Texas Alzheimer's Research and Care Consortium

Symposium 2025

Scientific Posters

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Scientific Posters

Poster Theme Group A1. Development of New Models and Analysis Methods

Poster # 1: NANOSCALE STRUCTURAL CHARACTERIZATION OF AMYLOID BETA 1-42 OLIGOMERS AND FIBRILS GROWN IN THE PRESENCE OF FATTY ACIDS

Presenting author: Dmitry Kurouski (TAMU)

Mono- and polyunsaturated fatty acids (FAs) are broadly used as food supplements. However, their effect on the aggregation of amyloidogenic proteins remains unclear. In this study, we investigated the effect of a large number of mono- and polyunsaturated, as well as fully saturated FAs on the aggregation of amyloid β1−42 (Aβ1−42) peptide. A progressive aggregation of this peptide is the expected molecular cause of Alzheimer's disease (AD), one of the most common neurodegenerative pathologies in the world. We found that arachidonic and stearic acids delayed the aggregation of Aβ1−42. Using Nano-Infrared spectroscopy, we found that FAs caused very little if any changes in the secondary structure of Aβ1−42 oligomers and fibrils formed at different stages of protein aggregation. However, the analyzed mono- and polyunsaturated, as well as fully saturated FAs uniquely altered the toxicity of Aβ1−42 fibrils. We found a direct relationship between the degree of FAs unsaturation and toxicity of Aβ1−42 fibrils formed in their presence. Specifically, with an increase in the degree of unsaturation, the toxicity Aβ1−42/FA fibrils increased. These results indicate that fully saturated or monounsaturated FAs could be used to decrease the toxicity of amyloid aggregates and, consequently, decelerate the development of AD.

Funding: NIGMS; COI: None

Poster # 2: IMPACT OF CIRCADIAN RHYTHM DYSREGULATION ON THE BRAIN-GUT-IMMUNE AXIS.

Presenting author: Emily Iglesias BS (TAMU)

Background: Circadian clocks throughout the body regulate physiological processes, such as the secretion of cytokines and growth factors, by aligning with the 24-hour solar light-dark cycle. This synchronization ensures that biochemical, physiological, and behavioral events occur at the "right" time of day. However, disruptions caused by shift work, jet lag, and irregular sleep patterns can lead to circadian dysregulation, which has been associated with health disorders like stroke, inflammatory diseases, and neurodegenerative disorders. The mechanisms underlying these effects remain unclear, but recent research suggests immune activation and inflammation may play a significant role. Given that the gut is rich in immune cells and metabolites influencing inflammation, this study hypothesizes that altered gut permeability and microbiota are key intermediaries linking shift work-induced circadian dysregulation to chronic inflammation and related pathologies. Additionally, changes in gut flora impact the gut-brain axis, potentially increasing blood-brain barrier permeability, promoting cytokine release, and contributing to neuroinflammation. Understanding these pathways could provide new insights into the connection between circadian dysregulation and systemic health outcomes. Methods: Young mice and rats (4-6 mo) were housed under a standard LD 12:12 cycle to establish baseline circadian rhythms, then split into two groups: one maintained on a fixed LD 12:12 cycle, and the other exposed to shifted LD 12:12 cycles (12hr advance/5d) for 80 days. After exposure, the shifted LD group returned to a regular LD 12:12 cycle for 7 months. Wheel-running behavior was monitored throughout. At study completion, animals were euthanized, and gut, spleen, blood, and fecal samples were collected for analysis. Results: The study implicates gut-immune interactions in mediating the effects of circadian dysregulation. Shifted LD cycles led to gut dysbiosis, compromised gut barrier integrity, and altered microbial composition, including

changes in Prevotella histicola and Clostridium difficile prevalence. These findings suggest that gut microbiota changes may contribute to inflammation, worsening stroke outcomes, and cognitive decline. Conclusion: Circadian dysregulation may impair gut function, leading to a proinflammatory state. Future studies should explore whether gut-targeted therapies, such as beneficial microbes or barrier-repair agents, can mitigate these effects.

Funding: Janell and Joe Marek '57 Alzheimer's Disease Research Fund and WoodNext Foundation; COI: None

Poster # 3: SHIFT WORK SCHEDULES ALTER IMMUNE CELL REGULATION AND ACCELERATE COGNITIVE IMPAIRMENT DURING AGING

Presenting author: Jocelin Reyes B.S (TAMU)

Background: Disturbances of the sleep wake cycle and other circadian rhythms precede age related deficits in learning and memory, suggesting that these alterations in circadian timekeeping contribute to the progressive cognitive decline during aging. Both age related dementia and altered regulation of circadian rhythms have been associated with immune cell activation and inflammation. Methods: We used C57Bl/6J mice exposed to shifted light-dark (LD) cycles (12hr advance/5d) during early adulthood (4-6mo) to test the long-term effects of circadian rhythm dysregulation on cognitive performance, immune cell regulation and hippocampal microglia at middle age (13-14mo). Results: Entrainment of the activity rhythm was stable in all mice maintained on a fixed LD 12:12 cycle, but was compromised during exposure to shifted LD cycles. Following exposure to experimental lighting conditions, re-entrainment of activity rhythm in shifted LD mice was marked by a delayed phase angle of entrainment and increased day-to-day variability in activity onset times that persisted into middle-age. These alterations in the light-dark entrainment pattern were closely associated with dramatic impairment in the Barnes maze test for the entire group of shifted LD mice at middle age, well before cognitive decline was first observed in aged (18-22mo) animals maintained on fixed LD cycles. In conjunction with the effects of circadian dysregulation on cognition, shifted LD mice at middle age were distinguished by significant expansion of splenic B cells and B cell subtypes expressing the activation marker CD69 or inflammatory marker CLIP, differential increases in CLIP+, 41BB-Ligand+, and CD74+ B cells in the meningeal lymphatics, alterations in subpopulations of T cell phenotypes in the spleen, and increased number and altered morphological state of microglia in the dentate gyrus. In mice exposed to shifted LD cycles, the expansion in splenic B cells was negatively correlated with cognitive performance such that when the number of B cells was higher, cognitive index scores were lower and performance was worse in the Barnes maze. Conclusion: These results indicate that disordered circadian timekeeping associated with early exposure to shift work-like schedules alone accelerates cognitive decline during aging in conjunction with altered regulation of immune cells and microglia in the brain.

Funding: Janell and Joe Marek '57 Alzheimer 's disease Research Fund, WoodNext Foundation and Texas Alzheimer's Research and Care Consortium; COI: None

Poster # 4: UTILIZING ATN PLASMA BIOMARKERS AND MACHINE LEARNING MODELS TO PREDICT EARLY ALZHEIMER'S DISEASE AMONG HABS-HD COHORT

Presenting author: Stella Anagnos, BS (UNTHSC)

Alzheimer's disease (AD) is a progressive condition of neurodegeneration in the brain resulting in a decline of cognitive function over time. Early detection of AD is essential for improving outcomes for Alzheimer's patients because of the irreversible nature of the neurodegeneration. Previous studies have demonstrated the predictive capabilities of amyloid, tau, and neurofilament biomarkers for denoting brain amyloidosis and how the biomarker of greatest predictive power is different depending on race and

ethnicity of the patient population. While most studies of ATN biomarkers predicting brain amyloidosis have been conducted in predominantly non-Hispanic White cohorts, further investigation of these biomarkers in different racial and ethnic groups is a growing focus. In this project, we investigated the role of ATN biomarkers Amyloid Beta (Aβ) 40, Aβ 42, T-Tau, ptau-181, and Neurofilament Light Chain (Nf-L) in support vector modeling (SVM) to predict amyloidosis in the HABS-HD cohort (N = 1,442, Amyloid Positive N = 108, Amyloid Negative N = 1,334). ATN Biomarkers were derived using single molecule array (SIMOA) technology on the HD-X platform. The HABS-HD cohort is a racially and ethnically diverse patient population consisting of non-Hispanic Whites, non-Hispanic Blacks, and Hispanics. By studying these biomarkers in this cohort, we were able to determine that SVMs with a combination of all ATN biomarkers (Aβ 40, Aβ 42, T-Tau, Ptau-181, and Nf-L) were the most successful at predicting brain amyloidosis in among non-Hispanic Whites (AUC = 0.88), non-Hispanic Blacks (AUC = 0.79), Hispanics (AUC = 0.88), and in the overall cohort (AUC = 0.82). Furthermore, we discovered that while the Aβ 42/40 ratio had the greatest predictive power among non-Hispanic Whites and in the overall cohort, pTau-181was the greatest driver in predicting brain amyloidosis in the non-Hispanic Black SVM model, and Nf-L was the greatest driver in predicting brain amyloidosis in the Hispanic SVM model. Moving forward, we will continue to investigate the relationship of these ATN biomarkers and work to incorporate more combinations of biomarkers as well as racial and ethnic groups until the most precise and accurate SVM models for predicting brain amyloidosis in each patient population can be achieved.

Funding: Research reported in this presentation was supported by the National Institute on Aging of the National Institutes of Health under Award Numbers R01AG054073 and R01AG058533, P41EB015922 and U19AG078109; COI: None

Poster # 5: THE MECHANISM BY WHICH THE NOVEL GENETIC RISK FACTOR SCULLY/HSD17♌10 CONTRIBUTES TO ADRD

Presenting author: Kyung-An Han (UTEP)

Background: The multifunctional mitochondrial enzyme Scully (Scu)/HSD17♌10 is linked to Alzheimer's disease (AD) because it binds to A♌ peptides and is overexpressed in the postmortem brains of AD patients. However, there is no in vivo evidence supporting this notion. Method: To narrow this knowledge gap, we investigated the role of Scu in dementia by measuring inhibitory control and memory in Drosophila and its interaction with Ab, Tau and exposomes. Result: We found that the Scu-deficient flies exhibit inhibitory control deficit and memory loss in an aging-dependent manner and interacts with the exposomes social stress and sleep loss. We identified the mushroom body as the major neural site for the Scu's role in the aging-associated cognitive decline. Scu/HSD17♌10 is known to be involved in steroid homeostasis in mammals and tRNA processing in Drosophila. We examine which Scu's function is important for its role in dementia. We found no genetic interaction of Scu with t-RNA processing molecules but found strong interaction with ecdysone, a major steroid hormone in Drosophila. Notably, Scu deficiency augments A♌ and Tau pathologies. Conclusion: Our findings not only advance the knowledge of how Scu contributes to dementia and ADRD pathogenesis but also provide a novel in vivo model system to validate GWAS and omics data obtained from human subjects.

Funding: This work was supported by the Orville Edward Egbert, M.D. Endowment fund, NIH NIGMS 1R16GM145548 and NIH NIMHD 3U54MD007592-29S5 grants; COI: None

Poster # 6: DETECTION OF TAU AGGREGATES IN ALZHEIMER'S PATIENTS BY SEED AMPLIFICATION ASSAY AND ITS APPLICATION FOR IDENTIFICATION OF TAU SEEDING INHIBITORS

Presenting author: Haley Evans, B.S. (UTH Houston)

Background: Accumulation of misfolded tau protein aggregates are a defining characteristic of Alzheimer's disease (AD). These pathological tau species propagate by templating their disease-associated conformation onto native tau, and incorporating this newly misfolded tau into the growing fibrils. Multiple lines of evidence suggest that this prion-like seeding mechanism underlies the stereotypical progression of tau pathology throughout the brain and thus represents a biologically-relevant therapeutic target. We have developed a tau Seed Amplification Assay (Tau-SAA) using the prion-like seeding capacity of disease-associated tau to mimic its propagation in a cell-free in vitro system. As such, Tau-SAA has immense potential for high sensitive and accurate detection of tau pathological aggregates in patients' samples as well as a drug screening platform for the discovery and development of therapeutics that target tau spreading in AD. Methods: Through several rounds of refinement, we optimized the Tau-SAA conditions including temperature, shaking frequency, and reaction volume. We then tested a cohort of AD and non-affected control brain homogenate samples to access the sensitivity and specificity of our assay. To access our platforms utility as a drug screening tool we tested 20 suspected amyloid inhibitors as well as several hundred additional FDA-approved and brain-penetrant compounds from a commercial library. Results: were analyzed in terms of percent inhibition of tau aggregation, half-maximal inhibitory concentration, maximum fluorescence, and the time-to-threshold. Results: Our data demonstrates Tau-SAA can accurately distinguish between AD and control samples and can detect the presence of tau seeds even at dilutions as extreme as 1,000,000 fold. Furthermore, through several rounds of adaptation, we have optimized the Tau-SAA for high-throughput drug screening. Conclusion: Detection of tau aggregates using Tau-SAA provides a practical method for identifying compounds that may inhibit tau aggregation and spreading. Our preliminary results demonstrate that known amyloid inhibitors halt tau aggregation and through screening of FDA-approved compounds we demonstrate that Tau-SAA may serve as a valuable tool for drug-repurposing and for the identification of novel compounds.

Funding: TARCC grant and NIH grant R61NS136666; COI: None

Poster # 7: PHENOTYPIC ANALYSIS OF PLCΓ2 VARIANTS WITHIN NOVEL LATE-ONSET ALZHEIMER'S DISEASE MOUSE MODEL

Presenting author: Juliet Garcia Rogers, BS (UTH San Antonio)

Background: Recent studies have linked PLCG2, the gene that codes for phospholipase C γ2 (PLCγ2), to late-onset Alzheimer's Disease (LOAD). PLCG2 polymorphisms are associated with reduced (P522R) or increased (M28L) risk for LOAD. The aim of our study is to compare difference in behavioral, biochemical, and histological phenotypes between PLCγ2 variants in a novel LOAD mouse model (LOAD2) with humanized Aβ, TREM2*R47H, and ApoE4. Methods: Males and female LOAD2 mice expressing wild type (WT), P522R, or M28L PLCγ2 were tested in the Barnes Maze test for spatial memory at 12 months, frailty analysis for aging phenotypes at 15 and 19 months, open field and novel object recognition for anxiety and recognition memory at 18 months, and fear conditioning for associative fear learning and memory at 21 months. Mice were euthanized at 23 months for histological and biochemical analyses. Results: M28L mice made significantly more errors during Barnes Maze training. Both M28L and P522R mice had significant deficits compared to LOAD2 mice during the memory-testing probe trial. Frailty testing revealed that in females only, M28L mice had higher Frailty Index scores than WT mice and P522R mice. Open Field and Novel Object Recognition testing showed no deficits in locomotion, anxiety, or recognition memory for any PLCγ2 genotype. When frailty was reassessed, there was an increase in the overall scores of all genotypes, with M28L still displaying the highest scores. There were no differences in associative fear learning or memory in these mice. Brain lipidomic analyses indicated differences in myelin related lipids between PLCγ2 genotypes and sex, with male P522R mice having a greater abundance of N-cerebrosides and N-sulfatides compared to their M28L and WT counterparts. Conclusions: In summary, mice expressing M28L and P522R PLCγ2

displayed minor but statistically significant deficits in learning and memory, sex-specific increases in frailty index scores and myelin associated lipid abundance, suggesting these variants may play a role in altering various phenotypes relevant to aging and LOAD. Future research will examine histological markers for various microglia, myelin, synaptic, and immune-cell markers in these mice, as well as explore the sex differences seen in our results.

Funding: NIA K01 AG066747, AARG-21-846012, NIA 3P30 AG013319-25S1; COI: None

Poster # 8: NOVEL TDP-43 ALS MODEL DRIVES MOTOR DYSFUNCTION AND PATHOLOGY IN MICE

Presenting author: Matthew Dopler, PhD (UTH San Antonio)

Background: Amyotrophic Lateral Sclerosis (ALS) is a rare neurodegenerative disease characterized by the death of the upper and lower motor neurons. Prognosis is a progressive weakness of skeletal muscles resulting in complete paralysis with the average survival rate of being 3-5 years. Accumulation of cytoplasmic insoluble phosphorylated TDP-43 is characterized in 95% of all ALS cases. There are currently no therapeutics targeting TDP-43 pathology and mouse models that replicate behavior, pathology, and change in TDP-43 solubility are needed. We developed and characterized a TDP-43 mouse model with 3 familial mutations (3X-TDP-43) under the control of tetracycline response system (Tet-off). The transgene expression was driven in the brain and spinal cord by the neurofilament heavy promoter (NEFH-tTA). Methods: TetO-3X-TDP-43 mice were crossed with NEFH-tTA mice. Expression of 3X-TDP-43 did not occur until after the mice were weaned at 20-22 days of age. Rotarod was conducted weekly to observe change in motor function. The number of days of mouse survival was recorded. Immunofluorescence and Western blots were conducted to study changes in pathology and biochemistry in mice. Results: Male mice expressing 3X-TDP-43 start showing motor dysfunction at 5 weeks of age with females showing dysfunction at 6 weeks of age. Motor dysfunction progressives up to death with the female mice survival range of 44-113 and male mice survival range of 48-80 days. Mice expressing 3X-TDP-43 showed increased GFAP in the brain suggesting increased gliosis. Post synaptic maker, PSD95, was decreased in mouse brain, suggesting a decrease in post synaptic density. Phosphorylated TDP-43 was observed in the brain and spinal cord, however this was shown to be localized to the neuronal nucleus. Conclusion: Compared to control mice, 3X-TDP-43 expressing mice showed increased and rapid motor dysfunction and decreased survival. Increase in astrogliosis and decrease in post synaptic density suggest an increase in neuronal damage and loss. Phosphorylated TDP-43 was shown to accumulate in the nucleus rather than resembling the hallmark cytoplasmic accumulation. Despite this limitation, we believe this model can assist in the development of therapeutics and increase our understanding of TDP-43 proteinopathy.

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Poster # 9: P2RY12 AS A REGULATOR OF MICROGLIAL PHENOTYPES AND FUNCTION IN NEURODEGENERATION

Presenting author: Teniade Adetona, BS (UTH San Antonio)

Background: Microglia play a critical role in responding to neurodegenerative cues, including those abundant in Alzheimer's disease. During neurodegeneration, microglia shift away from a homeostatic

phenotype as they react to pathology. This shift is partly mediated by the homeostatic microglial receptor, P2RY12, which promotes cell motility toward injury. Preliminary analysis indicates that levels of P2RY12 are higher in some neurodegenerative diseases when compared to Alzheimer's, suggesting that P2RY12 expression may vary depending on disease context. We hypothesize that microglia with higher levels of P2RY12 expression are less reactive in phenotype and therefore less responsive to neurodegenerative signals. Methods: To explore the role of P2RY12 in modulating microglial phenotypes and function, we generated tamoxifen-inducible conditional knockout mice (P2RY12 cKO; P2RY12fl/fl x Tmem119-2A-CreERT2). To assess the role of P2RY12 in rest-activity cycles, mice were exposed to 2 weeks of different environmental conditions: a standard 12 hr light - 12hr dark cycle, a 12 hr phase inversion, and constant darkness. Histological samples were collected to analyze cell morphology and P2RY12 expression in microglia via immunofluorescence microscopy. To determine behavioral effects of P2RY12 knockout, cognitive performance was measured using the Barnes maze task. Results: P2RY12 cKO mice entrained and responded to environmental conditions similarly to mice without Cre-inducible knockout, yet they exhibited hyperactivity, especially during the dark phase. During the Barnes maze, P2RY12 deficiency did not alter the time spent in the area surrounding the escape hole, nor did it affect activity during the trial as both were comparable between groups. Conclusion: Our findings suggest that conditional knockdown of P2RY12 may modify activity levels during specific environmental conditions, though further validation is ongoing. Based on the Barnes maze task, our findings suggest that P2RY12 deficiency may not alter spatial memory, though further analysis is ongoing to assess the effects of P2RY12 deficiency on spatial learning. Future work will further explore the hyperactive phenotype described and the therapeutic potential of inhibition of P2RY12 to mediate the progression of neurodegeneration.

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Poster # 10: SCOPIOUS BRAIN WAVES IN RAT MODELS OF ALZHEIMER'S DISEASE

Presenting author: Nastaran Lotfi, PhD (UTHealth Houston)

The gradual degeneration of neuronal populations in Alzheimer's disease (AD) results in significant cognitive impairments, irreversible memory decline, and other symptoms. While numerous studies focus on the cellular and cognitive aspects of AD, the neural circuits have received less attention due to their greater complexity, despite the fact that many network phenomena emerge from intricate interactions of these finer-grained parts. Electrophysiologically recorded subcortical local field potentials (LFPs) and extracortical electroencephalograms (EEGs) serve as primary sources of information about network dynamics, such as desynchronization and hypersynchrony. The recently established method of the Discrete Padé Transform (DPT) is a powerful tool for interpreting and understanding brain dynamics at the circuit level. The results show that LFPs consist of a few discrete, frequency-modulated waves-oscillons-embedded in a weak noise background. Oscillons seem to represent the true, physical oscillatory patterns in EEGs that were previously approximated by Fourier waves. For instance, a θ-oscillon is emulated by a Fourier-filtered θ-wave, while γ-oscillons (of which there are three) are typically rendered as "slow," "medium," and "fast" γ-waves. Although the traditional waveforms are useful in practical applications, they miss certain crucial aspects of LFPs, which are captured by the oscillons. Recent advancements in DPT allow for the processing of multiple signals at once, which resolves many practical difficulties in analyzing multichannel EEG recordings. Together, this set of tools provides a unique opportunity to study the multifaceted alterations in circuit dynamics caused by AD pathologies. Gaining insight into early disturbances in oscillon dynamics will lead to a better understanding of the circuit mechanisms of AD and help distinguish between healthy and AD-affected brain networks, both in humans and animal models. In this project, we aim to perform a comprehensive analysis of scopious oscillon dynamics in healthy and ADRD-affected humans and rodents at various stages of pathology development, which will establish new biomarkers of AD/ADRD through electrophysiological imaging.

Funding: R01AG074226; COI: None

Poster Theme Group A2. Genetics

Poster # 11: TOP ALZHEIMER'S DISEASE RISK ALLELE FREQUENCIES IN HABS-HD AFRICAN AMERICANS VS NON-HISPANIC WHITE AMERICANS

Presenting author: Reem Ayoub OMS-II (TCOM - UNTHSC)

Background: Alzheimer's disease (AD) is the most prevalent form of dementia, with African Americans (AA) being twice as likely to develop AD-related dementia compared to non-Hispanic whites (NHW). AAs also often present with more severe clinical symptoms at diagnosis. While most AD research focuses on individuals of European ancestry, genetic risk factors vary across populations. This study aims to investigate top AD risk alleles in AAs and NHWs from the Health and Aging Brain Study - Health Disparities (HABS-HD), with particular attention to the APOE ε4 allele, which has various effect sizes for AD risk among different ethnic groups. Methods: Genetic data from HABS-HD participants, including 616 AAs and 1098 NHWs, were analyzed to determine genotype frequencies across several single nucleotide polymorphisms (SNPs) of interest. APOE ε4 positivity and allele frequencies were evaluated in both populations. Statistical analyses were conducted to explore the differences in genotype frequencies and allele distributions between the two groups. Results: APOE ε4 positivity was higher among AAs (40%) compared to NHWs (30%). Significant differences in the distribution of known APOE4 variants were observed between the two groups. These findings suggest that AAs may carry a higher genetic burden for AD due to the increased prevalence of APOE ε4, which could explain their higher disease rates and more severe clinical outcomes. Discussion: While AAs have higher APOE ε4 positivity, it has been found that it carries a smaller effect size. These results underscore the importance of evaluating whole genetic and clinical risk factors in diverse populations. Future studies will assess other top AD risk alleles in AAs and compare these findings with those in NHWs and Mexican Americans. The data generated will contribute to developing a polygenic risk score tailored to different ethnic groups, improving the understanding and treatment of AD across diverse populations.

Funding: None; COI: None

Poster # 12: ANALYSIS OF ACE2 SNPS AS EPISTATIC RISK FACTORS FOR AD OUTCOMES

Presenting author: Amanda Tucker, BS (UNTHSC)

Background: Alzheimer's disease (AD) and AD-related dementias (ADRD) have no single identifiable cause but it is understood that many risk factors may interplay to create AD sub-phenotypes. The strongest genetic risk factor for development of AD/ADRD is the presence of the ε4 allele in the apolipoprotein E (APOE) gene, however, the allele frequency of ε4 and its impact on cognitive decline can vary significantly across racial/ethnic groups. Vascular disorders (e.g. hypertension or cardiovascular disease) are also strong risk factors for AD/ADRD. A multiethnic cohort study found that controlling for vascular disorders mediated the AD health disparity observed across racial/ethnic groups, suggesting vascular health has a significant influence on cognitive functions and neurodegeneration across these populations. Angiotensin-converting enzyme 2 (ACE2) genetic variants are risk factors for vascular disorders due the prominent role ACE2 plays in the renin-angiotensin-aldosterone systems as a key regulator of the vasculature. Recent studies suggest a potential interaction between ACE2 & APOE proteins, making ACE2 an interesting candidate for epistatic studies connecting vascular disorders and AD/ADRD risk factors. We hypothesize that ACE2 loci will have population-specific alleles associated with vascular disease and AD/ADRD, and that these contribute to group differences AD risk and

accelerated neurological dysfunction when found in epistasis with APOE ε4. Methods: We will conduct genomic association analysis of individuals enrolled in the Healthy Aging Brain Study-Health Disparities (HABS-HD) to identify ACE2 variants implicated in vascular disorders within Mexican-Americans, Black, and non-Hispanic White populations, controlling for APOE status. Formal epistasis testing will be conducted to determine if APOE/ACE2 gene-gene interactions differentially impact comorbidity-based risk for AD/ADRD in high-risk racial/ethnic populations. Conclusion: This study will extend an understanding of the interplay between genetic risk factors that differentially contribute to AD outcomes, specifically a co-occurrence of ACE2 SNPs and APOE status. We expect associations between cognitive decline/dementia and the presence of vascular diseases such as hypertension or cardiovascular disease in these populations. Overall, this project will begin to elucidate comorbidity and gene-gene interactions as a potential consideration for predicting AD risk and support future mechanistic studies on cellular phenotypes associated with epistatic effects.

Funding: This work is supported by the National Institute on Aging training fellowship (T32 AG020494), & IMSD Fellowship, Grant # 5 R25 GM125587-05 from the National Institutes of General Medical Sciences (NIGMS); COI: None

Poster # 13: DETERMINING THE IMPACT OF TOMM40 SINGLE NUCLEOTIDE POLYMORPHISMS ON METABOLIC SYNDROME AND WHITE MATTER HYPERINTENSITY VOLUME IN AFRICAN AMERICANS.

Presenting author: Christopher Purvis BS (UNTHSC)

Background: Single nucleotide polymorphisms (SNPs) in the TOMM40 gene have been implicated in Alzheimer's Disease (AD) susceptibility, independent of the well-studied APOE genotype. Furthermore, the SNP rs157582 has been associated with metabolic syndrome in African American populations, prompting an investigation into its potential effects on cognitive decline. Method: This study aims to elucidate the impact of 3 different rs157582 genotypes on metabolic syndrome variables and white matter hyperintensity (WMH) volumes in African Americans with mild cognitive impairment (MCI) and AD. Participants included African American adults diagnosed with MCI or AD and cognitively unimpaired (CU) recruited via the Health and Aging Brain Study - Health Disparities (HABS-HD). We analyzed seven key variables: diabetes diagnosis, HbA1c levels, glucose levels, hypertension diagnosis, dyslipidemia diagnosis, triglyceride levels, total cholesterol, and white matter hyperintensity volume. Genotypes for rs157582 were derived from the HABS-HD consortium Infinium Global Screening Array SNP (Illumina) data, and genotypes were tested for association with the metabolic and AD-related outcome variables. Result: Preliminary analyses indicate that individuals carrying the rs157582-T allele exhibited significantly higher rates of metabolic syndrome (i.e., diabetes, hypertension and/or dyslipidemia) diagnoses and indicators of elevated WMH volumes, suggesting a correlation between this genetic variant and both metabolic dysregulation and risk for cognitive dysfunction. Interestingly, the risk of this allele appears to stand independent of APOE allele e4 status, which has previously been linked to TOMM40 genetic associations. Additional studies of mediation/moderation effects of SNP and metabolic comorbidity on cognitive and AD-related imaging outcomes are pending. Conclusion: The findings suggest that the TOMM40 SNP rs157582 may play a crucial role in the intersection of metabolic syndrome and Alzheimer's disease risk among African Americans. This underscores the importance of genetic screening and metabolic assessment in high-risk populations, potentially informing targeted prevention strategies and interventions to mitigate cognitive decline in individuals at elevated genetic risk for AD.

Funding: HABS HD U19: NIH/NIA 1U19AG078109-01, Contact PI- Sid O'Bryant; COI:

Poster # 14: CORRELATION BETWEEN DNA METHYLATION IN ALZHEIMER'S DISEASE AND DEPRESSION-RELATED GENES AND GERIATRIC DEPRESSION SCALE SCORES AMONG HISPANIC TARCC PARTICIPANTS

Presenting author: Damariza Barraza, MS (UNTHSC)

The aim of this study is to examine the correlation between Geriatric Depression Scale (GDS) scores and DNA methylation profiles at known Alzheimer's disease (AD) and depression-related genes in a group of Hispanic participants. Previous research has identified a strong positive correlation between depressive symptoms and Alzheimer's disease, though the underlying mechanisms remain unclear. One potential mechanism is DNA methylation, an epigenetic modification influenced by environmental factors that affect gene expression. While DNA methylation has been associated with AD, depression, and other complex diseases, its specific effects on depression are less explored. Additionally, this study seeks to better understand the role of ancestry and environmental factors as moderators of the relationship between depression and AD. Using R, a linear regression analysis was conducted with CpG site methylation as the independent variable and GDS30 scores as the dependent variable, controlling for multiple covariates. The analysis was performed for both beta and M values. Results indicated that the cg25594636 site exhibited a direct relationship with GDS30, suggesting that higher methylation levels are associated with higher depression levels. In contrast, the cg03899372 site demonstrated an inverse relationship, indicating that higher methylation levels are associated with lower depression levels. The findings suggest a potential link between DNA methylation states and depression levels in this cohort. Future research should focus on tissue-specific CpG site expression to further elucidate the mechanisms underlying this association. Limitations of this study include the need for longitudinal data to establish causality and the adjustment for cell type proportions in future analyses.

Funding: None; COI: None

Poster # 15: INVESTIGATING GENETIC RELATIONSHIP BETWEEN CANCER AND ALZHEIMER'S DISEASE

Presenting author: Dipti Debnath, M.Pharm (UNTHSC)

Background: Among the leading causes of mortality and morbidity worldwide, Alzheimer's disease (AD) and cancer both pose significant challenges to the health of people all over the world. AD is the predominant form of dementia and is a gradually advancing neurodegenerative disorder marked by the buildup of neurofibrillary tangles and neuritic plaque. Cancer is a pathological condition characterized by impaired signaling and metabolism, resulting in unregulated proliferation and persistence of genetically modified cells. Multiple epidemiological investigations have shown a negative association between several cancer types and AD, indicating that cancer patients have a lower likelihood of getting AD, whereas those diagnosed with AD have a reduced prevalence of cancer. Methods: Leveraging existing large-scale genome-wide association studies (GWAS) on AD, and cancer (breast, prostate, lung, and colorectal) [Ntotal=300,000~600,000], we will assess the observed-scale SNP heritability and genome-wide genetic correlation using LD score regression (LDSC). Subsequently, the genome will be partitioned into more than 2000 LD-independent regions/loci, to assess for locus-based genetic correlation. First, we will apply LAVA (Local Analysis of Variance and Association) to assess heritability at each region for AD and four cancer traits. Significantly heritable regions will be followed up for assessment of genetic correlation. Results: The intensity and direction of shared genetic effects between AD and the four cancer types in a specific genomic area are identified by the local genetic correlation (rg), which ranges from -1 to 1. If the rg is positive, then there is a positive genetic association between AD and cancer in that region, and if it is negative, then there is an inverse genetic correlation. We are hypothesizing that several regions across genomes exhibit negative local genetic correlation (rg) between AD and cancers, identifying regions where genetic variants associated with a higher risk of Alzheimer's disease may be

protective against certain cancers. We will evaluate these regions for over-represented pathways. Conclusion: Pleiotropic loci may impact neurodegeneration and carcinogenesis differently, and we anticipate identifying regions of the genome with negative correlations may highlight pathways that are differentially regulated in the two conditions, thus expanding on possible biological underpinnings of AD and cancer's inverse relationship.

Funding: None; COI: None

Poster # 16: HISPANIC ANCESTRY AS A MODIFIER OF NEUROINFLAMMATORY GENE EXPRESSION IN SINGLE AND MIXED ETIOLOGY DEMENTIA

Presenting author: Elizabeth Ochoa Ph.D. (UTH San Antonio)

Background: Hispanic individuals are at a 1.5-times higher risk for Alzheimer's disease and related dementias yet remain underrepresented in research. Longitudinal Hispanic cohorts provide antemortem biospecimen, cognitive, and epidemiological data, and GWAS/admixture mapping analyses identify Hispanic ancestry as a modifier of Alzheimer's disease-associated gene expression. Additionally, antemortem-based studies suggest an altered pathological burden in Hispanic individuals, with neuropathological reports revealing a disproportional anatomy-dependent burden of Alzheimer's pathologies in Hispanic decedents. Despite these advances, few analyses investigate differential gene expression in dementia from postmortem brain of Hispanic decedents. To address the current knowledge gap, we investigated neuroinflammatory gene expression in Hispanic decedents with single or mixed etiology dementia. Method To quantify gene expression, RNA was extracted from postmortem frontal cortex brain tissue of Hispanic and non-Hispanic decedents with Alzheimer's disease (AD, n=6), cerebrovascular disease (CVD, n=6), or a mixture of the two etiologies (ADCVD, n=6). Following quality control, extracted RNA was hybridized to the NanoString Human Neuroinflammation panel, and gene expression counted via SPRINT nCounter. Analysis was completed with NanoString Advanced Analysis criteria via ROSALIND®. Low counts and low background genes were omitted from analysis. Result Comparison of Hispanic decedents with either AD or ADCVD to non-Hispanic decedents reveals shared pathway enrichment of the Astrocyte Function gene set. Respective to non-Hispanic decedents, we find two genes in Hispanic AD and seven genes in Hispanic ADCVD that are differentially expressed. Across all samples, gene expression analysis indicates P2RY12, NRP2, PRKACB, and seven other genes are increased at the transcript level in the frontal cortex of Hispanic decedents with CVD when compared to either Hispanic or non-Hispanic decedents with other etiologies. Conclusions: These preliminary findings suggest an ancestry- and etiology-specific transcriptional profile in CVD, and point to few genes modified by ancestry in AD and ADCVD. Ongoing experiments aim to determine differential gene expression relative to pathology, and to develop functional genetic models for screening. Overall, we seek to identify Hispanic ancestry- and disease-specific genes among dementia etiologies as an avenue for precision medicine dementia care among an at-risk, underrepresented population.

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Poster # 17: THE IDENTIFICATION OF A DISTINCT ASTROCYTE SUBTYPE THAT DIMINISHES IN ALZHEIMER'S DISEASE

Presenting author: Haichao Wei PhD (UTHealth Houston)

Background: Alzheimer's disease (AD) is characterized by the presence of two hallmark pathologies: the accumulation of Amyloid beta (Aβ) and tau proteins in the brain. There is a growing body of evidence suggesting that astrocytes, a type of glial cell in the brain, play crucial roles in clearing Aβ and binding to tau proteins. However, due to the heterogeneity of astrocytes, the specific roles of different astrocyte

subpopulations in response to Aβ and tau remain unclear. To enhance the understanding of astrocyte subpopulations in AD, we investigated astrocyte lineage cells based on single-nuclei transcriptomic data obtained from both human and mouse samples. Method: We analyzed a number of publicly available large datasets of single-nuclei RNA sequencing (snRNA-seq) studies from humans and mouse AD and control samples, and focused on astrocyte lineage cells. We characterized the diversity of astrocytes and identified global and subpopulation-specific transcriptomic changes between control and AD samples, and verified our findings by immunohistochemical staining. Result: We identified a specific astrocyte subpopulation marked by low levels of GFAP and the presence of AQP4 and CD63 expression, which showed functional enrichment in Aβ clearance and tau protein binding, and diminished in AD. We verified this type of astrocytes in mouse models and in AD patient brain samples, and found GFAPlowAQP4+CD63+ cell population further decreases with AD progression in human. Moreover, our findings unveiled significant alterations of the ligand-receptor interactions between astrocytes and other cell types. These changes underscore the complex interplay between astrocytes and neighboring cells in the context of AD. Conclusion: Overall, our work gives insights into astrocyte heterogeneity in the context of AD and reveals a distinct astrocyte subpopulation that holds potential for therapeutic interventions in AD. Targeting specific astrocyte subpopulations may offer new avenues for the development of novel treatments for AD. Spatial transcriptomic analysis for cell-cell communications are underway to further functional characterization.

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Poster # 18: APOE- RELEVANT TAU OLIGOMER POLYMORPHS DIFFERENTIALLY IMPAIR SYNAPTIC FUNCTIONING

Presenting author: Naomi Moreno, BS (UTMB)

Background: Apolipoprotein E (APOE), the strongest genetic risk factor for late-onset Alzheimer's disease, exist as 3 isoforms (APOE2, 3, 4) which differentially influence Alzheimer's disease risk. While it is known that the APOE isoforms uniquely influence overall tau pathology in disease, there remains a gap in knowledge concerning APOE isoform-specific influences on the conformational and functional properties of pathological tau aggregates. Method: Brain-derived tau oligomers were isolated from frontal cortex tissue of patients with various APOE genotypes. Proteinase K (PK) digestion and mass spectrometry were used to assess conformational properties of the APOE isoform-associated tau oligomers. Electrophysiology was used to assess functional properties of the APOE isoform-associated tau oligomers, especially regarding synaptotoxicity. Results: Tau oligomers demonstrate differential PK digestion resistance and cleavage site accessibility across APOE isoforms, suggesting conformational differences in tau oligomers across APOE isoforms. Tau oligomers also demonstrate differential impairment of synaptic plasticity across APOE isoforms, suggesting functional differences in tau oligomers across APOE isoforms. Conclusion: Tau oligomers associated with the different APOE isoforms present unique conformational properties and differentially impair synaptic functioning in an APOE isoform-dependent manner. These findings expand our understanding of how APOE isoform may influence AD risk by influencing pathological tau aggregation, and such APOE-isoform specific differences in tau aggregation can be used to enhance the development of personalized medicine based on APOE genotype.

Funding: AG067952, AG05402506; COI: None

Poster # 19: GENOTYPE-BY-ENVIRONMENT INTERACTION INFLUENCING WHITE MATTER HYPERINTENSITY: THE ROLE OF EDUCATION AND SEX

Presenting author: Renee Hernandez, BS (UTRGV)

Background: Increased white matter hyperintensity (WMH) volume is associated with cognitive decline and Alzheimer's disease (AD). Social determinants of health, such as education, and biological factors, such as sex, contribute to the risk of developing white matter lesions. Although these factors independently influence the risk of WMH, to our knowledge, this is the first study to examine their joint interaction in a statistical genetic linear mixed model. Methods: We analyzed MRI data from 318 Hispanic participants (178 males and 140 females; mean age of 60 years), estimating WMH heritability at 0.35 ($p=0.026$). We assessed the genotype-environment interactions (GxE) in the phenotypic determination of WMH using separate GxE models, where education (GxEd) or sex (GxSex) was the sole environment. Additionally, we assessed the effect of both environments in a joint interaction model. Results: When testing the GxSex against the polygenic model, the GxSex model showed significance at $p=0.048$. Similarly, when testing the GxEd against the polygenic model, the GxEd model showed an even greater significance at $p=0.001$. We then performed a novel interaction model that jointly modeled the interaction effects of education and sex. Relative to the GxE model with the higher likelihood (the GxEd model), the joint interaction model performed significantly better ($p=0.003$). Conclusion: Our joint interaction model revealed two key findings: (1) in females, the genetic correlation declines from one with increasing differences in the education environment, suggesting that the set of genes underlying WMH changes with differences in education. (2) In males, the additive genetic variance decreases with increasing education. Genes underlying WMH interact with education differently in males and females, potentially explaining the sex differences in ADRD. In males, increased education may lead to increased empowerment, resulting in a rise in the environmental variance of WMH (i.e., the environment is more influential). However, in females, increased education may alter gene interactions due to enhanced learning opportunities. Our findings emphasize the importance of joint GxE interactions by sex and education, providing valuable information for further research on education and dementia.

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Poster Theme Group A3. Human Neuropathology

Poster # 20: EVALUATING DIGITAL PATHOLOGY SOFTWARE: PERFORMANCE COMPARISON BETWEEN QUPATH AND HALO IN TAU PATHOLOGY ASSESSMENT

Presenting author: Angelique D. Gonzalez, BS (UTH San Antonio)

Background: The use of image analysis software has become more common in the field of pathology; however, many of these tools have been developed and optimized for cancer samples. Non-neoplastic brain tissue presents unique challenges for these tools due to lower cellularity and variability within the tissue morphology. In this study, we evaluated and compared two digital pathology software options' ability to quantify tau pathology in postmortem brain samples from the hippocampus and middle frontal gyrus (MFG). Methods: Immunohistochemistry was used to assess AT8 expression in 36 autopsied brains stratified according to CERAD-NP scores and Braak stages. Slides were digitized using Aperio Scan Scope XT (20x) and analyzed with QuPath and HALO IndicaLabs software. Optical density (OptD), percent positivity, and object density (ObjD) were measured with each. ObjD values were manually determined for each slide and used to validate digital measurements via ordinary least square regression models. Further analysis included Spearman's correlation and ANOVA ($P<0.05$). Results: Digital measurements correlated with manual ObjDs in both regions except for HALO-derived OptDs ($P>0.05$). HALO showed very strong relationships between digital and manual ObjDs ($\rho \geq 0.70$) in both regions, whereas QuPath showed a very strong relationship between these measurements in the hippocampus only. Significant differences were observed between HALO and QuPath ObjDs and OptDs ($P<0.01$). Significant differences between Braak stages were found for all QuPath measurements except MFG ObjDs ($P>0.05$). HALO-derived ObjDs and percent positivity values showed significant differences

between Braak stages (P<0.05), but OptDs did not (P>0.05). Conclusions: Digital and manual methods of quantification and scoring significantly correlated in both HALO and QuPath, thus supporting their effectiveness at accurately assessing tau pathology. QuPath's performance was more consistent in that all measurements showed significant correlations with manual analysis methods, and QuPath showed a greater ability to differentiate between Braak stages. However, stronger correlations between HALO ObjDs and manual techniques imply a more robust method for object detection and classification.

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Poster # 21: REGIONAL SIALYLATION PATTERNS IN CEREBRAL AMYLOID ANGIOPATHY

Presenting author: Caitlyn Fastenau, BS (UTH San Antonio)

Background: Glycosylation is the most common post-translational modification in the brain. Aberrant glycosylation patterns have been observed in cerebrospinal fluid and homogenized brain tissue of Alzheimer's disease (AD) cases. Our work has identified significantly increased α-2,6 N-sialylation of microglia within the parenchymal Aβ plaque microenvironment in AD brains compared to no plaque control regions. Thus, we hypothesized that increased microglia sialylation patterns were similar in brains with Alzheimer's Disease and Cerebral Amyloid Angiopathy (CAA) pathologies. CAA is defined as the deposition of amyloid beta aggregates in the vascular walls of cerebral arteries and arterioles. Method: The present study investigates sialylation patterns of microglia and endothelial cells of blood vessels in the frontal cortex across 30 post-mortem human brains with CAA+AD (N=11), AD (N=10), Control (N=9). Utilizing serial histologically stained slides, the area coverage of amyloid, α-2,6 sialylation, and microglia were quantified in vascular and perivascular regions (75 µm diameter around vessels). Results: We identified greater amyloid deposition in the perivascular region in CAA+AD cases compared to AD and Control cases. Additionally, we observed significant differences in vascular sialylation patterns across disease states. These included greater sialylation of leptomeningeal vessels compared to parenchyma in CAA+AD while greater parenchymal vessel sialylation was observed in AD. Lastly, we found a trending increase in microglia sialyation near parenchymal vessels in CAA+AD compared to Control cases. Conclusion: These findings suggest vessels in CAA+AD may be more vulnerable to pathological aggregation due to an increase with sialylation. Understanding vascular sialylation in the setting of CAA may provide novel insight into Aβ-blood brain barrier clearance and be relevant to adverse events observed in anti-amyloid therapies.

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Poster # 22: THE NUN STUDY: INSIGHTS FROM THIRTY YEARS OF AGING AND DEMENTIA RESEARCH.

Presenting author: Kyra M. Clarke, BS (UTH San Antonio)

INTRODUCTION The Nun Study is an iconic longitudinal study of aging and dementia on a cohort of 678 Catholic nuns from the School Sisters of Notre Dame. This study population offered a unique

opportunity to assess epidemiological factors contributing to dementia risk due to the participants' similar lifestyle, limiting potential confounds. Participants consented to undergoing annual neuropsychological assessments, allowing researchers access to convent archives and medical records, and post-mortem brain donation. This study investigated the associations between epidemiological factors, cognitive function, and brain pathology. Methods: We comprehensively reviewed the published literature reporting on or utilizing Nun Study data, with special focus on the study's design and key findings. Methods for collecting longitudinal data on participant cognitive health and neuropathological assessments are detailed, along with how these methods were changed or adapted over time. RESULTS Published findings from the Nun Study provided insight into the correlations between neuropathologies and cognitive function. Importantly, histological assessments revealed a high frequency of comorbid brain pathologies, with strong associations with dementia risk and rate of cognitive decline. Nun Study investigations also focused on identifying factors contributing to cognitive resilience despite the presence of brain pathologies. Early life cognitive ability was also found to influence late life cognitive health, suggesting "cognitive reserve" may be a viable target for preventative interventions in dementia. Conclusion: Decades of Nun Study research have made critical contributions to our understanding of Alzheimer's Disease and related dementias, highlighting continuing objectives for future research. Active research is still ongoing utilizing novel, modern computational techniques.

Funding: This research was supported by grants K08AG065463 (Flanagan ME as PI), U24NS133945 (Nelson PT, Flanagan ME, and Bumgardner C as PIs), R01AG072080 (Flanagan ME and Popko B as PIs), RF1AG072080 (Flanagan ME and Popko B as PIs), R01AG082118 (Cheng F, Flanagan ME, and Pieper AA as PIs), and P30AG066546 (Seshadri S and Maestre GE as PIs) from the National Institutes of Health. Additional support was provided by the Owen's Foundation Grant (Flanagan ME as PI) and the Baptist Foundation of San Antonio Endowment (Flanagan ME); COI: None

Poster # 23: UNDERSTANDING THE FORMATION OF HETEROMERIC AMYLOIDS BETWEEN TAU AND MUSASHI PROTEINS IN ALZHEIMER'S DISEASE

Presenting author: Abbigael Aday, BS (UTMB)

Background: Tauopathies are characterized by the accumulation of toxic tau species in the brain with oligomeric species being the most toxic form. Recent studies have also implicated RNA Binding Proteins, such as Musashi (MSI), in the onset and progression of several neurodegenerative diseases including Alzheimer's Disease (AD). Our lab has visualized co-localization between oligomeric tau and MSI1 and MSI2 in AD tissue, suggesting toxic crosstalk between tau and MSI proteins. In this study, we further investigated the relationship between MSI and Tau and the impact this relationship has on the formation of heteromeric amyloids. Methods: We performed sarkosyl fractionation on human AD brain homogenates to better understand oligomer and fibril formation of MSI and Tau in diseased brains. Immunofluorescence and IHC were used to visualize these aggregates spatially in tissue. We also performed primary neuron and cell-based assays to investigate the interplay between MSI and Tau and the potential formation of heteroligomers and heterofibrils. We performed RBP/RNA immunoprecipitation of MSI1 in the presence of naïve and pathogenic mutant tau species to understand the impact of tau on MSI function. Results: This study shows a dynamic interplay between Tau and MSI in AD brains and cell models suggesting bidirectional influence on protein aggregation. Our results also show that the presence of pathogenic tau greatly impacts the functionality of MSI which may contribute to RNA dysregulation in diseased tissue. Conclusions: Understanding the influence of RBPs on Tau aggregation and vice versa allows us to better understand disease pathophysiology and potential areas of therapeutic targets.

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Poster # 24: INVESTIGATING THE EFFECTS OF HUMAN BRAIN DERIVED TAU OLIGOMERS ON NEURAL STEM CELL DIFFERENTIATION

Presenting author: Adam Trupp BS (UTMB)

Background: Adult hippocampal neurogenesis is essential for memory, learning, and cognitive function, but is disrupted in Alzheimer's Disease (AD). Despite AD pathology, a subset of individuals, known as non-demented with Alzheimer's-like neuropathology (NDAN), retain cognitive abilities and increase the number of NSCs, suggesting resilient mechanisms. Tau oligomers have been identified as toxic proteins in AD-related neurodegeneration. This study investigates how brain derived tau oligomers (BDTOs), isolated from AD or NDAN postmortem brains, affect the differentiation and maturation of adult rat hippocampal neural stem cells (NSCs), aiming to uncover potential factors preserving neurogenesis in NDAN individuals. Methods: BDTOs were isolated from postmortem brains of AD and NDAN individuals. Adult rat hippocampal NSCs (SCR022) were cultured in expansion media supplemented with 20 ng/mL FGF-2. Cells were treated with either [50 nM] AD BDTOs, [50 nM] NDAN BDTOs, or vehicle control. After 24 hours of incubation, cells were fixed and stained with primary antibodies against DCX, GFAP, and counterstained with DAPI. Cells were also allowed to differentiate for 7-days, in differentiation media containing forskolin, then fixed and stained with antibodies against βIII-Tubulin, GFAP, and Nestin, with DAPI counterstaining. Images were captured using a Keyence microscope and quantitatively analyzed with ImageJ and Imaris software. Results: AD BDTO treatment significantly reduced overall cell number (DAPI+), indicating neurotoxicity, while NDAN BDTOs showed no such effects. AD BDTOs increased DCX+ cells at 24 hours as well as βIII-Tubulin+ and GFAP+ cells after 7 days, suggesting premature neuronal and glial maturation. Conclusion: AD BDTOs, in contrast to NDAN BDTOs, induce neurotoxicity and promote premature maturation in hippocampal NSCs, leading to a depletion of the NSC pool. Future experiments will investigate the molecular mechanisms underlying the premature maturation induced by AD BDTOs, as well as the non-toxic effects of NDAN BDTOs. Understanding these mechanisms could provide valuable insights into potential therapeutic strategies aimed at regulating neurogenesis and mitigating the cognitive decline associated with Alzheimer's disease.

Funding: R01-AG069433 (GT, MAM); COI: None

Poster # 25: EXPLORING THE ROLE OF NEURAL STEM CELL EXOSOMES IN MODULATING MICROGLIAL ACTIVATION IN ALZHEIMER'S DISEASE

Presenting author: Madison Kidd (UTMB)

Background: Adult neurogenesis, the generation of new neurons from neural stem cells (NSCs) in the hippocampus, is impaired in Alzheimer's disease (AD). We have previously shown that exosomes secreted by hippocampal NSCs (NSCexo) provide synaptic protection against amyloid oligomers and significantly impact microglial activation, which could underlie their protective mechanism against AD pathology. This study aims to investigate the mechanisms by which NSCexo activates microglia. Methods: Exosomes were isolated by serial ultracentrifugation from the conditioned media of adult rat hippocampus NSC (NSCexo) or mature neurons differentiated from NSCs (MNexo) and labeled with PKH26 red fluorescent dye. Human microglia (HMC3) were cultured in a complete growth medium and treated with labeled exosomes (NSCexo or MNexo; 3.6 x 10^3 exosomes/µl) PBS, or LPS. Twenty-four hours after the MNexo and PBS treatments, the culture medium was collected for cytokine analysis. The cells were washed and either fixed in 4% paraformaldehyde for immunofluorescence or lysed for western blot analysis. The culture medium for the LPS treatment group was changed every other day for 3 days. The cells were washed and fixed in 4% paraformaldehyde for immunofluorescence. Results NSCexo significantly promoted the release of the cytokines IL-8 and Serpin E1 in microglia compared to MNexo and PBS. MNexo alone prevented the release of IL-18, and MNexo and NSCexo inhibited the release of

IL-21. Immunofluorescence results suggest a change in the distribution of CD68 throughout the microglial cell body following NSCexo treatment compared to LPS, PBS, or MNexo. Conclusions Our data shows that NSCexo selectively activate microglia. IL-8 levels are reduced in AD patients, Serpin E1 regulates microglial motility and phagocytosis, and IL-18 plays a role in microglial activating and responding. MNexo and NSCexo inhibited the release of IL-21, which is increased in the brains of AD patients. Lastly, NSCexo treatment appeared to diffuse the lysosomal marker CD68 throughout the microglial cell body compared to PBS, LPS, and MNexo. Lysosomal migration from the perinuclear space to the cytoplasm has been associated with microglial phagocytosis. Thus, current studies are in progress to better understand the functional effects of these cytokines on microglial activity

Funding: R01-AG069433; COI: None

Poster # 26: AMYLOID B AND TAU OLIGOMERS DISRUPT BLOOD-BRAIN BARRIER IN A HUMAN BASED IN-VITRO MICROFLUIDIC NEUROVASCULAR UNIT MODEL

Presenting author: Zahra Kolahchi, MD (UTMB)

Background: Alzheimer's disease (AD) is the most common neurodegenerative disorder seen in age-dependent dementia and accounts for 60-70% of worldwide cases. A growing body of evidence supports the idea that neurovascular unit (NVU) dysfunction and blood-brain barrier (BBB) breakdown are major contributors for AD development. However, the mechanism underlying NVU dysfunction contributing to AD is still not fully understood. Methods: A three-dimensional in vitro NVU model was used as a compartmentalized microfluidic device. It contains five cell types in a dynamic and tunable microenvironment, resulting in an in vivo-like response. Each chip contains two fluidic compartments separated by a porous membrane. The vascular compartment is lined with endothelial cells (EC), while the brain compartment contains cortical neurons, astrocytes, pericytes, and microglia. Cultured cells on both sides of the porous membrane, provided cell-cell interactions resembling in-vivo microenvironment. Imitating AD pathophysiology, we evaluated the toxic effects of Amyloid β oligomers (Aβo) and Tau oligomers (TauO) by adding both to the brain compartment and adding only Aβo to the vascular compartment. We confirmed the aggregation of Aβ using Simple Western blot assay. Twenty-four hours after the treatment, indicators of permeability were measured using Dextran 3 kDa, and occluding levels. Results: After 24 hours of treatment, our preliminary data showed that Aβo and TauO produce cytotoxicity as indicated by an increased permeability, compared to the control chips. This toxic effect was supported by a significant increase in the crossing of Cascade Blue 3KDa between the compartments, as an indicator of increasing permeability, as well as a decrease in occludin levels. As the concentration of Aβo increased, a corresponding rise in permeability was observed. Although this suggests a trend towards higher permeability, a larger sample size (N) is needed to draw definitive conclusions. Conclusions: This is a human-based in vitro model that offers dynamic cell-cell interactions to investigate BBB function continuously with and without Aβo and TauO as well as discover therapeutic target capabilities. Our preliminary results suggest that Aβo and TauO provoke vascular cytotoxicity, BBB dysfunction and increased permeability. These data together suggest that NVU-on-a-chip is a good model for testing NVU dysfunction in AD

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Poster Theme Group A4. Molecular and Cell Biology

Poster # 27: NEUROPROTECTIVE EFFECTS OF TRANSITION METAL DICHALCOGENIDE NANOFLOWERS IN NEURODEGENERATIVE DISEASE

Presenting author: Harris Brown (TAMU)

Background: Parkinson's disease (PD) is the largest increasing neurological disorder and is characterized by the degeneration of dopaminergic neurons in the midbrain. While the exact etiology of neurodegeneration isn't completely understood, the build-up of alpha synuclein (α-syn) protein aggregates into cytotoxic oligomers and fibrils has been heavily implicated. Presence of aggregates induces cellular stress, mitochondrial dysfunction, disruptions in signaling pathways, and eventually cell death. Current treatments for PD are limited in that they are only used to mitigate symptoms, but none are capable of preventing or slowing the progression of toxic aggregates to other cells. Thus, the need for a neuroprotective therapeutic is immediate. Transition metal dichalcogenide (TMD) nanoflowers (NFs) are 2D nanomaterials that are biocompatible and induce cellular responses, however the exact molecular mechanisms in which molybdenum disulfide (MoS2) and molybdenum diselenide (MoSe2) enact their neuroprotective properties are currently under intense research Methods: TMD NFs were synthesized via hydrothermal synthesis reactions, and characterized using scanning electron microscopy to ensure correct morphology. Healthy brain cell lines have been administered MoS2 and MoSe2 to measure the cellular effects. Reactive oxygen species, mitochondrial impairment, cellular toxicity, and mitochondrial biogenesis assays were conducted. A simple in vivo C. elegans model were administered NFs and tracked for life span. The same experimentation was conducted in cells impregnated with α-syn fibrils to model PD pathology, and a genetically modified C. elegans strain that overproduce α-syn protein. Result: TMD NFs have shown no cellular toxicity, an ability to decrease reactive oxygen species, boost mitochondrial biogenesis, and increase mitochondrial health in both healthy cells and modeled PD cells impregnated with α-syn. When administered to C. elegans, varying increases in life span is observed. Conclusion: TMD NFs have indicated to be a promising neuroprotective treatment for PD, and holds promise as a therapeutic for other mitochondrial and neurodegenerative diseases like Alzheimer's.

Funding: NIH; COI: None

Poster # 28: KCNIP1 AT THE CONVERGENCE OF NUTRITIONAL DEFICIENCY, ION CHANNEL DYSFUNCTION, AND ALZHEIMER'S DISEASE

Presenting author: MS, Nishtha Khanna (Texas Tech HSC)

Background: Hyperexcitability of the hippocampal dentate gyrus (DG) is associated with impaired learning early in Alzheimer's disease (AD). The Mitochondrial Free Radical Theory of Aging suggests that oxidative stress (OS) contributes to AD pathogenesis. The vitamin A (VA) metabolite all-trans retinoic acid (ATRA) acts as an antioxidant and retinoic acid receptor (RAR) agonist, maintaining a homeostatic balance between α- and β-secretase activities. This balance collapses in AD, leading to amyloidosis. Our machine learning analysis of multiple post-mortem human hippocampus RNA-seq datasets identified KCNIP1, a protein important for Kv4 channel trafficking and DNA transcription, as the top-ranked gene in AD. Finally, recent preclinical studies have found a critical role of Kv4 channels, particularly Kv4.1, in early AD pathogenesis. Method: We employed a bioinformatics approach, complemented by a PubMed literature search, to investigate the mechanistic role of KCNIP1 as a nutrient sensor and as a transcription factor. Our analysis utilized Enrichr to identify transcription factor binding sites (TFBSs), which revealed both retinoic acid response elements (RAREs) and vitamin D (VD) response elements (VDREs) in the KCNIP1 promoter region. We then used JASPAR to quantify the strength of TFBS associations. Result: JASPAR analysis identified the presence of both RAREs (score of 0.88/1) and VDREs (0.80/1 for VDRE) on the promoter region of KCNIP1. Two RARE binding sites were identified in human, but mouse had only one RARE. Both human and mouse KCNIP1 had one VDRE binding site. The strength of the TFBS associations were considered to be strong. Conclusion: These bioinformatics results suggest a novel molecular mechanism of AD pathogenesis. TFBS analysis suggests that human KCNIP1 expression may be more dependent on vitamin A sufficiency in humans than in rodents. We propose that ATRA and/or VD depletion leads to KCNIP1 downregulation, impairing

Kv4.1 trafficking in DG granule cells, and ultimately impairs pattern separation in the DG. The dual roles of KCNIP1 in both Kv4 channel regulation and as a transcription factor highlight the potential significance of its downregulation in AD pathogenesis and/or progression. Validation and targeting of the KCNIP1/Kv4 pathway may present translational opportunities for AD prevention and treatment strategies.

Funding: NIH R01 AG073826; COI: None

Poster # 29: DIURNAL DIFFERENCES IN IMMUNE CELL TRAFFICKING THROUGH THE CENTRAL NERVOUS SYSTEM IN A 3XTG MOUSE MODEL OF ALZHEIMER'S DISEASE

Presenting author: Andrew Roarke Hynes, BS (UT Austin)

Numerous physiological processes are coordinated by an endogenous ~24h circadian clock, including immune function. For example, the circadian system regulates immune migratory factor expression, which impacts cell recruitment to peripheral tissues. This rhythmic regulation of immune cells is disrupted in inflammatory disorders, such as irritable bowel disease (IBD) and asthma. Infiltration of immune cells to the brain can trigger neuroinflammation, a critical feature of Alzheimer's Disease (AD). As up to 60% of AD patients experience disruptions to sleep-wake cycles and circadian rhythms, we posit disruption of circadian rhythms in peripheral immune cell trafficking through the brain as a potential mediator of AD pathology. To study this, immune cell subpopulations were assessed in neuro-immune interface tissues (i.e., meninges and deep cervical lymph nodes [dCLNs]) and brain using flow cytometry in adult (6-9 mos) and aged (18 mos) C57BL/6J and 3xTg mice during the middle of the light phase and middle of the dark phase. 3'Tag-Seq was also performed on meninges from these mice at 6 timepoints throughout the day to quantify rhythmic gene expression changes relevant to immune cell trafficking. We hypothesized that there would be time-of-day differences in immune cell subpopulation counts of adult C57BL/6J mice, and that these temporal differences would be blunted or absent in both aged and 3xTg mice. Preliminary results suggest higher presence of immune cell subpopulations (CD45+ cells, CD3+ cells, CD3+TCRβ+ cells, CD3+TCRβ+CD4+ cells, CD45R+ cells, and CD11b+CD115+Ly-6G- cells) during the dark phase in adult C57B/6J mice, with a cessation or reversal of this trend in aged and 3xTg mice. Additionally, there is rhythmic expression of the immune cell adhesion factor Vcam1 in the meninges with higher expression in the dark phase than in the light phase, which is also disrupted in aged mice. Results: gathered here could elucidate a mechanism of AD pathology; an important goal to the 55 million people living with AD, and other dementias, worldwide.

Funding: R01AG078758; COI: None

Poster # 30: TIME-RESTRICTED FEEDING AS A CIRCADIAN INTERVENTION AMELIORATES FEMALE-SPECIFIC COGNITIVE IMPAIRMENTS IN 3XTG-AD MICE

Presenting author: Brandy Routh, BS (UT Austin)

Background: Sleep and circadian disruptions are among the earliest behavioral manifestations of Alzheimer's disease (AD), implicating the circadian system in early disease etiology. In healthy individuals, a myriad of neurological processes are regulated in a circadian manner, including synaptic plasticity, neuroinflammation, and central nervous system energy homeostasis; however, it is unknown whether perturbation of daily rhythms in AD promotes neurodegeneration through dysregulation of these finely-tuned circadian processes. Here, we hypothesized that diurnal rhythms in transcriptomic profiles in the hippocampus may be dampened in early AD pathology, and that strengthening hippocampal rhythms could protect against AD cognitive deficits and pathology. Methods: To test hippocampal rhythmicity, we performed RNA sequencing on hippocampi isolated from adult (6-mo) C57BL/6 and 3xTg-AD mice at 6

time points throughout the day. To strengthen diurnal rhythms, in a separate cohort of mice, we implemented a time-restricted feeding schedule, in which food was offered for only 8 hours during the animal's active phase. Results: Intriguingly, 3xTg female mice showed a greater loss of rhythmicity in hippocampal gene expression compared to males, which may be concordant with human data showing a female prevalence in AD. In particular, female 3xTg-AD mice exhibited alterations in synapse-related pathways. After 6 weeks of time-restricted feeding, female 3xTg-AD mice improved spatial memory in a Barnes maze compared to mice maintained on ad libitum feeding. Conclusions: Our findings uncover female-specific dysregulated rhythms at the synaptic level in early AD pathology and highlight the potential of daily eating and fasting rhythms in the maintenance of synaptic balance. We further plan to perform transcriptomic and immunohistochemical analyses to determine if time-restricted feeding strengthened diurnal gene expression, reduced immune cell infiltration into the brain, and reduced microgliosis and amyloid pathology.

Funding: NIH R01AG062716; COI: None

Poster # 31: UNDERSTANDING THE ROLE OF MICROGLIAL PPARB IN ALZHEIMER'S DISEASE

Presenting author: Abhijeet A Patil, MS (UTH Houston)

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by amyloid-beta (Aβ) plaques, neurofibrillary tangles, and neuroinflammation, leading to memory loss and cognitive decline. Microglia, the immune cells of the central nervous system, play a critical role in maintaining brain homeostasis by clearing Aβ and modulating inflammation. Recent studies suggest that the nuclear hormone receptor PPARβ, involved in lipid metabolism and cell differentiation, is highly expressed in microglia, and significantly upregulated in the prefrontal cortex of AD patients. Additionally, the loss of Quaking (Qki), a PPARβ co-activator, has recently been shown to impair microglia phagocytosis and aggravate AD pathology in a mouse model. Currently, the role of PPARβ in AD pathogenesis is not fully understood. This research aims to quantify changes in microglial PPARβ expression in AD brains and investigate the impact of PPARβ loss on microglial function. Thus far, we have shown that microglial PPARβ is upregulated in late-stage AD, particularly in regions with relatively dense Aβ plaque burden. Future experiments will focus on characterizing disease pathology in the 5xFAD AD mouse model with conditional deletion of PPARβ in microglial cells. Together, we aim to identify PPARβ as a therapeutic target to mitigate AD progression.

Funding: MD Anderson Internal Funding; COI: None

Poster # 32: CHARACTERIZATION OF CHI3L1, A BIOMARKER FOR ALZHEIMER'S DISEASE

Presenting author: Qiang Wang, PhD (UTH Houston)

Background: Chitinase 3-like-1 (Chi3l1) encodes a chitinase-like soluble glycoprotein known for its role in promoting inflammation. In Alzheimer's Disease (AD) patients, Chi3l1 levels in cerebrospinal fluid (CSF) are significantly elevated, and multiple clinical studies have identified CSF Chi3l1 as a valuable biomarker for diagnosing, predicting, and monitoring AD progression. However, essential information about brain Chi3l1 expression and dysregulation is lacking at this time. Methodology: We performed single cell RNAseq analysis and immunofluorescence staining to identify the cellular source of Chi3l1 in the brain. In addition, we cultured primary brain cells to evaluate the conditions that lead to the secretion of Chi3l1. Moreover, we collected CSF and blood samples from wild-type, Chi3l1 knockout and aging mice, as well as AD mouse models to determine the levels of Chi3l1 in these body fluids. Results: We observed that astrocytes predominantly expressed Chi3l1 mRNA and protein in the brain. Primary

astrocytes continuously secreted Chi3l1 into the culture media and responded to inflammatory stimuli by escalating the levels of Chi3l1 production. Intriguingly, Chi3l1 levels increased with age and were significantly elevated in the CSF, but not blood, of mice harboring amyloid or tauopathy, two hallmarks of AD. Conclusions: We have found an exclusive expression of Chi3l1 by astrocytes in mouse brains and detected elevated CSF Chi3l1 levels in mouse AD models, which validates the clinical observations. In addition, heightened Chi3l1 production likely represents an astrocytic response to the inflammatory milieu, which is known to be an influential component in brain aging and AD pathogenesis.

Funding: NIH grants AG057587, AG074283, DK122708-03S1, BrightFocus ADR A20183775, and Brown Foundation 2020 Healthy Aging Initiative (W.C.); COI: None

Poster # 33: BIOGENESIS OF SOLUBLE AXL, A BIOMARKER FOR ALZHEIMER'S DISEASE

Presenting author: Sanming Li (UTH Houston)

Background: Axl is a microglial receptor that belongs to the TAM family of receptor tyrosine kinases. We previously reported that cytokine type I interferon (IFN-I) regulates Axl expression and promotes microglia-mediated synaptic loss under Alzheimer's disease (AD) conditions. Moreover, a truncated form, soluble Axl (sAxl), has been shown to be a biomarker for AD and its levels in the cerebrospinal fluid (CSF) are correlated with the cognitive trajectory of patients. The goal of this study is to comprehend the biogenesis of sAxl and elucidate the conditions that prompt sAxl production under AD-related settings. Methodology: We used microglial line BV2 cells and primary microglia cultures and performed kinetics studies to investigate how sAxl levels change over time after treatment with various immune stimuli. The cleavage of Axl into sAxl is known to be mediated by the A Disintegrin and Metalloproteinase (ADAM) family, which can be inhibited with specific ADAM inhibitors. We performed similar kinetics studies to investigate how different ADAM inhibitors would affect sAxl levels. In addition, we collected CSF and blood samples from AD mouse models and determined the levels of sAxl in these body fluids. Results: More than other treatments, IFN-I was highly effective in inducing sAxl production from both BV-2 and primary microglia cells. We observed that sAxl levels increased post-treatment with IFN-β in BV2 cells with delayed kinetics in comparison with other IFN-I-induced innate immune responders. In addition, we found that ADAM10/17 inhibition potently decreased sAxl production over time. Most significantly, sAxl levels were significantly elevated in the CSF, but not blood, of mice harboring amyloid or tauopathy, two hallmarks of AD. Conclusions: Type I interferon is a potent stimulator for Axl expression by microglia. Subsequent cleavage into sAxl is mediated by ADAM10 and ADAM17 jointly. These findings, for the first time, document a neuroinflammation-driven sAXl production with the implication of interferons as primary upstream initiators of sAXL biogenesis. Importantly, our detection of elevated sAxl in mouse AD models validates clinical observations and opens the door for mechanistic investigations on their functional involvement in disease pathogenesis.

Funding: NIH grants AG057587, AG074283, DK122708-03S1, BrightFocus ADR A20183775, and Brown Foundation 2020 Healthy Aging Initiative (W.C.); COI: None

Poster # 34: THE G-QUADRUPLEX HELICASE DHX36 REGULATES TRANSCRIPTION IN NEURONS

Presenting author: Vijay Kumar M J, PhD (UTH Houston)

Background: Chromatin remodeling and epigenetic regulation are vital players in aging. Chromatin structure states alter with age, leading to different epigenetic changes correlated with modified gene expression. However, the exact molecular factors mediating chromatin changes remain elusive. We showed that G-quadruplex (G4s) structures are overly stabilized during aging, and increased G4s can be

correlated with relaxed chromatin during aging. G4s (G4-DNA, G4-RNA) are non-canonical four-stranded structures and play an important role in transcription, replication, and translation. G4 helicases unfold the G4-DNA/RNA structures and modulate G4 landscapes in cells. Our data found that brain samples from aged mice contain more G4s than those of young mice. Mice treated with a small molecule G4 stabilizer develop cognitive impairment and accelerated brain aging. Thus, we hypothesize that reverting G4 stabilization could be a promising therapeutic strategy to prevent accelerated brain aging. Methods: By using a G4-DNA probe and mass spectrometry proteomic analysis, we identified that DHX36 is enriched in the aged brain. We used young and aged tauopathy mouse, Tau P301S to study mechanisms associated with aging, and age-related neurological disorders. We used the G4-specific antibody BG4 and G4-specific fluorescence probe N-TASQ to detect G4 structures and antibodies raised against DHX36 for immunohistochemistry. We used lentivirus to infect DHX36 in neurons and performed mRNA sequencing to identify the molecular and cellular targets of DHX36 linked to senescence and aging. Results: We discovered that DHX36 is significantly enriched in aged brains, likely indicating a compensatory mechanism to reverse G4 stabilization. We found that DHX36 expression is increased in aged Tau P301S mice compared to wild type. Our RNA-seq results show that DHX36 regulates the transcription of genes linked to chromatin organization, cell survival, aging, and cellular senescence. Conclusion Our study demonstrates that G4 homeostasis is imbalanced in the aged brain. Our RNA-seq data indicates that DHX36 regulates senescence-related pathways and aging. Our study will create a foundation for decoding the functions of G4s and DHX36 in regulating genes related to senescence and delineating molecular pathological mechanisms of age-related neurological disorders such as AD and ADHD.

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Poster # 35: MODULATION OF NEUROTOXIC REACTIVE ASTROGLIOSIS BY LRP1

Presenting author: Meng Wang, BS (UTH San Antonio)

Background: Repetitive traumatic brain injuries (rTBI) significantly increase the risks of Alzheimer's disease and related dementias (ADRD) as the patient ages. Often caused by falls and contact sport impacts, rTBI poses a pressing public health challenge. However, current treatments for ADRD after rTBI remain limited in efficacy. ADRD involves chronic neuroinflammation, which includes the conversion of astrocytes into a subtype of reactive astrocytes that are actively detrimental to neuronal function - neurotoxic reactive astrocytes. Markers of neurotoxic reactive astrocytes are substantially upregulated in brain tissue from ADRD patients, suggesting a negative role in disease pathogenesis. Targeting factors that modulate neurotoxic astrocyte reactivity could significantly preserve brain function in ADRD. This project investigates the role of astrocyte low-density lipoprotein receptor-related protein 1 (LRP1) in modulating neurotoxic astrocyte reactivity in the context of rTBI and aging. Method: We hypothesize that astrocyte-LRP1 protects brain function by reducing astrocyte susceptibility to transformation into neurotoxic reactive subtypes. Two aims are proposed: (1) to investigate if age and rTBI-induced neuroinflammation are associated with increased neurotoxic reactive astrogliosis and neurodegeneration, and (2) to determine if LRP1 loss/agonism alter astrocyte reactivity in response to inflammatory stimulus in vitro and in vivo. These aims will be achieved by employing a combination of in vitro experiments with primary astrocyte cultures, ex vivo analysis with human brain tissues, and in vivo studies using an astrocyte-specific LRP1 knockout mouse model. Single-cell RNA sequencing will be utilized to study gene expression changes elicited by astrocyte-LRP1 knockout. Result: Our results suggest that the loss of astrocyte-LRP1 is linked to expedited cognitive and motor decline with age in mice. Astrocyte-LRP1 loss increased neurotoxic reactive astrogliosis induced by neuroinflammatory stimulation in vitro and in vivo. Preliminary human tissue analysis also suggested increased neurotoxic reactive astrogliosis in patients with ADRD, especially those with chronic traumatic encephalopathy. Conclusion: The findings suggest

that astrocyte-LRP1 may protect against age-related brain functional decline by reducing astrocyte sensitivity to neuroinflammatory stimulation, such as in aging and rTBI. This may provide novel insights into the molecular mechanisms driving neuroinflammation and astrocyte reactivity, offering potential avenues for targeted therapies in ADRD and brain aging.

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Poster # 36: EFFECTS OF CALCIUM ON AUTOPHAGY IN ALZHEIMER'S DISEASE

Presenting author: Rachael Cundey, BS (UTH San Antonio)

Background: Calcium dysregulation is hypothesized to be linked to the accumulation of amyloid in Alzheimer's disease (AD). L-type calcium channel (LTCC) antagonists have been associated with reduced risk of dementia in humans, but the mechanism of this effect remains unclear. Method: We assessed the effects of isradipine, an LTCC antagonist, on autophagic gene and protein expression in wild-type and 5XFAD mice. We then used a neuron-specific Cav1.2 conditional knockout mouse to determine whether loss of the channel would mimic the action of isradipine, which could suggest isradipine acts on neuronal LTCC Cav1.2 to cause the observed changes in autophagic pathways. Result: We obtained mixed results in the isradipine-treated mice, with changes in gene expression suggesting an increase in autophagy at 6 but not 9 months of age while changes in protein expression were inconclusive. The neuronal Cav1.2 conditional knockout did not result in pro-autophagy changes in gene expression, and the resulting changes in protein expression may indicate accumulation of autophagosomes. Conclusion: Isradipine may promote autophagy in an age-dependent manner through mechanisms other than action at neuronal LTCC Cav1.2.

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Poster # 37: NANO GOLD ACTS AS A KINETIC STABILIZER TO PREVENT LOSS OF FUNCTION OF UNDRUGGABLE TAU RELEVANT TO ALZHEIMER

Presenting author: Sanjib Bhattacharyya, PhD (UTHealth Houston)

Background: Tauopathies, a spectrum of neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease, frontotemporal dementia, and others, are characterized by dysregulation of Tau protein. Herein, Tau undergoes hyperphosphorylation and acetylation and consequently dismantles from the microtubule cytoskeleton to form insoluble aggregates. Tauopathies remain a challenging pathological problem in the clinic Tau remains largely undruggable due to its intrinsic disordered nature and unavailability of complete X ray crystal structure. In addition to Tau hyperphosphorylation, AD patients often exhibit insulin resistance (IR); the connecting mechanism remains elusive. In our previous study with P301L Tau transgenic mice and okadaic acid induced mouse model of AD, we have witnessed that mice treated with pegylated gold nanoparticles improved their cognition and learning ability. In addition, pegylated gold particle treatment upregulated phospho-Akt, diminished phospho-Tau burden, and lowered circulating Tau levels in vivo. Method: In a top-down approach to demonstrate the molecular mechanism connecting IR and Tau hyperphosphorylation in AD, we used a neuronal cell line (N2A) as an in vitro model to study the effect of 5 nm spherical citrate-capped gold nanoparticles (5-AuCit). To induce metabolic stress, we treated the cells with sodium palmitate (PA), such that IR develops over time. We studied the functional consequences of metabolic stress by performing neuron firing experiments. In addition, we used flow cytometry and immunofluorescence (IF) to quantify and visualize changes in insulin binding by 5-AuCit treatment Results: IR in N2A cells was confirmed by reduced phospho-Akt signal on western blots. This was restored by the treatment with 5-AuCit or Sitagliptin (used as a

positive control). Besides phospho-Akt, 5-AuCit treatment also down regulated the expression of phospho-Tau and restored neuron firing impaired by IR. Sitagliptin and 5-AuCit also restored cellular glucose consumption that is impaired by PA. Conclusion: 5-AuCit improves glucose absorption, reverses IR, and restores neuronal firing in neuronal cells. In doing so, 5-AuCit could confer normogenic cell signaling in neuronal cells that is possibly compromised during AD pathogenesis. Further studies are warranted to decipher how 5-AuCit-mediated molecular neuronal changes ameliorate IR to reverse the progression of AD.

Funding: None; COI: None

Poster # 38: UNRAVELING THE ROLE OF CHITOTRIOSIDASE (CHIT1) IN ALZHEIMER'S DISEASE

Presenting author: Swati Mohapatra, PhD (UTHealth Houston)

Background: Alzheimer's disease (AD) is marked by pathological amyloid-beta (Aß) plaque accumulation and neuroinflammation. Chitotriosidase (CHIT1), a microglia-specific glycosyl hydrolase elevated in the cerebrospinal fluid of AD patients, may influence Aß dynamics through its interaction with the extracellular matrix (ECM). This study investigates the hypothesis that CHIT1 modulates Aß pathology and its role in alteration of microglial phagocytosis. Methods: We utilized Tg2576 mice, overexpressing the 695-amino acid isoform of human Alzheimer beta-amyloid (Aβ) precursor protein (APP695) containing a double mutation of Lys670Asn, Met671Leu (i.e., Swedish mutation) under the control of the hamster prion protein (PrP) promoter and human AD brains to assess CHIT1 levels, neuropathology, and microglial activation. We evaluated the CHIT1 activity, overall protein levels, and histological staining patterns in the CNS-niche of age-/sex-matched Tg2576 males and females. Further, we assessed the CHIT1 activity using the CHIT1 activity assay in cerebrospinal fluid samples from AD patients. To better understand the sex differences in microglial phagocytosis in aged Tg2576 brains, we assessed phagocytic ability using an ex-vivo coincubation assay. Results: Preliminary findings indicate that CHIT1 concentrations and enzymatic activity are significantly elevated in the cerebrospinal fluid of Alzheimer's disease (AD) patients and is also present at elevated levels in whole brain lysates from 20-21-month-old Tg2576 mice (*$p<0.05$; **$p<0.01$; n=7-8/grp). Notably, we have identified IBA1+ microglia colocalize with higher levels of CHIT1 through immunohistochemistry staining of brain sections from AD patients compared with non-AD controls (*$p<0.05$; **$p<0.01$; n=8-9/grp). We conducted ex vivo co-incubation experiments using synthetic FITC-conjugated Aβ1-42 with Percoll-enriched CNS mononuclear cells to assess microglial phagocytotic functionality. These experiments revealed that microglial phagocytic uptake of Aβ is reduced in aged Tg2576 female mice compared to their age-matched Tg2576 male littermates (*$p<0.05$; **$p<0.01$; n=3-6/grp). Conclusion: Our study provides the evidence that CHIT1 is significantly elevated in the CSF of AD patients and in the brains of aged Tg2576 mice, suggesting a potential role in AD pathology. The marked increase in CHIT1 levels correlates with the activation of microglia. Notably, our findings highlight sex differences in microglial function, particularly in the phagocytic uptake of Aβ.

Funding: None; COI: None

Poster # 39: OSTEOPONTIN SIGNALING IN CNS FIBROBLASTS INDUCES PERIVASCULAR SPACE REMODELING LEADING TO CEREBRAL AMYLOID ANGIOPATHY

Presenting author: Vasilia E. Kyriakopoulos, MS (UTHealth Houston)

Background: The accumulation of amyloid-beta (Aβ) in the cerebrovasculature is a hallmark of cerebral amyloid angiopathy (CAA). Recent studies have linked osteopontin (OPN) secretion to tissue fibrosis.

We utilized single-cell RNA sequencing (scRNAseq) and optical imaging to investigate how CNS fibroblasts remodel the perivascular space and contribute to the pathology of CAA through the accumulation of Aβ on the vasculature, with a focus on the role of OPN on perivascular fibrosis development. Methods: ScRNAseq was conducted on blood vessel-enriched brain samples from young (6 months) and aged (18 months) Tg2576 mice exhibiting type II CAA, along with age-matched wild-type littermate controls. Using CellChatDB scRNAseq analysis, we identified the main cell types involved in sending and receiving OPN signals, along with key ligand-receptor pairs in the OPN pathway. Using two-photon microscopy, we visualized the vasculature of Tg2576 mice and tracked the development of fibrosis by assessing structural changes in fibrotic collagen surrounding leptomeningeal vessels. Cortical and vascular amyloid were labeled with methoxy-X04 (10 mg/kg, i.p.), leptomeningeal vessels marked with tomato lectin AF649 (2%, 200 μL i.v.), and fibrotic collagen detected by second harmonic generation (SHG) at 405 nm. Image analysis was performed using 3D reconstruction in Arivis Vision 4D software. Results: SHG imaging of leptomeningeal vessels in Tg2576 mice showed increased fibrotic collagen and abnormal vascular structure with advancing age. ScRNAseq analyses revealed significant upregulation of OPN signaling in CNS fibroblasts of young Tg2576 mice. At the transcriptomic level, CNS fibroblasts are predicted as the primary senders of OPN mediating signals. The significant contributors to the OPN signaling network include the CD44 (OPN receptor), and integrins (ITGB1, ITGAV, ITGB5, ITGA8, and ITGA4). Our results further suggest that OPN signaling involves coordinated activity between fibroblasts, mural cells, and macrophages to regulate fibrosis in the perivascular space. Conclusion: The present study shows that OPN signaling in the perivascular space is promulgated by CNS fibroblasts and impacts cell-signaling in the perivascular space in type II CAA model mice.

Funding: Public; COI: None

Poster # 40: INVESTIGATING TDP-43 STRAIN VARIABILITY: IMPLICATIONS FOR TAU AGGREGATION AND NEUROTOXICITY

Presenting author: Alessia Sciortino, PhD (UTMB)

Background: The pathological aggregation of hyperphosphorylated, ubiquitinated and cleaved transactive response DNA-binding protein 43kDa (TDP-43) represents the defining feature of frontotemporal lobar degeneration with TDP-43 (FTLD-TDP) and amyotrophic lateral sclerosis (ALS). Additionally, misfolded TDP-43 has been shown to accumulate in patients presenting limbic-predominant age-related TDP-43 encephalopathy (LATE), including up to 57% of Alzheimer's disease patients, where it correlates with hippocampal atrophy, cognitive decline and more severe neuropathology. TDP-43 has been shown to colocalize with amyloid plaques and neurofibrillary tangles, suggesting a pathological synergy between TDP-43 and Aβ or tau. Interestingly, the distribution pattern of pathological TDP-43 in AD differs from that of FTLD and ALS, suggesting that different strains of TDP-43 might be involved in each of these diseases and drive the specific pathological outcomes. Methods: In this study, we aimed to investigate the neurotoxic effects of different TDP-43 strains in primary neuronal cultures. Pathological TDP-43 was isolated from the frontal cortex of AD, ALS and FTD patients, and characterized using biophysical and biochemical techniques. Subsequently, brain-derived TDP-43 was amplified using recombinant TDP-43 monomer. Tau-overexpressing primary neurons were exposed to these distinct TDP-43 variants and neurotoxicity was assessed using cell viability assays, while TDP-43 and tau pathology were investigated using protein blotting and imaging techniques. Results Treatment with pathological TDP-43 potentiated tau pathology, causing an increase in phosphorylated tau levels, and exacerbated neuronal damage. TDP-43 treated neurons exhibited morphological changes, and these were accompanied by the increased release of pro-inflammatory cytokines, such as IL-6 and TNF-alpha, and decrease of anti-inflammatory markers like IL-10. Conclusions Preliminary data highlight the interplay between TDP-43 and tau in the development of AD-like neuropathology and suggest the presence of strain-specific neurotoxic profiles.

Overall, our study emphasizes the importance of strain heterogeneity in the study of neurodegenerative diseases.

Funding: National Institute on Aging; COI: None

Poster # 41: NON-TOXIC TAU OLIGOMER POLYMORPH ISOLATED FROM NON-DEMENTED INDIVIDUALS WITH ALZHEIMER'S NEUROPATHOLOGY BRAINS.

Presenting author: Anna Fracassi PhD (UTMB)

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and the leading cause of dementia worldwide. Tau oligomers (tauO) are considered one of the most toxic species in AD, making them a compelling target for diagnostic and therapeutic development. However, approximately one-third of neuropathological autopsy evaluations reveal individuals with extensive AD pathology-such as neurofibrillary tangles (NFTs)-who exhibit no clinical signs of dementia. These individuals are classified as Non-Demented with Alzheimer's Neuropathology (NDAN). The similar NFT burden in NDAN individuals and AD patients suggests that tauO can propagate in a non-toxic form, raising the possibility that NDAN tauO may spread without causing neuronal death. We hypothesize that NDAN tauO are non-toxic, allowing them to spread without inducing neurodegeneration. To test this, brain-derived tau oligomers (BDTO) were isolated from both AD patients and NDAN individuals via immunoprecipitation, followed by biochemical and biophysical characterization and comparison. Differential proteinase K digestion revealed that AD-BDTO and NDAN-BDTO are distinct conformers. When hippocampal slices from mice were treated with NDAN-BDTO, they showed significantly less impairment of long-term potentiation (LTP) compared to those treated with AD-BDTO. Additionally, neuroblastoma cells exposed to various concentrations of NDAN-BDTO released lower levels of lactate dehydrogenase (LDH)-a marker of cytotoxicity-than those treated with equivalent concentrations of AD-BDTO. In vivo, intracerebroventricular (ICV) injections of AD-BDTO and NDAN-BDTO in wild-type mice revealed significant differences in their effects on key cellular pathways, particularly those related to apoptosis, autophagy, and neuroinflammation. NDAN-BDTO were notably less toxic than AD-BDTO, mirroring our previous findings in NDAN human brains. Our results support the hypothesis that NDAN brains harbor a non-toxic tauO that spreads without causing neuronal death or cognitive decline, marking the first characterization of its kind. These findings carry significant translational potential, suggesting that in the context of AD, the complete removal or inhibition of tauO may not be necessary; instead, conversion of tauO to a less toxic species may suffice to halt disease progression.

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Poster # 42: INTRINSIC DISORDER IN P53 AND ITS MUTANTS CAUSES AGGREGATION AND INACTIVATION OF DNA REPAIR

Presenting author: David Lynch PhD (UTMB)

Background: It has been reported that there is an excess of DNA damage, and a limited DNA damage response (DDR) in early Alzheimer's disease (AD). A crucial protein in the response to DDR is p53, known colloquially as 'the guardian of the genome'. If the activity of this protein is inhibited, then the cell may be unable to repair itself. p53 is an intrinsically disordered protein that forms oligomers and fibrils, similarly to Aβ and tau. The aggregates have been observed in cancer, along with multiple mutations that cause a loss of function and changes of conformation. They lose function, and can gain toxic functions in vitro, and it has been shown by our lab that they are present in AD patients. We hypothesize that the formation of p53 aggregates are more easily formed by specific p53 mutants, and that all aggregates have a low DNA binding capacity, which, in turn, limits their ability to effectively reduce damage to the cell.

Methods • Recombinant p53 proteins were made, consisting of both the wild type and mutant proteins. These proteins were then used to make aggregates. • The DNA binding capacity of the p53 proteins was determined via the use of consensus-sequence DNA probes. The DNA binding capacity was determined via the use of AFM and DNA-ELISA. • The ability of the p53 proteins to inhibit cell damage was determined by the use of comet assays in cell cultures exposed to toxic tau oligomers. Results: Recombinant wild type and mutant proteins were used, both with aggregates and without, in DNA binding assays. There is clear evidence of changes to DNA binding capacity, dependent upon the type of p53 protein. Moreover, mutant p53 showed a distinct decrease in its ability to prevent cell death compared to the wild type protein in comet assays. Conclusion: The mutant p53 proteins, both in aggregated and non-aggregated form, show clear signs of failing to bind to DNA as effectively as the wild type. Moreover, in the comet assays, this is clearly demonstrated when they fail to preserve the cells as well as the wild type materials.

Funding: National Institute of Health, National Institute on Aging; COI: None

Poster # 43: BRAIN-DERIVED TAU OLIGOMERS FROM AD, DLB, AND PSP INDUCE SENESCENCE IN MOUSE PRIMARY ASTROCYTE CELLS

Presenting author: Fadhl Al Shaebi (UTMB)

Background: Cellular senescence is a state of irreversible growth arrest characterized by the secretion of pro-inflammatory factors, which contribute to tissue dysfunction and chronic inflammation. In the central nervous system, senescent astrocytes exacerbate neuroinflammation, promote tau pathology, and impair neuronal function, driving the progression of neurodegenerative diseases such as Alzheimer's Disease (AD), Dementia with Lewy Bodies (DLB), and Progressive Supranuclear Palsy (PSP). Despite the recognized role of astrocyte senescence in these disorders, the specific influence of brain-derived tau oligomers (BDTOs) on senescence induction in astrocytes remains unclear. This study addresses this gap by investigating whether BDTOs from AD, DLB, and PSP differentially induce senescence in astrocytes. Methods: Primary astrocytes were isolated from WT (C57BL/6) mice and treated with BDTOs from AD, DLB, and PSP brains. Untreated astrocytes served as control. Cellular senescence was assessed using immunofluorescence and β-galactosidase staining to detect established senescence markers. Western blot and ELISA were used to quantify the secretion of senescence-associated secretory phenotype (SASP) markers, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). RNA sequencing will be conducted to analyze global gene expression changes and further elucidate the molecular pathways involved in BDTO-induced senescence. Results: Treatment with BDTOs induced significant senescence in primary astrocytes, with distinct variations in the extent of the effect across the groups. Astrocytes treated with AD-derived BDTOs exhibited the highest levels of senescence, as evidenced by a pronounced increase in SASP markers. DLB-derived BDTOs induced senescence to a slightly lesser degree than AD, indicating a lower but still significant pathogenic potential. PSP-derived BDTOs induced the lowest levels of senescence, highlighting disease-specific differences in the impact of tau oligomers on astrocyte senescence. Conclusion: The comparative analysis of BDTOs from AD, DLB, and PSP revealed the differential pathogenic potential of tau oligomers in driving astrocyte dysfunction and senescence, suggesting the existence of disease-specific tau polymorphs. Future studies will provide insights into the distinct or shared pathways by which tau oligomers contribute to neurodegenerative disease progression through astrocyte senescence. Results: may offer insights into novel therapeutic strategies aimed at mitigating astrocyte-driven neurodegeneration.

Funding: NIH; COI: None

Poster # 44: LOW-FREQUENCY ULTRASOUND THERAPY ALLEVIATES NEUROPATHOLOGY AND NEUROINFLAMMATION IN A TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE NEUROPATHOLOGY

Presenting author: Kafayat Oyejide, BS (UTMB)

Alzheimer's disease (AD) is the most common neurodegenerative disorder, and by 2060, approximately 16 million Americans are expected to be affected. The primary pathological hallmarks of AD in the central nervous system include the accumulation of extracellular amyloid beta (Aβ) plaques and intracellular hyperphosphorylated Tau neurofibrillary tangles (NFTs). Neuroinflammation is also thought to be a key driver of AD progression. Previous studies have shown that exposure to low-frequency ultrasound (LFU) can rejuvenate and extend lifespan in both cellular systems and whole organisms. Based on these findings, we hypothesize that LFU exposure may help reduce AD-related neuropathology and neuroinflammation. To test this, we exposed 18-month-old female 3xTg-AD mice to LFU every other day for four months. The mice were placed in warm water baths (33-35℃) and exposed to intermittent ultrasound pulses at 4 kPa intensity for 30 minutes per session. Protein analysis revealed a significant reduction in the astrocyte marker GFAP in the treated mice. Immunofluorescence (IF) experiments further showed decreased GFAP and IBA1 immunoreactivity in the hippocampus, particularly in the dentate gyrus (DG) and CA3 regions of LFU-treated mice. IF analysis also demonstrated reduced levels of PHF-Tau and Aβ throughout the hippocampus. These results suggest that LFU treatment has beneficial effects on AD pathology and neuroinflammation, potentially laying the groundwork for new translational therapeutic strategies for AD patients.

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Poster # 45: INVESTIGATING THE EFFECTS OF TAU OLIGOMER EXPOSURE AND LOW-LEVEL LASER THERAPY ON HIPPOCAMPAL NEURAL STEM CELLS.

Presenting author: Kevin Johnson (UTMB)

Background: Loss of hippocampal neurogenesis is an early event in the progression of Alzheimer's Disease (AD) resulting in progressive cognitive decline. Preservation of neurogenesis is correlated with cognitive resilience in cognitively resilient individuals with AD neuropathology (NDAN), and is therefore a therapeutic target for the treatment and prevention of AD. One of the early pathological features of AD is the formation and spread of tau oligomers (TauO), which have been shown to be biologically active and in some cases toxic. Here we investigate the effects of TauO on hippocampal neural stem cells and their differentiation in vitro and in vivo, and whether a non-invasive nano-pulsed laser therapy (NPLT) can mitigate these effects. METHODS: In vitro: Adult rat hippocampal NSCs were exposed to TauO following NPLT pretreatment and seeded on 96-well plates to assess cytotoxicity after 24-hour exposure. To characterize the effects of TauO on NSC differentiation, cells were seeded on laminin-coated chamber slides and fixed at 24-hours and after 7 days of differentiation to characterize their progeny. In vivo: 7-10-week-old male and female C57/Bl6J mice were injected ICV with TauO or ACSF, and sacrificed at 24-hours and 7 days post injection. Fixed brain tissue was immunolabeled for the markers of NSC proliferation and differentiation. Results: The cytotoxicity assay showed no effect of TauO on LDH release in either NPLT or sham treated NSC. Both TauO and NPLT increased total cell number at 24-hours and 7 days. Additionally, TauO increased the fraction of NG2+ oligodendrocyte precursor cells and decreased DCX+ neuronal progenitors. In the NPLT treated group, neither control nor TauO treated cells showed any change in NG2+ cell fraction, however both NPLT-treated groups showed decreased DCX+ fraction. In adult mice, ICV TauO injection decreased Sox+ nuclei in the dentate gyrus subgranular zone 24-hours after injection, indicating acute depletion of hippocampal NSC. 7 days after ICV TauO injection, Sox2+ NSC returned to control levels, but DCX+ neuronal progenitors were decreased. ConclusionS Our results suggest TauO may play a significant role in the decline of hippocampal neurogenesis seen in AD by modulating proliferation and differentiation of NSC, leading to their premature depletion.

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Poster # 46: LOSS OF ATAXIN-2 FUNCTION, BY DELETION OR POLYQ EXPANSION, PROMOTE DNA DAMAGE, TAU PATHOLOGY, AND TDP-43 MISLOCALIZATION IN NEURONS

Presenting author: Sagar Gaikwad, PhD (UTMB)

Background: The pathological accumulation of tau aggregates and the mislocalization of TDP-43 in neurons are hallmark features of several neurodegenerative diseases, including Alzheimer's Disease (AD), Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Lobar Degeneration (FTLD), Parkinson's Disease (PD) and Progressive Supranuclear Palsy (PSP). Expanded polyglutamine (polyQ) repeats in the Ataxin-2 (ATXN2) protein are known to cause spinocerebellar ataxia type 2 (SCA2), a disorder marked by parkinsonism, motor dysfunction, and cognitive decline due to neurodegeneration in the frontal lobe and cerebellum. PolyQ-expanded ATXN2 is also present in patients with ALS/FTLD, PSP, AD, and PD, suggesting its role as a genetic risk factor in multiple neurodegenerative diseases. Given the overlap of tau and TDP-43 pathology across these diseases, we investigated whether the loss of ATXN2 function, either by deletion or polyQ expansion, contributes to tau accumulation and TDP-43 mislocalization. Method: We utilized western blotting and immunofluorescence staining to assess tau and TDP-43 pathology in SH-SY5Y cells with ATXN2 depletion or PolyQ52 expansion. Co-immunoprecipitation (Co-IP) was used to study ATXN2's interaction with proteins involved in RNA processing, DNA repair, and chromatin remodeling. Long-amplicon qPCR (LA-qPCR) and chromatin immunoprecipitation-rechromatin immunoprecipitation (ChIP-re-ChIP) were employed to examine DNA damage and ATXN2 recruitment to sites of DNA double-strand breaks (DSBs), respectively. Result: Our findings indicate that (1) ATXN2 depletion and polyQ expansion significantly increased tau aggregation and nuclear loss of TDP-43 in SH-SY5Y cells. (2) PolyQ-expanded ATXN2 caused nuclear TDP-43 loss in SCA2 patient brains. (3) ATXN2 polyQ expansion induced nuclear DNA damage in neurons and patient brains, particularly in transcriptionally active gene-rich regions. (4) Wild-type ATXN2 facilitated the recruitment of TDP-43, Huntingtin, and Brahma-related gene 1 (BRG1) to DSB sites for DNA repair and chromatin remodeling, a process impaired by ATXN2 depletion. Conclusion: Our findings suggest that ATXN2 plays a critical role in maintaining neuronal integrity by regulating tau and TDP-43 homeostasis, DNA repair, and chromatin remodeling. Loss of ATXN2 function, through deletion or polyQ expansion, exacerbates tau pathology, nuclear exclusion of TDP-43, and DNA damage, positioning ATXN2 as a strong genetic modifier of several human neurodegenerative diseases.

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Poster # 47: UNRAVELING SYNAPTIC TAUOPATHY IN ALZHEIMER'S DISEASE: THE ROLE OF AB AND SELECTIVE NEURONAL VULNERABILITY IN TAU SPREADING AND SYNAPTIC DYSFUNCTION

Presenting author: Shrinath Kadamangudi (UTMB)

I: In Alzheimer's disease (AD), pathological tau spreading strongly correlates with cognitive impairment, making tau an effective treatment target. Aβ has been implicated in facilitating trans-neuronal tau spreading, whereas primary tauopathies (e.g. PART) exhibit limited tau spread and minimal cognitive decline. Our recent work demonstrated that Aβ oligomers (AβO) promote the general engagement of soluble tau oligomers (tauO) in human synaptosomes. However, the role of AβO in modulating synaptic tauO internalization, as well as the selective synaptic vulnerability of tauO, remains unclear. M: Our

translational paradigms use frozen post-mortem brain tissue from Control, PART, and AD patients. Synaptosomes from the temporal cortex were: a) incubated with recombinant tauO (± AβO) and oligomer binding/internalization quantified via flow cytometry (FC), b) analyzed by FC immunophenotyping to assess pre-/post-synaptic and glutamatergic/GABAergic tauO vulnerability, and c) microtransplanted onto frog oocytes to measure excitatory/inhibitory (E/I) ratios via two-electrode voltage clamp. Brain-derived tau oligomers (BDTO) from AD and PART hippocampi were co-immunoprecipitated and analyzed by LC-MS/MS to compare synaptic interactomes. TauO-synapse interactions were validated by EM immunogold. R: AβO significantly increased tauO binding and internalization in Control synaptosomes; tauO showed minimal auto assembly. AD synaptosomes (AβO+) mirrored greater tauO uptake compared to PART (AβO-). These effects were abolished by proteinase-K pre-treatment, implicating synaptic membrane proteins in AβO-mediated tauO internalization. The AD BDTO synaptic interactome was enriched in endocytic and cytoskeletal proteins, while PART BDTO were associated with pre-synaptic vesicle cycling proteins. EM immunogold confirmed tauO association with synaptic vesicles, while FC immunophenotyping revealed a 2.5-fold preference for pre-synaptic and GABAergic synapses. PART synaptosomes exhibited a unique reduction E/I ratio, correlating with PHF-tau-further suggesting tau-driven inhibitory synaptic dysfunction. C: This study demonstrates that AβO enhances tauO binding and drives its internalization through synaptic membrane proteins, revealing a selective vulnerability of pre-synaptic and inhibitory synapses to tauO. These findings challenge conventional focus on post-synaptic excitatory systems and emphasize the therapeutic potential of targeting Aβ-tau interactions and synaptic vulnerabilities in AD and related tauopathies.

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Poster # 48: CHROMATIN REMODELER BRG1 RECRUITS HUNTINGTIN TO REPAIR DNA DOUBLE-STRAND BREAKS IN NEURONS

Presenting author: Subrata Pradhan, PhD (UTMB)

Abstract: Background: Increasing evidence suggests that impaired DNA repair undermines genome integrity with concomitant aberrant gene expression, neuronal dysfunction, and premature death of neurons in several neurodegenerative diseases (NDDs) like, AD, PD, ALS, SCAs and HD. The genome-wide association study (GWAS) strengthens the evidence that there is a strong association between age at onset and genetic variants in DNA repair pathways in NDDs. The precise mechanistic pathways of DNA repair deficiency in neuronal death are unknown. Methods: A combination of biochemical (Mass-spec, ChIP, Co-IP), computational (Alpha fold modeling), and molecular approaches (LA-qPCR, PLA, immunohistochemistry, CRISPR- mediated locus-specific DNA damage) was implicated to study the potential role of wild-type huntingtin in Transcription coupled Non-homologous End Joining (TC-NHEJ) DNA repair during transcription in human SH-SY5Y and mouse striatal neuroblastoma cell lines, iPSC-derived striatal neurons, different mouse brains, postmortem patients' brain, and Drosophila. Results: Wild-type huntingtin (HTT) assembles TC-NHEJ proteins PNKP, Ku70/80, and XRCC4 with chromatin remodeler Brahma-related Gene 1 (BRG1) to resolve transcription-associated DNA double strand breaks (DSBs) in brain. HTT recruitment to DSBs in transcriptionally active gene-rich regions is BRG1-dependent while efficient TC-NHEJ protein recruitment is HTT-dependent. mHTT compromises TC-NHEJ interactions and repair activity, promoting DSB accumulation in HD tissues. HTT or PNKP overexpression restores TC-NHEJ in a Drosophila HD model dramatically improving genome integrity, motor defects, and lifespan. Conclusion: Our data suggest that wild-type HTT, in association with BRG1 efficiently repairs the DSBs in neurons. It is possible to extrapolate this mechanism to related neurodegenerative disorders.

Funding: RO1 NS130830 and R01 EY026089-01A1; COI: None

Poster # 49: BRAIN-DERIVED TAU OLIGOMER POLYMORPHS: DISTINCT AGGREGATION AND STABILITY PROFILES AND DIFFERENTIAL BIOLOGICAL ACTIVITY

Presenting author: Suhyeorn Park PhD (UTMB)

Aggregation of microtubule-associated tau protein is a distinct hallmark of several neurodegenerative disorders such as Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and progressive supranuclear palsy (PSP). Tau oligomers are shown to be the primary neurotoxic species that initiate aggregation and propagate prion-like structures. Furthermore, different diseases are shown to have distinct structural characteristics of aggregated tau, denoted as polymorphs. Here, we investigated the structural and functional differences of amplified brain-derived tau oligomers (aBDTOs) from AD, DLB, and PSP. Our results indicate that the aBDTOs possess different structural and morphological features that impact neuronal function, gene regulation, and ultimately disease progression. The distinct tau oligomeric polymorphs may thus contribute to the development of clinical phenotypes and shape the progression of diseases. Our results can provide insight into developing personalized therapy to target a specific neurotoxic tau polymorph.

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Poster # 50: INVESTIGATING THE ROLE OF SMALL NON-CODING RNAS IN ALZHEIMER'S DISEASE USING HUMAN INDUCED PLURIPOTENT STEM CELLS - DERIVED CELLS

Presenting author: Xiaoyong Bao (UTMB)

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and hippocampal atrophy. Recent studies suggest that small non-coding RNAs (sncRNAs), including microRNAs (miRNAs) and transfer RNA fragments (tRFs), play critical roles in gene regulation and may be involved in the pathogenesis of AD. Changes in tRFs expression have been observed in AD patients, particularly within the hippocampus, a region crucial for memory formation. However, the cellular origin of these tRF alterations remains unclear. Methods: To investigate the specific cell types responsible for tRF dysregulation in AD, we employed induced pluripotent stem cells (iPSCs) derived from both healthy and AD patients. Using these iPSCs, we differentiated them into neurons, astrocytes, and microglia, mimicking the cellular environment of the hippocampus. Modified high throughput sncRNA sequencing was conducted on each cell type to profile and compare sncRNA expression patterns. Bioinformatics analysis was applied to identify significant changes in sncRNA expression related to AD pathology. Results: Our analysis revealed that both neurons and astrocytes showed significant alterations in sncRNA profiles in the AD-derived cells compared to healthy controls. Notably, several miRNAs and tRFs, shown impacted by AD in hippocampus, also had similar AD-changed pattern in iPSC-derived neurons and astrocytes. In contrast, AD-changed sncRNA expression in hippocampus was not recapitulated in microglia, suggesting that the primary sncRNA-related changes in AD occur in neurons and astrocytes. In microglia, the sncRNAs most impacted by AD belong to SNORD family. Conclusion: These findings highlight the potential critical role of neurons and astrocytes in the tRF-mediated regulation of AD pathology, while microglia appear less implicated in these changes. Our study demonstrates the utility of iPSC-derived models in elucidating cell-type-specific molecular mechanisms in AD, offering potential insights for future therapeutic strategies targeting sncRNA pathways in cell-specific manners.

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Poster # 51: TARGETING AGGREGATION-PRONE REGIONS OF TAF15 IN FTD: TOWARD THERAPEUTIC INHIBITION

Presenting author: Katerina Konstantoulea, PhD (UTSW)

Frontotemporal dementia (FTD) is a neurodegenerative disorder where the abnormal aggregation of RNA-binding proteins contributes to neuronal dysfunction and degeneration. TAF15, a member of the FET family, has been recently shown to form amyloid fibrils that were isolated from the cortices of four patients diagnosed with frontotemporal lobar degeneration (FTLD), which leads to FTD. Despite this exciting finding highlighting the relevance of TAF15, the precise mechanisms driving TAF15 aggregation remain poorly understood. In this study, we aim to identify the key aggregation-prone regions (APRs) of TAF15 and explore their role in disease pathology, with the ultimate goal of designing targeted binders and inhibitors to prevent or modulate its aggregation. Through Thioflavin-T (ThT) fluorescence kinetics, we quantify and map the regions within TAF15 most prone to aggregation. These findings are being corroborated using transmission electron microscopy (TEM) to visualize the fibrillar structures formed by the aggregation of these specific regions. The seeding potential of these APRs will also be assessed, examining whether these regions can trigger and accelerate the aggregation of full-length TAF15. Building on these biophysical insights, we are creating a TAF15 biosensor to monitor aggregation in live cellular environments. This biosensor will allow us to assess the effects of APR-mediated aggregation and provide a platform for screening potential aggregation modulators. Ultimately, identifying these critical APRs will enable the rational design of small molecules or peptides that bind to these regions, to inhibit or alter the aggregation process. These inhibitors may provide a novel therapeutic approach to mitigating the neurodegenerative effects of TAF15 aggregation in FTD and other related diseases.

Funding: None; COI: None

Poster Theme Group B1. Biomarkers (non-neuroimaging)

Poster # 52: HEART RATE RESERVE, AGE, AND SEX ARE PREDICTIVE OF BIOLOGICAL SIGNATURES ASSOCIATED WITH ALZHEIMER'S DISEASE IN MIDDLE-AGED AND OLDER ADULTS

Presenting author: Jack Manning, M.S.Ed. (TAMU)

Background: The A/T/N framework provides a structured approach to incorporate Alzheimer's disease (AD) biomarkers - beta-amyloid ("A"), phosphorylated tau ("T"), and neurodegeneration ("N") - to enhance the classification of AD pathology. However, the A/T/N network is still lacking in its ability to determine specific cutoffs for each biomarker. An individual's ability to respond to a stressor is influenced by their reserve capacity, defined as the difference between baseline and maximal function. It is thought that cognitive function is preserved in older adults with greater cardiorespiratory capacity. The purpose of this abstract is to determine how cardiorespiratory reserve capacity jointly influences biomarkers associated with AD through the A/T/N framework. Method: Sixteen adults (63.3⌖66.4 yrs.; 10 female) completed a structural T1w MRI scan and a test of cardiorespiratory capacity (VO2max). Before the VO2max, resting heart rate was measured, and blood was drawn to assess plasma levels of phosphorylated-Tau181 (pTau181, pg/mL) and beta-amyloid40 (AB40, pg/mL). Heart rate was monitored during the VO2max, and maximal heart rate was acquired. Hippocampal volumes (H-VOL) were

calculated using FreeSurfer. VO2 reserve (VO2R) and heart rate reserve (HRR) were calculated by subtracting baseline from maximal values obtained during the VO2max test. A multivariate multiple linear regression was used to test the hypothesis that VO2R and HRR were significant predictors of the multivariate combination of [AB40 ("A"), pTau181 ("T"), and H-VOL ("N")], while considering age and sex as covariates. Result: The multivariate multiple regression indicated that HRR ($p<0.001$), age ($p<0.01$), and sex ($p<0.01$) jointly contributed to the multivariate outcome measures (A/T/N). VO2R failed to reach statistical significance ($p=0.68$). Conclusion: HRR emerged as a significant predictor of the combined A/T/N biomarkers. During VO2max participants typically stop the test before they hit their absolute maximal oxygen uptake capacity, making it unclear if VO2 plateaus. HRR on the other hand tends to plateau a few minutes before the end of the test, making it a more stable measure of reserve capacity. Exercise HRR may be a candidate for future investigations in those with and without AD to assess its relationship with diagnostic criteria.

Funding: Funding for this project was provided by a Texas A&M University College of Education and Human Development R3 award; COI: None

Poster # 53: WALKING SPEED RATHER THAN CARDIORESPIRATORY RESERVE IS PREDICTIVE OF PLASMA PTAU IN A PILOT SAMPLE OF MIDDLE-AGED AND OLDER ADULTS

Presenting author: Jenna Yentes, PhD (TAMU)

Background: Functional reserve of a biological system is related to resilience; whereas resilience is the ability to recover from a stressor, reserve is the capacity. Operationally defined, a system's reserve is the capacity difference between baseline and maximal function. Narrowing of reserves occurs with aging and represents a restricted capacity to respond to challenges and could lead to an increased vulnerability to disease or injury. When measured over time, trajectories of reserve may hold the promise of the early identification of accelerated cognitive decline and/or pathology. It is currently unknown if functional reserve in the locomotor and/or cardiorespiratory systems are predictive of markers of cognition (MoCA) and dementia (plasma phosphorylated tau181 (pTau181)). Method: Nine middle-aged (59.2+/-4.1 yrs.; 3 male) and 7 older-adults (70.8+/-5.2 yrs.; 4 male) completed the MoCA and blood draw for pTau181. Sleep quality, quality of life, physical activity, and number of falls were also collected. Participants underwent testing to determine reserve in walking speed, oxygen consumption (VO2), and heart rate by measuring baseline and maximal levels. Linear regression was used to determine significant reserve and covariate predictors of MoCA and pTau181. Result: Reserve measures were not predictive of the MoCA. The strongest predictor of increased pTau181 was a decreased walking speed reserve ($p=.05$). For a one unit decrease in walking speed reserve, pTau181 was likely to increase by half a unit (standardized beta=-.51). Walking speed reserve remained as the only predictor even when covariates such as age, sex, falls, activity, and sleep were added to the model. Conclusion: Cardiorespiratory fitness is considered a protective factor against cognitive decline; however, in this pilot study, we found no evidence of cardiorespiratory reserve and an association with MoCA or pTau181. Conversely, walking speed reserve - the difference between preferred and maximal walking speed - was predictive of an increase in plasma pTau181. Slow gait speeds have been linked to cognitive impairment and decline. However, a measure of reserve or capacity may better predict cognitive decline in prodromal stages. This preliminary work reinforces the potential of walking speed reserve as a likely biomarker of cognitive decline and/or dementia.

Funding: Funding for this project was provided by a Texas A&M University College of Education and Human Development R3 award; COI: None

Poster # 54: TOWARDS UNDERSTANDING THE METABOLIC SHIFTS IN THE BIOFLUIDS FOR ALZHEIMER'S PATIENTS

Presenting author: Narendra Kumar (Texas A&M UHSC)

Introduction: Recent studies suggest metabolic profiling of biological fluids has become a powerful tool for understanding normal physiology and the physiological and pathological changes that identify potential biomarkers as a signature for different diseases conditions onset, progression, and establishment. In the present ongoing study, the aim is to unveil metabolic shifts in biofluids such as serum and urine from a novel genetically modified mouse model that shows T2D associated Alzheimer Diseases like symptoms. A focused analysis for two distinct mass-to-charge (m/z) range: 50-250 and 500-2000, for small and medium range untargeted metabolomics was done. Additionally, a novel pilot experimental approach was used that could provide a comprehensive view of metabolic alterations with a potential to identify novel biomarkers to elucidate the alteration in biochemical pathways linking T2D to AD-like alteration in brain functions. Methods: Serum and urine samples were collected from the control and diseased mice and processed for LC-MS analysis. High-resolution LC-MS analysis was performed on samples using positive electrospray ionization (ESI) mode with data acquisition in MSE mode. MassLynx software was used for initial data processing and the removal of background noise signals. Results: Pilot analysis uncovered distinct variations in spectral peaks between control and diseased groups in both serum and urine samples across both the m/z ranges. In the 50-250 range, which primarily includes low molecular weight metabolites including organic acids, amino acids, and carbohydrates, significantly altered peak intensities were observed. The 500-2000 range, encompassing small peptides, lipids, and larger polar compounds, showed potential alterations in disease-associated proteins, modified peptides, or lipid profiles. Conclusion: This study demonstrates the proof of the concept on using pilot experimental approach towards potential identification of the linkage in metabolic disturbances in the two most widely disease of T2D and AD. The approach may provide a foundation towards identifying novel biomarkers for T2D-linked AD and the avenue for their preventative intervention.

Funding: None; COI: None

Poster # 55: RELATIONSHIPS BETWEEN THYROID AND COGNITIVE FUNCTION AMONGST OLDER RURAL WEST TEXANS: A PROJECT FRONTIER STUDY

Presenting author: Brennon Henderson BA (Texas Tech HSC)

Background: Thyroid function has been examined in recent years for its potential relationship with Alzheimer's Disease and age-associated cognitive decline. The O'Bryant group previously published a seminal article that associates thyroid dysfunction with cognitive impairment among aging rural West Texans. Using a female cohort from Project FRONTIER (PF; Facing Rural Obstacles to Healthcare Now Through Intervention, Education & Research), they found that high TSH (thyroid-stimulating hormone) and low FT4 (free thyroxine) levels were significantly correlated with poorer cognitive performance. With the subsequent growth of the PF database, the present study seeks to validate these associations using a larger sample size. Methods: After receiving the relevant PF patient information and demographic variables, participants with missing information, or TSH levels and/or FT4 levels beyond 4 SD outside the mean were excluded. Results: A total of 1155 patients were included in the final analysis. Mean age was 59 ± 12 years, and approximately two thirds were female (M-31%, F-69%). Patients were 97% white, with 57% claiming Hispanic, Latino, or Spanish ethnicity. The Repeated Battery for the Assessment of Neuropsychological Status (RBANS) was used as a measure of neuropsychological functioning. Regarding thyroid function, participants had received a diagnosis of hypothyroidism (17.7%), hyperthyroidism (1%), or euthyroidism (81.4%). The distributions of patients' TSH (mean =2.5 ± 1.9 mU/L) and FT4 (mean = 0.94 ± 0.26 ng/dL) levels from blood work at baseline were analyzed. Linear regression was used to examine associations between TSH levels, FT4 levels, and RBANS categories. A significant positive correlation between TSH level and the Visuospatial/ Constructional category (p=0.033) was found. Further subgroup analysis of this cohort is underway to investigate

whether any differences are noted when categorized by gender, origin, and ethnicity. Conclusion: Age-associated cognitive decline is multifactorial, and there may be links between certain aspects of cognition and thyroid function. Further research is warranted to better elucidate these relationships and better provide healthcare in rural West Texas populations.

Funding: Supported by the TTUHSC School of Medicine Medical Student Summer Research Program as well as the Year 2 Medical Student Research Program; COI: None

Poster # 56: V-SET AND IMMUNOGLOBULIN DOMAIN CONTAINING 4 AS A POTENTIAL PREDICTOR OF ALZHEIMER'S DISEASE AND ADVANCED AGING

Presenting author: Bowen Yang, BE (University of Houston)

Background: V-set and immunoglobulin domain containing 4 (VSIG4) emerges as a significant player in the immune system pathways. It has been previously identified as a predicted potential hub gene involved in brain aging and has been reported to have upregulated expression in AD, underscoring its importance in understanding these conditions. Objective: This study aimed to evaluate the diagnostic potential of serum VSIG4 and identify trends in serum VSIG4 in relationship with other biomarkers and neurological tests. Methods: ELISA was used to measure the serum concentration of VSIG4 in AD, compared to healthy subjects. The relationship between VSIG4 levels and the age of the subjects, as well as other AD-related serum proteins and various measures of cognition was examined. Results: VSIG4 was significantly elevated in the serum of AD patients compared to healthy controls ($p=0.0074$). Significant correlations were identified between serum VSIG4 and other notable proteins related to AD and inflammation, such as FABP3 and TNF-α. Significant correlations were also identified between VSIG4 concentration and the results of neurological tests. Conclusions: Serum VSIG4 may reflect neuroinflammation and altered lipid processing, affecting the cognitive performance of AD and aging.

Funding: R01AG062987; COI: None

Poster # 57: POPULATION-SPECIFIC EXTRACELLULAR VESICLE MICRORNA SIGNATURES IMPLICATED IN ALZHEIMER'S DISEASE

Presenting author: Kumudu Himali Subasinghe, MS (UNTHSC)

Background. Alzheimer's disease (AD) is a progressive neurodegenerative disorder that disproportionately affects different racial/ethnic groups, including Mexican Americans (MAs) and non-Hispanic whites (NHWs). Early alterations in the AD brain can propagate to local and peripheral cells through small extracellular vesicles (sEVs), which contain bioactive molecules such as microRNAs (miRNAs). miRNAs are selectively packaged into sEVs and transported across the blood-brain barrier to influence gene expression in target cells, thus offering a more accessible window into brain health in living humans. Oxidative stress (OS), a critical driver of both aging and AD pathology, has been shown to affect sEV release and composition, making sEV-derived miRNAs promising candidates for early biomarkers of AD progression. Objective. Here we aimed to identify AD-relevant miRNA signatures contained within sEVs that are released from neurons into (1) the blood of individuals with cognitive impairment or AD and (2) the supernatant of neuronal cell cultures exposed to OS. Methods. (1) Human plasma samples from the Texas Alzheimer's Research and Care Consortium were processed using a two-step method that involved precipitating total exosomes and capturing neuronal-enriched extracellular vesicles (NEEVs) with a biotinylated antibody against the neuronal surface marker CD171. NEEV-derived miRNAs were profiled using next-generation sequencing (NGS) and analyzed for differential expression between cognitively impaired and healthy control groups. (2) Human neuronal SK-N-MC cells were treated with hydrogen peroxide (H_2O_2) to induce OS in vitro. sEVs were isolated from the cell culture supernatant, and miRNAs were extracted from both sEVs and cells. miRNAs were sequenced

using NGS, and differentially expressed miRNAs were identified and validated via quantitative PCR. Results. (1) Our analysis revealed population-specific miRNA profiles in NEEVs from cognitively impaired individuals compared to healthy controls, with significant differences observed between MAs and NHWs, suggesting their involvement in AD pathophysiology. (2) An miRNA profile indicative of H_2O_2 exposure was identified in sEVs from SK-N-MC cells, which included six overrepresented and two underrepresented miRNAs associated with the NF-κB signaling pathway. Conclusion: sEV-derived miRNAs from both human plasma and neuronal cell models show potential as biomarkers for early AD detection, particularly in diverse populations such as MAs and NHWs.

Funding: Texas Alzheimer's Research and Care Consortium; COI: None

Poster # 58: ASSOCIATION BETWEEN INFLAMMATORY BLOOD BIOMARKERS AND CONVERSION TO ALL-CAUSE DEMENTIA IN A DIVERSE SAMPLE.

Presenting author: Juan Carlos Guerrero Garcia, M.D. (UTH San Antonio)

Background: Activation of microglia and astrocytes leads to the synthesis and release of inflammatory proteins, which elicits the deposition of Aβ and Tau proteins in Alzheimer's Disease (AD). Inflammatory proteins have the potential to serve as risk stratification and monitoring biomarkers, but additional clinical validation is lacking, particularly in diverse samples. This study aimed to assess the impact of blood inflammatory biomarkers on dementia risk in a diverse cohort. Methods: We included dementia-free TARCC participants with blood measurements of TNF-alpha and IL-6 at baseline. TNF-alpha and IL-6 were measured using the Meso Scale Discovery platform. Inflammatory markers were categorized by the upper quartile level versus the bottom three quartiles. Clinical dementia was ascertained using the NINCDS/ADRDA criteria. We used Cox Proportional Hazard models to assess the association between inflammatory markers and dementia risk. Model 1 adjusted for age, sex, education, and site, and model 2 additionally adjusted for vascular risk factors (BMI, diabetes, hypertension, hyperlipidemia and current smoking). Analyses were performed in the total sample and among Hispanics only. Result: We included 959 particiants (mean age 67.83±9.04 years, 67.26% female, 93.22% white and 48.18% Hispanics). Overall, 285 participants developed dementia over a mean follow-up of of 3.8±2.32 years. In model 1, participants who were in the upper quartile of IL-6 had a higher risk of all cause dementia (HR 1.45 [CI 95% 1.11-1.90], p=0.006). Model 2 showed similar results (HR 1.42 [CI 95% 1.08-1.86], p=0.0115). In the sub-analysis including only Hispanic participants, we did not observe significant associations between high IL-6 and incident dementia, in model 1 (HR 0.98 [95% CI 0.64-1.49] p=0.927) or model 2 (HR 0.98 [95% CI 0.63-1.51] p=0.936). No significant associations were observed between TNF-A and incident dementia. Conclusion: Our results suggest that increased IL-6 is related to an increased risk of all-cause dementia in the TARCC cohort. Interestingly, these results were not replicated in the Hispanic sample. Additional analyses are needed to expand the number of inflammatory biomarkers and their impact in the incidence of MCI and dementia and ascertain any potential differences in Hispanic samples. These analyses are underway.

Funding: P30 AG066546; COI: None

Poster # 59: CHARACTERIZING THE BIGGS BIOBANK: DEMOGRAPHICS, BIOSPECIMENS, AND BIOMARKERS IN A SOUTH TEXAS COHORT

Presenting author: Samantha Gates, BA (UTH San Antonio)

Background: The Biggs Biobank is a repository of biospecimens and associated data from participants located in South Texas. The Biggs Biobank primarily focuses upon neurodegenerative and age-related diseases affecting the central nervous system, but also co-enrolls from several community focused research studies, such as TARCC. Herein we report available demographics, biospecimen types, and

biomarkers. Methods: The Biggs Biobank was created in January 2020 and collects biospecimens and data from consented research participants and clinic patients at the Glenn Biggs Institute, as well as the associated South Texas Alzheimer's Disease Research Center (STAC). In addition to data derived from electronic medical records (EMRs) and research records, the Biggs Biobank regularly stores blood products and cerebrospinal fluid (CSF). This report includes data from participants consented from January 2020 to June 2024 (n=1,316 participants). Results: Upon consent, Biggs Biobank participants had an average age of 73.3 (SD=9.71) and 60% identified as female. The sample was predominantly white (95.4%) with 49.7% self-identifying as Hispanic. Of participants with a cognitive diagnosis, 322 had confirmed normal cognition, while most of the remaining sample had a diagnosis of mild cognitive impairment (n=273) or dementia (n=287). Stored blood and CSF biospecimens include EDTA plasma (n=1048), packed cells (n=1048), DNA (n=878), serum (n=872), PBMCs (n=499), and CSF (n=344). 132 participants have matched plasma and CSF. We analyzed 5,342 data points across 20 selected biomarkers. These biomarkers included: PET Scan (n=144), MRI (n=467), APOE genotype (n=541), p-Tau/Aβ42 (CSF: n=234), Aβ42 (CSF: n=225; plasma: n=271), t-Tau (CSF: n=377; plasma: n=242), p-Tau181 (CSF: n=225; plasma: n=36), NfL (plasma: n=396), GFAP (CSF: n=84; plasma: n=391), UCHL1 (plasma: n=242), Cystatin C (n=113), HbA1c (n=355), C-Reactive Protein (n=146), Homocysteine (n=130), Total Protein (CSF: 297), Glucose (CSF: 311), WBC Count (CSF: 163), RBC Count (CSF: 205), and Myelin Basic Protein (CSF: 2). Conclusion: The Biggs Biobank provides a robust resource of data and biospecimens for researchers interested in testing hypotheses related to aging and neurodegeneration. We are actively seeking collaborators to maximize the research potential of our biobank and accelerate the neurodegenerative research discovery process.

Funding: P30 AG066546; COI: None

Poster # 60: PLASMA P-TAU T217 LEVELS CORRELATE WITH NEURITIC PLAQUE DENSITY

Presenting author: Tiffany Kautz, PhD (UTH San Antonio)

Background: Alzheimer disease (AD) and primary age-related tauopathy (PART) commonly display co-pathologies, such as cerebrovascular disease (CVD), Lewy body disease (LBD), and limbic predominant age-related TDP-43 encephalopathy (LATE). We analyzed Texas Alzheimer's Research and Care Consortium (TARCC) participant post-mortem tissue and ante-mortem plasma (sample closest to death) to assess the correlation between various pathologic changes and plasma biomarkers. We also quantified p-tau burden in the hippocampal subregions, entorhinal cortex, and frontal neocortex, and compared this to plasma biomarkers. Method: Using the Quanterix HD-X platform, we analyzed the plasma levels of p-tau T181, p-tau T217, NfL, GFAP, Aβ-40, and Aβ-42 in the TARCC participants with AD, PART, LBD, LATE, CVD and combinations of these pathologies (n=16) (Table 1). P-tau burden in the tissue was quantified using Aperio ImageScope. Result: Analyses demonstrated a strong correlation between CERAD neuritic plaque score and plasma p-tau T217 levels. There was also a significant correlation between p-tau T181 levels and neuritic plaque density, but less significant than T217. Plasma p-tau T217 levels, however, did not correlate with the Braak stage, Thal phase or overall p-tau burden in the frontal neocortex or hippocampus. Conclusion: In conclusion, we found a strong correlation between plasma p-tau T217 levels and CERAD neuritic plaque score, but no correlation between plasma p-tau T217 and overall p-tau (AT8) burden in the frontal neocortex or hippocampus. This suggests that T217 correlates more specifically with neuritic plaques (which are composed of β-amyloid and p-tau) rather than neurofibrillary tangles and neuropil threads, explaining the previously described clinical correlation between plasma p-tau T217 levels and the presence of β-amyloid and tau in the brain (measured by amyloid- and tau-PET, as well as other plasma and CSF biomarkers).

Funding: P30 AG066546, TARCC; COI: None

Poster # 61: SERUM METABOLOME PROFILING IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT REVEALS SEX DIFFERENCES IN METABOLISM

Presenting author: Rocio Diaz Escarcega, PhD (UTHealth Houston)

Background: More women than men are affected by Alzheimer's disease (AD). Although women live longer than men, it is not longevity alone, but other factors, including metabolic changes, that also contribute to the higher risk of developing AD in women. Metabolic pathways have been implicated in AD progression, but studies to date have examined targeted pathways, leaving many metabolites unmeasured. Sex is often a neglected biological variable and most metabolomic studies have not been specifically designed to investigate sex differences in metabolomic profiles. Methods: We performed untargeted metabolomic profiling using serum from male and female patients with mild cognitive impairment (MCI), a common precursor to the development of AD, as well as matched controls. Results We discovered significant metabolic changes in individuals with MCI, with several pathways being strongly associated with sex. Peptide energy metabolism demonstrated sexual dimorphism. Lipid pathways exhibited the strongest differences between female and male MCI patients, including specific phosphatidylcholine lipids, lysophospholipids, long chain fatty acids, and monoacylglycerols. 1-palmitoleoyl glycerol and 1-arachidonoyl glycerol (1-AG) were higher in female MCI subjects than in male MCI subjects with no differences between control males and females. In cultured male and female astrocytes, 1-AG promoted epigenetic changes and chromatin remodelling in a sex specific fashion. Conclusion: In our study, we showed novel sex-specific metabolites in MCI patients that could serve as biomarkers of MCI in both sexes, help further define AD etiology, and reveal new potential prevention strategies for AD.

Funding: This work was supported by the Glenn Foundation, the American Federation for Aging Research (AFAR), the Texas Alzheimer’s Research and Care Consortium (TARCC), the Alzheimer’s Association, the National Institute on Aging (NIA), and the Huffington Foundation.; COI: None

Poster # 62: EXPLORING BIOMARKERS IN BACTERIAL AND VIRAL SEPSIS: INSIGHTS AND PARALLELS WITH ALZHEIMER'S DISEASE

Presenting author: Tatiana barichello (UTHealth Houston)

Background: Sepsis, a severe and life-threatening condition, results from an abnormal and dysregulated host response to infection, leading to organ dysfunction. It has been increasingly associated with long-term cognitive impairments and neurodegenerative diseases, particularly Alzheimer's Disease (AD). This study aims to investigate the similarities in plasma biomarker profiles between bacterial and viral sepsis, including COVID-19 and AD, focusing on markers related to neuroinflammation, neurodegeneration, and amyloidosis. Methods: In this prospective observational cohort study, plasma samples were collected from 263 adult patients diagnosed with bacterial sepsis (n = 122) and viral sepsis (n = 101) from intensive care units (ICUs) in Brazil. Additionally, plasma samples from AD patients (n = 20) and healthy controls (n = 20) were included. These samples were analyzed using the NULISA™ proteomic liquid biopsy platform, which targeted key inflammatory biomarkers, blood-brain barrier integrity, glial cell reactivity, amyloidosis, and markers of neurodegeneration. Comparative analyses were performed across the different groups. Results: Bacterial sepsis showed a biomarker profile more closely aligned with AD than viral sepsis, particularly with elevated levels of phosphorylated tau proteins (p-Tau231, p-Tau-217, p-Tau181), amyloid-beta peptides (Aβ1-42, Aβ1-40, Aβ1-38), and glial cells reactivity (SOD1, TARDBP, GFAP and CHI3L1) markers. In contrast, viral sepsis exhibited a distinct neuroinflammatory and amyloidogenic pathway. Amyloidosis markers were notably more elevated in women with bacterial sepsis. Conclusion: The findings suggest that bacterial sepsis shares significant pathological similarities with AD, potentially exacerbating AD-related neurodegenerative processes. Viral sepsis, while showing

some overlap with AD, appears to follow a different trajectory, highlighting the need for tailored therapeutic interventions for different sepsis types.

Funding: None; COI: None

Poster # 63: BRAIN-DERIVED TAU OLIGOMERS IN PLASMA BRAIN-DERIVED EXTRACELLULAR VESICLES: A POTENTIAL PREDICTIVE BIOMARKER FOR ALZHEIMER'S DISEASE.

Presenting author: Michela Marcatti, PhD (UTMB)

Alzheimer's disease (AD) is one of the most prevalent forms of dementia worldwide. Therefore, establishing specific predictive biomarkers to identify individuals at high risk of developing AD is crucial, facilitating early treatment during the preclinical stage. Recent investigations have focused on blood-based biomarkers, such as plasma brain-derived extracellular vesicles (pl-BDEVs) content, to detect alterations within the central nervous system (CNS). Although blood-based biomarkers for amyloid proteins (Aβ42/Aβ40 peptide, tau, and phosphorylated tau) demonstrate promising diagnostic accuracy and correlation with cerebrospinal fluid (CSF) and neuroimaging biomarkers in AD, the urgency of identifying predictive biomarkers remains essential. Blood total-tau primarily originates from non-brain sources, underscoring the importance of analyzing brain-derived tau (BDT) in pl-BDEVs as an AD and other neurodegenerative diseases biomarker. Longitudinal studies, which involve collecting repeated samples from a single patient over time, possess the potential to identify specific biomarker patterns during the preclinical stage of individuals who may develop AD. However, investigations have yet to focus on the role of oligomers, the most toxic species in AD. In this study, we enriched pl-BDEVs from CNS cell types (neurons, microglia, astrocytes, oligodendrocytes) from plasma samples longitudinally collected from participants enrolled in the Texas Alzheimer's Research and Care Consortium (TARCC), who were initially cognitively normal or displayed mild cognitive impairment (MCI), and later either progressed to AD (termed "converters") or remained cognitively normal/MCI (termed "non-converters"). We evaluated the isolated pl-BDEVs by nanoparticle tracking analysis (size, number, and distribution), and western blot (expression of extracellular vesicles markers: CD63, CD9, CD81, GM130). Moreover, we demonstrated the successful detection of brain-derived tau oligomers (BDTOs) in pl-BDEVs derived from plasma samples. Western blot, immunocharacterization, proteinase K digestion, and seeding propensity assay in Tau-RD P301S FRET biosensor cells served as preliminary analyses to characterize these BDTOs. This study addresses the need for predictive AD biomarkers by exploring previously unexplored BDTOs conformers in pl-BDEVs. Discovering distinct BDTOs in peripheral brain derived extracellular vesicles could enable preclinical forecasting and advance early-stage AD treatments.

Funding: NIH/NIA; COI: None

Poster # 64: ALZHEIMER'S DISEASE BLOOD BIOMARKERS AND APOE GENOTYPE: PRODROMAL STAGING

Presenting author: Bilal Kahn, BS (UTSW)

Background: The apolipoprotein E4 variant has been linked to an increased risk for developing Alzheimer's disease (AD). Plasma pTau217 levels along with APOE4 genotype information make possible a prodromal identification of high-risk for development of AD. Methods: The cognitively normal subjects in this study are part of The Risk Reduction for Alzheimer's Disease (rrAD) clinical trial (NCT02913664) to examine the effects of exercise and intensive vascular risk reduction on cognitive function in older adults at-risk for developing AD. We examined how APOE genotype influences blood biomarkers for AD (pTau217, and Aβ42/Aβ40) in an initial cohort of 215 rrAD subjects, age 60-84 years. Results: Mean blood levels of pTau217 were 60% higher in subjects with one or two APOE4

alleles and the level continued to rise over a 2-year period. Blood levels of Aβ42/Aβ40 were lower in subjects with APOE4 and continued to decrease over the 2-year period. Conclusion: Plasma pTau217 is able to detect prodromal AD in at-risk patients and may be useful for the identification of patients suitable for AD therapeutic treatment. Since significant biomarker elevations are related to the APOE4 genotype, APOE genotyping will be important for routine clinical practice soon, and future APOE therapies in the pipeline.

Funding: This work was supported by the NIA of the National Institutes of Health under award number AG084134; COI: None

Poster Theme Group B2. Neuroimaging

Poster # 65: CEREBELLO-CEREBRAL FUNCTIONAL CONNECTIVITY IN EARLY ALZHEIMER'S DISEASE

Presenting author: Chi-Ying (Roy) Lin, MD, MPH, FAAN (BCM)

Background: The cerebellum, typically less affected by Alzheimer's disease (AD)-related tau and beta-amyloid pathologies than other brain regions, has the potential to compensate for the diseased brain networks in AD. Although structural and functional alterations in the cerebellum have been observed in amnestic mild cognitive impairment (aMCI), its precise role in early-stages of AD remains to be fully defined. Method: We investigated the cerebellar lobule-specific cerebello-cerebral functional connectivity (FC) in 19 cognitively normal, 19 aMCI, and 18 mild AD individuals using resting-state functional MRI with seed-to-voxel analysis. We conducted two-group comparison using one-way ANOVA in the CONN toolbox (level of significance: peak voxel $p < 0.001$ and cluster threshold size p-FWE < 0.05). Cognitive assessments were administered within 2 weeks of imaging, including the Montreal Cognitive Assessment (MoCA), Clinical Dementia Rating (CDR), and AD Assessment Scale-Cognitive Subscale (ADAS-Cog-13). We studied the clinico-imaging correlation by examining the correlation coefficient between the clusters and the different cognitive measures using linear regression models. Result: Participants from three groups did not differ significantly on age, sex, and education attainment. Compared to controls, aMCI participants exhibited stronger FC between the left cerebellar Crus I and II and the supramarginal gyrus in the parietal lobe; in mild AD, stronger FC was observed between the left cerebellar lobule VIIb and the bilateral medial frontal cortex, as well as between the right cerebellar lobule VIIb and the right inferior frontal gyrus. Of note, there was no significant difference in cerebello-cerebral FC between the aMCI and mild AD groups. Interestingly, participants with worse cognitive function demonstrated stronger cerebello-cerebral FC: higher ADAS-Cog-13 total score and lower MoCA score were both associated with stronger FC between the right cerebellar lobule III and left cuneal cortex, and higher CDR global score was associated with stronger FC between the vermis VII and right angular gyrus. Conclusion: Our findings suggest that the cerebellum, particularly its cognitive lobules, may play a compensatory role in cognitive function during the early stages of AD. Identifying and leveraging these measurable changes in cerebello-cerebral functional networks in aMCI and mild AD could pave the way for novel therapeutic interventions.

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Poster # 66: LINKING FUNCTIONAL CONNECTOMICS AND PROTEOMICS TO LEARNING AND MEMORY DEFICITS IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

Presenting author: Elizabeth Hipskind, BS (BCM)

Background: Magnetic resonance imaging (MRI) can be used to non-invasively assess structural and functional changes in the brain over the course of Alzheimer's Disease (AD). Resting-state functional MRI (rs-fMRI) measures functional connectivity (FC), a measure of communication between brain regions. We aim to understand the relationship between FC changes in the brain with learning and memory decline over the course of AD. Furthermore, we aim to link these to underlying proteomic changes in AD. Method: The APP/PS1 mouse model of AD was assessed at 3 time points over the course of AD: 3-months (before plaque deposition), 6-months (beginning of plaque deposition), and 10-months (plaque accumulation). First, we used Morris Water Maze to assess spatial learning and memory. Next, we used rs-fMRI to measure FC between 30 brain regions. FC was measured in awake mice to avoid potentially confounding effects of anesthesia. We performed spatial proteomics in 9 brain regions. We used machine learning (ML) to identify functional connections between brain regions that predict learning and memory performance at 6- and 10-months. The proteomics data are being modeled to explain the underlying mechanisms. Result: At 6-months, we see the emergence of memory deficits in APP/PS1 mice, while both learning and memory deficits are seen at 10-months. We observed early functional hyperconnectivity (increased FC) at 3-months, which increased across time points. At 6-months, the largest predictor of spatial learning is the temporal-hippocampus connection, while the dentate gyrus-subiculum predicted spatial memory performance. At 10-months, ML identified the insula-ectorhinal cortex and cortical subplate-entorhinal connections as the best predictors of spatial learning and memory, respectively. We are modeling spatial proteomics in corresponding brain regions to understand the mechanisms of FC changes. Conclusion: In APP/PS1 mice, we observed increased FC prior to the onset of cognitive deficits, suggesting rs-fMRI may be a non-invasive tool for disease detection. We used ML to identify changes in FC that explain spatial learning and memory performance. Interestingly, the connections that best predict performance vary with age, suggesting memory is supported by different compensatory strategies across disease progression. Spatial proteomic profiles will enhance our understanding of AD's neurobiological underpinnings.

Funding: NIH 1R56AG071152, NIH 1R01AG081192; COI: None

Poster # 67: MODELING STRUCTURAL AND FUNCTIONAL CONNECTOMICS WITH COGNITIVE DEFICITS AND SPATIAL TRANSCRIPTOMICS IN A MOUSE MODEL OF TAUOPATHY

Presenting author: Elizabeth Hipskind, BS (BCM)

Background: Tau is a key pathological feature of Alzheimer's Disease (AD) and other tauopathies. Magnetic resonance imaging (MRI) allows for the non-invasive detection and monitoring of structural and functional connectivity (FC) in the brain. We aim to understand the relationships between cognitive decline with structural and functional changes in the brain over the course of tau accumulation. Additionally, we link these to spatial transcriptomic changes to understand the underlying mechanisms of tauopathy. Method: The rTg4510 mouse model of tauopathy was assessed at 3-months (before tau tangle formation), 6-months (beginning of tangle deposition), and 10-months (tangle accumulation, some neurodegeneration). First, we measured spatial learning and memory using Morris Water Maze. Next, we performed neuroimaging of structural and functional connectivity using diffusion tensor imaging and resting-state functional MRI (rs-fMRI), respectively. Rs-fMRI studies were done with awake mice to avoid the potentially confounding effects of anesthesia on brain function. We then conducted high resolution spatial transcriptomics. We will use a machine learning model to understand how structural and functional changes relate to learning and memory performance and gene expression over the course of tau accumulation. Result: At 3-months, we see deficits in spatial learning and memory in the rTg4510 mice, even before tau tangle formation. These deficits increased in the 6- and 10-month groups. FC was increased (hyperconnectivity) at 3-months, while we observed a mix of hypo- and hyper-connectivity at 10-months. The 10-month group also showed a decrease in structural connectivity (white matter fibers).

We are currently identifying changes in spatial transcriptomics at each time point. Finally, we will define key contributors to tau-mediated cognitive decline by using machine learning to model the relationships between learning and memory performance with structural and functional connectivity and transcriptomic changes. Conclusion: We use a novel machine learning approach to identify functional brain connections that support memory across disease progression, bridging the gap between brain function and behavioral performance. We will identify regional patterns of susceptibility using spatial transcriptomics to enhance our understanding of the neurobiological mechanisms of AD.

Funding: NIH 1R56AG071152, NIH 1R01AG081192; COI: None

Poster # 68: LEVERAGING MACHINE LEARNING AND FEATURE IMPORTANCE TECHNIQUES IN NEUROIMAGING TO IDENTIFY CRITICAL BRAIN REGIONS STRONGLY CORRELATED WITH ALZHEIMER'S DISEASE

Presenting author: Benjamin Black, BS (UNTHSC)

Background: Machine learning (ML) is an evolving field in artificial intelligence that allows researchers to find patterns in data. In Alzheimer's Disease (AD) research, ML models such as Support Vector Machine, which combine decision trees, are valuable in analyzing neuroimaging data. This study aims to identify significant brain regions correlated with AD and mild cognitive impairment (MCI) using neuroimaging metrics from diverse populations. Methods: This study utilized data from a multi-ethnic cohort comprising 2950 participants, including those with no cognitive impairment (NC), MCI, and AD. Participants self-identified as Hispanic, non-Hispanic White, and non-Hispanic Black. Imaging data, including magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and positron emission tomography (PET) scans, were collected. The study used DTI metrics such as radial diffusivity, mean diffusivity, axial diffusivity, and fractional anisotropy to examine the structural integrity of white matter tracts. A Support Vector Machine was applied to predict cognitive impairment based on neuroimaging data, with Tau and DTI scans as the independent variables. Results: The Support Vector Machine identified that Tau uptake in the posterior cingulate and lateral parietal regions were the most correlated with cognitive impairment across racial and ethnic groups. DTI data, particularly axial diffusivity, highlighted the corpus callosum as a significant region for AD diagnosis. The SHapley Additive exPlanations (SHAP) values further demonstrated that posterior cingulate and lateral parietal regions were the most important in predicting cognitive impairment. Conclusions: This study demonstrates that machine learning models, particularly Support Vector Machine, can effectively identify brain regions associated with AD and MCI. The posterior cingulate, lateral parietal, and corpus callosum regions are key areas of neurodegeneration across diverse populations. These findings suggest that Tau and DTI metrics, especially axial diffusivity, have the potential to serve as clinical tools for early diagnosis and prediction of AD. However, the accuracy of machine learning models is limited by the quality and scope of the data available, emphasizing the need for further research.

Funding: R01AG054073, R01AG058533, and U19AG078109; COI: None

Poster # 69: AT[N] NEUROIMAGING OUTCOMES IN ALZHEIMER'S DISEASE: ANALYSIS OF MITOCHONDRIAL ANCESTRY IN A DIVERSE POPULATION

Presenting author: Jiya Ghei, BA (UNTHSC)

Background. Alzheimer's disease (AD) is the most common cause of dementia worldwide, and growing evidence suggests significant disparities in genetic risk factors across different racial/ethnic groups. Previous studies also show that mitochondrial dysfunction is implicated in AD pathology and is associated with increased beta-amyloid plaque production, a hallmark finding of AD. Preliminary research findings link AD risk to certain mitochondrial haplogroups, which are similar combinations of

mitochondrial DNA single nucleotide polymorphisms (SNPs) that represent common maternal ancestry. While this association has been studied using non-neuroimaging biomarkers, the relationship between mitochondrial haplogroups and amyloid, tau, and neurodegeneration (AT[N]) neuroimaging outcomes in AD remains unexplored, particularly in a diverse, representative cohort. This study examines associations between mitochondrial genetics and imaging biomarkers, including Amyloid PET, Tau PET, cortical thickness, and white matter hyperintensity in a diverse population of Mexican Americans, African Americans, and non-Hispanic Whites. Methods. Genetic data and neuroimaging data were collected from the Health and Aging Brain Study - Health Disparities (HABS-HD). Mitochondrial DNA was isolated from buffy coat samples and genotyped into mitochondrial SNPs, which were analyzed using Haplogrep3 to generate mitochondrial haplogroups for each participant in each of the three ethnic groups. Covariates included age, sex, education, APOEe4 status, and the first two eigenvectors (EV1 & EV2) of the genetic similarity matrix assessed using principal component analysis. Linear regression models were generated to analyze the relationship between major mitochondrial haplogroups and neuroimaging biomarkers. Results. Our preliminary analyses indicated significant positive and negative associations between specific mitochondrial haplogroups and Amyloid PET accumulation in the Mexican American group. These associations were consistent across various brain regions of interest. Conclusion. These results highlight the value of further investigation into the relationship between mitochondrial genetics and AD risk and progression, especially using AT[N] neuroimaging biomarkers. As additional data from the HABS-HD cohort becomes available, our analysis will expand to include additional neuroimaging and genetic data (including mito-nuclear genetic interactions) from each of the three racial/ethnic groups in our study.

Funding: HABS-HD U19: NIH/NIA 1U19AG078109-01, Contact PI- Sid O'Bryant; COI: None

Poster # 70: NEURAL OSCILLATIONS,THETA-GAMMA COUPLING, HIPPOCAMPO-CORTICAL NETWORKS,DISCRETE PADÉ TRANSFORM (DPT),COGNITIVE NEUROSCIENCE,FREQUENCY MODULATION (FM) IN BRAIN RHYTHMS

Presenting author: chandan kumar behera, PhD (UTHealth Houston)

Background: Oscillations of synchronized extracellular fields, such as theta (θ) and gamma (γ) rhythms, are crucial in controlling neural activities that underpin cognitive processes like learning and memory. Traditional methods, like Fourier analysis, offer only limited insights into these brain rhythms due to their inability to fully capture transient and noisy dynamics. To address these limitations, a new analytical approach, the Discrete Padé Transform (DPT), has been developed. This technique can reveal new structural motifs within brain waves-oscillons-which are believed to reflect the actual physical organization of synchronized brain activity. Method: This project will leverage the DPT to analyze high-quality electrophysiological datasets from open-access repositories, including NSF/CRCNS and DANDI, along with data from our collaborator, Dr. Ji. In Aim 1, we will quantify how θ and γ oscillons modulate the spiking activity of place cells during spatial learning, focusing on both traditional amplitude modulation (AM) and frequency modulation (FM) formats. In Aim 2, we will investigate the interaction of θ and γ oscillons across multiple timescales to unravel the temporal architecture of information exchange in hippocampo-cortical networks. Results: While this is a proposal for future research, preliminary analyses using DPT have already demonstrated the presence of oscillons in neural recordings, showing that these frequency-modulated waves provide a more detailed understanding of brain rhythms than traditional AM-based approaches. By focusing on FM channels, this project expects to reveal new insights into the coordination of neuronal activity. Conclusion: This research promises to advance our understanding of how brain rhythms coordinate cognitive functions through FM-based information processing. The findings may reshape our understanding of neuronal synchronization and brain wave structures, potentially contributing to the development of diagnostic and therapeutic tools for neurological disorders, such as Alzheimer's disease and epilepsy.

Funding: NIH grant; COI: None

Poster # 71: HIGHER ALPHA7 NICOTINIC ACETYLCHOLINE RECEPTOR AVAILABILITY IN THE BRAINS OF OLDER, COGNITIVELY NORMAL INDIVIDUALS

Presenting author: Alejandra N. Woolsey, B.S. (UTSW)

Background: The alpha7 nicotinic acetylcholine receptor (α7-nAChR) binds amyloid beta 42 with high affinity and may play a role in cognitive function over aging and Alzheimer's disease. This study aimed to test for higher regional availability of the α7-nAChR in a large sample of older compared to younger individuals in stable health. Methods: Across four published and one unpublished study, adults (18 years) in stable health completed one 90-minute dynamic PET scan that began with a slow IV push of [18F]ASEM, a radiotracer that targets α7-nAChR. Studies that were leveraged for this pooled dataset from healthy individuals used identical [18F]ASEM PET methods and the same high-resolution research tomograph, HRRT (Siemens). Older adults (≥50 years) underwent neuropsychological assessments and met the criteria of a Clinical Dementia Rating total score =0, Mini Mental Status Exam score ≥27, and normal performance memory tests. Data from older individuals assessed with the same cognitive battery (n=33) were used to test the hypothesized relationship between high [18F]ASEM binding and lower cognitive performance. Participants were non-smokers and underwent structural magnetic resonance imaging to delineate nine brain regions. The regional [18F]ASEM total distribution volume (VT) was determined using Logan analysis with metabolite-corrected arterial input function. A mixed-factor analysis of variance was used to examine the relationship between age and [18F]ASEM VT. Within a subset of older adults, we examined associations between regional binding and cognitive factor scores using Pearson correlations. The Benjamini-Hochberg procedure was applied to control for false discovery rate. Results: Older adults (n=60) had higher [18F]ASEM VT (mean ±SE =23.07 ±0.57) compared to younger adults (n=24, 19.76 ±0.90, $F(1, 82) = 9.78$, $P=0.002$). The group difference in VT differed across the nine regions of interest ($F(8, 656) = 14.63$, $P<0.001$), with the largest group differences in the cerebellar cortex or striatum. Within the older individuals who underwent identical neuropsychological assessment (n=33), lower performance in verbal episodic memory correlated with higher α7-nAChR availability in all regions but hippocampus and striatum. Conclusions: [18F]ASEM PET data suggest a higher availability of α7-nAChR in cognitively normal older adults. The relationship between the receptor and cognitive performance in healthy aging warrants further study.

Funding: National Institute of Aging/NIH; COI: None

Poster Theme Group C1. Neuropsychiatry and Behavioral Neurology

Poster # 72: PILOT SCREENING FOR PRODROMAL SYNUCLEINOPATHIES IN POST-9/11 VETERANS WITH PROBABLE REM SLEEP BEHAVIOR DISORDER

Presenting author: Taryn White, BS; Dakota Broadway, MA (BCM)

Background: Post-9/11 Veterans are the next wave of aging Veterans to benefit from preventative interventions for Parkinson's disease (PD) and dementia with Lewy bodies (DLB). In our previous report (Jones et al., 2024), over 50% of post-9/11 Veterans screened positive for rapid eye movement (REM) sleep behavior disorder (RBD). Since over 70% of patients diagnosed with RBD progress to PD/DLB within 12 years, this pilot study examined prodromal clinical markers of PD/DLB and PSG-confirmed RBD in a cohort of post-9/11 Veterans enriched with potential risk factors for these conditions. We also explored whether presence of subthreshold parkinsonism was associated with other prodromal phenomena. Methods: Subjects with probable RBD according to the single question screen for RBD (n=12), recruited consecutively from the Translational Research Center for Traumatic Brain Injury (TBI)

and Stress Disorders (TRACTS) Houston cohort underwent standardized assessments for subthreshold parkinsonism, olfactory loss, orthostasis, excessive daytime sleepiness, depressive symptoms, post-traumatic stress disorder, TBI exposures, autonomic symptoms, and polysomnography (n=10). Subthreshold parkinsonism was defined as Unified Parkinson's Disease Rating Scale Motor score >3 excluding action tremor, in accordance with Movement Disorder Society Prodromal PD criteria. Results: All 12 subjects were males ([50%] black or African American, 3 [25%] Hispanic) of mean age (SD) 44.4 ± 6.7 years. PSG studies (n=10) showed REM sleep without atonia (n=5, 50%), obstructive sleep apnea (n=4, 40%) and preserved REM atonia (n=1, 10%). Mean (SD) Sniffin Sticks scores were lower in Veterans with subthreshold parkinsonism versus those without (9.4 ± 2.07 vs. 11.29 ± 0.76, 95% CI: 0.01-3.76, p=0.049). There were no significant group differences in other prodromal features. Conclusion: This pilot study suggests the presence of clinical markers of prodromal PD/DLB in post-9/11 Veterans with psychiatric comorbidities and histories of TBI. Larger, replicative studies are needed to assess synuclein-specific biomarkers and quantify REM sleep without atonia.

Funding: Center for Alzheimer's and Neurodegenerative Diseases at Baylor College of Medicine; VA CSR&D Career Development Award #IK2CX002363-01A1; Translational Research Center for TBI and Stress Disorders VA RR&D #B9268-X; COI: Drs. Jones, Jorge, and Marsh have received study drug support from Acadia Pharmaceuticals. Dr. Jorge has received study drug support for a VA Cooperative Studies Program trial from Pfizer Pharmaceuticals.

Poster # 73: COGNITIVE COST OF LONG SLEEP DURATION AND DEPRESSION

Presenting author: Vanessa Young, MS (UTH San Antonio)

Background: Sleeping more or less than 7-8 hours has been associated with an increased risk for cognitive decline and Alzheimer's disease (AD). It remains unclear how other co-occurring conditions, such as depression, may impact sleep, cognition, and AD onset. We examined the association between self-reported sleep duration and cognition and whether depression modified this association. Method: We included dementia-and-stroke-free participants from the Framingham Heart Study Third-Generation, Omni 2, and New Offspring Cohorts who completed their second examination between 2008-2011 (n=1,853; age 49.8[SD 9.2] years; 42.7%M). We derived a global composite cognitive score (GC) from Trail-B, Visual Reproduction (VR), Logical Memory (LM), and Similarities (ST). We categorized the participants into four depression groups: control -untreated with Centre for Epidemiologic Studies Depression Scale (CES-D)<16(n=1405), treated with CES-D≥16(n=198), treated with CES-D<16(n=250), and untreated with CES-D≥16(n=133). Regression models examined the associations between sleep duration categories (≤6h; >6-<9h [reference]; ≥9h), GC and individual tests, adjusting for age, sex, education, cohort, and time between sleep and cognitive assessments. We tested effect modification by depression group. Results: Relative to average sleep, long sleep (≥9h) was associated with worse GC ($\beta \pm$ SE: -0.25 ± 0.07; $p<0.01$), LM (-1.50 ± 0.60, $p=0.01$), VR (-1.80 ± 0.42, $p < 0.01$), and TMT-B (-0.09 ± 0.03, $p=0.01$), but not with ST scores (-0.06 ± 0.28, $p=0.84$). These associations were not seen in short sleep (<6). We observed significant interactions between sleep duration and depression in their associations with GC ($p =0.03$), Trail-B ($p=0.01$), VR ($p=0.06$), and ST ($p=0.03$). Except for those treated with CES-D<16, we found that long sleep duration was associated with poorer GC and VR scores in three groups: untreated CES-D≥16 (GC: -0.60 ± 0.26, $p =0.02$; VR: -3.70 ± 1.70, $p=0.03$); treated CES-D≥16 (GC: -0.74 ± 0.30, $p=0.02$; VR: -4.30 ± 1.89, $p=0.03$); and control (GC: -0.18 ± 0.09, $p=0.04$; VR: -1.30 ± 0.55, $p=0.02$). Long sleep duration was only associated with Trail-B (-0.29 ± 0.13, $p=0.02$) among those untreated with CES-D≥16. Conclusion: Associations between long sleep duration and cognitive tests were stronger in adults with CES-D≥16, regardless of depression treatment status. This suggests complex interactions between sleep, depression, and cognition. Longitudinal studies with objective measures are warranted.

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Poster # 74: EVALUATION OF THE NEUROLOGICAL EFFECT OF YOUNG CSF ADMINISTRATION IN AGED RATS SUBJECTED TO THE ISCHEMIC STROKE MODEL

Presenting author: Victória Linden de Rezende (UTHealth Houston)

Aging is a risk factor for the development of several conditions, including ischemic stroke (IS). The pathophysiological process of IS involves neuroinflammation, cell death, and disruption of the blood-brain barrier(BBB). In this context, systemic interventions have been explored to restore damaged cells' functionality. Although the brain has barriers that prevent the free transport of substances from the periphery to the central nervous system, cerebrospinal fluid(CSF) can freely flow into brain tissue, which is important in maintaining the organ's homeostasis. A recent study demonstrated the ability of young CSF to improve memory function and to increase the proliferation and differentiation of oligodendrocyte progenitor cells in the hippocampus of aged rats and in primary OPC cultures. Thus, this study analyzed the protective effect of CSF administration of young rats (10 weeks) on aged rats (12 months) after they were subjected to IS. The animals were divided into four groups: I) Sham+artificial CSF; II) IS + artificial CSF; III) Sham+young-CSF; IV) IS+young-CSF. The permeability of the BBB was assessed 24 hours after IS and CSF infusion. In addition, the animals were evaluated for neurological scores (24h, 10 days, and 20 days post-IS) and subjected to behavioral tests to assess locomotor and anxiety-related behaviors (22 days post-IS). The results showed BBB disruption in the cerebellum and hippocampus, but not in the cortex after IS. Additionally, young CSF was able to prevent BBB disruption. Furthermore, neurological deficits were observed in animals that suffered IS compared to the control group, and CSF administration appeared to be effective in protecting the brain from neurological damage. Interestingly, an increase in the number of rearings was observed in the IS+artificial CSF group compared to the Sham+artificial CSF group, and young CSF was effective in reducing the number of rearings in the IS+young CSF group compared to the IS+artificial CSF group. Regarding the plus maze test, no significant changes were observed in the evaluated groups. In this regard, it can be concluded that young CSF appears promising in reducing the damage caused by IS; however, further studies are needed to understand its therapeutic mechanisms better.

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Poster Theme Group C2. Neuropsychology

Poster # 75: ACCULTURATION MODERATES THE RELATIONSHIP BETWEEN STRESS APPRAISAL AND MEMORY: RESULTS FROM THE HEALTH AND AGING BRAIN STUDY-HEALTH DISPARITIES STUDY (HABS-HD)

Presenting author: Jordana Breton, BA (UT Austin)

Background: Stress exposure (SE) and appraisal (SA) are distinct components of the stress process and differentially contribute to late-life cognition among ethnic/racial minorities. For example, lower memory in Black, compared to White, older adults is partly explained by higher SE among Black older adults. In contrast, higher SA may offset differences in memory between Black and White adults. These associations might be critical to examine among Latinos, given that they report the same or more SE than their White counterparts, but appraise these situations as less stressful. Lower levels of acculturation may represent a source of resilience that modify the effects of SE and SA on memory among older Latinos.

We examined whether the relationship between chronic SE and SA on memory was moderated by acculturation among Latino older adults. Methods: We used data from 1,004 Latinos (63.03 ± 7.88 years) from the Health and Aging Brain Study. Chronic SE was the total number of events reported as ongoing for 6 months; SA was the reported severity of those endorsed events. Acculturation was measured by the Short Acculturation Scale for Hispanics. Our outcome was a memory score, which consisted of total learning and delayed recall trials from the Spanish-English Verbal Learning Test. Linear regressions controlling for age, sex, education, and SE were used to examine the SA x acculturation interaction on memory. The SE x acculturation interaction on memory model was adjusted for age, sex, education, and additionally adjusted for SA. Results: There was a significant interaction between SA and acculturation for memory (B = -0.513, p = 0.047, R2 = 0.002), such that higher SA was associated with better EM in those with low acculturation, but worse memory in those with high acculturation. There were no reliable effects for SE on memory (B = -0.437, p = 0.359, R2 = -0.001). Conclusion: Findings revealed that SA differentially impacts memory in Latinos with low and high levels of acculturation. Lower levels of acculturation may be linked to protective sociocultural factors that buffer against the negative effects on memory of high SA.

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Poster # 76: AGE-RELATED DIFFERENCES IN MOOD AND MOTIVATION IN A COMMUNITY-BASED SAMPLE OF HEALTHY YOUNGER AND OLDER ADULTS.

Presenting author: Anika Bhatia BS (UT Dell)

Objective: Previous research suggests that age-related changes in cognition over the lifespan can contribute to declines in motivation and goal-directed activity. The current study aimed to (1) compare self-reported symptoms of mood (anxiety and depression) and motivation (apathy, anhedonia, and fatigue) in a community-based sample of younger (ages 18-30) and older (ages 60-80) adults, and (2) examine the interrelationships between these metrics. Based on prior work, we hypothesized that older adults (OA) would report fewer mood and greater motivation symptoms than younger adults (YA) on all three measures. Methods: The sample included 36 younger and 30 older adults recruited from the community as part of a larger study. All participants completed self-report questionnaires assessing anxiety (GAD-7), depression (PHQ-9), apathy (DAS), anhedonia (DARS), and fatigue (MFI), which were administered and scored according to standardized procedures. Results: The YA group endorsed significantly more symptoms than the OA group on the GAD-7 (Eta2=0.191), PHQ-9 (Eta2=0.123), and the Executive subscale of the DAS (Eta2=0.399), while OAs obtained significantly higher scores than the YA group on the Mental Fatigue subscale of the MFI (Eta2=0.065). There were no significant between-group differences on the DARS nor the remaining subscales of the DAS and MFI. Both mood measures were significantly correlated with each other (R2=0.41) and with the Executive subscale of the DAS (R2=0.28-0.30), which, in turn, shared modest correlations with a subset of DARS subscales (R2=0.07-0.14) but was unrelated to the other two DAS subscales (Emotional and Behavioral Apathy) and to any of the MFI subscales. Conversely, a significant positive correlation was shared between all subscales of the MFI and DARS (R2=0.13-0.48), both of which showed greater internal consistency between subscales (DARS: R2=0.59-0.89; MFI: R2=0.63-0.79) than the DAS (R2=0-0.42). Conclusions: Results point to a higher co-occurrence of anxiety, depression, and cognitive effort avoidance (executive apathy) in community-dwelling younger vs. older adults and suggest that emotional and behavioral aspects of apathy may be more closely related to fatigue and anhedonia. Findings also raise concerns about the internal consistency of the DAS, which we plan to explore further in our future work.

Funding: The Alzheimer's Association; COI: None

Poster # 77: DATA PRIVACY CONCERNS OF OLDER ADULTS PARTICIPATING IN A DIGITAL MONITORING STUDY AND RESPONSE TO AN EDUCATIONAL INTERVENTION

Presenting author: Rachel E. Mis, PhD (UT Dell)

Background: Passive monitoring of digital activities is a promising tool for assessing real-world cognitive and functional abilities in older adults. However, little is known about how data privacy concerns may be a barrier to research with these technologies, or how to educate older adults on mitigating privacy risks. The purpose of this study was to a) characterize the data privacy concerns of older adults enrolling in a passive digital monitoring study and b) determine if a brief educational intervention would lessen these concerns. Method: Thirty-eight older adults (Mean age: 74.92±5.26 years) with and without neurocognitive disorders (Mean MoCA-blind: 18.60±2.80) enrolled in this study. At baseline, participants answered questions addressing concerns about privacy of online/tech-related data in general, data privacy specific to the present study, and knowledge on maintaining general data privacy on a scale of 0 (strongly disagree) to 10 (strongly agree). An educational presentation reviewing data protection measures used in this study (e.g., specifying data collected/not collected, instruction on how to turn off collection of specific data elements, data deidentification) was delivered via Zoom, after which data privacy concerns were re-assessed. Paired t-tests examined changes in participants' responses following the intervention. Result: At initial onboarding, participants expressed greater concern related to data privacy in general (mean: 7.58±2.66) compared to this study specifically (mean: 4.84±3.56), $t(37)=5.16$, $p<.001$, $d=.84$. Following intervention, participants' study-related privacy concerns were reduced at a moderate effect size, $t(37)=3.44$, $p=.001$, $d=.56$, and at a small-to-moderate effect size for general data privacy concerns, $t(37)=2.31$, $p=.03$, $d=.38$. The intervention did not significantly affect participants' perceptions of their general data protection knowledge, $t(37)=1.35$, $p=.19$, $d=.22$. Conclusion: Older adults enrolling in a study on passive digital monitoring of real-world behaviors were more confident in the privacy of their online/tech-related data in the study despite having general data privacy concerns. A brief educational intervention was effective in further reducing participants' concerns specific to the study and in general. Our results suggest older adults' data privacy concerns may be attenuated through awareness and education by research teams conducting digital monitoring studies. Limitations and future directions are discussed.

Funding: R01AG077017, TARCC Fellowship Grant 956044; COI: None

Poster # 78: ENHANCING COGNITIVE FUNCTION IN PRIMARY PROGRESSIVE APHASIA: A STUDY OF HD-TDCS EFFECTS ON PRE-SMA AND LIFG

Presenting author: Paulina Devora, MS (UTD)

Objective: To evaluate and compare clinically meaningful effects of High-Definition transcranial Direct Current Stimulation (HD-tDCS) targeting the pre-supplementary motor area (preSMA) versus left inferior frontal gyrus (LIFG) in patients with primary progressive aphasia (PPA). Methods: Ten sessions of open label active HD-tDCS were administered to patients with PPA targeting either preSMA (n = 4) or LIFG (n = 4). Neuropsychological testing was performed using standardized measures at baseline and after completion of intervention (immediately and 8 weeks after). Clinically significant change was defined as an improvement of at least 1 z-score or 10 t-score points compared to baseline. Results: Two patients (one from each group) showed significant improvement in processing speed (Trails A) and executive function (Trails B) at 8 weeks. In the LIFG group, half of the patients showed immediate improvement in working memory, while 25% of the preSMA group showed improvement at 8 weeks. Visual memory (Rey-O

complex figure-- immediate and delayed recall) showed varying results, with up to 75% of the LIFG subjects showing improvement in immediate recall immediately after treatment and around 50% of the LIFG subjects with improvement in delayed recall. Verbal learning (Hopkins Verbal Learning Test) showed improvement, with 25-50% of subjects showing various improvement in total learning, immediate, and delayed recall across times. For letter fluency (FAS), 25% and 50% of the LIFG subjects showed improvement at immediate and 8-week time points, respectively. For category fluency (animals), 50% of the preSMA subjects showed improvement at 8 weeks, and 50% of the LIFG subjects showed improvement at both time points. In both groups, single subjects showed isolated worsening in verbal memory and visuospatial function (Rey-O copy). Discussion: Although up to 50% of all participants across stimulation sites showed clinically significant improvement, highest percentage of patients who had improvements were noted in the LIFG group in immediate measures of verbal fluency and verbal/visual memory. Despite the small sample size, these preliminary findings suggest that HD-tDCS may help improve various cognitive symptoms in PPA. These preliminary results suggest that targeting different brain regions with HD-tDCS could be a promising approach for alleviating cognitive challenges in PPA.

Funding: None; COI: None

Poster # 79: EVALUATING A TWO-STEP COGNITIVE SCREENING PROCESS USING THE BRIEF DEMENTIA SCREENING INDICATOR AND COGNITIVE SCREENING TESTS

Presenting author: Hanna Hausman, PhD (UTH San Antonio)

Background: Early identification of individuals at risk for dementia is crucial for improving treatment outcomes and reducing healthcare costs. Combining demographic and health information with cognitive screening may enhance dementia risk detection in primary care settings. This study aimed to evaluate the effectiveness of the Brief Dementia Screening Inventory (BDSI) in identifying individuals at risk from dementia and then to determine if combining BDSI and cognitive screening results improves classification of cognitive functioning and clinical practice efficiency. Methods: 153 English-speaking, older adults (>62 years; 76% male) were recruited from two dementia clinics in the Southern United States (Texas and Louisiana). Participants were administered the Mini-Mental State Examination (MMSE), BDSI, and a brief cognitive assessment tool, the Quick Mild Cognitive Impairment (QMCI). Participants were identified as cognitively normal (CN) or cognitively impaired (CI) based on prior neuropsychological testing. Cognitively normal individuals with scores ≥ 5 on the Geriatric Depression Scale - Short Form were excluded from the study. Detailed sensitivity/specificity, receiver operating characteristic (ROC) curve, and classification accuracy analyses were conducted on BDSI alone then combined with each cognitive screener. Results: Using an established dementia risk cutoff score of ≥ 22, the BDSI demonstrated limited sensitivity (30.30%) and strong specificity (93.10%) in identifying individuals at risk for dementia. The combination of BDSI and QMCI yielded slightly better classification accuracy than BDSI and MMSE. The BDSI-MMSE correctly classified 63.4% of cases but missed 83.3% of impaired cases, whereas the BDSI-QMCI correctly classified 64.7% of cases but missed 74.2% of impaired cases. Conclusions: The BDSI alone demonstrates high specificity; therefore, those identified as high risk likely are, and they should be referred for further evaluation. This strong specificity is valuable, as it may help avoid unnecessary burden, tests, and costs for the individual. However, given its low sensitivity, the BDSI does not reliably rule out cognitive impairment. Combining the BDSI with a cognitive screener may improve efficiency in identifying high-risk individuals in primary care settings, facilitating earlier interventions. However, it should be noted that this approach still misidentifies many CI individuals as CN, warranting further research into its utility.

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Poster # 80: CORRELATION BETWEEN COGNITIVE IMPAIRMENT AND PAREIDOLIA IN OLDER ADULTS

Presenting author: Laureen Phelps, MS (UTH San Antonio)

Background: Pareidolia is defined as the misperception of meaningful images in ambiguous patterns. Prior research has demonstrated that the Montreal Cognitive Assessment (MoCA) significantly predicts pareidolia responses. Additionally, the Noise Pareidolia Task (NPT) has shown potential to be an effective tool for differentiating between Lewy Body Dementia (LBD) and other dementias. However, few studies have examined the use of the NPT from the National Alzheimer's Coordinating Center (NACC) Lewy Body Module in a large sample exhibiting mixed cognitive diagnoses. Objective: Determine the relationship between cognitive ability or impairment, and pareidolia in older adults (who likely have Lewy Body Dementia or Alzheimer's Disease) in a mixed sample. Methods: Subjects from the NACC were selected if they completed the MoCA and the NPT(n=453) and were divided into two groups based on MoCA scores: <26 = impaired (n=299), ≥26 = normal cognition (n=154). A Pearson product-moment correlation was conducted to evaluate the relationship between the total raw MoCA scores and NPT scores. A simple linear regression was run to determine the predictive relationship between MoCA groups and NPT scores. Results: There was a significant positive relationship between MoCA and NPT scores. Face ($r(453) = 0.47$, $p<0.01$), noise ($r(453) = 0.40$, $p<0.01$), and total correct ($r(453) = 0.47$, $p<0.01$). The linear regression demonstrated statistically significant models (face correct $F(1,451) = 125.69$; noise correct $F(1,451) = 87.02$; total correct $F(1,451) = 130.34$) with MoCA performance status accounting for 21% (face), 16% (noise), and 22% (total) of variance in participant scores on the NPT. This indicates that the remaining variance may be related to other factors, including Lewy Body Dementia, Parkinson's Disease, or Alzheimer's Dementia. Conclusion: These findings confirm the hypothesis that MoCA scores can significantly predict NPT scores in both impaired and unimpaired individuals.

Funding: None; COI: None

Poster # 81: VARIATIONS IN COGNITIVE AND EVERYDAY FUNCTIONING ACROSS RACIAL/ETHNIC GROUPS WITH MILD COGNITIVE IMPAIRMENT

Presenting author: Alyssa Kaser, BA (UTSW)

Background: Individuals with mild cognitive impairment (MCI) may experience subtle deficits in everyday functioning, though research on extent of functional decline and relationship to cognition across racial and ethnic groups is limited. This study examined the relationship between everyday functioning and cognitive performance in a diverse, community-based sample of older adults with MCI. Methods: 651 participants with MCI were utilized from the Health and Aging Brain Study-Health Disparities (HABS-HD): 165 non-Hispanic White (NHW), 236 non-Hispanic Black (NHB), and 250 Hispanic (MAge=69.84, 63.96, 64.06; MEducation=15.18, 14.37, 9.90; %Female=40, 54, 63, respectively). Everyday functioning was estimated using the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) and its six domains. Neuropsychological test scores were converted to z-scores and averaged to derive domain-specific (memory, attention/executive functioning, language) and global cognition scores. Analyses of variance/covariance assessed between-group differences in demographics, neuropsychological performance, and functional ratings. Non-parametric bivariate correlations examined associations between cognitive and functional performance across racial/ethnic groups. Results: Cognitively, significant group differences were found in memory ($p<.001$, $\eta^2=0.05$, NHW z-scores<NHB & Hispanic) and attention/executive functioning ($p=.004$, $\eta^2=0.04$, Hispanic z-scores<NHB), with lower z-scores indicating poorer performance. Functionally, the NHB group had significantly higher CDR-SB scores ($M=1.37$) than NHW ($M=1.12$, $p=.003$) and Hispanic groups ($M=1.20$, $p<.001$) after covarying for

demographics and global cognition (p<.001, partial η^2=.03). Significant group differences were observed in CDR memory (p=.001, η^2=.02, Hispanic>NHB), orientation (p<.001, η^2=.02, NHB>NHW), and home/hobbies (p=.001, η^2=.02, NHB>Hispanic) domains, with higher scores indicating greater impairment. Greater functional impairment was weakly associated with lower memory (r=-.16, p=.01) and attention/executive functioning (r=-.18, p=.007) scores in the Hispanic group, but no associations were found in NHW or NHB groups. Conclusions: Patterns of cognitive and functional performance varied across racial/ethnic groups in this sample of community-dwelling older adults with MCI. NHB participants were rated as having greater functional difficulties than NHW and Hispanic groups, despite better memory and attention/executive functioning, even after adjusting for demographics and global cognition. Furthermore, cognition was differentially related to functioning across groups, suggesting that factors beyond cognitive decline may contribute to functional variability and highlighting the need for individualized, culturally sensitive assessments of subtle functional changes.

Funding: None; COI: None

Poster # 82: EXPLORING THE RELATIONSHIP BETWEEN TRAUMATIC BRAIN INJURY HISTORY AND COGNITIVE IMPAIRMENT IN A DIVERSE COMMUNITY-BASED SAMPLE

Presenting author: Diamond Lee, M.S (UTSW)

Objective: Research suggests that traumatic brain injury (TBI) with/without loss of consciousness (LOC) may impact cognition later in life; however, there is a paucity of research investigating this association in diverse samples. In a racially diverse, community-based sample, this study aimed to investigate 1) the prevalence of self-reported concussion across racial/ethnic groups, and 2) whether a history of TBI and LOC is associated with cognitive impairment while controlling for ethno-racial background. Methods: Participants from a population-based multiethnic cohort (N=769; Mage=61.8; Meduc=14.5; 61% Female; 45% Black, 40% White, 10.6% Hispanic/Latinx, and 1.6% Asian) completed a brief neurocognitive assessment and the Texas Evaluation of Concussion History (TECH) survey. A consensus diagnosis of +/- cognitive impairment was made based on +/- subjective complaint and review of cognitive data. Descriptive statistics were gathered to determine the prevalence of concussion history (+/- LOC) across ethno-racial groups. Multiple logistic regression analyses examined whether concussion history +/- LOC was associated with a later diagnosis of cognitive impairment. Results: Thirty-two percent of the sample reported concussion history (Mconcussions= 2.55), 49.5% of which involved LOC. Fewer Black individuals reported concussion (25.3%) and LOC (35.7%) compared to their White (43.3%, LOC=55.7%) and Hispanic/Latinx (33.1%, LOC=58.1%) counterparts (ps<.01). Self-reported concussion history (OR=2.81, 95%CI=[0.71-11.4], p=.14) and LOC (OR=1.1, 95%CI=[0.90-1.31], p=.39), controlling for age, sex, education, and ethno-racial background, did not predict later cognitive diagnosis (impaired/not impaired). Conclusion: Findings revealed differential rates of self-reported concussion among racial/ethnic groups, but history of concussion +/- LOC was not associated with cognitive impairment diagnosis in this sample. Future research is needed to explore the impact of the number and severity of TBI on later cognition in community samples as well as the impact of health literacy on self-identification of concussion history.

Funding: None; COI: None

Poster # 83: MONTREAL COGNITIVE ASSESSMENT MEMORY SCORES AND ALZHEIMER'S DISEASE NEUROPATHOLOGICAL CHANGE

Presenting author: Oscar Kronenberger (UTSW)

Background: The Montreal Cognitive Assessment (MoCA) Memory Index Score (MIS) incorporates points for correct responses to category and multiple-choice cues. Previous research suggests that the MIS may identify episodic memory deficits in Alzheimer's disease (AD) better than MoCA total score (TS) or free recall score (FRS), although its relationship with AD neuropathology has not been explored. The current study compared MIS, TS, and FRS scores in predicting post-mortem AD neuropathology. Methods: National Alzheimer's Coordinating Center data for participants with postmortem neuropathology data were selected based on the following criteria at initial MoCA assessment: 1) aged 50+, 2) clinical diagnosis of mild cognitive impairment or dementia with global Clinical Dementia Rating score of 0.5 or 1, and 3) MoCA TS>= 10. The sample of 658 individuals (Mage=75.85 [SD=10.53], Meduc=16.22 [SD=2.83]) were mostly White (93.5%) and male (60.3%). Binary logistic regression models assessed how baseline TS, FRS, and MIS predicted AD neuropathology, using Alzheimer's Disease Neuropathological Change (ADNC) scores according to the 2012 NIA-Reagan Criteria, dichotomized as absent (none/low ADNC) or present (intermediate/high ADNC). Demographic variables (age, education, sex, race, and ethnicity) were included in each model. Results: The sample demonstrated a mean baseline TS of 18.29 (SD=4.49), FRS of 0.87 (SD=1.35), and MIS of 6.08 (SD=4.11). The average time between MoCA and death was 3.68 years (SD=1.79). Of the sample, 454 (69.0%) had intermediate/high levels of ADNC upon autopsy. All three regression models were significant, with age and MoCA scores predicting ADNC (ps<.001). Along with demographics, the TS had an overall classification accuracy (CA) of 71.1% (B=-0.09, Nagelkerke R^2=0.11; Wald=18.94, odds ratio [OR]=0.91) FRS had a CA of 70.1% (B=-0.28, Nagelkerke R^2=0.11; Wald=20.56, OR=0.75) and the MIS had a CA of 70.2% (B=-0.12, Nagelkerke R^2=0.12, Wald=25.94, OR=0.89). Conclusions: Baseline TS, FRS, and MIS contributed similarly to logistic regression model accuracy in predicting intermediate/high levels of ADNC at autopsy, with odds of intermediate/high ADNC decreasing by approximately 9%, 25%, and 11% for every one-unit increase in TS, FRS, and MIS, respectively. These results suggest that the MIS is roughly equivalent to TS and FRS for predicting AD neuropathology at autopsy.

Funding: None; COI: None

Poster # 84: EVALUATION OF THE MONTREAL COGNITIVE ASSESSMENT MEMORY INDEX SCORE (MIS) FOR PREDICTING AMNESTIC MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S CLINICAL SYNDROME

Presenting author: Oscar Kronenberger (UTSW)

Background: The Montreal Cognitive Assessment (MoCA) Memory Index Score (MIS) may have prognostic utility for predicting the progression of mild cognitive impairment (MCI) to Alzheimer's Clinical Syndrome (ACS). We evaluated the prognostic utility of the MIS, compared to MoCA total score (TS), free recall score (FRS), combined TS+MIS, and a previously recommended cutoff algorithm (TScutoff<20+MIScutoff<7), for identifying MCI to ACS converters over one, three, and five annual follow-ups. Methods: National Alzheimer's Coordinating Center data for 2900 individuals aged ≥50 with MCI at baseline MoCA and at least 1 annual follow-up visit were used. ROC curves examined the prognostic utility of baseline MoCA scores (TS, FRS, MIS, and TS+MIS) for identifying individuals with MCI who developed ACS by each follow-up. Area under the curve (AUC) and sensitivity and specificity at optimal cutoffs were examined, and results were compared with the previously recommended predictive cutoff algorithm. Results: Conversion to ACS increased over the first (13%), third (27%), and fifth follow-up (34%). All MoCA scores identified ACS progressors at each follow-up timepoint (ROC ps<.001). AUC ranges were similar across follow-ups for TS (0.63-0.70), FRS (0.70-0.73), MIS (0.71-0.74), and TS+MIS (0.70-0.74). Although differences were modest, FRS (ps<.02) and MIS (ps<.01) better classified ACS converters by the third and fifth follow-up visits when compared to TS, and TS+MIS had superior classification to the TS at all three timepoints (ps<.001). The MIS had higher classification than the FRS at the first follow-up only (p=.009). Despite these differences, no MoCA scores achieved sensitivity ≥70 and specificity ≥70 simultaneously. The previously recommended

algorithm displayed unacceptably low sensitivity (range=0.10-0.27) but good specificity (range=0.92-0.96). Conclusion: While MoCA scores significantly classified ACS conversion from a heterogeneous MCI sample, cutoff scores with acceptable sensitivity and specificity for identifying who will progress could not be derived. Concurrent with previous research, delayed recall performance was a particularly meaningful indicator of future ACS progression, with only a small advantage of the MIS over the FRS at the first follow-up. Future research may explore if MoCA scores yield more prognostic utility in conjunction with other ACS features such as genetic, blood, cerebrospinal fluid, or neuroimaging biomarkers.

Funding: None; COI: None

Poster # 85: DEMOGRAPHIC EFFECTS ON THE MONTREAL COGNITIVE ASSESSMENT IN A COMMUNITY-BASED SAMPLE

Presenting author: William Goette, PhD (UTSW)

Objective The Montreal Cognitive Assessment (MoCA) is a popular cognitive screening measure. It is routinely interpreted via a simple cut-score for impaired versus non-impaired, despite evidence of demographic disparities in MoCA performance. This study extends previous analyses of demographic effects on the MoCA to better understand the implications of simple cut-scores. Participants and Methods Data were obtained for 678 participants (MAge = 61.04 [SD = 9.82], MEdu = 14.63 [SD = 2.30]) from the Dallas Hearts and Minds Study, the third wave of the community-based, longitudinal Dallas Heart Study. Included participants were determined to be cognitively unimpaired by consensus diagnosis based on neuropsychological test performance and blinded to MoCA scores. Bayesian generalized linear regression was utilized to examine the effect of age, education, sex, race, ethnicity (Hispanic/non-Hispanic), and literacy (Wechsler Test of Adult Reading raw scores) on MoCA scores. Due to small cell sizes, race was collapsed to White (n=322) and non-White (n=346; Black=86.42%, Asian=1.45%, American Indian/Alaskan Native=1.45%, multiple races=2.89%, "Other"=7.80%). Results MoCA scores ranged from 13-30 (M=24.21 [SD=3.43]), and 61% of the sample scored below the 26-point cut-score. Credible effects for age, education, and race on MoCA raw score were found (Adjusted-R2 = 0.31 [95% CI: 0.24-0.37]). Holding age and education constant, White-identifying persons are predicted to score 2.47 points higher on average than non-White peers. Adding literacy to the regression improved overall model performance (Adjusted-R2=0.46 [95% CI: 0.40-0.52]) and reduced the effect of race by more than half (predicted difference = 0.98 points). Moderately sized racial differences (White>non-White) were found for the cube, rhinoceros, serial 7s, sentence repetition, abstraction, and list recall items. Small racial differences (White>non-White) were observed for the clock numbers, clock hands, digits backward, and vigilance items. Conclusions Results highlight the influence of age, education, and literacy on MoCA performance. Consistent with prior research on the effects of educational quality, literacy considerably reduced racial group differences, but there remained a difference of about one point. These findings raise concerns about universal cut-scores as these may result in elevated false positives among older, non-White adults with fewer years of education and/or with lower literacy.

Funding: None; COI: None

Poster Theme Group D1. Dementia Care Research (nonpharmacological)

Poster # 86: PRECISION HEALTH FOR DEMENTIA: THE HOUSTON COHORT ENROLLED

Presenting author: Fatima I. Chavez, MPH (BCM)

Background: We aimed to establish a precision medicine workflow for Alzheimer's disease and related dementias (AD/ADRDs) and assess its impact. AD/ADRDs are clinically, pathologically, and genetically heterogeneous. Precision medicine promises individualized etiologic diagnosis, and ultimately targeted therapies. Method: As of October 2024, 115 participants had been enrolled from the highly diverse Houston community, Baylor College of Medicine, Harris Health, the Michael E. DeBakey VA Medical Center, and Kelsey-Seybold Clinic. These include Individuals with established AD/ADRD, mild cognitive impairment (MCI), or no known cognitive impairment (NCI). Participants received (i) comprehensive neurologic and neuropsychological assessments (NACC Uniform Data Set), (ii) brain MRI and amyloid PET, (iii) CAP-CLIA whole genome sequencing; in some cases, tau PET and blood-based biomarkers also were obtained. Genome data were filtered using a virtual gene panel specifically developed for this project. All subjects were consented for comprehensive disclosure of dementia risk. RESULT Participants had a mean age of 69 years, were 56% female, and were representative of Houston's diversity. Following baseline assessments based on clinical consensus diagnoses, 39% of subjects enrolled in the precision medicine study had normal cognition, 33% mild cognitive impairment, and 20% AD/ADRD. Data will be presented summarizing highly penetrant Mendelian AD/ADRD alleles identified, including SORT1, risk factor alleles, including GBA, and other medically actionable alleles. Plasma pTau217 provided excellent discrimination between the consensus-based NCI and MCI vs AD diagnoses. A subset of participants and caregivers completed pre and post disclosure surveys. To date, we have not detected increased participant worry; moreover, the majority reported making behavioral changes to improve brain health, including increasing mentally stimulating activities, exercise, and/or dietary modifications. Conclusion: Overall, our experience and emerging results establish feasibility and will inform implementation of precision health for dementia, incorporating CAP-CLIA grade whole genome sequencing with disclosure to participants.

Funding: BCM, NIH; COI: None

Poster # 87: RISK PROFILES OF ALZHEIMER'S DISEASE AND RELATED DEMENTIAS CARE PARTNERS: A LATENT PROFILE ANALYSIS TO INFORM INTERVENTION

Presenting author: Matthew Lee Smith, PhD, MPH, CHES (TAMU)

Objectives: To investigate how profiles of caregiver burden, depression, and social disconnectedness associate with emotional well-being, care experiences, and engagement in a problem-solving intervention among care partners of individuals with Alzheimer's disease and related dementias (ADRD). Methods: Ninety-five ADRD care partners enrolled in the Care Partners of persons with Dementia Problem-Solving Training (CaDeS) trial and completed trial baseline questionnaires. Latent Profile Analysis identified distinct participant clusters based on caregiver burden, depressive symptoms, and social disconnectedness. Multivariable linear regression models with backwards elimination determined factors associated with identified profiles, and group comparisons examined intervention engagement. Statistical significance was set at $p<0.05$. Results: Two profiles emerged: Profile 1 (n=56) was characterized by lower burden, depressive symptoms, and disconnectedness compared to Profile 2 (n=39). Profile 1 was associated with higher life satisfaction ($p=0.02$), more social support ($p=0.02$), and less resentment towards caregiving ($p<0.001$) than being in Profile 2. Both groups had similar intervention attendance (median=100% both groups) and engagement (median=5 and 5.1 out of 6). Conclusion: Two profiles emerged with different well-being and social dynamics, but engagement in the intervention was similar. Multifaceted approaches are needed to improve their health and well-being as well as the health and well-being of their care recipients.

Funding: TARCC; COI: None

Poster # 88: CAIDE DEMENTIA SCORE AND COGNITION ASSOCIATION IN DEMENTIA-FREE HISPANICS FROM THE HABS-HD COHORT

Presenting author: Abigail Mendoza, Medical Student (UNTHSC)

Background: Hispanics have a higher prevalence of cardiovascular risk factors compared to its non-Hispanic White counterparts. Studies have consistently shown a positive association between cardiovascular risk factors and cognitive decline. The Cardiovascular Risk Factors, Aging, and Incidence of Dementia risk score (CAIDE) predicts the risk of dementia later in life. CAIDE has been utilized in primarily non-Hispanic Whites. The aim of this study is to examine the relationship between CAIDE scores and cognitive function in Hispanics from the Health and Aging Brain Study (HABS-HD). We hypothesize that a higher CAIDE score will be associated with poorer cognitive performance in this cohort. Methods: Data from 1116 dementia-free Hispanic participants were analyzed. CAIDE was used as a predictor of cognitive performance on multiple cognitive domains. Cognitive scores were converted to Z scores, except for the MMSE, with lower Z scores meaning worse performance. CAIDE scores were used as a continuous variable; and were also categorized into two groups: low risk (CAIDE score < 9), and high risk (CAIDE score > 9). Linear regression was used to estimate the association between CAIDE and cognitive performance while adjusting for APOE4 status. Results Sixty-eight percent of the total sample were female, mean age 61 (9.26), and 11 (4.54) years of education. Twenty-four percent of the sample were APOE4 carriers. Participants in the high-dementia risk group were older, had less years of education, higher systolic blood pressure and BMI compared to the low-dementia risk group. Cognitive performance was significantly lower in the high-risk group participants except for SEVLT delayed and FAS. Linear regression showed that CAIDE risk scores significantly predicted MMSE, Trails A, Trails B, and DSS, after adjusting for APOE4 status. Results: did not change when using CAIDE as a binary variable. Conclusion: Our analysis suggests that higher CAIDE risk scores are associated with poorer performance in multiple cognitive domains. Further research is needed to validate the utility the CAIDE dementia score to predict cognitive decline in this population. This can aid targeted interventions to reduce dementia risk.

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Poster # 89: DEVELOPMENT OF AN EDUCATIONAL SUPPORT GROUP PROGRAM FOR CAREPARTNERS OF HISPANIC AND LATINO INDIVIDUALS WITH LANGUAGE-PROMINENT DEMENTIA

Presenting author: Giselle Yoshimoto (UT Austin)

Background: Aphasia is a common speech and language symptom of Alzheimer's disease and related dementias (ADRD). When aphasia results from a neurodegenerative disease, symptoms progressively worsen, leading to increasing communication challenges for affected individuals. Latino and Hispanic populations are disproportionately affected by ADRD, yet there is a shortage of culturally and linguistically appropriate resources and evidence-based support for carepartners of those living with language-prominent dementias. The development of interventions that address the cultural, linguistic, and practical needs of carepartners of those with language-prominent dementia is essential to improving their quality of life. Method: This study aims to examine the impact of participation in an educational support group program on the quality of life, communication, and wellbeing of carepartners of Latino and/or Hispanic individuals with dementia affecting speech and/or language. The development of the educational support group program was informed by themes identified in focus groups conducted with carepartners and individuals with progressive aphasia (PA), independently. The focus groups involved discussion over the challenges of living with PA and providing care, in addition to the desired topics, resources, and

desired speech-language pathologist (SLP) support for the program. The educational component (phase 1) included support group meetings where carepartners learned about PA and dementia, managing symptoms, communication strategies and technology, self-care, coping strategies, social work, and planning for the future. As an augment to the support group, carepartners had the opportunity to opt into "Ayúdame," an on-demand text-message-based support service. Following the educational component, participants entered an implementation phase (phase 2) where they practiced communication strategies with their partners in communication training sessions supported by an SLP. Result: Although data collection is ongoing, preliminary results indicate that both individuals with PA and their carepartners benefitted from the program, demonstrating improvements in quality of life and communication. Conclusion: The current study demonstrates the need and preliminary benefits of a educational support group program developed for carepartners of Latino and/or Hispanic individuals with dementia affecting speech and language. Additional cohorts will complete the educational support group program to further refine content prior to constructing a website where modules will be provided in Spanish.

Funding: None; COI: None

Poster # 90: A MITOCHONDRIAL BASED INTERVENTION FOR MILD COGNITIVE IMPAIRMENT (MCI) USING PHOTOBIOMODULATION, METHYLENE BLUE, AND MEDIUM CHAIN TRIGLYCERIDES

Presenting author: Hunter Dutkiewicz, BS (UT Austin)

Background: Mild Cognitive Impairment (MCI) is a significant predictor of Alzheimer's Disease (AD) and other types of dementia. Moreover, MCI is often considered a preclinical stage of AD and is characterized by impairments in cognitive function. Photobiomodulation (PBM), low-dose methylene blue (MB), and medium-chain triglyceride (MCT) supplementation have been demonstrated to enhance cognition and may serve as a multilevel, mitochondrial intervention for MCI. We aim to improve cognitive function by improving mitochondrial function and decreasing oxidative stress, which may improve neuronal metabolic function, thereby improving neurophysiology and cognitive abilities. Method: Participants with MCI, aged 65 years or older, will be randomly assigned to receive active treatment or sham placebo. Their vitals will be taken, and they will complete cognitive testing. During cognitive tests, a functional near-infrared spectroscopy (fNIRS) recording will be taken to measure cerebral hemodynamics. Afterward, they will receive either transcranial PBM or a sham condition, followed by a second fNIRS recording. They will then take home a light-emitting diode (LED) PBM device for daily use, along with daily low doses of MB and MCT oral supplementation, for 60 days. Participants will maintain a daily log and have weekly check-ins with experimenters. After 60 days, they will return to the lab for vitals and cognitive tests. Participants will return their PBM devices, be debriefed, and be compensated for their participation. Results: We have shown a dampened cerebral hemodynamic response from a single PBM session in older adults as compared to younger adults. However, we expect daily PBM to yield a higher cerebral oxygenation response. Repeated PBM and MB have improved cognition previously. Therefore, we expect cognitive performance to improve in the treatment group compared to the sham group. Conclusion: A mitochondrial-targeted treatment for MCI using PBM, MB, and MCT has both empirical and theoretical efficacy support. It may prove to be a first line of defense in patients at high risk of developing AD and dementia. This study reinforces the potential of mitochondrial noninvasive interventions in mitigating cognitive decline, warranting further investigation into their long-term benefits and mechanisms of action in AD.

Funding: Supported by the Oskar Fisher Project; COI: None

Poster # 91: EFFECTIVENESS OF CLOSED-LOOP THETA-BURST STIMULATION ON COGNITIVE CONTROL IN YOUNG ADULTS

Presenting author: Minsu Zhang, MS (UT Austin)

Background: Cognitive decline in conditions such as Alzheimer disease (AD) affects a significant proportion of our society. Recent transcranial magnetic stimulation studies demonstrated that theta-burst stimulation (TBS) on the left dorsolateral prefrontal cortex improved various cognitive functions in cognitively normal older adults and those diagnosed with AD. We developed a closed-loop brain stimulation where a real-time brain-computer interface(BCI) decodes the individual's contingent negative variation (CNV), an electroencephalography biomarker of cognitive control, and delivers TBS upon false negative outputs of the BCI. We examined the effectiveness of our intervention on cognitive performance in seven cognitively normal young adults. Method: A session consisted of Baseline, Closed-loop TBS (CL-TBS), intermittent-TBS (iTBS), and cognitive battery blocks. Baseline and CL-TBS blocks composed of four blocks with 26 CNV task trials. Electroencephalography data from the Baseline blocks was used to train the BCI. During CL-TBS blocks, a 2-s TBS train was delivered at the end of a false negative BCI trial. iTBS with 600 pulses was delivered in the iTBS block. Batteries were assessed following the baseline, iTBS, and CL-TBS blocks and consisted of Go/NoGo tasks and visual working memory tasks. Result: Grand-averaged CNV amplitude increased in CL-TBS blocks as hypothesized. Online BCI and the baseline cross-validation accuracies were all above chance-level and validated the feasibility of the CNV-BCI. CNV task accuracies were all above 95% during Baseline and CL-TBS blocks, suggesting ceiling effects. CNV task response time (RT) decreased but the variance increased during CL-TBS blocks. This may be due to the practice effect and requires comparison with a within-subject sham control. Go/NoGo task RT was largely consistent across all conditions. Working memory accuracy increased after both iTBS and the CL-TBS blocks marginally. Conclusion: A major observation was that CL-TBS after i-TBS resulted in increased CNV amplitude and working memory accuracy. However, this was not accompanied with the enhancement in CNV task accuracy or shorter RT. We suspect that this is due to the combination of shortage of stimulation dosage of a single session and ceiling effect with young adult samples. Further data collection from within-subject sham control and older adults samples will follow.

Funding: TARCC Investigator initiated grant; COI: None

Poster # 92: ETHNORACIAL AND BILINGUAL DISPARITIES IN SPEECH-LANGUAGE INTERVENTION FOR PRIMARY PROGRESSIVE APHASIA

Presenting author: Rylee Manning, M.Sc., M.Phil. (UT Austin)

Background: Primary Progressive Aphasia (PPA) and Primary Progressive Apraxia of Speech (PPAOS) are neurodegenerative syndromes characterized by early speech and/or language impairments with relatively spared cognition. Though there is no cure to ameliorate these symptoms, available evidence has demonstrated the benefits of speech-language intervention for people with PPA (Wauters et al., 2023). A scoping review revealed that most intervention research focused on PPA and PPAOS has been conducted in monolingual English speakers (Grasso et al., 2023), despite estimates indicating that most of the world's population speaks more than one language. The current systematic review was conducted to characterize the ethnoracial and linguistic diversity of participants represented in the nonpharmacological intervention literature conducted in individuals with PPA and PPAOS. Method: Building on a previously conducted systematic review for PPA/PPAOS (Wauters et al., 2023), additional papers published between 2021 and 2024 were added to the current review. New data fields were also extracted from each study in order to characterize variables associated with ethnoracial and linguistic diversity. This included but was not limited to: migration history, race, ethnicity, occupation status, years of education, languages spoken by participants, and inclusionary/exclusionary criteria. Results: Ongoing data extraction from N=149 studies indicates that there is a significant lack of diversity in the current literature, with an overrepresentation of White, monolingual English-speakers. Of the studies that formally reported on participants' racial identity (n=9), 89% of participants identified as White. Of only three studies that

reported on participants' ethnicity, 66% identified as Hispanic or Latino. The majority of prior studies citing language proficiency as inclusionary criteria overwhelmingly reported English proficiency as inclusion criteria. Conclusion: Given the lack of ethnoracial and linguistic diversity in the current literature, the reported benefits of evidence-based speech-language treatment options for PPA/PPAOS are not directly generalizable to these underrepresented groups. Increasing ethnoracial and linguistic diversity in intervention research is paramount, as racial and ethnic minorities are at a greater risk of developing Alzheimer's disease and related dementias. In order to reduce health disparities perpetuated by the lack of representation in the field, concerted efforts must be taken to achieve equitable service provision.

Funding: None; COI: None

Poster # 93: EXPLORING NEUROLOGISTS' PERSPECTIVES: BARRIERS AND FACILITATORS IN IMPLEMENTING COGNITIVE CARE PLANNING

Presenting author: Shaoqing Ge, PhD, MPH, RN (UT Austin)

Background: The global population is aging rapidly, leading to a significant rise in age-related cognitive disorders. Cognitive decline and dementia are critical health issues affecting older adults, threatening their independence and quality of life. Alzheimer's disease and other dementias not only impact individuals but also place a heavy burden on families, caregivers, and healthcare systems worldwide. Addressing cognitive health in aging populations has thus become a priority in global health initiatives but few studies have examined the formal process of cognitive care planning amongst neurologists. Method: This qualitative study used semi-structured interviews to examine neurologists' experiences, attitudes, and perceptions of implementing Cognitive Care Planning (CCP) in their practice. Participants were recruited from one medical center in Seattle, WA, using a purposive sampling approach. The interview guide was informed by the updated Consolidated Framework for Implementation Research (CFIR). From June to December 2023, we conducted audio-recorded Zoom video conferencing interviews with seven neurologists, each lasting 45 to 60 minutes. All data were stored, managed, and analyzed using Dedoose Software. Deductive content analysis was employed to code interview data, deriving codes and subcodes from the pre-existing CFIR framework. Result: The study identified several barriers to CCP integration, including limited treatment options, fear and shame associated with cognitive decline, complex health problems of patients, and patient willingness. Additional challenges included lacking technology integration, appointment structure, specialty-specific demands on providers, organizational constraints like staffing and appointment time limitations, and a shortage of referral resources. Despite these barriers, neurologists also noted facilitators such as sufficient caregiver support, integrating a health champion, and making CCP appointments flexible and adaptable to patient needs. Conclusion: The insights from this study highlight the practical challenges and opportunities associated with CCP implementation. By identifying key facilitators and barriers, the findings aim to inform strategies that enhance the feasibility and effectiveness of CCP, ultimately improving cognitive health outcomes and overall quality of life for patients with cognitive impairments and their families.

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Poster # 94: A SCOPING REVIEW OF AURICULAR POINT ACUPRESSURE EFFECTS IN PERSONS WITH COGNITIVE IMPAIRMENT AND DEMENTIA

Presenting author: Bianca Shieu, PhD, RN (UTH San Antonio)

Background: Auricular Point Acupressure (APA), a non-invasive modality of auricular therapy, is extensively used for managing many health issues. These include cancer-associated pain, persistent lower

back discomfort, and dysmenorrhea among oncology patients, and benefits for the mental health population, including those experiencing depression, anxiety, or sleep disturbances. However, its effects on individuals with cognitive impairment and dementia have been less explored. This review aims to provide a comprehensive overview of the application of APA specifically for individuals with cognitive impairment and dementia. Methods: We followed PRISMA guidelines and meticulously searched seven English and Chinese electronic databases. Our search strategy utilized a combination of relevant keywords and MeSH terms. Two investigators independently screened the titles and abstracts of the retrieved articles, followed by a full-text review to identify eligible studies. Any disagreements were resolved through discussion or by consulting a third investigator. Data extraction was carried out using a standardized form, capturing study characteristics, intervention details, and outcomes. The quality of evidence was assessed using the Mixed Methods Appraisal Tool, and data synthesis was performed through narrative synthesis. Results: Our results demonstrated that APA can effectively manage chronic pain, enhance daily living activities, improve mental status and cognition, reduce constipation, and enhance sleep quality in this population. Conclusion: Overall, APA has shown its potential and benefits for persons with cognitive impairment and dementia. More randomized controlled trials are needed to provide further evidence.

Funding: UT Health Start-Up Fund; COI: None

Poster # 95: CAREGIVER BURDEN IN ALZHEIMER'S DISEASE AND RELATED DEMENTIAS (ADRD) IN THE SOUTH TEXAS ADRC (STAC)

Presenting author: Natalia Monroy, BS (UTH San Antonio)

Background: Dementia is a neurodegenerative disease that results in progressive declines in behavior, cognition, and functional independence. As the disease evolves, patients become increasingly dependent upon caregivers for managing all aspects of daily life. These shifts in responsibility often resulting in greater caregiver distress and burden. Prior research has shown cultural and ethnic differences in caregiver burden, but there is little research exploring differences in caregiver burden within South Texas. We analyzed levels of caregiver distress within our South Texas ADRC (STAC) cohort to determine whether caregiver burden differed by ethnicity. We also reviewed whether caregiver burden and depression were associated to reported hours of care. Methods: A total of N = 39 patient/caregiver dyads were enrolled in the STAC and chose to participate in the Caregiver Repository. All caregivers completed demographic questionnaires summarizing hours of care, as well as the Zarit Burden Interview, and the Patient Health Questionnaire (PHQ-9). Results: were analyzed using R statistical software. Ethnicity groups were compared with independent t-tests on measures of depression and caregiver burden. Results: The total STAC cohort is comprised of 51% Hispanic participants; However, only N = 13 enrolled in the Caregiver Repository (33%), $t(38) = 4.36$, $p < 0.05$. When compared to non-Hispanic caregivers, Hispanic caregivers showed higher levels of burden ($p<.0005$), despite similar levels of depression ($p = .668$). The overall sample showed a non-significant, but trending relationship between hours of reported caregiving and perceived distress, $r(37) = .23$, $p = .159$, and levels of depression, $r(37) = .133$, $p = .418$. Conclusion: These findings suggest that our South Texas Hispanic caregivers are experiencing higher levels of perceived distress, despite similar levels of reported depression when compared to non-Hispanic caregivers. Future analyses will explore caregiver distress stratified by clinical syndrome and disease staging, as well as incorporating other social determinants of health.

Funding: None; COI: None

Poster # 96: PARTICIPANTS' PERSPECTIVES ABOUT THE EFFECTS OF PROBLEM-SOLVING TRAINING (PST) ON CAREGIVER BURDEN AND DEPRESSION AMONG ADRD CARE PARTNERS

Presenting author: Kristin Wilmoth, PhD (UTSW)

Background: Participants in the Care Partners in Dementia Problem-Training (CaDeS) study were care partners of a person with Alzheimer's Disease or related dementias (ADRD). Care partners often experience caregiver burden and emotional distress as they try to balance their caregiving responsibilities with other areas of their lives. In a TARCC-funded randomized controlled optimization trial of CaDeS, Problem-Solving Training (PST) - and its Spanish-language equivalent Descubriendo Soluciones Juntos (DSJ) - demonstrated efficacy for improving caregiver burden (as measured by the Zarit Burden Interview) and depressive symptoms (as measured by the Patient Health Questionnaire-8), regardless of the number of PST/DSJ sessions with or without follow-up booster sessions. Method: Care partners were randomized to receive three or six sessions of PST/DSJ with or without (±) booster sessions. Herein, we report care partner participants' perceptions on PST/DSJ, including their satisfaction (Client Satisfaction Questionnaire-8; CSQ-8, possible range 0-32), confidence being able to apply the PST/DSJ strategy in the future (0-10 scale, completed by participant and PST Coach), and subjective impression of change in caregiver burden and depression (much worse, worse, the same, better, much better), all collected at 6-months post-baseline. Result: Ninety-five care partners completed the intervention. Initial exploration identified no differences in any measure by intervention arm; therefore, we pooled all participant data across intervention arms. Participants (n=91) reported high satisfaction (CSQ-8 M=27.0, SD=4.4) with PST/DSJ. Both participants (n=90, M=8.5, SD=1.3) and coaches (n=95, M=7.4, SD2.0) reported high confidence for applying the PST/DSJ strategy to future goals/problems. For subjective change in caregiver burden (n=88), 60 (68.2%) of partners said they got better/much better (remaining n=25, 27.5% said they stayed the same). For subjective change in depression (n=91), 66 (72.5%) of partners said they got better/much better (remaining n=28, 31.8% stayed the same). Conclusion: Care partners reported high satisfaction with PST/DSJ and were generally confident in their ability to apply the PST/DSJ strategy to future goals/problems. For each outcome (burden, depression), over two-thirds of participants reported subjective improvement. Findings from this study further support, from the perspective of ADRD care partners, the benefits of PST/DSJ.

Funding: TARCC Collaborative (#1029417, PI Juengst) & TARCC Jr Investigator (#1286993, PI Wilmoth) Research Grants; COI: None

Poster # 97: ENGINEERING THERAPEUTICS BY DECODING FEATURES DRIVING AMYLOID ASSEMBLY IN ALZHEIMER'S DISEASE.

Presenting author: Nikolaos Louros, PhD (UTSW)

Background: Recent advancements in cryogenic electron microscopy (cryo-EM) have revolutionized our understanding of amyloid fibrils, shedding light on the intricate structural landscape underlying amyloidogenic diseases. This transformative technique has unveiled the polymorphism inherent to amyloid fibrils, linking distinct structural variants to specific pathological phenotypes. These structural insights have raised several open questions, including the impact of extrinsic factors on amyloid toxicity, or the extent to which intrinsic structural elements of amyloids contribute to fibril nucleation, polymorphism, and propagation. Results: To better understand the intrinsic determinants of amyloid fibrils formed by tau and amyloid beta peptide (Aβ) in Alzheimer's disease (AD) and other tauopathies, we performed rigorous thermodynamic profiling of their polymorphic cryo-EM structures. Coupled with dimensionality reduction, our profiling pinpoints specific key local motifs that consistently drive fibril maturation in AD and CTE tau ex vivo strains, and act as disease classifiers driving the formation of different disease-related tau/Aβ strains. Using biophysical techniques and cryo-EM, we find that these local sequence motifs concurrently act as nucleators of tau, mediate its disease-related polymorphism, and regulate the propagation of ex vivo tau aggregates in cells. We find that they promote co-aggregation of "vulnerable" brain proteins, which could explain the apparent selective vulnerability of neurons, and trigger amyloid co-deposition, specifically of medin and Aβ in the brain vasculature, leading to cerebral

amyloid angiopathy (CAA). Leveraging this knowledge and AI-based rational design, however, we developed de novo therapeutic agents targeting AD amyloids in vitro, in cells, and in animal models, promoting their clearance by utilizing these identified key amyloidogenic motifs as functional interaction sites of high specificity. Conclusions: We find that local amyloid motifs are intrinsic determinants of amyloid strain nucleation, polymorphism, and seeding. Our findings show that these elements are hotspots promoting co-aggregation of other (non-self-aggregating) brain proteins, suggesting that this interaction may be relevant to selective cellular vulnerability. Considering the intrinsic "stickiness" that these local motifs exhibit, we have utilized this property to develop a novel platform for anti-amyloid agents that specifically target AD amyloid strains and block further aggregation in disease models.

Funding: Endowed Scholar Award, UT Southwestern Medical Center; COI: None

Poster # 98: NON-INVASIVE NEUROMODULATION USING TRANSCRANIAL PHOTOBIOMODULATION TO ENHANCE COGNITIVE FUNCTION IN HEALTHY ADULTS: MEG/EEG EVIDENCE

Presenting author: Tyrell Pruitt, PhD (UTSW)

Background: Transcranial photobiomodulation (tPBM) is a non-invasive neuromodulation technique that has shown promise in improving cognitive function and neurophysiological activity. This study aims to assess the efficacy of tPBM in modulating brain activity across multiple regions, with implications for nonpharmacological therapeutic interventions in dementia care. Previous work has demonstrated tPBM's capacity to enhance brain function, but no studies have concurrently utilized magnetoencephalography (MEG) and electroencephalography (EEG) to measure its effects. Methods: Twenty-five healthy adults (mean age 25.6 ± 4.8 years) participated in a study assessing the effects of 1064-nm laser tPBM delivered to the right prefrontal cortex for 8 minutes. MEG and EEG data were recorded simultaneously for 6 minutes before and after the stimulation. Power spectral densities (PSDs) were calculated across multiple frequency bands, and changes between pre- and post-tPBM recordings were evaluated using cluster-based permutation analysis with family-wise error correction ($p < 0.05$). Results: tPBM induced significant increases in alpha (8-12 Hz) and beta (13-30 Hz) frequency power across cortical regions, particularly within the ipsilateral hemisphere. MEG and EEG source imaging revealed enhanced activity not only near the site of stimulation but also in remote regions, including the parietal and occipital lobes. These widespread effects suggest that tPBM can modulate cognitive networks, potentially contributing to improved brain function in dementia care settings. Conclusion: This study provides strong evidence that tPBM can significantly influence neural activity in regions associated with cognitive function, offering a nonpharmacological approach to enhancing brain health. The use of MEG and EEG as complementary tools provides a detailed map of the neuromodulatory effects of tPBM. These findings underscore the potential for integrating tPBM into dementia care as a therapeutic strategy to enhance cognitive performance and neuroplasticity.

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Poster Theme Group D2. Psychosocial Factors and Environmental Design

Poster # 99: PRELIMINARY EVALUATION OF CHRONIC STRESSORS IN HISPANIC ADULTS AT RISK FOR NEURODEGENERATIVE DISEASE

Presenting author: Valentina R. Garbarino, PhD (UTH San Antonio)

Background: Chronic stress increases the risk of mild cognitive impairment and Alzheimer's disease, a neurodegenerative disease which is 1.5-fold more prevalent in Hispanic than non-Hispanic white populations. Methods for quantifying risk of neurodegenerative disease driven by stress(ors) are lacking. Therefore, we aim to evaluate a stress-related transcriptional profile, the Conserved Transcriptional Response to Adversity (CTRA) for the ability to predict neurodegenerative disease risk influenced by chronic stress. To this end, a sub-study to evaluate perceived stress and collect blood samples to assess the CTRA, was added to ongoing longitudinal population studies at South Texas Alzheimer's Disease Research Center. Method: Hispanic participants over the age of 65 who consented to the sub-study completed the Perceived Stress Scale (PSS), the Brief Resilience Scale (BRS), filled out an open-ended survey on stress inducing and stress relieving factors, and provided a blood sample for peripheral blood mononuclear cell isolation to later be used to quantify transcriptional outcomes relevant to the CTRA. Cognitive status was determined as part of the parent studies. Only females were included in this preliminary analysis. Result: Hispanic females with MCI had lower resilience to stress based on the BRS questionnaire (Mean ± SEM: 3.42 ± 0.299) than age matched controls (4.27 ± 0.224; P= 0.0417). There was a significant and expected correlation between participant BRS and PSS scores (R2= -0.898, P< 0.0001). No differences were observed between the NC and MCI group in age or level of education. The greatest stressors reported by this cohort of Hispanic female individuals were concerns for their families and their own health. The greatest stress relievers reported by this cohort were interactions with friends and family members and watching television. Conclusion: Sample collection is ongoing, but preliminary analyses revealed a significantly reduced level of resilience to psychological stress in Hispanic females with MCI compared to NC controls. Future directions include analysis in a larger sample size to include males and the analysis of the CTRA in the PBMC samples to determine if there are specific transcriptomic changes that may associate with perceived stress and predict individual risk of stress exacerbated neurodegenerative disease.

Funding: This work was supported by the South Texas Alzheimer's Disease Research Center (P30AG066546); COI: None

Poster # 100: IMPACTS OF IMAGEABILITY OF ARCHITECTURE ON BRAIN HEALTH: A SYSTEMATIC LITERATURE REVIEW

Presenting author: Cristian A. Maestre, BSArch (UTRGV)

Background: Neuroscience applied to architectural design offers new avenues to understand the impacts of the built and natural environments in the brain, including neural pathways, mediators, and contexts. The positive impact of architecture on neuroscience can be explored through the concept of imageability, which relates to the distinct and memorable features of a place. Imageability is a component of urban design and planning that has been recognized for its potential to enhance people's perceptual and emotional engagement with their environment. Nevertheless, evidence supporting specific strategies and impacts on brain health is still unclear and has not been systematized. This systematic review aimed to characterize and summarize the evidence on the importance of imageability of architecture and related pathways for brain cognitive and psychological health. Method: This systematic review was conducted following the PRISMA guidelines. Our keywords included imageability and architecture, environment, built environment, neuroarchitecture, aphantasia, urban design, memorability, visual recall, mental visualization, architectural features, façade, wayfinding, familiarity, vividness, cognition, expectations, green walls, biophilia, aesthetics, emotions, embodied cognition and embodiment. We searched electronic databases for studies showing the relationship among imageability, architecture, and neuroscience. From the 5,270 identified articles, we included 56 original peer-reviewed articles. Result: The findings suggest that environments with high imageability are correlated with better cognitive and psychological health, high emotional engagement, and enhanced social connectivity. Studies have also highlighted that high-imageability environments enhance livability, promote wayfinding, and support physical activity. However, some gaps were identified, including the need for standardized methods to assess imageability

and its impact on brain health by examining brain structures and function with imaging studies. Conclusion: Imageability seems to plays an important role in creating environments that promote cognitive and psychological health, physical activity and foster a sense of community belonging. Future research should focus on developing objective, replicable methods for evaluating imageability and exploring the neural paths that underlie its effects.

Funding: This work was supported by 1DP1AG069870-01 (GEM); COI: None

Poster Theme Group E1. Dementia Care Practice (descriptive research)

Poster # 101: VIRTUAL CAREGIVER SUPPORT PROGRAM IS FEASIBLE AND ACCEPTABLE TO CAREGIVERS OF VETERANS WITH DEMENTIA DURING CARE TRANSITIONS

Presenting author: Molly Horstman, MD, MS (BCM)

Background: Hospital GamePlan4Care is a virtual evidence-based caregiver support intervention designed for use during care transitions from hospital to home. Our objective was to test the feasibility and acceptability of Hospital GamePlan4Care. Methods: We recruited caregivers of Veterans with dementia hospitalized at the Houston VA. All caregivers received the intervention, which included a Care Transitions handbook, the Hospital GamePlan4Care website, and four phone calls with a dementia care specialist to tailor the intervention. The website includes skills training relevant to care transitions, including how to conduct a medication review, managing delirium after discharge, learning new medical tasks, and managing dementia behaviors. Feasibility was assessed with participant recruitment and enrollment rates. Acceptability was assessed 30 days post-discharge with the Acceptability of Intervention Measure and a semi-structured interview. Interview transcripts were analyzed using Rapid Qualitative Analysis. Results: Of the 43 caregivers approached, 22 caregivers (10=spouse, 7=adult child, 2=parent, 1=sibling, 1=other relative, 1=friend or neighbor) enrolled. Mean caregiver age was 62.8 years (SD 16.8), and 90% were female. Seven were non-Hispanic black, nine were non-Hispanic white, and six were Hispanic. The median number of years of caregiving was 3 (IQR 6.5 years). Sixteen caregivers completed 30-day data collection. All caregivers agreed or completely agreed with "Hospital GamePlan4Care meets my approval," and 14 agreed or completely agreed with "Hospital GamePlan4Care is appealing to me." Caregivers reported the intervention "came at the right time." Caregivers felt the information was easy to access, and appreciated having multiple formats (e.g. handbook, website, emails, phone calls). However, the amount of content on the website was overwhelming and repetitive to some. The dementia care specialist was a source of emotional support and encouragement, and caregivers appreciated learning about available VA resources, such as respite care. Caregivers reported limited time to engage in the training due to competing demands following hospital discharge. Conclusion: Hospital GamePlan4Care was feasible and acceptable to caregivers during care transitions. Based on the pilot, we reduced the amount of training in Hospital GamePlan4Care to better fit caregivers' needs. Next, we will compare Hospital GamePlan4Care to a Health Education Control in a pilot randomized controlled trial.

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Poster # 102: IMPLEMENTING A NEUROPLASTICITY CARE TOOL KIT WITH STAFF CARING FOR DEMENTIA PATIENTS WITH BPSD

Presenting author: Sandra Petersen, DNP, APRN, FNP/GNP-BC, PMHNP-BE, FAANP (UT Tyler)

Background: Dementia is a progressive neurodegenerative disorder characterized by cognitive decline, affecting millions worldwide. Recent advancements in neuroplasticity-the brain's ability to adapt and

reorganize itself by forming new neural connections-offer promising inroads for therapeutic interventions. Training healthcare staff to harness neuroplasticity could significantly enhance the quality of care for dementia patients. Objective: This study aims to develop and evaluate a training program for healthcare staff focused on utilizing neuroplasticity principles to improve cognitive and functional outcomes and decrease the behavioral and psychological symptoms of dementia (BPSD) in patients with progressive neurocognitive decline. Methods: The training program was designed based on current neuroplasticity research and included modules on emotional connection and social connection, physical exercise, and cognitive stimulation with overarching personalized care strategies. An initial cohort of cohort of 30 assisted living memory care communitiess participated in the program, which was delivered through a combination of workshops, online courses, and hands-on practice. Pre- and post-training assessments were conducted to measure changes in staff knowledge, confidence, and application of neuroplasticity techniques. Results: Preliminary findings indicate a significant increase in staff knowledge and confidence in applying neuroplasticity-based interventions. Patients under the care of trained staff showed improvements in cognitive function, mood, and ability to participate in daily living activities. Notably, the integration of aroma therapy, music, physical exercise and social engagement activities was associated with the most substantial benefits. Conclusion: Training healthcare staff to utilize principles of neuroplasticity is a feasible and effective approach to enhancing dementia care. The program not only improves staff competencies but also positively impacted patient outcomes. Future research should explore long-term effects and scalability of the training program across different healthcare settings. Keywords: Dementia, Neuroplasticity, Healthcare Training, Cognitive Stimulation, Patient Outcomes

Funding: Private; COI: None

Poster Theme Group F2. Nonhuman

Poster # 105: THE EFFECT OF TRAUMATIC BRAIN INJURY ON ALZHEIMER'S DISEASE PROGRESSION IN TGF344 RAT MODEL

Presenting author: Dr. Lubna Mahmoud (UTMB)

Traumatic brain injury (TBI) is a risk factor for Alzheimer's disease (AD). However, the underlying mechanisms are still not completely understood. Our overall goal is to determine the effect of TBI on the onset and progression of AD pathology and memory dysfunction in the TgF344 AD rat model displaying the full spectrum of human AD pathology. We have previously shown increased accumulation of Aβ plaques in TgF344-AD rats subjected to TBI at an age when the AD pathology is still not developed. Here we aimed to study whether TBI also affects neurological and cognitive functions in TgF344-AD rats Methods: Female and male TgF344-AD rats (3 months old) were randomized to receive parasagittal fluid percussion injury (TBI), sham injury or no injury (naïve) (N=16 rats/group). Neurobehavioral tests (beam walk, beam balance, neuroscore) were performed on post-injury days 1-3 and 3 months after injury. The working memory paradigm of the water maze test was performed 3 months after injury. Results: TBI TgF344-AD rats performed significantly worst in the beam balance, beam walk and neuroscore tests on days 1-3 after injury when compared to sham and naïve groups (2-way ANOVA). Three months post-injury, TBI rats performed significanly worst in the neuroscore test (2-way ANOVA) and in the water maze test (RM one way ANOVA) when compared to sham and naïve groups. Conclusions: These results, and our previous data, show that TBI increases the severity of neurological and cognitive dysfunction and the accumulation of Aβ plaques in TgF344-AD rats.

Funding: NIH/NINDS 1R01NS128808; COI: None

Poster # 106: PERINEURONAL NETS (PNN) IN NON-TRADITIONAL ANIMAL MODELS: RELEVANCE TO BRAIN HEALTH AND ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Presenting author: Esperanza Isabel Alaniz, MS (UTRGV)

Background: Perineuronal nets (PNN) are extracellular molecules released by neurons and glial cells that modulate functions by encapsulating inhibitory cells and neurites. Animal research suggests PNNs are related to memory formation, retention, and extinction, making PNNs relevant for the study of Alzheimer's disease and related dementias (ADRD). According to the National Institutes of Health, Alzheimer Disease affects an estimated 6.9 million Americans as of 2022. Our goal is to quantify the change in number and area of PNNs in the gray short-tailed opossum (Monodelphis domestica) and Syrian hamster (Mesocricetus auratus), hypothesizing differences in the number and density of PNNs per brain area. Methods: One adult Monodelphis and 1 adult Mesocricetus were transcardially perfused with 4% paraformaldehyde, brains were collected and sliced at 35 µm. PNNs were identified using immunohistochemistry with Lectin. Image J software and a modified stereology method were used to quantify PNNs. Areas quantified included the Medial Preoptic Area (MPO), Primary Motor Cortex (M1), Primary Somatosensory cortex (S1), External Cortex of the Inferior colliculus (ECIC), Ventral Nucleus of the Lateral Lemniscus (VNLL), Ventrolateral Tegmental (VLT), Superior Colliculus (SC), and Substantia Nigra (SN). The area of 10 PNNs per brain region were compared between the species. Results Preliminary results revealed that the average area of PNNs in the SC was 301 um2 and 126 um2 for the SN, with 70 PNNs in the SC and 54 PNNs in the SN of the Monodelphis. In the Mesocricetus, the M1, S1, and ECIC had larger, more prominent cellular bodies and seemed to contain less branching networks that overlapped with other PNNs. In the MPO area in the forebrain, and VNLL and VLT areas in the midbrain, networking branches were more visible and similar to those of the Monodelphis in the SN, although the PNN areas were larger. Conclusion Our findings align with the literature regarding how PNNs are expressed. These findings may contribute to understanding the pathophysiology of AD/ADRD and we propose the Monodelphis and Mesocricetus as models for aging disorders. Henceforth, we will increase our sample size and use novel memory/behavioral paradigms to study memory and its relation to PNNs.

Funding: 1K01HL145339-01A1 (PI: Gil); COI: None

Poster # 107: ALZHEIMER'S DISEASE AND HIV-1 COMORBIDITY

Presenting author: Jose Rios, BS (UTRGV)

Alzheimer's disease (AD) is a devastating neurodegenerative disease characterized by a progressive impairment of cognitive functions. An estimated 39 million people were living with HIV. HIV-associated neurocognitive disorder (HAND) is a common primary neurological disorder associated with HIV infection of the central nervous system, despite successful virologic control with combination antiretroviral therapy (ART). A new challenge looms as individuals living with HIV age and reach age-related neurodegenerative diseases such as AD. Over 50% of the US HIV-positive population is aged 50 years or older, mainly due to the successful treatment regimens helping HIV-positive adults survive for decades with HIV. Evidence of AD-associated pathology in people living with HIV (PLWH) has been reported. There is concern that AD may become prevalent with an earlier onset of cognitive decline or accelerate the disease progression. Therefore, there is a pressing unmet need to study HIV and AD comorbidity. Our central hypothesis is that HIV promotes the onset of cognitive decline in AD mouse models. In this study, we used Tau transgenic mice as an AD model and the chimeric HIV (EcoHIV) model for HIV. We infected Tau with EcoHIV before the cognitive decline started and determined its effect on cognition decline using novel object recognition (NOR) to test cognitive decline. NOR task performance is quantified using the Recognition Index (RI) = Time(novel)/[time(novel) + time(familiar) x100. At two weeks post-EcoHIV of Tau and wild-type (WT) mice, no significant effect was found on RI ($p>0.05$). This indicates that EcoHIV is not able to promote a cognitive decline in the Tau mouse model after two weeks of post-EcoHIV infection in male and female mice. However, in five weeks of

post-EcoHIV infections, the RI of Tau male and female mice infected with EcoHIV was significantly lower than WT infected with EcoHIV ($p<0.05$), indicating that the EcoHIV produced cognitive decline in Tau mice. These data indicate that EcoHIV can promote the onset of cognitive decline in the Tau mice model and provide critical new data by revealing that HIV can interfere with the onset of AD-related cognitive decline. This work is supported by NIH grants (AG084378).

Funding: This work is supported by NIH grants (AG084378); COI: None

Poster # 108: THE INFLUENCE OF AGE AND BIOLOGICAL SEX ON SHORT-TERM MEMORY IN THE SYRIAN HAMSTER (MESOCRICETUS AURATUS)

Presenting author: Laura Emma Garcia (UTRGV)

Background: Aging plays an important role in cognitive function, memory, and mental health. As we age, some cognitive functions may change or become impaired. Aging is also a critical risk factor for Alzheimer's Disease and related dementias. For this reason, it is important to develop animal models to study the biological mechanism of aging and ADRD. The present study used the Syrian hamster (Mesocricetus auratus) as a model. Methods - Three cohorts of male (n=28) and female (n=36) subjects, including young (PND 161), middle (PND 354), and old aged (PND 602), were randomly chosen. Memory experiments were conducted using a 16-hole board apparatus. Holes were categorized as a zone to collect data. Zone 6, in the center, contained the stimulus odor for the control/treatment conditions during trial 2. A preexposure trial was completed for 3 minutes to collect data on zone preference and expose hamsters to the apparatus. Subjects were exposed to either clean or dirty bedding (corr. opposite-sex odors). Animals were placed in the hole board for five 3-minute trials; Preexposure, Treatment/Exposure, and Memory tests 1-3. The inter-trial intervals for tests 2 and 3 were 15 and 30 minutes, respectfully, from time of exposure to treatment/control. Results - Males had more overall entries into the stimulus zone (6) compared to females $F(1, 41) = 10.507$, $p=0.002$, there was no significant interaction between sex and trials $F(3,123) =1.648$, $p=0.182$. There was no sex difference in overall entries into a neutral zone (1) $F(1, 41) =0.012$, $p=0.914$. There was no significant interaction between sex and trials $F(3, 123) =0.603$, $p=0.614$. There was no significant interaction between age and trials; old cohort - $F(1,41) = .260$, $p=.613$; middle cohort - $F(1,41) = 1.526$, $p=.224$; young cohort - $F(1,41) = .143$, $p=.7.07$. Conclusion: Our results provide evidence that the Syrian hamster is a potential animal model for investigating sex differences/aging in learning and memory. Males approached a social stimulus more often than females, and the middle-aged cohort demonstrated a higher main effect during memory trials. These findings have implications for ADRD biological mechanisms research.

Funding: NIH Grant 5K01HL145339-03; COI: None

Poster # 109: DEVELOPING NOVEL THERAPEUTIC INHIBITOR PEPTIDES FOR ALZHEIMER AND RELATED DISEASES

Presenting author: Ayde Mendoza-Oliva, PhD (UTSW)

Background: Tauopathies such as Alzheimer's disease (AD) result from the abnormal assembly of tau protein into amyloid fibrils. Currently, there is no approved drug to stop tau aggregation. Our work focuses on developing peptide inhibitors that bind to growing tau fibrils, preventing their extension. A report from another group focused on short inhibitory peptides, but we found that these only functioned when pre-incubated with tau seed assemblies. We hypothesized that longer tau sequences would have higher binding energy and might more effectively cap fibril growth. Furthermore, we predicted that the strategic introduction of large, hydrophobic residues would disrupt protofilament extension without affecting initial binding to the fibril end. Methods: We used Rosetta, a structural prediction algorithm, to identify sites where tryptophan substitutions were predicted to meet these criteria. We tested a panel of

candidates and selected those that potently inhibited seeded aggregation by AD and corticobasal degeneration (CBD) homogenates in wild-type (WT) tau HEK biosensor cells. These cells expressed the repeat domain of tau fused to fluorescent proteins complementary for fluorescence resonance energy transfer (FRET). Results: We identified specific tau substitutions that blocked the seeding process and promoted the clearance of AD and CBD-seeded aggregates in cells. After selecting one of these inhibitors, we determined the minimum size required to retain its inhibitory effect in cells. This is crucial as we now aim to explore gene therapies or pharmacological treatments using this inhibitor. Currently, we are standardizing a WT tau neuronal biosensor derived from iPSCs to validate the inhibitory effect observed in HEK biosensors. Our goal is to elucidate the mechanism of action of this inhibitory peptide and assess its function in vivo Conclusion: By identifying key tau substitutions, we developed an inhibitor that blocks seeding and disrupts the maintenance of pathological aggregates in cells. Success in this effort could introduce a new treatment strategy for AD, related tauopathies, and potentially other amyloid protein assembly disorders.

Funding: TARCC Junior Investigator Research Grant; COI: None

Poster Theme Group G1. Epidemiology

Poster # 110: HOUSEHOLD ENVIRONMENTS AND COGNITIVE DECLINE AMONG MIDDLE-AGED AND OLDER ADULTS IN CHINA: EXPLORING GENDER, AGE, AND RESIDENTIAL VARIATIONS

Presenting author: Xi Pan, Ph.D. (TXST)

This study examined the relationship between household environments and trajectories of cognitive function among middle-aged and older adults in China and its urban/rural, gender, and age variations. We estimated multi-level linear growth curve models using a representative sample of 16,111 respondents aged 45 years and over from the China Health and Retirement Longitudinal Study (2011-2018). Older people who lived with a spouse, but not with children, and those with higher living expenditures, better housing quality, and indoor clean fuels for cooking had a slower cognitive decline. Living arrangement more strongly predicted men's cognitive decline, while living expenditure, solid fuel use, and housing quality significantly predicted only women's cognitive decline. Only for older adults and rural residents, those living alone had significantly faster cognitive decline than those living with a spouse only. These findings underscore the importance of improving the living conditions of older adults to help alleviate their cognitive decline.

Funding: None; COI: None

Poster # 111: INTERACTION BETWEEN ALCOHOL USE AND APOE E4 AND ITS ASSOCIATION WITH FOUR COGNITIVE DOMAINS AMONG AMERICAN OLDER ADULTS FROM DIVERSE

Presenting author: Edna Patricia Mendoza, M.S. (UNTHSC)

Background: Alzheimer's disease and related dementias pose significant public health challenges, with their complex etiology involving both genetic and environmental factors. Previous research suggests that genetics may influence the relationship between alcohol use and cognition, with the APOE ε4 allele potentially moderating this association. Light to moderate alcohol consumption has been found to have a protective effect on cognition, especially in individuals carrying the APOE ε4 allele, while heavy drinking is linked to poorer cognitive outcomes. This study examines the interaction between alcohol use and APOE ε4 allele on the associations with cognitive domains in diverse populations. Method: The study has

a sample size of 3,227 individuals aged 50+, comprising African Americans (n=770), Mexican Americans (n=1,231), and non-Hispanic Whites (n=1,226) from the Health and Aging Brain Study - Health Disparities. Linear regression was employed to explore the association between alcohol use and related risky drinking patterns, measured by the Alcohol Use Disorders Identification Test (AUDIT) total score, and four cognitive domains: episodic memory, executive function, processing speed, and language, measured by various standardized neuropsychological tests. The model also evaluated if and how such associations were moderated by the APOE ε4 allele. Analyses were stratified on AA, MA, NHW individuals. Results: Significant interaction effects on episodic memory and language domains were observed among MA and NHW individuals. For NHW, those with higher AUDIT scores who are carriers of two APOE ε4 alleles showed a decrease in episodic memory and language performance. In contrast, non-APOE ε4 carriers exhibited improvements in these domains with higher AUDIT scores. Among MA, the opposite pattern emerged: APOE ε4 carriers experienced improvements in episodic memory and language domains, while non-APOE ε4 carriers showed declines with higher AUDIT scores. No interaction effects were found significant among AA individuals. Conclusion: These findings suggest that the interaction between alcohol use and APOE ε4 status significantly influences cognitive outcomes differently across ethnic groups. This highlights the importance of considering ethnic/racial backgrounds when assessing the impact of lifestyle factors on cognitive health in older adults. Further research is needed to understand the mechanisms underlying these interactions to develop targeted interventions for at-risk populations.

Funding: None; COI: None

Poster # 112: CAIDE DEMENTIA SCORE ASSOCIATION WITH MRI MEASURES OF NEURODEGENERATION IN HISPANICS FROM THE HABS-HD COHORT.

Presenting author: Joshua Manning, BS (UNTHSC)

Background: The Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) score quantifies individual risk of developing dementia. In non-Hispanic White and African American cohorts, higher CAIDE scores have been associated with neurodegeneration in brain regions associated with Alzheimer's Disease (AD) and increased white matter hyperintensities (WMH) volume. These associations have not been adequately investigated in Hispanic populations. This study analyzes if CAIDE scores are associated with neurodegeneration in AD signature regions and WMH volume in Hispanics. Methods: Hispanic participants from the HABS-HD cohort (n=936) underwent an interview, cognitive testing, clinical labs, and a 3T MRI. CAIDE scores were used as a continuous and categorical variable (low-risk = CAIDE < 9; high-risk = CAIDE ⌑9). Baseline characteristics between low-risk and high-risk groups were compared with t tests for continuous variables and chi-squared tests for categorical variables. Using FreeSurfer, we segmented T1-weighted volume scans, derived right- and left-hippocampal volume, total hippocampal volume and mean cortical thickness in meta-regions of interest (ROIs) (right and left entorhinal cortex + fusiform, inferior temporal, and middle temporal cortex) and estimated intracranial volume (ICV). WMH volume was measured from FLAIR using the Statistical Parametric Mapping Lesion Segmentation Tool. Linear regression was used to find an association between CAIDE scores, cortical volume and WMH volume, adjusted for ICV, APOE4 status, and the MRI scanner. MRI volumes were log transformed due to non-normality. Statistical analyses were performed in SPSS software. Results:The high-risk group was significantly more female, less physically active, and had lower left and right hippocampal volume, meta-ROI volume and THV ($p < .001$). No significant difference was found for WMH volume ($p = 1.0$) or ICV ($p = 0.11$). Linear regression showed that CAIDE scores significantly predict left, right and total hippocampal volumes, and meta-ROI volumes ($p < .001$), but not WMH volume ($p= 0.91$). Conclusion: These results suggest that CAIDE scores can predict neurodegeneration in Hispanic populations. Neurodegeneration and cardiovascular risk assessments were largely developed using non-Hispanic White cohorts and have not been sufficiently vetted for use in Hispanic populations. Future studies may indicate the need for a risk score specifically developed for Hispanic populations.

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Poster # 113: SUBCLINICAL KIDNEY IMAGING ABNORMALITIES ON MRI ARE ASSOCIATED WITH POORER COGNITIVE FUNCTIONING IN COMMUNITY-BASED RACIALLY/ETHNICALLY DIVERSE OLDER ADULTS

Presenting author: Emily Powell BS (UT Austin)

Objective: Black and Latino older adults are disproportionately impacted by Alzheimer's disease and related dementias (ADRD) and have higher rates of kidney disease. Although ADRD has been tied to overt chronic kidney disease, limited research has been performed regarding the link between kidney health and cognition in older adults without kidney disease (eGFR > 60 ml/min/1.7m2). This study therefore used novel renal MRI markers to investigate and establish a link between latent kidney function and microstructural damage and cognition in a sample of racially/ethnically diverse older adults. Method: 19 predominantly female (84%), community-dwelling adults (age 67.2 ±7.4) were enrolled. Standard labs including serum creatinine-based eGFR (eGFR 81.4±13.1) were measured. Cognition was assessed using the California Verbal Learning Test- III (CVLT) and the Delis-Kaplan Executive Function System (DKEFS). Participants underwent MRI exams of the brain and kidneys (anatomical, diffusion, angiography, and phase contrast) at a 3T Siemens Vida scanner to assess total kidney volume, microstructure (FA, ADC) and kidney volume normalized renal artery blood flow (RBF, ml/min/100g). Result: Bivariate correlations revealed renal FA was significantly associated with performance on demographically adjusted measures of verbal learning (CVLT Total Trial 1-5 scaled score: r =. 49, p = .02), and executive functioning (Trails Number-Letter Switching scaled score: r = .48, p = .03; Category Switching scaled score: r =.47, p = .03). On bivariate regression analysis, only renal FA (B = 0.51, p = .03), but not brain FA (B = 0.23, p = .30) was a significant predictor of verbal learning. On univariate RBF was significantly associated with verbal recall (CVLT Short Delay Free Recall scaled score: r = .37, p = .05; CVLT Long Delay Free Recall scaled score: r = .49, p = .02). Kidney ADC and eGFR were not associated with cognition. Conclusion: Renal MRI markers of microstructural integrity and blood flow are linked with cognitive performance in older adults, with renal FA showing a stronger correlation with cognition than global brain FA. Results: suggest early detection efforts targeting subclinical kidney disease may reduce risk for cognitive decline in later life.

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Poster # 114: ASSESSING FOR HEALTHCARE DISPARITIES IN HISPANIC DEMENTIA PATIENTS WHO PRESENT TO A NEUROCOGNITIVE CLINIC

Presenting author: Gabriela Cruz, BS (UT Houston)

Background: It is estimated that 13% of Hispanics who are aged 65 years or older have AD/ADRD. When compared to non-Hispanic whites, Hispanics are also 1.5 times more likely to develop AD/ADRD and develop clinical symptoms earlier. Further, it has been shown that Hispanics have less health insurance coverage and healthcare utilization rates than non-Hispanic whites. The purpose of this cross-sectional study is to identify healthcare gaps in Hispanics who present for the first time to our neurocognitive clinic in order to develop a pilot outreach program. Methods: A chart review was conducted for new patients who attended our neurocognitive clinic between September 16th, 2024 and October 3rd, 2024. Variables obtained include patient race/ethnicity, Spanish speaking only, age, sex, referrals, MMSE/MOCA scores, anxiety/depression scores, dementia symptom onset, and medication status. Results: Of the 51 new

patients who were included, 17.6% identified as Hispanic, and 11.7% were Spanish speaking only. The mean age of Hispanics and non-Hispanics was 76 (9.8) and 73.7 (9). The mean MMSE or MOCA score for Hispanics and non-Hispanics was 15 (7.2) and 22.4 (5.6). Hispanic patients were referred from a PCP 66.6% and neurologist 11.1% of the time. Non-Hispanic patients were referred from a PCP 52.3% and neurologist 26.1% of the time. 44.4% of Hispanics and 30.9% of non-Hispanics were already on medication for dementia when presenting to the clinic. And 44.4% of Hispanics and 40.4% of non-Hispanics were either prescribed or had their dementia medication dose increased during the visit. Conclusion: Our study demonstrates that Hispanics were older, more progressed, and more likely to be referred from a PCP than non-Hispanics. Consistent with these findings, our pilot community outreach and education program is tailored to increase awareness of AD/ADRD symptoms, promote lifestyle modifications to manage risk factors for AD/ADRD, and stress the importance of consistent and timely medical care. Plans to expand the scope of this study and to identify strategies to address disparities are underway.

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Poster # 115: ASSOCIATION OF HEARING LOSS TO INCIDENT-ALL CAUSE DEMENTIA IN THE FRAMINGHAM HEART STUDY

Presenting author: Dr. Francis Kolo (DVM, PhD) (UTH San Antonio)

Background: Age-related hearing loss has been identified as a significant, potentially modifiable risk factor for cognitive impairment and dementia. Our study indicated that individuals with hearing loss experienced a higher cognitive decline rate than those with normal hearing. We found a correlation between elevated PTA thresholds and an increased incidence of dementia outcomes. Methods: Our study examined the link between hearing loss and dementia in 924 individuals from the Framingham Heart Study over 15 years. We defined HL as PTA (0.5-4.0 kHz) > 25 dB, in the better ear and we additionally considered PTA as a continuous variable (at each of .5, 1, 2, and 4 kHz frequencies). Continuous monitoring was used to identify dementia cases, with cognitive impairment assessments beginning with the Mini-Mental State Examination. Diagnoses were committee-based, utilizing medical records, neurologic evaluations, neuroimaging, and sometimes autopsy results. DSM-IV criteria were used for all-cause dementia, and NINCDS-ADRDA and NIA-AA criteria for Alzheimer's, with PET scans providing additional amyloid and tau data. Results: During the 15-year follow-up period, 113 participants were diagnosed with incident all-cause dementia. From the incident cases, 89 participants were diagnosed with Alzheimer's disease. We found a higher risk (90%) of developing all-cause dementia in the participants with any hearing loss (Hazard Ratio [HR]:1.90, 95% confidence interval [CI]: (1.09, 3.28), p=0.02), after 15 years of follow-up. Additionally, we observed a 74% risk of developing AD with any hearing loss, however, this was not statistically significant (HR: 1.74, 95%CI: (0.94, 3.23), p=0.08) Conclusions: Midlife hearing loss was associated with a doubling of dementia risk, suggesting a potential causal or biomarker role for midlife hearing loss in the prevention of late-life dementia

Funding: This work was supported by the Multidimensional Assessment of Brain Health (AG066524), P30AG066546 (South Texas Alzheimer's Disease Research Center) at San Antonio and FHS: AG054076, AG049607 grants; COI: None

Poster # 116: CHARACTERIZATION OF GUT MICROBIAL COMPOSITION IN ALZHEIMER'S DISEASE.

Presenting author: Jessica Valdez Ponce, MS, MB(ASCP) (UTH San Antonio)

Background: Despite scientific advances in the field of Alzheimer's disease (AD) and related dementias (ADRD), the causes are not completely understood. As the aging population grows, so does the need for early interventions. New evidence suggests microorganisms' dynamics contribute to health and disease, and the gut microbiome may play a role in ADRD. Recent studies indicate differences in gut microbiota composition between AD and non-AD patients, and a reduced abundance of Barnesiella intestinihominis has been related to cerebral small vessel disease. Although promising, studies are limited by a lack of larger samples, diversity, or microbial metabolomic output. This study aims to characterize the gut microbial composition and its metabolic yields in older adults to understand the interrelationships of the gut microbiota and their metabolic yields in ADRD. Methods: Participants were recruited from TARCC, MarkVCID, and the South Texas ADRC. The study was conducted remotely. Stool sample collection was performed using OMNIgene Gut, which allows for stabilization of the microbial DNA for gut microbiome sequencing, and the OMNImet GUT, which contains a preservative for quantitative fecal metabolomic profiling. Participants reported dietary intake via the Diet History Questionnaire III (DHQ-III) and received questionnaires on health status, medication use, and vascular risk factors. Subjective cognitive decline was assessed with the Everyday Cognition test (participant and informant). Baylor's Alkek Center for Metagenomics and Microbiome Research will perform whole-metagenome sequencing, and the metabolomic profiling will be performed by METABOLON. These will be completed at the end of 2024. Result: As of August 2024, n=161 participants were enrolled in the study. The sample includes participants aged 74+/- 8 years, 64% women, 66% self-identified as Hispanic, and 25% have a diagnosis of MCI/AD. Additional information, including neurological outcomes, will be obtained from the parent study. Preliminary analysis will relate bacterial abundance, diversity, and metabolomics to clinical diagnosis, neuropsychological domains, and neuroimaging markers. Conclusion: This study has the potential to identify gut microbial changes related to ADRD and related endophenotypes in a diverse sample, paving the way for larger efforts. The valuable data generated by this grant will be available to the scientific community.

Funding: TARCC grant 2020-58-81-CR; COI: None

Poster # 117: ENHANCED COGNITIVE RESERVE IN THE RIO GRANDE VALLEY LATINO POPULATION: THE IMPACT OF HIGH FAMILISM AND HEALTHY LIFESTYLE CHOICES

Presenting author: Chun Xu (MD, MSc, PhD) (UTRGV)

Background: Incidence of cognitive impairment has been increasing among U.S. Latinos. Age of onset is even earlier in this population. Better lifestyle and high level of familism have been suggested for some chronic conditions including cognitive impairment in non-Latino populations. However, very limited study was found in Latino population. Material and Methods: Self-reported Latino participants from communities in Brownsville, Harlingen, and Edinburg, Texas were recruited into this study. Information on demographics, medical and family history, lifestyle, cognitive impairment assessment using the Montreal Cognitive Assessment (MoCA), and familism variables were collected. Multivariable regression models were used to compare familism and other variables (social-demographic factors, lifestyle, MoCA scores) across groups. Results: We observed a high prevalence of Alzheimer's disease (AD) and MCI (60%) in the studied RGV Latino population. Higher levels of familism were negatively correlated with cognitive impairment (P=0.038), particularly with factor 4 using factor analysis. These associations remained significant after adjusting for gender and education using multiple logistic regression. In addition, The APOE ♏4 allele was significantly associated with AD (P<0.05). AD and MCI were significantly associated with low levels of physical activity, older age, and lower education. After adjustment, the association with low physical activity remained significant (P<0.05). Conclusions: Our study highlights a high prevalence of AD and MCI, along with their comorbidity with diabetes, hypertension in the RGV Latino population. This is the first research to identify a higher level of familism

as a protective factor, linked with cognitive reserve and diabetes prevention in RGV Latino community. Additionally, several risk factors, including older age, lower education levels, and reduced physical activity, were associated with AD and MCI, emphasizing the importance of targeted interventions. These findings demonstrate the importance of culturally sensitive strategies to improve health disparities and health outcomes in this underserved population. Further research is necessary to validate these findings and to develop effective interventions tailored to the unique needs of the RGV Latino community.

Funding: None; COI: None

Poster # 118: ENVIRONMENTAL POLLUTANTS AND COGNITIVE DECLINE: EXPLORING BIOCHEMICAL MARKERS IN OLDER ADULTS. PRELIMINARY REPORT

Presenting author: Juan Carlos Lopez-Alvarenga. M.D., D.Sc. (UTRGV)

Background: The neurocognitive decline is significant in public health among those over 65. Prior research indicates that environmental contaminants, particularly heavy metals like cadmium (Cd) and mercury (Hg), correlate with deleterious cognitive effects in adults. In addition, metabolites resulting from nicotine biotransformation, such as cotinine, have been associated with cognitive effects, but the findings are inconsistent. This study examines the relationship between biochemical traits and metabolites linked to environmental pollution and memory recall performance in a representative sample of the U.S. population with age >60 from the NHANES 2011-2012 dataset. Our main goal was to analyze the relationship between metabolites and memory recall assessed with animal fluency and the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) tests. Methods: We performed a cross-sectional analysis including 1,573 participants aged 60 and above (mean age 69.6 years, SD 6.7). The participants were 20% Hispanic, 51% non-Hispanic white, and 52% female. Obesity and overweight were found in 36% and 37% of the population, respectively. We correlated 147 metabolites with memory recall and transformed them into z-scores based on CERAD and animal fluency aggregated assessments. Using appropriate covariate adjustments, we used an elastic net regression technique to find metabolic components linked to memory recall. Results: Out of the 147 metabolites examined, 12 had a moderate association with memory recall (F1). The metabolites included essential biochemical markers such as urine albumin, creatinine, cholesterol, testosterone, globulin, albumin-to-creatinine ratio, hydroxy-cotinine, cotinine, estradiol, calcium, ALT, and glucose. Furthermore, the elastic net identified three metabolites-manganese, N-acetyl-S-(phenyl)-L-cysteine, and alpha-linoleic acid-were identified as correlating with memory recall performance. Conclusion: Our study suggests that many biochemical variables, including markers of environmental exposure, correlate with cognitive function in elderly individuals. These findings highlight the need for additional investigation to elucidate the processes behind the association between neurocognitive deterioration and environmental contaminants. Addressing these environmental factors may enhance tactics for avoiding or alleviating cognitive impairment in aging populations.

Funding: KL2 Gibss Institute San Antonio; COI: None

Poster # 119: CULTIVATING AWARENESS: AN OVERVIEW OF THE SOUTH TEXAS RIO GRANDE VALLEY ALZHEIMER'S DISEASE RESEARCH CENTER

Presenting author: Tania Vargas (UTRGV-SOM)

Background: Hispanics remain an under-studied population in dementia research which challenges the understanding of risk factors and experiences related to Alzheimer's disease and related disorders (ADRD). In this report, we aimed to characterize the demographic and health-related conditions associated with ADRD in the Rio Grande Valley (RGV) cohort of the South Texas Alzheimer's Research Center (STAC) study. Methods: We analyzed cross-sectional data of 110 participants and summarized

demographic (by age, sex, and education) and clinical (body mass index, blood pressure, diabetes, dyslipidemia, smoking, and history of cardiovascular diseases) data between Hispanics and non-Hispanics. Cognition was evaluated with the Montreal Cognitive Assessment (MOCA) and total scores were standardized based on age, sex, education and language of preference. Dementia was a Clinical Dementia Rating (CDR) ≥1.0; mild-cognitive impairment (MCI) was defined as a CDR equal to 0.05. Statistics included adjusted (by demographics) regression models examining the association of clinical variables with standardized -MOCA-score, MCI and dementia. Results Overall, the mean is 65.4±12.9y, 65.5% (n=72) are women, and 83 (75.4%) are Hispanics. A total of 20 (19.1%) participants had a CDR≥1.0, whereas 57 (24.2%) and 28 (26.6%) had a CDR of 0 and MCI; respectively. Compared to non-Hispanics, Hispanic participants had lower years of education (14 vs. 16y), had a higher prevalence of diabetes mellitus (14.8% vs. 34.9%; P=0.045) and dyslipidemia (62.6% vs. 37.0%; P=0.010). Regression models showed that each unit increase in office diastolic blood pressure (BP) was associated with lower standardized-MOCA (β-0.044; 95% confidence interval [CI], -0.085 to -0.004); this association remained significant only in Hispanics (β-0.050; 95% CI, -0.099 to -0.001). We also observed that a higher diastolic BP was associated with MCI and only in Hispanics (Odds ratios, 1.10; 95% CI, 1.01-1.20) and Dementia (OR, 1.11; 95% CI, 0.99-1.25). Conclusion: Our results emphasize the importance of early identification and management of clinical preventable risk factors to potentially mitigate cognitive impairment and dementia risk in Hispanics. The STAC cohort will provide valuable and unique information regarding disparities in dementia research in Hispanics, which can guide targeted interventions aimed at preserving cognitive health in aging populations from underrepresented groups.

Funding: 5P30AG066546-04; COI: None

Poster Theme Group G2. Health Services Research

Poster # 120: OFF-LABEL ANTIPSYCHOTIC USE AMONG PERSONS WITH ALZHEIMER'S DISEASE AND ALZHEIMER'S RELATED DEMENTIAS

Presenting author: Youngran Kim, PhD (UTHealth Houston)

Background: Neuropsychiatric symptoms (NPS) are present in the majority of patients with Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD). Although non-pharmacological treatments are recommended as first-line interventions, antipsychotics are frequently used off-label to manage disruptive behaviors in older adults with dementia. This study aims to examine patterns and trends in antipsychotic prescribing, focusing on different healthcare provider types. Methods: We identified Medicare beneficiaries aged 65 and older with AD/ADRD in Texas from 2017 to 2022, focusing on those enrolled in Part D prescription benefits. Individuals with bipolar disorder, schizophrenia, or other psychotic disorders were excluded to specifically examine potential off-label antipsychotic use. Prescription claims for antipsychotics, including original prescriptions and refills, were analyzed. The residential status of beneficiaries at the time the prescription was filled was categorized as home, assisted living facility, nursing facility, or other. Prescriber types were grouped into four categories: psychiatrists, primary care physicians, other specialty physicians, and advanced practice registered nurses/physician assistants (APRN/PAs). Results: The overall prevalence of off-label antipsychotic use was 12.7% between 2017 and 2022, ranging from 12.1% to 13.3% annually. Quetiapine was the most frequently prescribed antipsychotic (61.2%), followed by Risperidone (14.7%) and Olanzapine (9.6%). Only 6.3% of antipsychotic prescriptions were written by psychiatrists. The majority (56.8%) were written by primary care physicians, particularly for nursing facility residents (81.4%). Other specialty physicians accounted for 16.9% of antipsychotic prescriptions, with a higher percentage prescribed to individuals living at home (24.1%) compared to those in assisted living facilities (9.4%) or nursing facilities (8.1%). APRN/PAs were responsible for 19.6% of antipsychotic prescriptions, with a larger share dispensed to residents of assisted living facilities (36.2%). Over the study period, the proportion of prescriptions written by primary care physicians decreased from 65.3% to 48.4%, while

those by APRN/PAs more than doubled from 12.6% to 28.7%. Conclusion: Off-label antipsychotics were predominantly prescribed by primary care physicians; however, their share significantly decreased over time, while prescriptions written by APRN/PAs increased substantially. This shift may reflect the growing role of APRN/PAs in the primary care of individuals with dementia.

Funding: TARCC Junior Investigator Research Grant 2024; COI: None

Poster Theme Group G3. Prevention (nonpharmacological)

Poster # 121: SOCIAL-EMOTIONAL AND LIFESTYLE RISK FACTORS ASSOCIATED WITH SUBJECTIVE MEMORY PROBLEMS AMONG NON-HISPANIC BLACK AND HISPANIC MEN WITH CHRONIC CONDITIONS

Presenting author: Matthew Lee Smith, PhD, MPH, CHES (TAMU)

Background. Subjective memory problems are defined as worsening thinking abilities that include forgetfulness and difficulties with recall and decision making. While subjective memory problems may not be verifiable by common cognitive assessments, they may be indicative of cognitive declines and the earliest stages of mild cognitive impairment. Subjective memory problems are thought to be driven by disease states, unhealthy lifestyles, limited mental stimulation, and inadequate social engagement, but these relationships are understudied within communities of color. The purpose of this study was to identify social-emotional and lifestyle risk behaviors associated with subjective memory loss among community-dwelling non-Hispanic Black and Hispanic men ages ≥40 years with ≥1 chronic condition. Methods. Data were analyzed from a non-probabilistic national sample of 1,982 non-Hispanic Black (58.2%) and Hispanic (41.8%) men collected with an internet-delivered questionnaire. The binary dependent variable was whether the participant self-reported having memory problems (0=no, 1=yes). A binary logistic regression model with backward stepwise entry was fitted to identify factors associated with subjective memory problems. Primary covariates of interest included social-emotional (e.g., depression, social disconnection, stress) and lifestyle risk behaviors (e.g., physical activity, sleep, alcohol consumption, tobacco use, cannabis use). The model adjusted for sociodemographics and disease characteristics. Results. On average, participants were age 56.6 (±10.02) years [range 40 to 93 years] and reported 3.9 (±2.8) chronic conditions. Six percent (n=116) of participants self-reported subjective memory problems. Concerning social-emotional risk factors, feelings of social disconnectedness (OR=1.27, P=0.019) increased the odds of reporting subjective memory problems. Concerning lifestyle risk factors, men who reported sleep problems in the past week (OR=1.08, P=0.019) and cannabis use in the past month (OR=1.66, P=0.021) were more likely to report subjective memory problems than those who did not report sleep problems or cannabis use, respectively. Discussion. Findings reinforce the importance of social engagement and sleep hygiene for brain health. Although cannabis use may be helpful to manage chronic disease symptomatology, it's association with subjective memory problems requires additional research. Prevention efforts are needed to facilitate social connection and promote healthy lifestyle behaviors for chronic disease self-management among non-Hispanic Black and Hispanic men with chronic conditions.

Funding: Texas A&M Triads for Transformation (T3) initiative; COI: None

Poster # 122: RELATIONSHIPS BETWEEN VITAMIN B12 DEFICIENCY, GERIATRIC DEPRESSION, AND HISPANIC ETHNICITY: A PROJECT FRONTIER STUDY

Presenting author: Hamza Hashmi (Texas Tech HSC)

Background: Previously, we described health disparities in Vitamin D (VD) status, geriatric depression, and Hispanic ethnicity (HE) in an aging West Texas population from Project FRONTIER (Facing Rural Obstacles to Health Care Now Through Intervention, Education, and Research; PF). To further explore the impact of nutritional deficiencies on mood disorders in an aging population, we examined relationships between Vitamin B12 (VB12) status, geriatric depression, and HE. Methods: A cohort of 299 PF participants (mean age 62.6 ± 11.8 years old, 70.9% female, 40.5% HE) was used. We examined relationships between VB12 level, Geriatric Depression Scale (GDS) score, consensus depression diagnosis, and HE status. GDS total score ranged from 0 to 30 points and was further subcategorized into Dysphoria, Meaninglessness, Apathy, and Cognitive Impairment. Standard correlation and regression analyses were performed, and we utilized the Mann-Whitney U test to compare group differences between HE and non-HE subgroups. Results: A significant negative correlation was found between VB12 level and geriatric depression ($p = 0.019$). VB12 level was further significantly negatively correlated with Dysphoria ($p = 0.005$) and Meaninglessness ($p = 0.026$). Additionally, we found a significant negative association between VB12 level and depressive symptoms ($p = 0.0383$). In terms of ethnic disparities, HE participants had lower VB12 levels ($p = 0.0216$) and higher geriatric depression symptoms ($p = 0.0029$) compared to their non-HE counterparts. Conclusion: Our results suggest that VB12 deficiency is associated with geriatric depression in a rural underserved West Texas population, highlighting a potential link between nutritional status and chronic disease that may contribute to AD pathogenesis and/or progression. Of note, the GDS subfactors Dysphoria and Meaninglessness were significantly correlated with VD levels in our previous study. Given that depression is one of the many comorbid conditions that frequently occur with cognitive decline in the elderly, our study highlights a need for further research into the potential benefits of nutritional supplementation in older adults. Our study also identifies ethnic disparities in VB12 status and depressive symptoms in a largely underrepresented and understudied rural population. These disparities are important to consider when investigating areas to improve healthcare in West Texas.

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Poster # 123: EFFECTS OF TRANSCRANIAL INFRARED LASER STIMULATION ON BRAIN RHYTHMIC ELECTRICAL ACTIVITY AND COGNITIVE AGING

Presenting author: Jay Rose (UT Austin)

Background: The US population of older adults is expected to rapidly increase in the coming years and the prevalence of dementia will increase proportionally, putting an enormous strain on the health care system. The development of effective interventions that target cognitive aging and prevent or delay neurocognitive disorders is of great importance to public health. Transcranial Infrared Laser Stimulation (TILS) is a non-invasive intervention that has been found to modulate mitochondrial respiration and cerebrovascular functions in young and older human brains. In older adults, TILS is being investigated as an intervention against cognitive decline, and studies using both single and repeated weekly treatments have found improvements in some tasks of executive function, attention, and reaction time. Research on the electrophysiological effects of TILS is in early stages, with studies on young adults showing TILS increases alpha and beta power in frontal and parietal brain regions. This study seeks to fill the gap in the literature on the effects of TILS on electrophysiology and executive function in aged brains. Methods: In this placebo-controlled clinical trial, we examined neurocognitive effects of an 8-minute session of TILS (250 mW/cm2, 1064 nm) by recording older adults' brain electrophysiology using quantitative EEG before, during and after TILS or sham stimulation. To assess cognitive symptoms, participants completed three cognitive tests (Trails A and B, and digit symbol substitution) immediately before and after treatment. Results Results showed significantly increased alpha and beta power density in the TILS

group compared to sham placebo, with TILS effects lasting post-treatment. No significant group cognitive effect was found after a single TILS; however, a significant moderating effect of systolic blood pressure and LDL cholesterol on change in Trails B performance was found in the TILS group, indicating older people with worse cardiovascular measures improved less. Conclusions The results from this study help us to further understand the electrophysiological and cardiovascular mechanisms via which photobiomodulation results in cognitive enhancement and implicate that repeated sessions of TILS over multiple weeks may be needed before improvements in cognitive functioning can be seen in a cognitively older adult population.

Funding: Elhapa Foundation, Oskar Fischer Project; COI: None

Poster # 124: ORAL HEALTH BEHAVIORS, HEALTHCARE UTILIZATION, AND ALZHEIMER'S DISEASE: A CASE-CONTROL STUDY

Presenting author: Zarna Lalwani, BDS (UT Houston)

Background: Oral health challenges are prevalent among dementia patients, particularly those with Alzheimer's Disease (AD), due to cognitive decline and communication difficulties. Despite its impact, oral care for dementia patients often receives insufficient attention, leading to issues such as tooth decay and gum disease. This study investigates the oral health practices of participants at the UTHealth Neurocognitive Disorder Center (NCDC) to identify oral health behaviors and barriers to dental care. Additionally, it explores the association between AD, previous infections, inflammation, and dental issues with and without dental care. Methods: A survey was given to patients and caregivers during their visits at the NCDC that assessed AD risk factors, oral health practices, history of dental issues, utilization of dental services, and related barriers. Patients with a final diagnosis of AD were categorized as cases, while healthy individuals and those with other neurological conditions served as controls. Analysis was conducted using SPSS version 29.0. Preliminary statistical analyses were performed including chi square, fishers exact, and ANOVA. P-values of <0.05 were considered statistically significant. Results: Of the 124 participants, 52 (41.9%) were diagnosed with AD. Overall, 55.6% were female, 90.3% were Caucasian, and 93.5% were non-Hispanic. 81.4% of participants brushed their teeth at least twice a day, and 59% used dental floss to clean their teeth at least once a day. Statistically significant dental problems included those with a dental diagnosis (gum disease, mouth sores, cavities, mouth sores, halitosis), and symptoms of mouth/teeth/gum bleeding. Statistically significant healthcare utilization variables include those with dental symptoms and also had subsequent dental care, as well as the variables for dental cleanings, and crown/bridge procedures. Conclusion: Enhancing oral health practices in AD is crucial for overall well-being, reducing systemic complications, and possibly contributing to AD prevention through proactive oral hygiene and effective dental care utilization. Tailored interventions addressing barriers to care can mitigate oral health disparities and improve outcomes. Evaluating dental and oral health history could guide preventive strategies against AD, highlighting the essential role of comprehensive oral care in dementia management.

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Poster # 125: THE FEASIBILITY OF REMOTELY DELIVERED BLOOD FLOW RESTRICTION TRAINING IN CAREGIVERS OF ADULTS WITH ALZHEIMER DISEASE OR OTHER DEMENTIAS

Presenting author: Prof. Dr. Murat Karabulut, PhD (UTRGV)

Background: More than 16 million Americans provide more than 17 billion hours of unpaid care for adults with Alzheimer Disease (AD) or other dementias. Family caregivers are at increased risk for many health issues such as depression, anxiety, stroke, and cardiovascular disease. Caregivers of adults with AD or other dementias represent a section of the population with low levels of physical activity (PA) and they face challenges in finding ways to participate in PA. The purpose of this study was to evaluate the feasibility of remotely delivered blood flow restriction (BFR) training in caregivers of adults with AD or other dementias in the Lower Rio Grande Valley region. Methods: Caregivers of adults with AD or other dementias attended 30-minute group exercise sessions 2x/wk for 8 weeks. Exercise sessions were delivered in their homes on a tablet computer over video conferencing software. Ten caregivers of adults with AD or other dementias enrolled and nine of them completed the 8wk intervention. Results: Even though one subject was not able to complete the training due to the caretaker's health issues, the satisfaction rate of remotely delivered BFR training was still over 80%. Nine caregivers of adults with AD or other dementias attended 100% of the group exercise sessions. Retention rate and compliance with BFR training with video conferencing were 90% and 100%, respectively. The average Likert scale responses were 4.8 or higher for terms like "pleasurable", "pleasant", "enjoyed it", "refreshing", "felt good" and "strong sense of accomplishment". Conclusion: The findings indicate that BFR training delivered by group video conferencing is a viable and potentially effective method for promoting and enhancing PA among caregivers of adults with Alzheimer's or other dementias.

Funding: UTRGV FACULTY SEED RESEARCH GRANT; COI: None

Poster Theme Group H. Novel Statistical Methods

Poster # 126: MULTI-STUDY TRANSCRIPTOMIC ANALYSIS OF ALZHEIMER'S BRAIN TISSUE

Presenting author: Fernando Koiti Tsurukawa (Texas Tech HSC)

The majority of existing studies on Alzheimer's Disease (AD) transcriptomic data consider differential expression-based analysis, which are univariate by design and often miss the multivariate nature of genetic interactions, neglecting the potential importance of non-differentially expressed genes in classification tasks.Several existing studies report analyses of single datasets but results are often not replicated in other datasets. Our explorative study is based on three datasets, all of which are transcriptomic analyses sampled from postmortem human brain tissue, comparing neuropathologically diagnosed AD cases with control patients with normal cognitive and functional diagnostic.Our methods include feature selection to narrow down the set of potential genes followed by performance evaluation of gene subsets to identify genes associated with AD in a multivariate modeling approach.Through our methods, several genes are implicated in AD without being significantly differentially expressed, such as RLBP1, BRINP3, C17orf58, TRIB1 and SHISA4. Moreover, genes SCG3, CLK4, STARD7 and WNT7B are only able to obtain 70% accuracy scores in a univariate approach but display consistent performance when paired with other genes when evaluated across all three datasets.Our research suggests that both KCNIP1 and SLC38A2 may be involved in AD through a previously unexplored mechanism. KCNIP1, nominated in Agora in 2018, may be involved in AD pathophysiology through its interactions with calcium signaling pathways and trafficking of potassium channels, which are critical for maintaining neuronal function and integrity, while SLC38A2 encodes a sodium-coupled neutral amino acid transporter and is implicated in amino acid metabolism and neurotransmitter synthesis. We observe several epigenetic associations with AD. As far as we know, those genetic associations are not yet documented in publications. Our goal is to emphasize the integration of machine learning techniques beyond traditional gene differential expression analyses and report the caveats of using specific datasets from different studies. We designed a machine learning based pipeline and present the gained insights

from the multi-study multivariate analysis of three datasets along with the caveats of such analysis and the recommendations to follow.

Funding: None; COI: None

Poster # 127: CHARACTERIZATION AND COMPARISON OF ATROPHY AND HYPOMETABOLISM PATTERNS IN ALZHEIMER'S DISEASE

Presenting author: Annie Dang, MS (UTH San Antonio)

Background: The A/T/N (amyloid/tau/neurodegeneration) biomarker framework for Alzheimer's disease (AD) is used to create homogenous groups based on pathology. Presence of atrophy on structural MRI or hypometabolism on PET can be used to indicate positive "N", despite evidence to suggest that atrophy and hypometabolism in AD may be differently distributed. Here, we characterize the regional and network patterns of atrophy and hypometabolism in AD and compare their behavioral associations. Method: BrainMap databases (voxel-based morphometry - VBM; voxel-based physiology - VBP) were used to identify AD studies for meta-analysis. 412 VBM (atrophy) contrasts and 462 VBP (hypometabolic) contrasts were identified. Activation likelihood estimation was performed separately for VBM and VBP to identify cross-study convergence of brain alteration patterns. Mango was used to visualize results, quantify spatial overlap between VBM and VBP, and determine behavioral associations of altered regions. Meta-analytic connectivity modeling was used to build VBM and VBP network models. Results: VBM and VBP analysis showed vastly different patterns of change, with VBM changes predominantly affecting the bilateral parahippocampus, bilateral temporal gyrus, and insula, and VBP changes predominantly affecting the posterior cingulate and bilateral parietal lobes. Behavioral analysis showed that VBM regions loaded most strongly on explicit memory and emotion while VBP regions loaded mostly strongly on reasoning, explicit memory, and social cognition. Both VBM and VBP alterations occurred in a network-based pattern. Conclusion: VBM and VBP patterns of alteration appear distinct, aligning with different behavioral changes. This dissociation may well reflect distinct underlying neuropathologies. Ongoing work focuses on evaluating the ability of VBM and VBP network models to diagnose and detect disease progression along the AD continuum.

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Poster # 128: PSYCHOMETRIC DETERMINATION OF BIOMARKER RESILIENCE

Presenting author: Donald R. Royall, MD (UTH San Antonio)

Background: Many persons may be "resilient" to dementia-related biomarkers. We can now isolate the effects of individual biomarkers and identify resilient cases. Here we examine apolipoprotein E (APOE) ε4 allelic burden (APOE4). Methods: We used our previously validated "Line of Identity" (LOI) algorithm (Royall & Palmer, 2024). The δ "TARCC to ADNI" (dT2A) homolog was used. ε4 burden was coded as the number of alleles. "CR" captures all variance in dT2A residual to APOE4's effect. Results: N = 2215 /3497 (56.1%) were NHW and 1230 (35.2%) MA. Ethnicity significantly moderated APOE4's association with dT2A [by ΔCHI SQ (df 1) = 5.43, $p < 0.05$]. The association was weaker in MA ($r = 0.15$) than NHW ($r = 0.21$). So, we analyzed each separately. Figure 1 presents NHW LOI results. N = 1053 /2215 (47.54%) were afflicted. N = 1162 (52.46%) were resilient. Figure 2 presents MA results. N = 289 /1230 (23.50%) were afflicted. N = 940 (76.50%) were resilient. In both demographics, all ε4 carriers were afflicted, afflicted subjects had higher ε4 burdens: by ANOVA [in NHW: $F(1, 2213) = 8412.90$, $p < 0.001$; in MA: $F(1, 1228) = 7665.26$, $p < 0.001$], higher CDRSB at baseline: [in NHW: $F(1, 2207) = 172.76$, $p < 0.001$; in MA $F(1, 1228) = 31.25$, $p < 0.001$], and at 48 months [in NHW: $F(1, 1049) = 105.41$, $p < 0.001$; in MA: $F(1, 586) = 32.00$, $p < 0.001$]. Afflicted NHW had faster conversion to clinical "AD" over 48 months [Cox's $F(98, 102) = 2.52$, $p < 0.001$). Afflicted MA did not convert faster in

that interval [F (68, 26) = 1.51, p =0.12). In both demographics, affliction class predicted CDRSB independently of CR, survived adjustment for APOE2, but was fully attenuated by APOE4. Conclusions: MA are less strongly impacted by APOE, a higher fraction are resilient, and the afflicted class is not at greater risk for prospective conversion. Our classifiers are specific to ε4's effect, survive adjustment for competing dementia risks, and can be assigned by psychometric assessment alone. This raises a strong challenge to the A/T/N(X) diagnosis of "AD".

Funding: Julia and Van Buren Parr Professorship in Psychiatry; COI: The authors have disclosed their invention of δ, its homologs and orthologs to the University of Texas Health Science Center at San Antonio, which in turn holds a patent relating to the use of a non-overlapping set of δ-related blood-based biomarkers as predictors of Mild Cognitive Impairment (MCI) in non-Hispanic whites (U.S. Patent 13/943,654: "A Serum Biomarker Screen for the Diagnosis of Clinical and Pre-clinical Alzheimer's Disease in Non-Hispanic Populations"). There are no other patents, products in development or marketed products to declare.

Poster # 129: PYTHON-BASED MACHINE LEARNING FOR THREE-DIMENSIONAL HUMAN BRAIN MODEL SEGMENTATION AND ANALYSIS

Presenting author: Morgan Mekale Smith, MS (UTH San Antonio)

Background: Neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, cause atrophy of specific regions of the brain. Atrophy assessment in the clinical setting is accomplished via magnetic resonance imaging and other neuroimaging modalities. Post-mortem assessment of macroscopic features is standard in neuropathologic evaluations but is often semi-quantitative and subjective. Previously, we demonstrated three-dimensional (3D) models can be generated from autopsied brains for visualization and tissue processing. Python coding software, with many tools for object/data manipulation, visualization, and analysis, could serve as a potential research approach for automated analysis of neuroanatomical structures (by mesh segmentation) to quantitatively measure atrophy using machine learning (ML). Methods: Imported .obj files of 3D scanned brain tissue were visualized and manipulated via several Python modules. The .obj files of 3D brain models were simplified using mesh decimation via Python coding software. Based on readily identifiable gyri and sulci, 3D models were segmented and annotated. Segmented models were exported from Blender into a Python-based ML pipeline. Using manual mesh segmentation of healthy brain models, annotated 3D scanned mesh data was used to train various ML models. Trained models were then used to predict labels for unannotated data, and performance was assessed via evaluation metrics for each ML algorithm. Results: Through Python-based ML, we determined physical properties and completed texture mapping to segment three-dimensional models based on identifiable gyri and sulci. Our methods demonstrated random forest and decision tree classifiers generated predictions with the highest accuracy, average precision, and recall scores when assigning annotations to unannotated data. These algorithms also demonstrated the lowest hamming loss scores compared to the other evaluated ML models. Conclusion: Our findings provide support for the utilization of ML techniques to identify specific sub-regions and measure atrophy from 3D brain models. Future validation against other imaging modalities, like magnetic resonance imaging, is necessary to confirm model consistency of surface mesh segmentation. Our data suggests that ML techniques in conjunction with the Blender application can be utilized to accurately identify anatomical structures of the brain. We believe these tools have broad applicability in neuropathology practice, research, and education.

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