thus trigger neuronal hyperexcitability characteristic of AD. Here, we asked the question: does BIN1 mediate LVGCC surface localization in neurons to induce calcium influx and resultant neuronal hyperexcitability? To determine whether BIN1 mediates LVGCC surface localization, we overexpressed human neuronal isoform 1 of BIN1 via lentiviral transduction in primary hippocampal neurons. Lentivirus encoding an mCherry fluorophore was utilized as a negative control. Following transduction, cell surface biotinylation and immunoprecipitation were performed to isolate surface proteins. We subsequently ran western blots (WB) to compare surface LVGCC expression across conditions. Additionally, live-cell calcium imaging was utilized to assess whether BIN1 induces increased calcium influx and whether this increase is due to LVGCCs. Our preliminary WB results suggest a trending increase in LVGCC surface expression when BIN1 is overexpressed. Preliminary live-cell calcium imaging data revealed a trending increase in calcium influx via surface LVGCCs when BIN1 is overexpressed. Replicates of these experiments will be performed to validate these findings. Ultimately, this project will confer an enriched understanding of BIN1. Identifying how BIN1 mechanistically contributes to neuronal hyperexcitability will enable novel therapeutic strategies targeting a leading genetic risk factor for AD.

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Abstract Title: Identification of novel activity-related transcripts using laser capture microdissection and RNA sequencing	
McKnight Institute(Arizona, Gainesville, Miami, UAB): Arizona	PI Lab: Huentelman

Identification of novel activity-related transcripts using laser capture microdissection and RNA sequencing

Mario Mosqueda, Monica Chawla, Leigh Nicholson, Matt De Both, Carol Barnes, and Matt Huentelman

Activity-regulated genes (ARGs) are genetic regions that respond to neuronal cell activity changes. ARGs are important in neuronal health and disease, and play a central role in memory formation and plasticity. Arc (activity regulated cytoskeleton associated protein) is a prototypical ARG wherein neuronal depolarization results in increased transcription as well as a time-related differential compartmentalization of Arc RNA from the neuronal soma into the dendrites. To identify novel ARGs we laser capture microdissected four hippocampus cell compartments in the CA1, CA3b, CA2, and dentate gyrus regions including their soma and dendritic fields individually. The experimental cohort was comprised of six-month-old F-344 rats at multiple time points (10, 30 min, 1, 2, 4, and 24 hours; n=6 per time point) following maximal electroconvulsive shock (MECS). We used RNA sequencing and performed differential expression analysis to identify transcripts that were altered by MECS both in quantity and by compartment (soma vs. neuropil). We found eight novel activity-regulated genes that exhibited Arc-like transcriptional response profiles characterized by the following aspects; transcripts were (1) not differentially compartmentalized at rest, (2) significantly increased in expression in the soma compartment before the neuropil, and (3) not previously reported as an ARG. We validated one of these novel ARGs, Trib 1 (Tribbles Pseudokinase 1), using chromogenic in situ hybridization (RNAScope; ACD Bio). Trib1 expression was quantitated by pixel intensity analysis of images captured by the Aperio ImageScope in the same soma and neuropil regions of the hippocampus. The RNAScope results confirmed our RNA-sequencing findings and demonstrated that Trib1 exhibits both a transcriptional and compartmentalization response similar to Arc, positioning Trib 1 as a novel activity-regulated transcript. Trib1 is a pseudokinase that plays a role as a molecular scaffold to initiate degradation of its substrates via the ubiquitin proteasome system. One such substrate is C/EBPalpha; a member of a family of proteins with known roles in cognitive function. Trib1 has also been found to interact with and regulate various MAP kinase family members. Based on our observations, we propose that Trib1 is a new activity-regulated transcript and encourage future evaluations of Trib1 and the role it may play in activity-regulated neural cell physiology.

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Abstract Title: Electrophysiological Signatures of Novel Language Learning in the Earliest Stages

McKnight Institute(Arizona, Gainesville, Miami, UAB): Gainesville	PI Lab: Brain Language and Bilingualism Lab – Dr. Eleonora Rossi

ABSTRACT

Previous research has examined the ways in which the learning of a second language in adulthood can promote cognitive and neural changes. However, little is known about the earliest stages of novel language learning in adults and how it may impact neurobehavioral signatures of language and cognition. This study aimed to investigate how the earliest neural signatures of novel language learning may be impacted by variables such as Age of Acquisition (AoA), proficiency in the second language, and general cognitive measures such as working memory and inhibitory control. Spanish-English bilinguals (n=37) participated in a 10-day mini-longitudinal study in which they completed Dutch lessons through Rosetta Stone. Event Related Potentials (ERPs) were examined at pre and post-test to investigate neural changes of Dutch language encoding using a Semantic Categorization Task (SCT). The results show a reduced N400 across learned vocabulary at post-test, indicating rapid neural adaptation. Both bilingualism factors and inhibitory control were shown to have an impact on the N400, with higher bilingual experience leading to reduced N400s for cognates, and better inhibitory control leading to smaller N400s for cognates and larger N400s for non-cognates. Working memory did not significantly affect N400 amplitude. These results suggest that bilingualism may aid in the lexicalization of similar words across languages, while higher inhibitory control can prevent cross-linguistic interference from cognates. This study demonstrates the ways in which individual differences can modulate the earliest signs of language learning and expands current literature on the neuroadaptation that occurs alongside language learning.

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Abstract Title: A novel multi-modal magnetic resonance imaging technique to measure the concentration and ratio of iron products in a phantom of cerebral cavernous malformation.	
McKnight Institute(Arizona, Gainesville, Miami, UAB): UAB	PI Lab: Bolding

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The evolution of magnetic resonance imaging (MRI) has permitted the detection of angiographically occult vascular malformations, including cerebral cavernous malformations (CCMs). Although relatively rare, CCMs are vascular lesions found predominantly in the brain and may cause severe symptoms, including seizure, headache and stroke. CCMs frequently hemorrhage and are permeated or surrounded by iron-rich blood breakdown products (BBPs) whose ratios change in characteristic ways over time. Iron present in BBPs is believed to have a strong positive correlation with CCM disease severity. Additionally, iron in vascular brain lesions disrupts the inhomogeneity of the MRI magnetic field, generating susceptibility artifacts that make these lesions difficult to interrogate with MRI. Quantitative susceptibility mapping (QSM) has shown potential to quantify total lesional iron content by measuring tissue magnetic susceptibility. However, QSM cannot differentiate between various chemical forms of iron. Our team proposes a novel multi-modal MRI technique, *FerroQuant*, for detecting recent hemorrhage within a CCM lesion by measuring the concentration and ratio of BBPs and how they change over time. We hypothesize that combining QSM with imaging techniques sensitive to different forms of iron (T1 and T2 mapping) will allow simultaneous independent measurement of multiple BBPs.

Methods: Preliminary work was done on a CCM phantom, which consists of jelly beads made from a mixture of red-colored liquid containing 2g of Iron (III) citrate (0.1g Fe^{2+}) and sodium alginate spherified in a Calcium lactate solution. Three gelatin molds were embedded with the iron-containing jelly beads to mimic CCM lesions and validate QSM acquisition. MRI images were acquired at 3.0T. MRI data were analyzed using FSL. To validate our QSM estimates, the mean susceptibility values of the CCM phantoms were correlated with the QSM-derived iron measurements in human patients.

Results: The iron-embedded jelly beads appeared hyperintense on the QSM maps compared to the nearby gelatin mold. The susceptibility of iron in these phantoms, as demonstrated by QSM, averages about 2ppm, similar to the iron content of human CCM lesions, as documented in literature (Tan et al., 2014). Therefore, in this experiment, we were able to successfully estimate the iron concentration using QSM.

Limitations and conclusions: 1). Factors like inflammation, edema, and tissue type that are present in humans and can influence the MRI signal are not present in the phantoms. Future studies will use ferritin and multiple iron products to estimate the iron concentration and ratio of soluble and insoluble iron products with QSM as an index for iron concentration.

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Abstract Title: Exploring Rare Childhood Diseases through Neural Organoid Generation	
McKnight Institute: Arizona	PI Lab: Huentelman Lab

Abstract: Rare neurological disorders in children are inadequately diagnosed and treated, resulting in a decrease in quality of life through symptoms such as developmental delay, reduced cognitive and motor abilities, and regression. Improving both the diagnostic process for children with these disorders, as well as focusing on a personalized drug testing model would significantly increase the quality of life for these children and their families. Brain-specific organoid generation is a novel technique that allows for reproducible and versatile modeling of neurodevelopmental processes and associated disorders. In this study we used forebrain neural organoids generated from iPSCs with patient-specific genetic mutations to study genotypephenotype relationship in vitro.

We generated patterned forebrain, dorsal and ventral, neural organoids with CRISPRintroduced clinically-validated disease-causing point mutations identified in children with rare disorders (in the genes DOCK3, GABRA1, HNRNPH2, MTFMT, WDR45) and wildtype control (WT). Organoids were grown over a 100-day period and collected at longitudinal timepoints for analysis. Immunofluorescence, RT-qPCR, and single-cell sequencing was performed. RT-qPCR quantification of SOX and PAX1 confirmed expected neurodifferentiation and maturation of organoids during the optimization stage. Immunofluorescence of sectioned organoids confirmed mature neurons via beta-tubulin III staining, as well as region specific brain structures. The presence of different cell types, including astrocytes, inhibitory neurons and excitatory neurons, were seen in all five mutant and wildtype organoids, and cell proportions between timepoints and region (dorsal or ventral) were measured. Cell proportions showed differences across mutation, region, and timepoint, such as astrocytes being predominantly present in dorsal organoids compared to ventral, regardless of mutation and timepoint, and excitatory neurons having a higher proportion in WT dorsal/ventral organoids on day 50 compared to all mutants except HNRNPH2 ventral organoids.

We successfully used neural organoids generated from cells containing patient-specific mutations to investigate phenotypic changes. Organoids represent an efficient and reproducible in vitro disease model for neurodegenerative diseases, specifically due to their ability to be generated from mutation-carrying iPSCs.

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Abstract Title: Employing sexually dimorphic risk for metabolic syndrome to identify Alzheimer's disease risk promoting or protective genes	
McKnight Institute: Gainesville	PI Lab: Gemma Casadesus

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Metabolic syndrome (MetS) is a central risk factor for Alzheimer's disease (AD) development, which, like AD, evolves in a sexually dimorphic pattern, whereby males exhibit increased susceptibility to metabolic syndrome yet, compared to females, are less likely to develop AD. The mechanisms that underlie the pathogenic link between MetS and AD or the root of sex differences in AD development remain poorly understood. Utilizing this relationship, we aim to identify genetic drivers of AD risk in metabolicallystressed females or, alternatively, neuroprotective genes in males. To explore this link, we placed male and female APP/PS1 mice, which mirror the sexually dimorphic pattern of AD development in humans, on a "Western" high-fat diet (HFD) or a control diet to determine the longitudinal metabolic, ADpathological, and hippocampal transcriptome responses. We characterized metabolic dysfunction through physiological measures including glucose and insulin tolerance testing, pathology through quantification of soluble and insoluble amyloid-beta, and transcriptomic signature through bulk RNA sequencing. Our findings indicate a powerful CNS sexually-dimorphic transcriptomic response to MetS that is inverted to the observed degree of metabolic dysfunction; females demonstrate an advanced disease state compared to males despite their relative physiological resilience to HFD. Using AI-powered statistical analyses, we identified key genes implicated in AD development that are differentially expressed across sex. Together, these findings have the potential to inform precision medicine.

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Abstract Title: Post-stroke whole body vibration therapy alters transcriptome and reduces cognitive deficits in middle-aged rats.	
McKnight Institute: Miami	PI Lab: Raval

ABSTRACT

Post-stroke whole body vibration therapy alters transcriptome and reduces cognitive deficits in middle-aged rats.

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Stroke is a leading cause of death in the United States, and frailty is linked to increased risk and severity of stroke. Post-stroke physical frailty often accompanies cognitive deficits. Both physical and cognitive deficits in stroke survivors can be reduced by rehabilitative exercise. However, adherence to rehabilitative exercise is often poor due to various factors including preexisting health conditions, motivation, and cost. Effective and affordable rehabilitation interventions are crucial to minimize post-stroke deficits and the overall burden of stroke. Our published studies have demonstrated that an exercise mimetic, low frequency whole body vibration (WBV; 40Hz) therapy, ameliorates both motor and cognitive deficits in a rat model of stroke [1,2]. Our studies have also demonstrated that post-stroke WBV therapy reduces ischemic brain damage, however the underlying mechanisms by which WBV induces ischemic protection and cognitive improvement remain elusive. In the current study, we hypothesize that WBV treatment improves post-stroke outcomes by altering the expression of key genes implicated in stroke recovery. Middle-aged female Sprague-Dawley rats were randomized to sham or transient middle cerebral artery occlusion (tMCAO; 90 min) surgery after which they received no treatment (tMCAO+No-WBV) or WBV (tMCAO + WBV) for 15 minutes twice a day for a week. Following WBV, cortical tissue was collected for analysis of gene expression via RNA sequencing (RNAseq) and gene enrichment analysis via Enrichr. Upon analysis of the RNAseq data, we observed that 89 genes were significantly up regulated, and 180 genes were significantly down regulated ($p<0.0001$) in the tMCAO + WBV group as compared to tMCAO + No-WBV group. The significantly upregulated genes with the greatest increase in fold change include Kif21a, LOC103689968, and AABR07051308. In regard to genes that were reduced in expression, SYNJ1, TLR3, and VPS37C demonstrated the greatest significant decrease in fold change. Enrichment analysis revealed that the genes with greatest decrease in fold change, namely SYNJ1, TLR3, and VPS37C are all involved with neuroinflammation, with the most down regulated gene, VPS37C, being implicated in innate immune system function. The observed WBV induced transcriptional reprogramming may reduce post-stroke inflammation thus improving stroke outcomes, and future confirmatory studies are needed to establish WBV therapy for stroke rehabilitation.

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Abstract Title: Pseudotime Analysis of Alzheimer's Disease: Identifying Key Genes of Molecular Progression in the brain and candidate RNA blood biomarkers	
McKnight Institute: Arizona	PI Lab: Huentelman

Pseudotime Analysis of Alzheimer's Disease: Identifying Key Genes of Molecular Progression in the brain and candidate RNA blood biomarkers

Piras IS, Song S, Naymik M, Ecca F, Huentelman MJ.
Translational Genomics Research Institute, Early Detection and Prevention Division

Pseudotime (PT) methods are machine learning-based algorithms designed to extract latent temporal information from cross-sectional data. We applied PT analysis to publicly available bulk tissue RNA-profiling data obtained from post-mortem brain and blood samples of Alzheimer's disease (AD) and non-demented (ND) donors.

We utilized data from the Accelerated Medicine Partnership-AD (AMP-AD) repository from eight brain regions: ACC, DLPFC, FP, IFG, PCC, PHG, STG and TCX. We first extracted PT trajectories with the phenoPath method, investigating the correlation with clinical and neuropathological variables, including Clinical Dementia Rating, Braak stage, disease status, and amyloid plaque density. We detected a significant correlation in 83.8% of the variable/pseudotime comparisons. We identified 866 genes significantly correlated with pseudotime, with concordant directions across all eight brain regions ($|r|$ ^{3} 0.4; Benjamini and Hochberg (BH) adj-p < 0.05). We observed consistent patterns at the cell-specific gene level across brain regions, with a significant increase in gene expression across PT for astrocyte, microglia, oligodendrocyte, and endothelial cell genes, and a significant decrease for both excitatory and inhibitory neuron genes. We conducted multi-brain coexpression network and key driver analysis across all datasets, identifying 358 significant key drivers, with 65 of them
associated with PT in all the 8 brain regions. Notably, 9 genes were significant key drivers in 7 distinct brain regions: CRYM, DRD1, GABRA4, KCNV1, LAMP5, PCP4. PCSK2, RASGRP1 and ZCCHC12. Finally, we extracted the pseudotime trajectory using the DDRTree method from two independent blood RNA profiling datasets from Gene Expression Omnibus (GSE63060 and GSE63061). After cross-referencing the results with the 866 genes significantly associated in brains, we identified an overlap of 112 genes also significantly associated in blood in both datasets ($|r|$ ^{3} 0.4; BH adj-p < 0.05).

In conclusion, our results highlighted key genes associated with AD, which might be useful targets for repurposed drugs or new molecule screening. Further in vitro and in vivo studies are warranted to validate the functional relevance of these genes. Additionally, we identified candidate blood-based RNA biomarkers that might predict AD onset before clinical symptoms appear. Validation in longitudinal studies will be a central step in assessing the applicability of these biomarkers in clinical practice.

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Abstract Title: Stopping Before the Finish Line: Exploring Differences in Dropout and Readmission Rates for Older Adults in Substance Use Disorder Treatment

McKnight Institute: Gainesville	PI Lab: Dr. Ben Lewis; Florida Recovery Center

ABSTRACT:

BACKGROUND

Substance use disorder (SUD) is a chronic condition characterized by compulsive use of substance despite harmful consequences. Substantive literatures have described individuals in treatment for SUDs, and investigated predictors of treatment success. However, the vast majority of this literature focuses on typical treatment-seeking samples, among which aging adults are underrepresented. Exceptionally few studies have explicitly focused on older treatment-seeking individuals. The current study employed a matched-sample design to examine differences in subject-reported measures of mood, craving, abstinence self-efficacy, and need for treatment. Additionally, age group effects on rates of dropout from treatment and readmissions to treatment were investigated.

METHOD

The study sample included matched samples of older (age 55+; n = 235) and younger (age 3040; n = 235) individuals in residential treatment for substance use. Matching was conducted by education, profession, and sex. Group differences were examined using logistic regression and t-tests. Importantly group differences in affect, craving, and abstinence self-efficacy were examined at both treatment initiation (relevant for dropout analyses) and discharge (relevant for readmission analyses).

RESULTS

Older adults ceased treatment against the advice of their treatment team more often than younger adults (p=.03). Moreover, older adults appeared more likely to return to treatment, albeit with trend-level significance (p=.08). Interestingly, despite these objective measures of treatment success, older adults reported less symptoms of anxiety & depression, rated their craving as substantially lower, and endorsed markedly higher confidence in their ability to maintain abstinence.

DISCUSSION

Taken together, these results suggest that older adults may be at greater risk of both dropping out of treatment early, and/or returning to treatment. Although our analyses cannot speak to causation, age differences in self-reported measures suggest that older adults may be more confident in their own capacity to function outside of treatment, potentially leading to higher dropout rates. Importantly, the readmission data highlight that at the group-level, such confidence is likely misplaced. Further exploration of these relationships may improve treatment services for aging populations.

First Author (Last name, first name): Raciti, Federica Maddalena	Presenter (if someone other than First Author):
Abstract Title: Auditory and Vestibular Consequences of Mild Traumatic Brain Injury	
McKnight Institute: Miami	Lab: Suhrud Rajguru

ABSTRACT

Traumatic brain injury (TBI) represents a public health challenge, with significant and enduring consequences for individuals and communities. While the immediate effects of TBI are widely acknowledged, its long-term impact extends beyond cognitive and motor functions to encompass a diverse range of sensory dysfunctions often overlooked in clinical assessments. Among these less-explored yet clinically significant outcomes are hearing and balance impairments. The CDC estimates that auditory and vestibular loss affects 8 to 67% of TBI patients, with prevalence largely contingent upon injury severity. In cases of moderate to severe TBI, auditory and vestibular losses typically result from conductive or mixed mechanisms, often secondary to temporal bone fractures. In mild TBI these dysfunctions primarily manifest as sensorineural, stemming from transient or permanent damage to hair cells and the associated neural pathways. Despite hearing and balance impairments being common post-concussive symptoms, there's limited understanding on the temporal dynamics and the pathophysiology of these phenomena. In this work we characterize relevant short- and long-term changes in auditory and vestibular activity in an ecologically valid mTBI model (n=6 male Brown Norway rats, 14-16 weeks). The closed head injury was induced using the accelerated weight drop system, simulating a single controlled weight drop (450g at 1 meter). Threshold values of auditory brainstem responses (ABRs) and cervical vestibular myogenic potentials (cVEMPs) evoked by pure tone bursts at different frequencies (ABR 2, 4, 8, 16, 24, 32 kHz cVEMP 1, 8 kHz) were evaluated prior the injury and monitored up to 28 days post-concussion. Previous studies in mTBI rat models revealed complete recovery of their cognitive and motor functions within three days from the injury. Here we observe the same recovery timeframe for post-concussion changes of cVEMP and ABR responses to low and high frequency stimuli respectively. In contrast, changes in ABRs evoked by low frequency stimuli remain significant until 14 days after mTBI. Notably, mild head trauma does not affect cVEMP responses to 8 kHz stimuli. Overall, these results show the complex dynamics of mTBI-induced auditory and vestibular dysfunctions highlighting the importance of considering sensory outcomes alongside cognitive and motor assessments in TBI research and clinical practice. The detailed characterization of auditory and vestibular functional outcomes in the established model will help delving deeper into the molecular mechanisms driving these sensory dysfunctions, ultimately improving therapeutic interventions for TBI patients.

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Abstract Title: Recurrent hypoglycemia exposure results in cognitive impairment via increased platelet dysfunction in aged insulin-treated diabetic male rats.	
McKnight Institute: University of Miami	PI Lab: Dr. Kunjan R. Dave

ABSTRACT

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Nearly 16.5 million senior adults in the USA (≥65 years old) have diabetes. Long-term diabetes is associated with worse cognitive outcomes. Intensive antidiabetic therapy increases the risk of recurrent hypoglycemia (RH) in subjects with diabetes. We have previously shown that RH exposure to insulin-treated diabetic (ITD) rats leads to impaired spatial learning and memory[1]. However, the mechanism by which RH exposure leads to cognitive impairment is unknown. Chronic cerebral hypoperfusion plays a role in the development of vascular cognitive impairment and dementia. Platelet activation is one of the mechanisms responsible for deficits in cerebral perfusion. An earlier study demonstrated that two mild/moderate hypoglycemia exposures to type 2 diabetes patients activate platelets[2]. Therefore, we evaluated the role of platelet dysfunction in RH exposure-induced cognitive impairments in diabetic rats. We hypothesize that RH-exposure to diabetic rats leads to cognitive impairment via increased platelet dysfunction-induced cerebral hypoperfusion. In this abstract, we evaluated the effect of RH exposure to aged ITD rats on platelet dysfunction. Aged male (21±0 months old) streptozotocin diabetic rats were treated with insulin 2-3 weeks after diabetes induction and were exposed to either hyperinsulinemic euglycemia (control) or hyperinsulinemic hypoglycemia. The extent of platelet dysfunction was quantified using an in vivo model of thrombosis. Briefly, either 7 days after 5-day RH (sub-acute) or 3 days after 6-week RH (chronic), the carotid artery was attached to the jugular vein using a shunt containing a pre-weighed suture, and blood flow was allowed for 15 min. The suture was withdrawn and weighed to quantify clot deposition in the suture. In the sub-acute RH exposure experiment, the clot weight in the RH-exposed ITD rats (29±3 mg, n=7) was 88% higher ($p<0.01$) than in the controls (15±1 mg, n=6). The clotting time for the RH-exposed ITD rats (5.04±0.48 min, n=7) was significantly shorter ($p<0.05$) than in the controls (6.76±0.30 min, n=6). Our results show that 5-day RH exposure increases platelet dysfunction in aged male ITD rats when determined 7 days post-exposure. In the chronic RH exposure experiment, the clot weight in RHexposed ITD rats (28±3 mg, n=6) was 66% higher ($p<0.01$) than in the controls (17±1 mg, n=7). Our results indicate hypersensitivity of platelets following RH exposure to aged ITD male rats. In the future, we plan to evaluate the role of platelet dysfunction in RH exposure-induced cognitive impairment in ITD rats. **References:** 1) Transl. Stroke Res. 2019;10(1):78-90.; 2) Diabetes Care. 2018;41(12):2625-2633. **Acknowledgement:** NIH (NS122808), Evelyn F. McKnight Brain Institute at the University of Miami.

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Abstract Title: Effects of chronic yagus nerve stimulation in aging	
McKnight Institute: Gainesville	PI Lab: Bizon

Effects of chronic vagus nerve stimulation in aging

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The aging population is at significant risk for cognitive decline, which adversely affects activities of daily living and overall quality of life. This decline is mediated in part via age-related changes in excitatory/inhibitory (E/I) signaling in the brain, as well as increases in inflammation, both of which disrupt cognitive function. Electrical vagus nerve stimulation (VNS), an FDA-approved treatment for epilepsy, shows promise in enhancing neuroplasticity and reducing inflammation, suggesting that it may counteract age-related cognitive deficits. The broad goal of this research program is to address several potential beneficial effects of VNS in aging: first, to investigate whether VNS can remediate age-related impairments in cognitive tasks mediated by the hippocampus and prefrontal cortex (PFC); second, to determine if VNS can attenuate ageassociated E/I dysregulation and impaired synaptic function in the hippocampus and PFC; and third, to determine how VNS affects peripheral and brain markers of inflammation in aged rats. Aged male and female FBN rats (24 mo.) were surgically implanted with a cuff electrode around the left vagus nerve and received daily 1-hour sessions of VNS using parameters previously demonstrated to enhance cortical plasticity and various forms of learning (100 stimulus trains/session at 30Hz, 700 μA, 120 μs biphasic pulse width, 0.8 s train duration), or a sham control procedure, for at least 30 sessions, during which experiments were conducted to gather data for the study's objectives. Preliminary data indicate that this VNS regimen significantly improves working memory performance in aged rats, and significantly alters the profile of cytokine expression in aging. These findings, along with published data across species, suggest that VNS may serve as a promising intervention to mitigate cognitive decline and improve overall brain health in the aging population.

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Abstract Title: Electronic cigarette vapor exposure impairs catecholamine metabolism responsible for observed post-stroke cognitive decline	
McKnight Institute: Miami	PI Lab: Raval

Electronic cigarette vapor exposure impairs catecholamine metabolism responsible for observed post-stroke cognitive decline

Vicente A. Sanchez[1], Hari Pradhyumnan[1], Gina G. Perez[1], and Ami P. Raval[1, 2]

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Widespread usage of nicotine-containing electronic cigarettes (EC) has raised the importance of characterizing how vaping affects stroke outcome [1]. Our published study showed that just 16 days of EC exposure results in worsened post-stroke cognitive decline in young rats of both sexes [2]. Furthermore, our study demonstrated that EC exposure altered brain energy metabolism. Brain energy metabolism can impact neurotransmitters (NT) metabolism and NT are vital for cognitive function. Therefore, the current study investigates how EC exposure affects NT metabolism in the brains of rats before and after induction of ischemia. Adult Sprague-Dawley rats of both sexes were randomly allocated to air or EC (5% nicotine Juul pods) exposure for 16 nights. After exposure, brain cortexes were collected from a cohort of rats for unbiased global metabolomic analysis. A second cohort was exposed to transient middle cerebral artery occlusion (tMCAO; 90 min) or sham surgery and survived 21 days. After 21 days rats were perfused with saline and 4% paraformaldehyde. The brains were sectioned coronally (10ìm) for immunohistochemical staining. Three serial sections per animal starting at -5.30mm from Bregma were stained with anti-tyrosine hydroxylase (TH) antibody to visualize dopaminergic cells in the ventral tegmental area (VTA). Estimated population of TH-positive cells in the VTA was obtained using a brightfield stereoscope and the optical fractionator probe function in

StereoInvestigator software with a counting frame of 50x50ìm and ~30 sampling sites per section. Initial quantification shows that EC reduces number of TH-positive neurons. Metabolomic analysis indicated that EC resulted in 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 rats. Observed changes in NT metabolites due to EC were more prominent in females than males. Altered NT metabolism and release may be in part responsible for the observed poststroke cognitive decline. Because of the relative novelty of EC, what impact EC has on NTs remains elusive and understanding the effects of EC on NT will help elucidate how EC exposure exacerbates ischemic brain damage.

Acknowledgements: We thank Ms. Ofelia Furones-Alonso for surgical and technical support.

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Abstract Title: Exploring the link between blast-induced hearing loss and the progression of Alzheimer's disease

McKnight Institute: Miami	PI Lab: Suhrud Rajguru

ABSTRACT

Introduction: Exposures to hazardous noise causes irreversible injury to the structures of the inner ear, leading to changes in hearing and balance function with strong links to age-related cognitive impairment. While the role of noise-induced hearing loss in long-term health consequences, such as progression or development of Alzheimer's Disease (AD) has been suggested, the underlying mechanisms and behavioral and cognitive outcomes or therapeutic solutions to mitigate these changes remain understudied. The goal of this study to characterize the association between blast exposure, hearing loss, and the progression of AD pathology, and determine the underlying mechanisms.

Methods: To this aim we acquired wild-type (WT) and 3xTg-AD mice, a well-established experimental model of AD pathology. Female and male mice of 4 months of age were randomly assigned at the beginning of the study to no blast or blast-exposed groups. Blast injury was carried out in an ecologically valid oxyacetylene gas tube. Functional outcomes and cognitive, affective and anxiety deficits were assessed at different time points using auditory functional tests (auditory brainstem response (ABR) and cervical vestibular evoked myogenic potential) and behavioral assessments (novel object recognition, water maze, open field) over 3 months. In addition, we performed western-blot and immunohistochemistry analysis to examine expression levels of amyloid beta (Aβ), Tau, and inflammasome proteins in the peripheral auditory system and multiple brain regions including auditory cortex and brainstem after blast exposure.

Results: We found that blast injury led to auditory sensorineural cell loss with a consequent combination of temporary and permanent hearing and balance impairment. Mice behavioral analysis revealed that both WT- and 3xTg-blast mice as well as 3xTg sham animals had challenges with the novel object recognition. In open field, 3xTg blast mice exhibited significant increases in fecal boli when compared to WT mice while 3xTg animals (sham and blasted) showed a decrease in overall mean speed, total distance traveled and mobility while time spent at the center of the arena and frequency zone transition center-border increased noticeably. In addition, Aβ, Tau and inflammasome proteins were elevated in cochlea as well as brainstem and cortex of 3xTg mice suggesting an involvement of pyroptosis related mechanisms in the impact of hearing loss on the onset and progression of cognitive decline in AD pathology.

Conclusions: Our results suggest a strong correlation between early hearing loss and progression of AD pathology. Preventive and therapeutic strategies aimed at attenuating hearing loss could be beneficial in delaying the onset of Alzheimer's disease.

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Abstract Title: Oral contraceptive treatments increase cerebral sphingolipid and ceramide metabolites and post-stroke cognitive deficits in female rats	
McKnight Institute: Miami	PI Lab: Raval

ABSTRACT

Oral contraceptive treatments increase cerebral sphingolipid and ceramide metabolites and post-stroke cognitive decline in female rats

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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 the focus of this 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. Additionally, the most pronounced effects of OC use occur early in treatment, distinct from the long-term risks of myocardial infarction, venous thromboembolism, and stroke, notably in smokers [2]. OC exposure increases female susceptibility to stress hormone effects on memory, fear conditioning, and emotion regulation [3]. Our understanding regarding the contribution of short-term OC exposure on the severity and consequence of stroke injury is sparse, and a goal of this study. Adolescent and adult Sprague-Dawley female rats were randomly (n = 8/group) exposed to either placebo or OC for 16-21 days. Brain tissue was then harvested to obtain an unbiased global metabolomic profile (performed by Metabolon Inc.), complemented with western blot analysis, microglial morphological 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 increased ($p<0.05$) in OC-exposed brains as compared to placebo, with more pronounced changes in adolescent rats compared to adults. S1P, regarded as a “double-edged sword” in the pathogenesis of brain-related disorders, plays a key role in synaptic transmission, neuronal autophagy, and neuroinflammation [4]. Preliminary results indicate that Sphingosine Kinase 2 (SphK2) and S1P Receptor 3 (S1PR3) are significantly aggregated while S1P Lyase (S1PL) is significantly decreased upon OC exposure. S1P3 is crucial in inflammation, thereby modulating microglia activation and oligodendrocyte function and impacting both inflammatory and neurodegenerative processes. Understanding how OC affects brain metabolism, S1P function, and cognitive function, particularly across different ages and durations, is crucial for assessing stroke risks in OC users.

Acknowledgements: We thank Ms. Ofelia Furones-Alonso for surgical and technical support. References:

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Title of Abstract: The Importance of Tissue Identity in MRI-derived tDCS Models	

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique in which electrodes are applied to the surface of the skin to deliver electrical currents of 2mA-4mA and modulate the neuronal cell environment [1]. Prior research shows that tDCS can remediate cognitive functions in older adult populations [1]. To predict tDCS, the finite element method has been used, where tissues in the head are segmented based on their identities in Magnetic Resonance Imaging (MRI) data. These tissues may affect the distribution of electrical current due to their conductivity values, which represent the ability of a medium to pass electrical current[2]. In this project, we aimed to perform a sensitivity analysis to investigate how individual tissue may contribute to the obtained current density (J) value when comparing multiple segmentation models containing different numbers of head tissues. Six models were created for analysis, named M1-M6. M6 was assigned as the reference model, containing the tissue identities typically used in the field, while M1-M5 were derived models used to analyze significance. Each of M2 – M5 included one additional tissue outside M6 to isolate their sole contribution to the current density. M2 adds blood vessels, M3 eyes, M4 fat, and M5 separates bone into cancellous and cortical tissues. M1 contains 11 tissues (eyes, blood, cancellous and cortical bone, muscle, and fat are included). Four human participants (two males, and two females) were segmented into M1-M6. Tissue segmentation and volume meshing were completed in Simpleware, and ROAST-generated artificial electrodes were converted and added to the model. Electrodes were placed at the F3 (cathode) and F4 (anode), with 2mA as input current. COMSOL was used to generate electric fields using the AC/DC module. Tissues were assigned the following conductivity values: 0.126 S/m (white matter), 0.276 S/m (grey matter), 0.165 S/m (CSF), 0.01 S/m (bone), 1.0E-09 S/m (air), 0.465 S/m (skin), 0.16 S/m (muscle), 0.25 S/m (fat), 0.67 S/m (blood vessels), 0.5 S/m (eyes), $2.14E^{-02}$ S/m (cancellous bone), and $5.52E^{-03}$ S/m (cortical bone)[4][5]. The white matter and grey matter masks were isolated and combined to compute current density values in the brain. Current density values isolated in the brain region for M1-M6 were tested for significance via a Welch's t-test in RStudio**.** The results showed statistical significance ($p < 0.05$) for M1 (all tissues, median = 0.020381 Am^{-2}), M4 (fat, median = 0.018377 Am^{-2}), and M5 (cortical and cancellous bone, median = 0.015608 Am^{-2}) showed a p-value <0.001. The models examining the blood (M2, $p = 0.763$, median = 0.01622 Am^{-2}) and eye (M3, $p= 0.443$, median = 0.01623 Am^{-2}) masks separately were not significant. This observation was likely due to their smaller size and localized position with respect to the electrodes and the brain[3]. Similarly, the significance seen in the remaining models (e.g., fat and composite bones) may be caused by the larger coverage area related to the electrode location and the brain.

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Abstract Title: Electronic cigarette exposure worsens stroke induced inflammation and cognitive deficits in female rats.	
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Electronic cigarette exposure worsens stroke induced inflammation and cognitive deficits in female rats.

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The innate immune response plays a crucial role in the pathogenesis of ischemic stroke and a key component of the innate immune response is the inflammasome. In a published report, we observed amplified inflammasome activation after ischemia in the brains of nicotine exposed female rats [1]. Apart from conventional cigarettes, nicotine is the main ingredient of currently popular electronic cigarette (EC) devices and because of its relative novelty, our understanding of what impact EC has on the brain is limited. In a recent publication, we demonstrated that EC exposure exacerbates ischemic brain damage in female rats [2]. Therefore, the current study aims to investigate the impact of EC exposure on post-ischemic inflammasome activation in the brains of male and female rats. Since microglia play a key role in both innate and adaptive immune responses following ischemia, we also aim to evaluate the impact of EC exposure and ischemic episode on microglial activation in rat brains. Adult Sprague-Dawley rats of both sexes were randomly assigned to air/EC vapor (5% nicotine Juul pods) exposure for 16 nights, followed by transient middle cerebral artery occlusion (tMCAO; 90 mins) or sham surgery. Animals were then divided into two cohorts. In the first cohort, cortical brain tissue was collected from animals 24h after tMCAO/sham surgery and used for western blotting of inflammasome proteins including Caspase-1, Interleukin-1b (IL-1b), apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and gasdermin-D (GSDMD). Female animals exhibited elevated levels of caspase-1 and ASC proteins in the ipsilateral cortex post-stroke. In a subsequent study, rats were sacrificed 21 days post-tMCAO for immunohistochemistry analysis of microglial marker ionized calcium-binding adapter molecule-1 (Iba-1). The estimate of activated microglia was obtained across three serial coronal sections (10μm) using the optical fractionator probe function in StereoInvestigator software with a counting frame of 100x100μm and approximately 40 sampling sites per section. Results indicated increased activated microglia in the cortex of female rats exposed to EC, potentially contributing to exacerbated infarction post-stroke.

Acknowledgements: We thank Ms. Ofelia Furones-Alonso for surgical expertise.

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Abstract Title: Development of *SLC6A1* Knock-out Zebrafish and Drug Screening Pipelines to Identify Treatments for *SLC6A1* Neurodevelopmental Disorders	
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ABSTRACT

SLC6A1 neurodevelopmental disorders (*SLC6A1*-NDD) are rare neurological conditions that result in epilepsy, autism spectrum disorder (ASD), and severe developmental, motor, behavioral, and intellectual disabilities in children. The *SLC6A1* gene encodes for the protein GABA transporter 1 (GAT1). GAT1 is required for reuptake of the inhibitory neurotransmitter, GABA, into the pre-synaptic nerve terminal. Despite the severe symptoms associated with *SLC6A1*-NDD, non-seizure and behavioral symptoms are not well characterized. Thus, *SLC6A1* knock-out (KO) zebrafish models were generated to assess non-seizure and behavioral symptoms associated with SLC6A1-NDDs. Locomotor and behavioral phenotyping assays were compared across multiple generations (F0 and F2) of zebrafish larvae harboring various indel mutations in *SLC6A1.* Guide efficiencies, exon location, and indel size were compared across mutant lines to assess impacts of indel mutations on behavioral phenotypes. Sequencing analyses and bioinformatic tools were used to compare predicted impacts of indel mutations on GAT1 function. Artificial intelligence tools were used to identify FDA-approved therapies hypothesized to upregulate and/or compensate for loss of GAT1 and prepare for future drug screening. Together this work provides the framework for comparative behavioral studies and therapeutic options for the assessment and treatment of non-seizure phenotypes associated with GAT1 loss-of-function mutations.

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Abstract Title: Causal relationship between sleep duration and Alzheimer's disease: insights from Mendelian Randomization and Latent Causal Variable analysis	
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ABSTRACT

Causal relationship between sleep duration and Alzheimer's disease: insights from Mendelian Randomization and Latent Causal Variable analysis

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The identification of modifiable risk factors, including lifestyle-related habits, offers opportunities for disease risk reduction or prevention. Sleep disturbances, such as insomnia, sleep apnea, and restless leg syndrome, encompass a wide category of conditions that affect sleep. Several studies have linked sleep disturbances with an increased risk of Alzheimer's Disease (AD).

To explore the causal relationship between sleep disturbances and AD risk, we conducted mendelian randomization (MR) and latent causal variable (LCV) analysis using sleep duration (SD) as the exposure and AD as the outcome. We leveraged publicly available Genome-wide Association Studies (GWAS) summary statistics from self-reported and accelerometer-derived SD from the UK Biobank (PMIDs: 30846698, 30952852) and six AD GWAS. We ran LCV analysis as a discovery analysis using three AD GWAS as exposure (GCST90012877, GCST007320, and GCST90027158), and then focused on the significant phenotypes for the MR analysis, using the same sleep GWAS and also three additional AD GWAS (PMIDs: 2416273, 24162737, 30820047). Inverse Weighted Variance (IWV) was employed as our primary analysis, and subsequently we used MR-Egger and Weighted Median methods. We tested for heterogeneity using the Cochran Q test.

LCV analysis revealed a significant association of self-reported long sleep (gcp = -0.644; p = 2.04E-13) and accelerometer-derived sleep duration standard deviation (gcp = -0.507; p = 0.031). We focused on these phenotypes in the MR study, but did not validate the results using the same three AD GWAS. However, we replicated the results on one of the three other GWAS (b = -22.4; p = 4.9E-09). The results were not significant when we used MR-egger (b = -18.5; p = 0.260) and Weighted Median methods (b = -21.0; p = 0.518). Three SNPs were responsible for the signals (rs4577128, rs4727449, and rs79456170; p < 0.001), located in *PRKCA*, *STAG3,* and *COMETT* genes.

Our results do not suggest clear evidence of a causal association between SD and AD. Although the results were highly significant with two different methods in two independent GWAS, we failed to find consistency across the different datasets. Other studies failed to detect evidence of causal association between SD and AD by MR (PMIDs: 35918656 and 33150399). However, a recent study (PMID: 38301285) using the English Longitudinal Study of Ageing, was able to identify increased risk of dementia and AD associated with long sleep. The risk of AD associated with SD might be potentially independent from genetic factors but mediated by other processes such as astrocyte and microglia dysregulations (PMIDs: 35755779, 29563238).

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Investigating age-related changes of mPFC neural responses to ventral hippocampus Abstract Title: stimulation	
McKnight Institute: Arizona	PI Lab: Barnes

ABSTRACT

Investigating age-related changes of mPFC neural responses to ventral hippocampus stimulation

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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 of 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 LFP and unit activity. However, 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 25 individual biphasic electrical pulses (halfwidth: 0.5 ms) ranging in amplitude from 100-600 μA with a 30s interval between pulses across the CA1 layer in iHC and vHC of anesthetized male F344 young (10 months, n = 3) and old (24 months, n = 2) rats. We simultaneously recorded evoked neural activity along the dorsoventral length of the mPFC using Neuropixels 2.0 probes. Recordings were obtained from all 4 shanks spanning 3.84 mm along the DV axis of the mPFC including the prelimbic(PL) and infralimbic(IL) regions (areas 24b and 25). Along the ML axis, the shanks span 720 μm from layer II/III to layer VI. Upon stimulating either the iHC and vHC, we observed that increasing the stimulus amplitude resulted in a decrease in response latency and increase in the magnitude of the LFP response across the mPFC, with a larger relative increase in response to iHC stimulation compared with vHC. We also observed a layer-specific difference in evoked response amplitudes with relatively larger responses in the mPFC layers V/VI compared to layers II/III across all rats and stimulation conditions. Notably, the magnitude of LFP response in the IL regions of the mPFC was larger than in the PL in young rats across stimulation conditions. In old rats, this increase in response magnitude in the IL region was not observed. The LFP response magnitude to iHC/vHC stimulation also correlated with increased firing of mPFC neurons. The relative increase in the number of mPFC neurons activated by the stimulation was more in the IL region compared to the PL region in young rats, while in old rats, the similar response magnitude resulted in a similar number of neurons activated in both subregions. It appears that the vHC drive to the IL is greater than that to the PL in young rats, and this difference does not emerge in old rats.

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Age-related changes in medial prefrontal cortex-ventral hippocampus theta power Abstract Title: interactions during a spatial working memory task	
McKnight Institute: Arizona	PI Lab: Barnes

ABSTRACT

Age-related changes in medial prefrontal cortex-ventral hippocampus theta power interactions during a spatial working memory task

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Neural ensembles in hippocampus and mPFC play a crucial role in memory-guided navigation and decision making, a process susceptible to decline with age in mammals. These regions are connected via a unidirectional projection from the ventral hippocampus to the mPFC and damage or inhibition of this circuit leads to impairments in spatial alternation tasks (Wang et al, 2006). Rats with mPFC lesions show an impairment on spatial working memory tasks, while rats with hippocampus lesions are impaired in both spatial and working memory tasks. To test the interaction between these regions we used a spatial alternation task consisting of two interleaved components: “outbound” (working memory) and “inbound” (spatial memory). Behavioral data from young (10-13 mo) and old (24-26 mo) rats tested on this task reveals that aged rats are slower to learn both components of the task. A major deficit was observed in the aged rats’ performance on outbound trials even after reaching criteria. Because the outbound component of the task requires coordination between the hippocampus and mPFC, these interactions could be impaired in aged rats. In order to investigate the mechanisms underlying agerelated impaired performance on this task, we implanted young (n=9) and old (n=3) rats with hyperdrives in both structures. Electrophysiological recordings were collected from the ventral CA1 region of the hippocampus (vHC) and in the prelimbic (PL) and infralimbic (IL) regions of the mPFC as the rats performed the spatial alternation task. Looking at electrophysiological activity prior to the rat making a choice, we observed robust theta activity (8-12Hz) in both the mPFC and vHC regions in young and old rats. Separating trials by correct and incorrect performance, we replicated the observation that theta power on correct trials was higher than on incorrect trials in the mPFC (O’Neil et al., 2013), and that this power difference was seen in both age groups. In the vHC, there was no difference in theta power between correct and incorrect trials. In young rats, there was reduced correlation of mPFC-vHC theta power prior to incorrect trials compared to correct trials. In old rats, there was no difference in mPFC-vHC theta power on the basis of performance. Overall, while there was no difference in the absolute theta power in either the vHC or mPFC regions between age groups, the theta power correlation between the regions was reduced in aged rats compared to young rats.

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Abstract Title: Block of sortilin binding in progranulin gene therapy enhances rescue of microgliosis and microglial lipofuscinosis in progranulin-deficient mice

McKnight Institute: UAB	PI Lab: Erik Roberson

ABSTRACT

Loss-of-function mutations in the progranulin (*GRN*) gene which encodes a lysosomal glycoprotein, lead to neurodegeneration. Individuals with mutations in both progranulin alleles have a complete loss of the progranulin protein resulting in a lysosomal storage disorder, neuronal ceroid lipofuscinosis (NCL). Progranulin haploinsufficiency notably causes frontotemporal dementia (FTD), an early-onset dementia characterized by degeneration of the frontal and temporal lobes of the brain. Both patient populations exhibit gliosis, increased levels of lysosomal proteins, and lipofuscinosis. Progranulin-deficient mice exhibit similar pathologies with increased gliosis and lipofuscinosis throughout the brain. Restoration of the progranulin protein is a rational therapeutic strategy using AAV-progranulin gene therapy. Previous data has shown that AAV-progranulin gene therapy with a blocked carboxy terminus to block progranulin's interaction with sortilin corrects lipofuscinosis and microgliosis in progranulin-deficient mice. This led us to ask whether blocking progranulin's carboxy-terminal domain would be a more effective therapeutic than progranulin with normal sortilin binding in correcting these phenotypes. To answer this question, we compared the effects of AAVs expressing progranulin with and without carboxy-terminal modifications that block sortilin binding. We found superior correction in several outcome measures with the carboxy terminally blocked progranulin, including more effective correction of microgliosis, microglial lipofuscinosis, and microglial morphology. These findings suggest that blocking progranulin's carboxy terminus and its interaction with sortilin enhances progranulin gene therapy's ability to correct microgliosis and microglial lipofuscinosis.

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Abstract Title: Ovarian Hormones Tune Amygdala Inhibition to Drive Anxiety-Like Behavior Across the Reproductive Cycle

McKnight Institute: UAB	PI Lab: Dr. Elizabeth Lucas

Abstract:

In both humans and rodents, high levels of ovarian hormones reduce anxiety, but the cellular mechanisms driving this effect remain enigmatic. The basolateral amygdala (BLA) regulates anxiety, but little is known about the regulation of BLA function across the female reproductive cycle. Using mice as the model species, we first conducted single nucleus sequencing of the BLA in males and females in the high (proestrus) versus low (diestrus) hormone stages of the reproductive cycle. We observed profound changes of the transcriptional landscape of most BLA cell types in proestrus females compared to diestrus females and males. All neuronal subtypes expressed the progesterone receptor and estrogen receptor alpha, but estrogen receptor beta expression was limited to one type of principal neuron and parvalbumin-expressing interneurons (PVIs). Considering that BLA activity is tightly regulated by PVIs, we targeted this neuronal population for subsequent electrophysiological and behavioral experiments. We performed whole-cell patch clamp electrophysiology in BLA PVIs in proestrus females, diestrus females, and males and observed effects of both sex and estrous cycle. BLA PVIs were hyperpolarized and received fewer excitatory postsynaptic currents in proestrus versus diestrus. However, we also observed increased intrinsic excitability and reduced frequency of inhibitory postsynaptic currents in females versus males independent of estrous cycle. We next harnessed chemogenetics to depolarize BLA PVIs in males, proestrus females, and diestrus females to establish a causal relationship between the observed electrophysiological changes and regulation of anxiety-like behavior across the reproductive cycle. We found that activation of BLA PVIs reversed the anxiolytic effects of proestrus in the elevated plus maze and open field tests but decreased social interaction in females compared to males independent of estrous stage. Ongoing work is monitoring *in vivo* activity of additional interneuron and principal neuron populations across the estrous cycle in these behavioral assays. Contrary to current models, our data suggest that increased BLA PVI activity promotes, rather than inhibits, anxiety-like behavior. Our work further implicates a role for biological sex and cycling ovarian hormones in regulating the critical balance of excitation and inhibition in the BLA to guide behavior.

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Abstract Title: Identifying peripheral immune response signature dependent on Parkinson's disease progression	
McKnight Institute: Gainesville	PI Lab: Malu Gamez Tansey

ABSTRACT

Identifying Peripheral Immune Response Signature Dependent on Parkinson's Disease Progression:

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Disrupted immune function is a significant component of Parkinson's disease (PD) and inflammatory cytokines in the blood may serve as biomarkers to identify early PD. However, there is significant variability in circulating cytokine levels due to circadian rhythm, diet, and environmental exposures. Stimulation-based assays may be more sensitive to underlying immune dysfunction, potentially allowing us to observe immune deficits in patients prior to the development of motor symptoms in PD. To investigate this, peripheral blood mononuclear cells were collected from healthy controls, early and moderate PD, and prodromal PD individuals with REM sleep behavior disorder who are likely to convert to PD. Monocytes and T-cells were isolated, plated, and treated with vehicle or a stimulation paradigm (interferon gamma for monocytes, CD3/CD28 beads for T cells) for 72 hours to assess stimulation-based responses rather than baseline differences. Flow cytometry was used to analyze monocyte and T-cell subtypes, activation, mitochondrial health, and lysosomal activity. The cultured media was analyzed for cytokine secretion using Meso Scale Discovery assay. We observed that later stages of PD are associated with a more proinflammatory monocyte composition, and T-cells from later stage PD patients showed lower fractions of functional mitochondria after stimulation. Prodromal PD cells exhibited higher stimulation-dependent secretion of TNF, IL-1β, and IL-8 relative to early and moderate PD, as well as a distinct signature of immune activation relative to healthy controls. These findings reflect observable immune dysfunction based on PD progression, indicating potential in blood stimulation-based assays as biomarkers for early PD identification.

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Abstract Title: MD simulations of rare Alzheimer’s disease–associated APOE isoforms, such as APOE3Christchurch, highlight unique structural, conformational, and dynamical features.

McKnight Institute: UAB	PI Lab: Erik Roberson

The lipid carrier protein Apolipoprotein E (APOE) is the strongest and most well-known risk factor for late onset Alzheimer's disease (AD). The three most common alleles are APOE3, APOE2, and APOE4 which provide neutral, decreased, and increased risk of developing AD, respectively. Several rare variants in APOE have been identified, through a case study and genome wide association study, to be protective against AD. These rare variants include APOE3-Christchurch (R136S), APOE3-Jacksonville (V236E), and APOE4R251G. Previously, we examined common and rare APOE isoforms in a lipid-free state. This study was limited by the starting structure, as APOE begins in a closed state with the C-domain against the N-domain, allowing for few observable changes on a nanosecond timescale. Additionally, APOE is largely in a lipidbound state in vivo and undergoes distinct structural changes to become lipid-bound. Therefore, examining APOE in a more extended lipid-bound conformation may elucidate changes caused by these substitutions that would have otherwise gone undetected. We have obtained a starting lipidated APOE structure, provided by Prakashchand et al., which was generated from coarse-grained molecular dynamics (MD) simulations of a mutant APOE structure (PDBID: 2L7B) in the presence of DPPC lipid molecules. Using this structure, we subsequently converted the mutant APOE to three separate APOE3 molecules using PyMOL after energy minimization. After 300 ns of equilibrated simulation of each lipid-protein complex, we generated a representative structure which was used to convert APOE3 to the remaining APOE isoforms, except for APOE4-R251G which was generated from a representative APOE4 structure. Three replicate simulations for each variant, each with 300 ns of equilibrated simulation, were used for subsequent analysis. Types of analysis included examining changes in APOE structure, conformation, dynamics, and lipids binding interactions. Results indicate that APOE3-Ch has similar conformation stability and dynamics to APOE2. Another variant of which we know very little, APOE4-R251G, appears largely distinct in conformational stability and has different dynamics compared to its most closely related isoform APOE4. Analysis of rare APOE isoforms, in the context of common APOE isoforms, provides insight into unique and shared characteristics of each that could be predictive of downstream functional changes resulting in altered AD risk. This work was supported by the NIH R01AG068395, NIH R01AG081228 and Alzheimer’s Drug Discovery Foundation.

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Abstract Title: Factors associated with verbal memory performance in rural residents of the United States.	
McKnight Institute: Arizona	PI Lab: Huentelman

Factors associated with verbal memory performance in rural residents of the United States.

Harshini Venkatachalam, Megan Johnson, Matt De Both, Marcus Naymik, Meredith Hay, Roberta Brinton, Carol Barnes, Lee Ryan, and Matt Huentelman

Residents of rural areas are often underrepresented in research studies and clinical trials of all types. This is true for cognitive aging research and dementia-focused clinical trials. Evidence suggests that rural residents are at higher risk for dementia, demonstrate an enrichment for known risk factors, and typically receive delayed diagnoses compared to non-rural residents. We sought to investigate the factors that are associated with cognitive performance in nondemented residents of rural zip codes in the United States. We utilized our internet-based study, MindCrowd, which is over ten years old and has collected cross-sectional cognitive data from over 40,019 rural U.S. zip code residing participants. We focused here on the results from MindCrowd paired associates learning, a verbal memory task that includes three rounds of 12 word-pairs and yields a final scored result ranging from 0-36. The basic demographics of the MindCrowd rural cohort is as follows: 75% aged 50 and older, 90% White, 5% Hispanic, 19% male, and 26% high school education or less. Of note, only 12.6% of this cohort endorsed having no health/medical conditions while that same percentage is approximately doubled when the MindCrowd cohort as a whole is considered. The three most prevalent factors in rural participants are hypertension (42%), having a second-degree relative with Alzheimer's disease (31%), and depression or anxiety (26%). The three factors with the largest impact on verbal memory performance in the rural cohort were age (p=1.32e-13, beta=-0.17 word pairs per year), sex (p=7.88e-06, beta= -2.0 word pairs if male), and education (p=3.18e-05, beta=1.5 word pairs per milestone). Of note, the beta values for the three strongest predictors of verbal memory performance - age, sex, and education - were found to be similar when comparing rural and non-rural participants. Other demographic, health, medical, and lifestyle factors that had a significant influence on performance in rural residents included; number of daily prescription medications, stroke, and smoking status. In this large study of residents of rural U.S. zip codes, we demonstrate that the strongest predictors of verbal memory performance have similar impacts in rural and non-rural residents. We further characterize other factors that impact verbal memory performance within the rural cohort. While preliminary, this study represents one of the largest investigations of cognition in rural residents of the U.S. This study is a collaboration with the Precision Aging Network research team.

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Key Words: rural | cognition | disparity | equity | memory

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Abstract Title: CRISPR screening of genes associated with neuronal pentraxin 2 gene expression in human iPSC-derived glutamatergic excitatory neurons	
McKnight Institute: Arizona	PI Lab: Barnes

TITLE: CRISPR screening of genes associated with neuronal pentraxin 2 gene expression in human iPSCderived glutamatergic excitatory neurons

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Neuronal pentraxin 2 (NPTX2 or Narp), an immediate early gene enriched at the excitatory synapse of glutamatergic neurons and inhibitory parvalbumin interneurons, is critical in the dynamic regulation of homeostatic scaling of synaptic activity in response to stimuli (Tsui et al., 1996; Xu et al., 2003; Chang et al., 2010). Studies suggest that NPTX2 gene and protein expression is downregulated with aging and greatly reduced at the onset of cognitive impairment in Alzheimer's Disease (Hanson, 2017; Xiao et al., 2017). Glycopeptiforms of NPTX2 have also been implicated in contributing to cognitive resilience in aging populations (Buchman et al.2024). Reprogrammable human induced pluripotent stem cells (hiPSCs) derived from human adult cells alongside CRISPR gene editing present an innovative approach to investigate these complex cellular mechanisms (Romito and Cobellis., 2015). Brain derived neurotrophic factor (BDNF) signaling has been identified as an upstream bidirectional modulator of expression NPTX2 (Giacobbo et al., 2018; Mariga et al., 2015) but showed low expression levels in hiPSC-derived glutamatergic neurons (bitbio®). In this study, we utilize hiPSC-derived excitatory glutamatergic cortical neurons, generating CRISPR-ready excitatory glutamatergic neurons (bitbio®) to 1) perform a dose-dependent experiment to assess the effects of enriched BDNF in culture medium on NPTX2 mRNA expression over days of treatment; 2) establish a protocol to quantify mRNA levels of NPTX2 using reverse-transcription quantitative polymerase chain reaction (RTqPCR) readouts and validate a knockdown of NPTX2 in these excitatory glutamatergic neurons; and 3) further develop a protocol for knockout of NPTX2 by optimizing synthetic guide RNA (sgRNA) delivery. Dosedependent BDNF treatment did not show a significant main effect of BDNF on NPTX2 mRNA expression levels across a 14-day time course experiment in these excitatory neurons. We have established a RT-qPCR method to quantify mRNA levels of NPTX2 with siRNA-knockdown and sgRNA treated neurons compared to control. We plan to further screen other highly correlated target genes with NPTX2 including SCG2, RIMBP2, ARHGEF7, CHGB and TRIM9 through delivery of each sgRNA. The findings here should provide insights into the mechanisms by which additional pathways interact with NPTX2 to produce NPTX2's function in circuits critical for optimal cognitive function.

Keywords: NPTX2, iPSCs, Glutamatergic Neurons, CRISPR, RT-qPCR

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Abstract Title: Differential effects of chronic oral THC consumption in young and aged rats	
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With the increased legalization of recreational and medicinal cannabis, use is growing rapidly amongst older adults. As the number of older adults in the US is expected to reach 90 million by 2050, it is imperative to better understand the cognitive impacts of cannabis use in this population. We evaluated the effects of chronic oral administration of delta-9-tetrahydrocannabinol (THC; the primary psychoactive component of cannabis) on a delayed response task that assessed PFC-dependent working memory and on the Morris 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 prior to drug administration. As expected, aged rats were impaired relative 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. Working memory performance was assessed after three weeks of daily consumption. There were no effects of THC on working memory in young adults; 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; however, THC did not enhance spatial learning in either age group. These findings suggest that THC does not impair and can provide benefit to cognition in older subjects. While data showing pro-cognitive effects of THC in older subjects are of particular interest, the neural mechanisms underlying such effects are poorly understood. Changes in glucose utilization and metabolism within the CNS are well documented with age and are linked with cognitive decline as well as neurodegenerative conditions such as Alzheimer's disease. To better understand the relationship between brain metabolism and cannabis use, a second experiment testing the effects of chronic oral THC consumption on brain metabolism in aging was done using Matrix-assisted laser desorption/ionization mass spectrometry (MALDI Imaging). For this study, young and aged rats consumed control or THC gelatin for three weeks, after which they were euthanized for brain tissue collection and processing. Initial results indicate that chronic oral THC causes brain region-specific alterations in levels of a range of small molecules, notably among those associated with monoamine metabolism in prefrontal cortex