TEXAS Alzheimer's Research and Care Consortium

a Darrell K Royal Texas Alzheimer`s Initiative

TARCC 2023 Scientific Symposium – Advances in Alzheimer's Disease Science, Research, and Care

Thursday, January 26, 2023

8:00 am – 5:00 pm

AT&T Executive Education and Conference Center at UT Austin

1900 University Avenue

Austin, Texas 78705

http://www.txalzresearch.org/research/symposia/

Agenda

7:15 am — Breakfast Available
Ampitheater 204 (Level M2)

8:00 am — Welcome, State of the TARCC, and Speaker Introduction
Munro Cullum, PhD (UT Southwestern)
Ampitheater 204 (Level M2)
Facebook Live
YouTube Live

8:15 am — Introductory Address
Ronald C. Petersen, MD, PhD (Mayo Clinic)
Ampitheater 204 (Level M2)
Facebook Live
YouTube Live

8:45 am — Q&A

9:00 am — BREAK

9:30 am — Data Blitz from TARCC Scientists
Moderated by Rodrigo Morales, PhD (UT Health Houston)
Ampitheater 204 (Level M2)
Facebook Live
YouTube Live

Presenters:

Transcranial focused ultrasound: Next generation image guided therapies of the brain
Bhavya Shah, MD (UT Southwestern)

Sexually dimorphic blood-brain barrier responses in Alzheimer's disease
Elvis Cuevas, PhD (UT Medical Branch at Galveston)

Relationship between age-related cognitive impairment and circadian timekeeping
Karienn A. de Souza, PhD (Texas A&M University Health Science Center)

Sleep & cognition in Parkinson's disease with and without RBD
Vanessa Young, MS (UT Health San Antonio)

Understanding neurological diseases and aging
Celso Catumbela, MS (UT Health Houston)

Glial lipid droplet formation is neuroprotective and requires AD risk genes
Matthew Moulton, PhD (Baylor College of Medicine)

Clinical utility of cognitive variability in dementia evaluations
Bonnie M. Scott, PhD (UT Austin Dell Medical School)

The role of vitamin A in Alzheimer's disease
J. Josh Lawrence, PhD (Texas Tech University Health Sciences Center)

TARCC studies of AD-related peripheral markers of mitochondrial dysfunction
Nicole Phillips, PhD (UNT Health Science Center)

Stiff and disruptive brain vasculature in Alzheimer's disease: Impact of blood pressure dysregulations
Jesus Melgarejo, MD, PhD (UT Health Rio Grande Valley)

Alzheimer's disease and related disorders following traumatic brain injury
Christian Lobue, PhD (UT Southwestern)

RNA-binding proteins (RBPs) musashi and tau in Alzheimer's disease
Mauro Montalbano, PhD (UT Medical Branch at Galveston)

GamePlan4Care – Online translation of REACH II intervention
Jinmyoung Cho, PhD, FGSA (Texas A&M University Health Science Center)

Phenotypic analysis of PLCγ2 variants within novel late onset Alzheimer's disease mouse model
Juliet Garcia Rogers, BS (UT Health San Antonio)

Clinical research at UT Health Houston
David Hunter, MD (UT Health Houston)

Cerebello-hippocampal connectivity in mild cognitive impairment and mild dementia due to AD
Chi-Ying (Roy) Lin, MD (Baylor College of Medicine)

Closed loop brain stimulation as a potential intervention for cognitive decline
Minsu Zhang (UT Austin Dell Medical School)

Role of methylation in risk for cognitive impairment in Mexican Americans
Ann Abraham Daniel, MSc (UNT Health Science Center)

Neuropsychological profile of aging in mild intellectual disability: A case report
Lubnaa Abdullah, PsyD, ABPP (UT Health Rio Grande Valley)

11:30 am BREAK

12:00 pm Oskar Fischer Lecture Series Keynote Address: *Exploring genetic studies on human neurodegenerative diseases*
Professor Peter St. George-Hyslop, MD, FRCPC, FRS
University of Cambridge Institute for Medical Research
Zlotnic Family Ballroom 4-5-6 (Level M1 Lower)
Facebook Live
YouTube Live

2:00 pm Poster Session
Classrooms 103 and 104 (Level M1 Upper)

3:30 pm *Problem solving training (PST) for English- and Spanish-speaking care partners of adults with Alzheimer's and Alzheimer's-related dementia*
Shannon Juengst, PhD (TIRR Memorial Herman and UT Southwestern)
and Kristin Wilmoth, PhD (UT Southwestern)
Ampitheater 204 (Level M2)
Facebook Live
YouTube Live

4:15pm *Alzheimer's biomarkers among diverse populations in the HABS-HD study*
Sid O'Bryant, PhD (UNT Health Science Center)
Ampitheater 204 (Level M2)
Facebook Live
YouTube Live

4:45 pm Poster Winner Announcements and Closing Statements
Ampitheater 204 (Level M2)
Facebook Live
YouTube Live

Texas Council on Alzheimer's Disease and Related Disorders

Marc Diamond, M.D., Chair, *Dallas*

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Byron Cordes, LCSW, C-ASWCM, *San Antonio*

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Ana Guerrero Gore, *Galveston*

Char Hu, Ph.D., *Austin*

Mary Ellen Quiceno, M.D., *Dallas*

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Staff: Lynda Taylor, MSW, *Texas Department of State Health Services*

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TEXAS Alzheimer's Research and Care Consortium
a Darrell K Royal Texas Alzheimer`s Initiative

The Texas Alzheimer's Research and Care Consortium (TARCC) was established by state law in 1999 and formally funded with a $2 million state appropriation in 2005. Initially comprised of four statewide medical institutions with the goal of improving the diagnosis, treatment, and prevention of Alzheimer's disease (AD) and related disorders through collaborative efforts, the consortium has grown to a membership of ten medical institutions.

TARCC has greatly increased Texas' capacity to advance research and discovery to improve early diagnosis, treatment, and prevention of Alzheimer's disease and related brain disorders through the accumulative appropriation of more than $60 million from 2006 to 2023. This funding allows TARCC to:

- Enable cutting edge research to enhance our understanding, detection, surveillance, treatment, and prevention of Alzheimer's disease and related disorders.
- Promote a comprehensive model of care that embraces caregivers as well as patients across the state
- Establish interdisciplinary scientific collaborations among Texas medical research institutions and AD researchers to create valuable statewide resource for the study of Alzheimer's disease and related brain disorders
- Offer support and growth opportunities to junior investigators to build a core for Texas' scientific future

The state legislative investment in TARCC has resulted in the awarding of more than $110 million in additional outside federal and foundation grants since 2010, with projects addressing disease biomarkers, identification of disease characteristics in Hispanic populations, phenotyping dementia characteristics, studies of caregiver support, and proteomic studies of dementia.

Managed by a Scientific Director with the support of a member-based Steering Committee, the scientific and medical training the medical institutions represent set the research agenda for the state appropriated funds. TARCC is proud to partner with leading medical, scientific, and academic partners to move closer to improved progression and eventual eradication of neurodegenerative disease.

http://www.txalzresearch.org
http:///www.facebook.com/txalzresearch

TARCC MEMBER INSTITUTIONS

Baylor College of Medicine
Texas A&M University Health Science Center
Texas Tech University Health Sciences Center
University of North Texas Health Science Center
UT Austin Dell Medical School
UT Health Science Center at Houston
UT Health Science Center San Antonio
UT Medical Branch at Galveston
UT Rio Grande Valley School of Medicine
UT Southwestern Medical Center

Scientific Posters

Poster Theme Group A: Basic Science and Pathogenesis

A1. Development of New Models and Analysis Methods

Poster #1

DEVELOPMENT OF AN AGE-DEPENDENT COGNITIVE INDEX: RELATIONSHIP BETWEEN IMPAIRED LEARNING AND DISTURBANCES IN CIRCADIAN TIME KEEPING

Presenting author: Karienn de Souza, PhD (Research Assistant Professor, Texas A&M University)

Background: Preclinical quantitative models of cognitive performance are necessary for translation from basic research to clinical studies. In rodents, non-cognitive factors are a potential influence on testing outcome and high variability in behavior requires multiple time point testing for better assessment of performance in more sophisticated tests. Thus, these models have limited translational value as most human cognitive tests characterize cognition using single digit scales to distinguish between impaired and unimpaired function. To address these limitations, we developed a cognitive index for learning based on previously described scores for strategies used by mice to escape the Barnes maze. Methods: We compared the cognitive index and circadian patterns of light-dark entrainment in young (4-6mo), middle-aged (13-14mo) and aged (18-24mo) mice as cognitive changes during aging are often accompanied by pronounced changes in sleep-wake cycle. Following continuous analysis of circadian wheel-running activity (30-40d), the same cohorts of mice were tested in the Barnes maze. Results: Aged mice showed significant deficits in the learning and memory portions of the Barnes maze relative to young and middle-aged animals, and the cognitive index was positively correlated to the memory portion of the task (probe) in all groups. Significant age-related alterations in circadian entrainment of the activity rhythm were observed in the middle-aged and aged cohorts. In middle-aged mice, the delayed phase angle of entrainment and increased variability in the daily onsets of activity preceded learning and memory deficits observed in aged animals. Learning-impaired mice were distinguished by a positive relationship between the extent of Barnes-related cognitive impairment and variability in daily onsets of circadian activity. Conclusion: While it is unclear whether changes in the sleep-wake cycle or other circadian rhythms play a role in cognitive impairment during aging, our results suggest that circadian rhythm perturbations or misalignment may nevertheless provide an early predictor of age-related cognitive decline.

Funding Disclosure: Joe Marek 57 Alzheimer's Disease Research Fund

Poster Theme Group A: Basic Science and Pathogenesis

A1. Development of New Models and Analysis Methods

Poster #2

UNDERSTANDING AMYLOID BETA, TAU OLIGOMERS INTERACTIONS AT LOW-DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 1 (LRP1) USING FLOW CYTOMETRIC PROXIMITY LIGATION ASSAYS

Presenting author: Danielle Jamison, BS (Graduate Student, University of Texas Medical Branch at Galveston)

Background: Alzheimer's Disease (AD) is characterized by three neuropathological hallmarks: amyloid plaques, neurofibrillary tangles, and neurodegeneration (A+T+N+). Oligomers of the proteinaceous components of the plaques and tangles, amyloid beta (AβO) and tau (tauO), respectively, are recognized as the true toxic species of the disease. Postmortem identification has resulted in the discovery of individuals that are Non-Demented with Alzheimer's Neuropathology (NDAN; A+T+N-). These A+T+N- individuals are resilient to the cognitive damage caused by the oligomers, and thus, represent an incredibly useful tool in understanding the mechanism by which these oligomers enter the synapse to induce toxicity. Previous work from our lab has demonstrated that tauO can outcompete AβO from a protein substrate at the synapse. Low-density lipoprotein receptor-related protein 1 (LRP1) is a tau monomer transporter; therefore, it is logical to hypothesize that LRP1 is also acting as a transporter of tauO at the synapse. This work sought to ascertain the interaction of and differences between AβO and tauO at LRP1 in synaptosomes from human control, A+T+N+ patients, and A+T+N- individuals. Methods: We use flow cytometric proximity ligation assays to investigate exogenous AβO and tauO interaction with LRP1 in synaptosomes isolated from human control hippocampal tissues. The interaction of endogenous tau at LRP1 was examined in synaptosomes isolated from human control, A+T+N+ patients, and A+T+N- individuals' frontal cortex. Results: The presence of 0.5 μM exogenous tauO significantly decreases the interaction of 2.5 μM AβO at LRP1. Mean and median fluorescence data from PLA-positive synaptosomes is highest for A+T+N- individuals, followed by A+T+N+ patients, and lastly, lowest in control subjects. Conclusions: The above data suggests that tauO and AβO compete for the binding site of LRP1 and that generally, A+T+N- individuals' LRP1 engages endogenous tau more efficiently than both control and A+T+N+ patients, possibly leading to differences in uptake of endogenous tau and confirming distinct molecular characteristics between A+T+N+ patients and A+T+N- individuals. Future studies will use proteinase K treated synaptosomes to determine if the difference in engagement of tau at LRP1 may translate to differences either in rate and/or quantity of internalization in control, A+T+N+ patients, and A+T+N- individuals.

Funding Disclosure: UTMB Presidential Scholars Program; NIA R01AG073133

Poster Theme Group A: Basic Science and Pathogenesis

A1. Development of New Models and Analysis Methods

Poster #3

FLOW CYTOMETRY PROXIMITY LIGATION ASSAY: A METHOD TO STUDY HUMAN SYNAPTIC PROTEIN-PROTEIN INTERACTIONS

Presenting author: Michela Marcatti, PhD (Postdoctoral Fellow, University of Texas Medical Branch at Galveston)

Synaptic dysfunction often underscored by altered interaction of key synaptic protein, plays an important role in the pathophysiology of many neurological disorders, including Alzheimer's disease (AD). The limitations associated with employing fresh human brain tissues led to the development of methods to isolate detached-and-resealed synaptic terminals, known as synaptosomes, from cryopreserved human brain tissues. Synaptosomes have become important model systems for studying human synaptic functions, since they are more accessible than ex vivo brain slices or primary neuronal cultures. Many technical approaches have been used to study synaptosomes such as immunostaining, flow cytometry, and immunoprecipitation. Here, we established a method to detect protein-protein interactions (PPI) at the human synapses with high specificity and sensitivity by applying flow cytometry proximity ligation assay to synaptosomes (syn-FlowPLA). We established the optimal conditions for synaptosome fixation and permeabilization, and primary antibody concentrations, and then we performed syn-FlowPLA on synaptosomes isolated from human frontal cortex (FC) and hippocampus (HP). We detected the known synaptic interaction between the pre-synaptic N-methyl-D-aspartate glutamate receptors (NMDARs) and postsynaptic density protein 95 (PSD95), as well as the interaction between two proteins that are not expected to interact, such as the mitochondrial superoxide dismutase 2 (SOD2) and PSD95, as a negative control. Syn-FlowPLA provides rapid analyses with increasing target sensitivity, comparing with the other techniques used to study synaptosomes. Most importantly, Syn-FlowPLA allows to study PPI within the synaptic volume, excluding the other neuronal compartments. Our data encourage the possibility to use syn-FlowPLA as an important tool to identify synaptic interactors that can be useful for the study of AD and other neurodegenerative diseases characterized by synaptic dysfunction.

Funding Disclosure: NIH/NIA 1R01AG072883

Poster Theme Group A: Basic Science and Pathogenesis

A1. Development of New Models and Analysis Methods

Poster #4

PATTERN DYNAMICS OF BRAIN WAVES AFFECTED BY ALZHEIMER'S DISEASE

Presenting author: Clarissa Hoffman, BS (Graduate Student, UT Health Science Center Houston)

Background: We focus on understanding the impact of Alzheimer's Disease (AD) pathology at the neurocircuit level. The main physiological manifestation of circuit activity is the synchronized extracellular field, which gives rise to the recorded local field potential (LFP). These fields are widely studied using a variety of methods which primarily address time-localized (instantaneous) or the time-averaged characteristics of LFPs. Methods: We propose an alternative approach that focuses on the morphologies of waveforms-the patterns of the brain waves over finite timescales. Specifically, we use two independent methods for quantifying the structural regularity and irregularity of brain waves and correlate the resulting "stochasticity scores" with behavior. The first, quantifies the pattern's consistency with the underlying mean. The second, measures how "structured" or "orderly" (e.g., periodic-like or time-clustered) the pattern is. Results: Our previous work in wild-type mice revealed a curious interrelationship between morphologies of θ-waves, γ-waves, and sharp wave events (SWE) and the animal's speed and acceleration. We also noticed spatial clustering of waves with different morphology along the animal's trajectory, reminiscent of hippocampal place fields. Based on these observations, we studied circuit activity of hippocampal networks in AD brains and found a number of alterations in LFP rhythmicity. For example, there is a loss of distinct quiescence and movement states in the AD model, indicating an ambiguity of physiological context. Furthermore, the coupling of waveform patterns with speed is weaker in the θ and SWE in AD, yet, the strength of coupling between γ-patterns and speed is strengthened revealing potential θ-γ dysfunction. Additionally, the spatial selectivity of patterns is lost in AD, suggesting that damaged synaptic circuits compromise wave patterning and information exchange between brain regions. This failure to discriminate environmental position may be a potential cause of pattern dysfunction, and thus memory loss in AD. Conclusions: These differences in brain wave patterns can be used to better understand and potentially to detect circuit-level pathologies in AD brains. Overall, these results offer a novel perspective on studying the structure, the dynamics, and the functionality of the brain waves and will provide a deeper understanding of AD at a neurocircuit level.

Funding Disclosure: NIH R01AG074226, NIH R01NS110806, NSF 1901338, NIH R01NS097764

Poster Theme Group A: Basic Science and Pathogenesis

A1. Development of New Models and Analysis Methods

Poster #5

FK506 IMPROVES OBJECT RECOGNITION IN AGED, BUT NOT TGF344-AD RATS

Presenting author: John Broussard, PhD (Assistant Professor, UT Health Science Center Houston)

Background: Alzheimer's disease (AD) is the most prevalent age-related neurodegenerative disorder for which there is no cure. This has been disappointing because many new compounds and biologics show promise initially, only to fail in clinical trials or become restricted later. One reason for this setback is the insufficient understanding of the complex pathophysiology of AD, resulting in a lack of reliable biomarkers to measure disease progression. Another factor impeding successful translation from preclinical to clinical outcomes is that transgenic models of AD capture. Methods: We implanted 32-channel electrode arrays into the CA1 subfield of 18-month-old WT and TgF344-AD (n=6/group) rats. Fourteen days after implantation, we recorded the single unit and local field potential activity while rats performed an object location recognition task. Animals were given either i.p. injections of saline or 10 mg/kg of FK506, a calcineurin inhibitor (Tacrolimus), an immunosuppressant drug commonly used in organ transplant patients. Following injection, we recorded the training of animals to an identical object pair. One day later, we assessed spatial memory of animals by moving the object to a novel location, and recording the interaction of the animals with both objects. Results: Aged TgF344-AD rats exhibited impairments in object location recognition memory compared to their WT cohorts. Additionally, TgF344-AD rats exhibited impairments in the neurophysiological results from their hippocampal place cells, as evidenced by AD related changes in spatial information content, place cell stability, and in-field firing rates. The TgF344-AD animals also exhibited significantly weaker theta oscillations than WT rats. Administration of 10 mg/kg FK506 significantly improved memory performance in aged WT, but not TgF344-AD rats. Further, FK506 increased the in-field firing rate of place cells in WT animals, and object location recognition memory was enhanced. However, FK506 did not improve place cell properties or performance in TgF344-AD rats. Conclusion: These findings support the notion that altered electrophysiological properties of place cells may contribute to learning and memory deficits observed in AD. However, the effects of calcineurin inhibition through FK506 may not improve electrophysiological measures or behavioral outcomes during advanced stages of AD-related neurodegeneration.

Funding Disclosure: NS118329, NS109118

Poster Theme Group A: Basic Science and Pathogenesis

A1. Development of New Models and Analysis Methods

Poster #6

PHENOTYPIC ANALYSIS OF PLCΓ2 VARIANTS WITHIN NOVEL LATE ONSET ALZHEIMER'S DISEASE MOUSE MODEL

Presenting author: Juliet Garcia Rogers, BS (Graduate Student, UT Health Science Center San Antonio)

Background: Recent genetic studies have strongly linked PLCG2, the gene that codes for phospholipase C gamma 2 (PLCγ2), to Late-onset Alzheimer's Disease (LOAD). PLCG2 contains two polymorphisms associated with reduced (P522R) and increased (M28L) risk for LOAD, yet how PLCG2 contributes to LOAD pathogenesis and progression remains poorly understood. The aim of our study is to analyze how PLCγ2 variants modulate phenotypic traits such as memory, aging, and metabolism using a novel LOAD mouse model (LOAD2). Methods: Three groups of LOAD2 mice were used in this study expressing Wild Type (WT), P522R, or M28L PLCγ2. At 12 months of age, spatial learning and memory differences between mouse lines were measured using the Barnes maze. At 14 months of age, frailty, a clinical syndrome associated with the aging process and adverse outcomes, was assessed for each mouse line. Lastly, at 16.5 months of age, non-fasting blood glucose was measured for each mouse line. Results: The results from Barnes Maze indicated all mice learned how to escape the maze; however, M28L mice made significantly more errors during training and both M28L and P522R mice had significant deficits compared to controls during the memory-testing probe trial (Two-way ANOVA). Frailty testing revealed that in females only, M28L mice had higher Frailty Index scores than WT mice (One-way ANOVA; $p<0.032$) and P522R mice ($p=0.016$). Additionally, a notable decrease in whole body weight occurred in female mice expressing either M28L or P522R PLCγ2 compared to WT mice ($p=0.016$ and $p=0.020$). There were no significant weight differences in the males. Non-fasting blood glucose results indicated no major differences between PLCγ2 variants. Conclusion: In summary, mice expressing M28L and P522R PLCγ2 displayed deficits in learning and memory, as well as sex-specific increase in frailty, suggesting these variants may play a role in altering various phenotypes relevant to aging and LOAD. Future research on this cohort of mice will examine longitudinal changes in behavior and frailty in addition to analyzing brain pathology to further characterize the role of PLCγ2 variants in LOAD progression.

Funding Disclosure: NIH

Poster Theme Group A: Basic Science and Pathogenesis

A2. Genetics

Poster #7

MITOCHONDRIAL GENOME-WIDE ASSOCIATION STUDY INVESTIGATING INDICES OF MITOCHONDRIAL DYSFUNCTION IN MEXICAN AMERICANS COMPARED TO NON-HISPANIC WHITES

Presenting author: Danielle Reid, PhD (Postdoctoral Fellow, University of North Texas Health Science Center)

Background: Mexican Americans (MAs) are the fastest growing subpopulation within the Hispanic/Latinx population. Common risk factors for developing cognitive impairment (CI) in MAs include stroke, diabetes, obesity, and depression. Although the reason for the association between cognitive decline and the comorbidities remain unknown, the prevalence of these comorbid conditions varies greatly across different race/ethnic backgrounds. For example, diabetes is three times more prevalent among MAs relative to their non-Hispanic White (NHW) counterparts. Mitochondrial dysfunction is implicated in both AD and diabetes, and due to the prevalence of metabolic comorbidities in MAs, mitochondrial DNA (mtDNA) damage may be particularly important. Additionally, mtDNA itself can accumulate reactive oxygen species (ROS) damage and elicit pro-inflammatory processes when released, thus increasing one's risk for morbidity. Previously we reported MAs exhibited elevated levels of oxidative mtDNA damage compared to NHWs, which was associated with AD, sex, tobacco abuse, and education. In this study, we hypothesize that mitochondrial SNPs in the MA population will be associated with indices of mitochondrial dysfunction (e.g., mtDNA copy number [CN] and 8oxoG variants), especially those diagnosed with AD and/or diabetes, compared to NHWs. Methods: Whole mtDNA was amplified from both extracted buffy coat PBMCs and plasma from approximately 600 MA and NHW TARCC participants using REPLI-g® Human Mitochondrial DNA Kit and sequenced via Illumina NextSeq. We propose to perform a mitochondrial genome-wide association study to identify mitochondrial SNPs associated with mitochondrial oxidative damage and altered mtDNA CN in MAs compared to NHWs. Analyses will control for covariates such as, age, sex, education, diabetes, tobacco abuse, and depression. Results: By utilizing NGS technology we expect to investigate haplogroup effects, private mutations, and low frequency heteroplasmic SNPs to better understand population-specific risks for mitochondrial dysfunction in connection to complex age-related disease. Conclusion: This study will determine if mitochondrial dysfunction is a considerable clinical risk factor for AD and type-2 diabetes in MAs compared to NHWs. The results may also show sex differences potentially pointing to contributing mechanisms relating to disease development. Altogether the data could help identify targets for precision-based approaches to help reduce risk for disease.

Funding Disclosure: R25GM125587, U54MD006882

Poster Theme Group A: Basic Science and Pathogenesis

A2. Genetics

Poster #8

POPULATION-SPECIFIC MITOCHONDRIAL STRESS INDICATORS ASSOCIATED WITH ALZHEIMER'S DISEASE IN MEXICAN AMERICANS AND NON-HISPANIC WHITE TARCC PARTICIPANTS

Presenting author: Isabelle Gorham, BS (Graduate Student, University of North Texas Health Science Center)

TARCC-Based Project

Background: Alzheimer's disease (AD) is the most prevalent form of dementia and is one of the leading causes of death in America. Age is known to be the biggest risk factor for AD, and Mexican Americans are one of the fastest aging populations in America. Mitochondrial stress and dysfunction are key players in the progression of AD and are also known to be impacted by lifestyle and environmental exposures/stressors. Mitochondrial dysfunction can cause the release of mitochondrial DNA (mtDNA) extracellularly, which can be detected in the peripheral blood (i.e., plasma). This project aims to identify population-specific differences in mitochondrial stress and dysfunction detectable in the blood.
Methods: DNA was extracted from 200uL of participant plasma and buffy coat using the Mag-Bind® Blood & Tissue DNA HDQ 96 kit (Omega Bio-tek) according to the manufacturer's specifications. mtDNA and nuDNA copy number was assessed through absolute quantitative PCR (qPCR), targeting the mitochondrial minor arc (MinArc), and the nuclear-encoded beta-2-microglobulin gene (B2M). Data was stratified by population and sample type and linear regressions were performed to adjust for batch effects and identify factors that may influence this phenotype of mitochondrial dysfunction. Results: Population-specific differences in factors contributing to the mtDNA phenotype were observed at the $p < 0.05$ level. In the Mexican American cohort, there was a significant relationship between cellular mtDNA:nuDNA ratio (quantified from buffy coat) and BMI, Clinical Dementia Rating Sum of Boxes score (CDRSum), and education. Further, there was a relationship between cell-free mtDNA copy number (quantified from participant plasma) and education, and CDRSum. In the non-Hispanic cohort, there was a significant relationship between cellular mtDNA:nuDNA ratio (from buffy coat) and sex, age, and CDRSum. No predictors of interest were associated with cell-free mtDNA in the non-Hispanic White cohort.
Conclusions: Evidence supports that there are population-based differences in which factors may be predictive of this blood-based phenotype of mitochondrial dysfunction. Mexican American populations seem to be more heavily influenced by environmental factors (BMI and education) whereas the Non-Hispanic population seems to be more heavily influenced by non-environmental factors (sex and age).

Funding Disclosure: TARCC

Poster Theme Group A: Basic Science and Pathogenesis

A2. Genetics

Poster #9

DIFFERENTIAL GENE EXPRESSION SIGNATURES IN PERIPHERAL BLOOD OF COGNITIVELY IMPAIRED MEXICAN AMERICANS

Presenting author: Talisa Silzer, PhD (Medical Communications Associate, University of North Texas Health Science Center)

TARCC-Based Project

Background. Mexican Americans (MAs) are one of the fastest growing aging sub-populations in the United States. They are known to experience earlier and more severe forms of cognitive impairment and may suffer from distinct forms of Alzheimer's disease (AD) that are more metabolically driven. The literature concerning AD-related disparities in MAs is sparse. Additionally, few groups have examined AD-related gene expression alterations, particularly not in peripheral blood. Methods. Here we conducted differential gene expression analysis using RNA-seq data from peripheral blood of aging MAs (N=48) enrolled in the Health and Aging Brain Study - Health Disparities (HABS-HD) cohort. Results. We identified 30 significantly differentially expressed transcripts mapping to 29 unique genes; 15 genes were down-regulated and 14 were up-regulated. Gene enrichment analyses point to biological processes such as synaptic dysfunction, inflammation, cell development/differentiation, cell death, epigenetic modifications, and RNA processing. Several of the biological processes enriched among patients with mild cognitive impairment (MCI) overlap with known pathological features of AD. As such, gene expression signatures in peripheral blood may serve utility in identification of therapeutic targets or key processes contributing to AD pathology. Future Directions. Future studies will be focused on replicating these findings in a larger Mexican American cohort and comparing differentially expressed genes to other ethnic populations such as Non-Hispanic Whites.

Funding Disclosure: TARCC 2020 (Phillips), TARCC 2018 (Barber), R01AG070862 (Barber), R01AG054073 (O'Bryant), R01AG058533 (O'Bryant), P41EB015922 (O'Bryant), U19AG078109 (O'Bryant)

Poster Theme Group A: Basic Science and Pathogenesis

A2. Genetics

Poster #10

FREQUENCIES OF THE TOP ALZHEIMER'S DISEASE RISK-CONFERRING ALLELES DIFFER AMONG MEXICAN AMERICANS AND NON-HISPANIC WHITES IN THE HABS-HD COHORT

Presenting author: Mohammad Housini, MS (Graduate Student, University of North Texas Health Science Center)

Background: Alzheimer's Disease (AD) and related dementias are a significant burden on our aging population. Here we evaluate the top 10 AD risk alleles previously reported in the literature (Kunkle et al., 2019) among Mexican Americans and non-Hispanic whites enrolled in the Health & Aging Brain Study - Health Disparities (HABS-HD) cohort to determine whether allele frequencies vary based on ethnicity. Methods: DNA was extracted from buffy coat samples (n = 1635) on the Hamilton robotic system with the Mag-Bind Blood & Tissue DNA HDQ 96 Kit. Genotyping was performed per manufacturer's protocol using the Illumina Infinium Global Screening Array (GSA) and analyzed with Genome Studio 2.0. Samples with call rates less than 98% were repeated or excluded. Allele and genotype frequencies of the top ten AD risk alleles from Kunkle et al. (2019) were calculated using standard statistics in the HABS-HD cohort. Result: Our data suggest that allele and genotype frequencies differ significantly between Mexican Americans and Non-Hispanic Whites for eight of the ten SNPs assessed. Conclusion: Given the high heritability of AD, significant differences in the frequencies of the most important AD SNPs between MA and NHW participants points to underlying etiological differences across ethnic and racial groups. We plan to expand and continue this work in African Americans and further elaborate on these differences to promote ethnicity targeted diagnostics and help reduce health disparities in medicine and science.

Funding Disclosure: R01AG054073, R01AG058533, R01AG070862, T32AG020494, U19AG078109, and partially grant #RP17301 from Cancer Prevention and Research Institute of Texas (CPRIT)

Poster Theme Group A: Basic Science and Pathogenesis

A3. Human Neuropathology

Poster #11

ASSESSMENT OF TAU PHOSPHORYLATION AND B-AMYLOID PATHOLOGY IN HUMAN FOCAL CORTICAL DYSPLASIA WITH DRUG-RESISTANT EPILEPSY

Presenting author: Joaquin Lugo, PhD (Associate Professor, Baylor University)

Background: Epilepsy can be comorbid with cognitive impairments and behavioral problems. These commodities can be aggravated by drug-resistant seizures, which affect 30-40% of patients with epilepsy. In some types of refractory epilepsies, such as temporal lobe epilepsy (TLE) or focal cortical dysplasia (FCD) surgical resection of the seizure focus can reduce or eliminate the seizure burden. Histological examination of brain biopsies from these epilepsies have shown the presence of β-amyloid (Aβ) plaques/deposits or hyperphosphorylation of the protein tau (p-tau), and the p-tau aggregates neuropil threads (NT) or neurofibrillary tangles (NFT). These are neuropathological hallmarks of Alzheimer's disease (AD), which could represent a possible mechanism underlying the cognitive deficits associated with epilepsy. Methods: To further determine whether AD-like pathology is a common feature of drug-resistant epilepsy we used immunohistochemistry to identify p-tau and Aβ deposits in cortical biopsies from patients with FCD. Results: Our findings further confirmed the existence of p-tau related NT and NFT pathology as well as some Aβ deposits in FCD cases with drug-resistant seizures. Robust p-tau immunoreactivity was found mostly in the brain biopsies from older patients while Aβ deposits were found in samples from all ages. Conclusions: Overall, our findings support that AD-like pathology occurs in human epilepsy and suggest that these Aβ and p-tau deposits may contribute to the cognitive comorbidities in cases with severe epilepsy. However, mechanistic studies are required to determine if this AD-like pathology results in memory deficits in experimental models of epilepsy.

Funding Disclosure: None

Poster Theme Group A: Basic Science and Pathogenesis

A3. Human Neuropathology

Poster #12

VITAMIN A DEFICIENCY DRIVES ALZHEIMER'S DISEASE PROGRESSION THROUGH DYSREGULATION OF GLUCOCORTICOID SIGNALING

Presenting author: J. Josh Lawrence, PhD (Associate Professor, Texas Tech University Health Sciences Center)

Background: Glucocorticoids (GCs) play a key role in cellular activity, stress, and immunity. GCs bind mineralocorticoid and GC receptors centrally and play a significant role in hippocampal-dependent learning. There is a strong connection between dysregulation of the hippocampal-pituitary-adrenal (HPA) axis, GC overexposure, increased serum levels of pro-inflammatory cytokines, and the pathogenesis of Alzheimer's disease (AD) and major depressive disorder (MDD). There is also increasing evidence linking Vitamin A (VA) deficiency in AD. All-trans retinoic acid (ATRA) is the bioactive derivative of VA. Previous studies in rats have shown that VA deficiency leads to an increase in serum GC levels but all-trans retinoic acid (ATRA) treatment can reduce these levels to baseline. Relatedly, previous studies suggest that VA improves symptoms of AD and its progression in vitro and in vivo. Finally, VA deficiency impairs hippocampal-dependent learning. In this study, we investigated the most dysregulated ATRA-sensitive pathways in the human hippocampus in AD. Methods: We performed an in silico experiment via Ingenuity Pathway Analysis (IPA) from the publicly available human AD hippocampal transcriptomic data generated by van Rooij and colleagues (2019) using 673 ATRA-sensitive genes from the literature. Results: The top ATRA-sensitive canonical pathway was GC receptor signaling (p=4.86E-34). The most dysregulated ATRA-sensitive gene was UQCRC2 (p=6.51E-16), which was downregulated within mitochondria. A total of 36 genes, including NDUFA genes, in the Mitochondrial Dysfunction pathway were dysregulated (p=2.27E-21), further linking ATRA deficiency to mitochondrial dysregulation in human AD. Our analysis also reveals that the neuroinflammatory signaling pathway was also a statistically significant canonical pathway (p=1.58E-22) that is associated with immune response genes and cytokines as well as their transcription factor (NF-kB1), all of which are activated in a chronic stress response, AD, and MDD. Finally, our IPA analysis demonstrated that the top Upstream Regulator was tretinoin (ATRA itself), validating the ATRA sensitivity of our enriched gene set and the regulation of the GR pathway. Conclusion: Our study provides a wealth of new knowledge regarding interactions between ATRA availability, ATRA-sensitive genes, GR signaling, and mitochondrial function. Understanding these pathways can help identify novel therapeutic strategies for AD.

Funding Disclosure: NIH/NIA R01 AG071859-01A1

Poster Theme Group A: Basic Science and Pathogenesis

A3. Human Neuropathology

Poster #13

ALZHEIMER'S DISEASE CIRCULATING-EXOSOMES ARE PROINFLAMMATORY IN RECIPIENT BRAIN MICROVASCULAR ENDOTHELIAL CELL IN AN RNA-CARGO-DEPENDENT MANNER

Presenting author: Jiani Bei, MS (Research Associate, University of Texas Medical Branch at Galveston)

Dysregulation of the neurovascular unit and blood-brain barrier (BBB) dysfunction are critical pathophysiological events in neurodegenerative diseases, including Alzheimer's disease AD. Loss of the barrier properties is a major component of the pathology and progression of AD. Breakdown of the BBB in AD has been documented by multiple independent postmortem human studies. Furthermore, in early-stage AD patients treated with amyloid-modifying therapies, amyloid related imaging abnormalities (ARIA)-vasogenic edema and ARIA-microhemorrhage have been identified and both are related to BBB dysfunction. BBB dysfunction was proposed as an early biomarker of human cognitive dysfunction independent of Tau- and β-amyloid. Mounting evidence show that apolipoprotein E (apoE) encoded by the APOE gene plays critical roles in regulation of the neurovascular unit and BBB. APOE4 accelerates BBB dysfunction. Extracellular vesicle (EVs) transfer functional mediators to neighboring and distant recipient cells. There has been increased interest in studying the potential of exosomes (Exos) in AD, mainly focusing on their protein contents, i.e. Tau- and β-amyloid (Aβ)-containing Exos. We purified circulating Exos from severe AD patient (AD-Exos) and Ctl (Ctl-Exos) sera using size-exclusion chromatography (SEC), which avoids aggregation and decreased integrity of Exos, compared with ultracentrifugation. EV-specific assays validated Exo particle size (50-150 nm) and qualities, exclusively from synaptosome-sized particle (0.6 μm to 1.6 μm). Exo size and morphology were not significantly altered between groups. Exosomal particle counts were measured using our nanoparticle tracking analysis system, which showed that Exo counts are not statistically different between groups. Next, we treated human BMECs with AD-Exos vs. Ctl-Exos for 72 hrs prior to measuring the transendothelial electrical resistance, fluidic force microscopy-probed lateral binding force between living BMECs, and immunofluorescence staining of major TJ and AJ proteins. We found that AD-Exos downregulate paracellular expressions of TJ Zo-1 and AJ VE-cad and attenuated the recipient BMECs barrier function. To identify the functional cargos in AD-Exos, we employed saponin-assisted active permeabilization to pretreat exosomal cargos with RNase. Such pretreatment mitigated the detrimental effects of AD-Exos on recipient BMECs barrier function. Conclusion: AD-Exos weaken the BBB in an exosomal RNA cargo-dependent manner.

Funding Disclosure: R21AI154211, R21AG066060, John Sealy Chair Alzheimer’s Disease

Poster Theme Group A: Basic Science and Pathogenesis

A3. Human Neuropathology

Poster #14

REARRANGEMENT OF AMPA RECEPTORS IN NON-DEMENTED WITH HIGH PATHOLOGY INDIVIDUALS

Presenting author: Berenice Adriana Gutierrez PhD, (Postdoctoral Fellow, University of Texas Medical Branch at Galveston)

Background: Alzheimer's disease (AD) is the most common form of dementia in the ageing population. The diagnosis is made at the clinical level since the definitive diagnosis requires a brain biopsy to confirm the presence of amyloid beta and hyperphosphorylated tau protein aggregates. Stunningly, histopathologic findings of AD have been found on postmortem brain tissue of individuals who did not develop dementia throughout their lifetime - non-demented with high pathology (NDAN). We propose that postsynaptic receptors in NDAN individuals, such as AMPA receptors, have a different structure and function that confers them protection from the effects of amyloid beta and possibly tau oligomers (e.g., disruption of calcium homeostasis) that lead to the clinical symptoms of dementia. Method: To determine whether there is a difference in the structure and function of AMPA receptors, we analyzed the proteomic and transcriptomic data of 30 individuals: 7 controls (absence of AD histopathologic findings; 3 males and 4 females), 15 AD (7 males and 8 females), and 8 NDAN (2 males and 6 females). From the three groups, we obtained the fractional contribution of each AMPA receptor subunit, performed correlation analyses within the subunits to predict the stoichiometry of the receptor, and ran a gene ontology analysis from the most significant genes that interacted with the AMPAR subunits. Results: The proteomic and transcriptomic data showed changes in the expression, organization, and synaptic remodeling of AMPA receptors in control, AD and NDAN individuals. AMPA receptors in the three groups participate in neuronal and synaptic signaling pathways, however NDAN individuals additionally show a very robust participation in cellular respiration pathways, indicating that there is a strong compensatory process and better integration of synaptic function and mitochondrial energy management in these individuals. Conclusion: We found differences at the structural and functional level of postsynaptic receptors in control, AD, and NDAN individuals. The AMPA receptor remodeling and compensatory cellular respiratory pathways in NDAN individuals may contribute to block the disruption of intracellular calcium homeostasis and synaptic transmission produced by amyloid beta oligomers; all these preventing NDAN individuals from developing cognitive impairment.

Funding Disclosure: R01AG070255

Poster Theme Group A: Basic Science and Pathogenesis

A3. Human Neuropathology

Poster #15

AUTOPHAGIC RESPONSE TO ALZHEIMER'S DISEASE BIOMARKERS IN DEMENTED AND COGNITIVE INTACT INDIVIDUALS WITH AD NEUROPATHOLOGY.

Presenting author: Pietro Scaduto, PhD (Postdoctoral Fellow, University of Texas Medical Branch at Galveston)

Sporadic Alzheimer disease (AD) is by far the most common form of dementia characterized by abnormal accumulation of toxic oligomers that leads to formation of plaques, neurofibrillary tangles, and ultimately neuronal deficit and loss of cognitive ability of the subject. In recent years, several reports have described rare individuals, referred to "Non-Demented with Alzheimer's Neuropathology" (NDAN), showing severe neuropathological signs, though remaining cognitive intact. The existence of these unusual cases suggests that there is a natural way for the human brain to resist (or significantly delay) the neurotoxic events that normally lead to cognitive impairment in AD. We hypothesized that one of those potential protective mechanism could be the enhancing autophagical efficency. Autophagy is an intracellular system designed for the degradation of long-lived proteins and organelles in lysosomes, and it has been suggested that its alterations may be involved in abnormal accumulation of toxic proteins. Autophagy activity naturally reduces with age, that is the major risk factor of AD. In individuals with AD pathology this reduction is exacerbated and significantly reduced compared to non-AD age matched individuals. Here we analyzed autophagic levels of mRNA from hippocampus cognitively normal, AD, NDAN donors. Using available online RNA-sequencing dataset we separate CTRL (N=28), AD (N=29), and NDAN (N=14) based on braak stages and cognitive test. We first perform Pearson correlation analysis of those autophagy and mitophagy genes with levels of AD biomarkers available for this cohort: immunohistochemistry of Aβ and pTau, and ratios between most toxic with non-toxic biomarkers species Aβ42/Aβ40 and pTau/Tau. Then we compare the differences between AD and NDAN in terms of difference in absolute correlation from CTRL. We found that autophagy genes from NDAN subjects responded more to the AD pathology compare to AD subjects, significantly to pTau-ihc and Aβ42/Aβ40, and a similar trend to pTau/Tau. This evidence suggests that proper response of key mRNAs autophagy elements may contribute to preservation of cognitive integrity in the face of profuse AD neuropathology as observed in NDAN individuals.

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Poster Theme Group A: Basic Science and Pathogenesis

A3. Human Neuropathology

Poster #16

IDENTIFICATION OF A-2,6 SIALYLATION IN HUMAN NEURODEGENERATION AND MOUSE MODELS OF ALZHEIMER'S DISEASE

Presenting author: Caitlyn Fastenau, BS (Graduate Student, UT Health Science Center San Antonio)

Background: Research shows evidence of increased sialylation in AD tissue homogenate, yet we lack an understanding of spatial distribution and cell specificity in the brain tissue microenvironment. Sialylation is the glycolytic linkage of sialic acid (SA) bonds onto glycoconjugates. According to the Religious Orders Study and Memory Aging Project (ROSMAP) dataset, AD patients have increased RNA expression of sialyltransferase ST6Gal1, enzyme that transfers α-2,6 SA onto terminal sugars, and neuraminidase-1, enzyme that cleaves α-2,6 SA. Increased expression is correlated with neuritic plaques. Yet, it is unclear how changes in SA levels and spatial distribution contributes to AD progression. Thus, our first goal was to better understand sialylation patterns relative to amyloid pathology by investigating microglia due to partial regulation by sialylation. Our previous work focused on the 5XFAD mouse model of amyloid-beta (Aβ) pathology and demonstrated significantly increased levels of α-2,6 sialylation in 5XFAD compared to WT. While sialylation patterns were strongest in the plaque microenvironment, we concluded increased sialylation was more pronounced on microglia compared Aβ plaques. To further explore AD, we investigated sialylation patterns with respect to tau pathology. Methods: In this study, we utilized brain tissue from the 5XFAD mouse model, rTg4510 mouse model of tau pathology, and post-mortem human brain tissue. A plant-derived lectin was used to recognize α-2,6 SA bonds. Aβ plaques, neurofibrillary tangles, microglia, and α-2,6 SA were histologically labelled in cortical brain tissue and imaged with confocal microscopy for quantification. Results: Qualitatively, α-2,6 SA levels displayed a microglial-like phenotype in 5XFAD cortical brain tissue. Similarly, the rTg4510 and human AD case had the same α-2,6 sialylation patterns resembling reactive microglia. Importantly, immunofluorescent co-labeling allowed visual confirmation of α-2,6 sialylation colocalizing with IBA1 labeled microglia in rTg4510 and human AD. Conclusion: Preliminary data proposes reactive microglia are sialylated in murine models of AD and human AD. These histological findings provide emerging evidence for microglia sialylation in neurodegeneration and moves us toward our overall hypothesis that region- and cell-type specific changes in sialylation during aging regulate microglia dysfunction and protein aggregate pathology observed in aging and ADRD.

Funding Disclosure: None

Poster Theme Group A: Basic Science and Pathogenesis

A3. Human Neuropathology

Poster #17

ASSOCIATION OF GUT MICROBIOME AND ALZHEIMER'S DISEASE NEUROPATHOLOGIC MEASURES IN MIDDLE-AGED INDIVIDUALS: A CROSS-SECTIONAL STUDY

Presenting author: Yannick Joel Wadop Ngouongo, PhD (Postdoctoral Fellow, UT Health Science Center San Antonio)

Background: Recent research suggests imbalances in gut microbiota may contribute to the pathogenesis of neurological disorders, including Alzheimer's disease (AD). AD is characterized by the accumulation of misfolded amyloid-β (Aβ) oligomers and neurofibrillary tangles composed of hyperphosphorylated tau protein. Those accumulations trigger neuroinflammation leading to synapse loss and neuronal death. Fecal microbiota transplantation has been shown to reduce amyloid plaques in mouse AD models. In humans, patients with AD have decreased abundance of microbes with neuroprotective effects in their guts. Finally, we have shown that Barnesiella intestinihominis, a bacterium excreting neuroinflammatory metabolites, is associated with dementia endophenotypes in middle-aged individuals. However, the association between gut dysbiosis and Aβ and tau in humans is still poorly understood. Method: In this cross-sectional study, we used stool specimens and neuropathological measures of 140 middle-aged individuals (mean age 56, 54.3% women) from the Framingham Heart Study to estimate the link between shifts in gut microbiota composition and PET Aβ and tau deposit levels in several brain regions. We quantified the gut microbiome composition using the 16S rRNA gene sequencing method and performed multivariable association analysis, adjusting for age, sex, and BMI. Result: Our results indicate a negative correlation (adjusted p-value < 0.0001) between tau levels in the inferior temporal cortex and the abundance of several genera, including Butyricicoccus, Ruminococcus, and Pseudobutyrivibrio. Similarly, we observed a negative correlation between Aβ deposit levels and genera Ruminococcus and Bifidobacterium. Conclusion: Together, our results suggested that the accumulation of Aβ plaques and tau tangles are associated with a decreased abundance of butyrate-producing bacteria in the human gut.

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Poster Theme Group A: Basic Science and Pathogenesis

A3. Human Neuropathology

Poster #18

DNA DAMAGE AS AN EARLY MARKER OF SENESCENCE IN TAUOPATHIES

Presenting author: Anner Harris, BS (Graduate Student, UT Health Science Center San Antonio)

Background: Hyperphosphorylated tau accumulation in neurons and astrocytes is a pathological hallmark of a class of neurodegenerative disorders known as "tauopathies", such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE). Previous research investigating the toxic effects of astrocytic tau pathology identified the DNA damage marker p16 in astrocytes from post-mortem human cases of AD and FTD. DNA damage is a marker of cellular senescence, a state in which cells undergo irreversible cell cycle arrest. Senescence initiation can also be identified via the expression of phosphorylated histone H2AX (gamma-H2AX) and cyclin-dependent kinase inhibitor p21. Senescence in astrocytes leads to reduced functional support for neurons. While recognized, the role of senescent astrocytes in tauopathies is not well understood. Here, we sought to determine how expression of other DNA damage markers, gamma-H2AX and p21, may vary across different tauopathies. Method: Immunohistochemistry was performed on postmortem human frontal cortex tissue of CTE (N=3), AD (N=3), PSP (N=3), CBD (N=3) and glioblastoma (GBM) (N=1) cases with antibodies against markers of early senescence gamma H2A.x (yH2A.x) and p21. Positively stain nuclei were quantified. Immunofluorescence was employed on the previously mentioned cases using either glial fibrillary acidic protein (GFAP) or NeuN antibodies in conjunction with yH2A.x or p21 markers in order to qualitatively measure the prevalence of senescent astrocytes and neuron in tauopathies. Result: Immunohistochemistry revealed yH2Ax expression was observed in AD, PSP, and CBD cases. From immunofluorescence experiments, yH2AX co-stained expression in astrocytic and neuronal in AD and CBD cases. Minimal expression of yH2Ax was revealed in the CTE case. Results from p21 stains were inconclusive. Conclusion: Overall, results indicate that DNA damage may be broadly associated with astrocytes in tauopathies. Utilizing alternative approaches to recognize and evaluate astrocyte senescence in post-mortem human tissue will provide further insight into these findings.

Funding Disclosure: None

Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #19

INTACT AUTOPHAGY AND REDUCED TAUOPATHY IN NON-DEMENTED INDIVIDUALS WITH ALZHEIMER NEUROPATHOLOGY

Presenting author: Anna Fracassi PhD (Postdoctoral Fellow, University of Texas Medical Branch at Galveston)

Background: Alzheimer's disease (AD) is a terminal neurodegenerative disease and the most common cause of dementia. Notably, some individuals, here referred to as Non-Demented individuals with Alzheimer Neuropathology (NDAN) are cognitively intact despite the presence of neuropathology consistent with fully symptomatic AD and have decreased tau oligomers at synapses. Accumulating evidence proposes that autophagy, the major cell mechanism responsible for removing protein aggregates and reportedly a primary route of clearance for tau in healthy neurons but disturbed in AD, is required for synaptic functions including neurotransmission and synaptic plasticity. Thus, the understanding of the neuroprotective mechanisms to evade cognitive decline to preserve synaptic functional integrity is important for the development of therapeutic approaches to prevent dementia. Method: Here we evaluated autophagy as a key protective mechanism for maintenance of cognitive integrity in NDAN subjects by efficient removal of tau oligomers. Using postmortem hippocampal samples from age matched NDAN (n=7), AD (n=7) and healthy controls (n=6), we performed immunofluorescence and comparative western blot analyses for regulatory molecules and ATGs (autophagy-related genes) involved in autophagy. Tauopathy was accessed by the expression and phosphorylation levels at Ser202/Thr205 (AT8), Thr231 (AT180) and Ser396 (PHF13.6) of tau oligomers. Results: We found that NDAN subjects have significantly increased regulatory mTor, Raptor, Beclin-1, and Atg16L, Atg12, Atg3, Atg5, Atg7, LC3AB, and proteasomal PSMA5 but not lysosomal LAMP1 as compared to AD. Expression levels were comparable with healthy controls. Autophagic proteins, except p62, were negatively correlated to tau oligomer (>65 kDa), not to total tau (>45 kDa), indicating autophagy being specific to tau oligomer clearance. Tau oligomer expression and levels of phosphorylation at Ser202/Thr205, Thr231, and Ser396 were significantly reduced in hippocampal tissue in NDAN as compared to AD, also confirmed by immunofluorescence analyses of Tau tangles. Conclusion: Our results indicate, for the first time, intact autophagy and associated reduced tauopathy as one of protective mechanism in cognitive intact NDAN. This novel observation supports the potential of autophagy-induced strategies in AD therapeutics.

Funding Disclosure: Supported by NIH/NIA grants R01AG069433

Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #20

AMYLOID BETA OLIGOMERS PROMOTE UPTAKE OF TOXIC TAU OLIGOMERS IN HUMAN SYNAPTOSOME

Presenting author: Shrinath Kadamangudi, MPhil (Graduate Student, University of Texas Medical Branch at Galveston)

Objective: In Alzheimer's disease (AD), predictable spreading of tau pathology correlates well with progressive cognitive impairment, thus constituting a likely effective treatment target. Numerous investigations postulate the influence of amyloid-beta on trans-neuronal pathological tau spreading and emerging evaluations of primary tauopathies (e.g. Primary Age Related Tauopathy) observe limited tau spreading alongside little-to-no amnestic changes. The synergy of amyloid-beta and tau has often been studied through a protein- or receptor-mediated substrate (e.g. LRP1 and alpha-2-adrenergic-receptors), however this approach has failed to provide effective therapeutic targets. Toxicity induced by the biophysical interaction these amyloid moieties with the microenvironment, such as the formation of donut-like annular assemblies of soluble amyloid-beta, has gained recent traction; this phenomenon, however, remains largely unstudied within the context of pathological tau spreading. To this end, we investigated the influence of soluble amyloid-beta-oligomers (AbO) on non-receptor-mediated binding and uptake of toxic tau-oligomers (tauO) in human synaptosomes. Methods: We employed synaptosomes isolated from autopsy frontal cortex specimens of 3 non-demented individuals with no evidence of AD neuropathology. First, synaptosomes were pre-treated with concentrated proteinase K (PK) to enzymatically cleave synaptic surface proteins. Synaptosomes were then incubated with tauO (2.5um) alongside various concentrations of fluorescently labeled preformed amyloid-beta-oligomers (0, 2.5uM, 5.0uM, and 10.0uM). After extensive washing, the resulting oligomer binding and uptake (measured as residual oligomer presence after secondary PK treatment) was determined using flow-cytometry and EM. Results: Despite the absence of surface proteins, we 1) found a near linear increase in synaptic tauO binding and 2) increased synaptic tauO uptake (particularly at higher AbO concentrations [5-10uM AbO], as a function amyloid-beta-oligomers. A qualitative assessment of EM negative stain images validated the quality of our synaptosome preparations, while decreased immunolabelling for synaptic surface markers validated the efficiency of our pre-PK treatment. Conclusions: This study is the first to investigate the impact of soluble amyloid-beta-oligomers on toxic tau-oligomer binding and uptake in a non-receptor-mediated fashion at the synaptic interface directly using post-mortem human brain tissue. If validated, these findings could underscore the need to better understand and develop therapies around the biophysical influences of amyloid proteins.

Funding Disclosure: R01AG073133 to GT

Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #21

SINGLE-NUCLEI ANALYSIS OF HIPPOCAMPI FROM WILD-TYPE MICE AFTER INTRACEREBROVENTRICULAR INJECTION OF NEURAL STEM CELL-DERIVED EXOSOMES

Presenting author: Salvatore Saieva, PhD (Postdoctoral Fellow, University of Texas Medical Branch at Galveston)

Neural stem cells (NSC) and adult neurogenesis are known to modulate synaptic plasticity and cognitive function. Decreased number of NSC have been reported in Alzheimer's Disease (AD), whereas their increase is associated with improved learning and memory. However, an increased neurogenesis does not correlate with preserved cognition, thus suggesting that other mechanisms involving increased numbers of NSC promote the preservation of memory. NSC are also known to secrete exosomes, namely microvesicles containing cell-specific cargos of biomolecules, that can be taken up by other cells, thus modulating their function. We and others have shown that NSC-derived exosomes (NSCexo) injected in brains of AD transgenic mice models ameliorated the cognitive decline and decreased the binding of toxic oligomers to synapses. The exact mechanisms by which NSCexo provide protection to synapse is still under investigation, although initial deep sequencing analyses show that elements of neuroinflammation seem to modulate NSCexo-mediated neuroprotection. Our long-term goal is to find the specific genes regulated by NSCexo that may be responsible for the cognitive resilience and the overall improvement of CNS function. As preliminary investigation, we injected fluorescent-labeled NSCexo in mice to identify which cell types internalize the exosomes. Furthermore, to shed light on this mechanism, we here show the results of a single-nuclei gene expression investigation on hippocampi isolated from mice injected with NSCexo, compared to not-injected mice. These investigations allowed us to determine cell-specific changes in gene expression after NSCexo injection, thus indicating which cell types are more likely to drive exosomes-mediated neuroprotection.

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Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #22

SIGNIFICANT CHANGES IN THE EXPRESSION OF BODY FLUID TRNA-DERIVED FRAGMENTS IN ALZHEIMER'S DISEASE

Presenting author: Wenzhe Wu, PhD (Research Scientist, University of Texas Medical Branch at Galveston)

Alzheimer's disease (AD), the most common type of dementia, is affecting approximately six million Americans aged 65 years and older. Significant efforts have been made to identify the disease mechanisms and treatment strategies. However, the cure or prevent strategies are extremely limited. Biomarker signatures are thought to withstand rigorous validation and ultimately provide the tools necessary to enable the clinical development of neurotherapeutics. Several biomarkers, including amyloid and/or tau in body fluids are promising to be associated with the development of AD. However, given the nature of AD being pathologically heterogeneous, an expansion of the AD biomarker toolbox is urgently needed. tRNA-derived RNA fragments (tRFs), a family of recently discovered small non-coding RNAs (sncRNAs), have been found to be significantly altered in the hippocampus tissues of AD patients, and the expression change in some tRFs shows age- and stage-dependent. To access whether the changes of tRFs can be also detectable in more accessible tissues, we compared sncRNA profile in cerebrospinal fluid (CSF) and serum samples from patients with or without diagnosed AD, using phosphor- small-RNA-seq and qRT-PCR validation. We found that the dominant sncRNAs in CSF and serum belong to tRFs. Using a limited number of CSF samples, we found that tRFs from the 5'-end of tRNA GlyCCC2 (tRF5-GlyCCC2) and ProAGG (tRF5-ProAGG) were enhanced in CSF of AD patients. Interestingly, serum tRF5-ProAGG expression was significantly reduced in AD patient and correlated to the AD disease severity, supporting that tRFs are promising in serving as AD diagnostic biomarkers.

Funding Disclosure: R21AG069226 NIH/NIA

Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #23

PERIPHERAL INFECTION ACCELERATES THE ALZHEIMER'S DISEASE PATHOLOGY

Presenting author: Vijayasree V. Giridharan, PhD (Postdoctoral Fellow, UT Health Science Center Houston)

TARCC-Based Project

Background: The etiology of late-onset Alzheimer's disease (AD) is still unclear. Our previous studies demonstrated the impact of infection on cognitive dysfunction and amyloid-beta (Aβ) accumulation in wild-type rodent models of bacterial meningitis and sepsis. We next sought to explore the role of peripheral infection on AD pathology in a transgenic mouse model. Methods: To test our hypothesis, 50-day-old male APP/PS1 mice were subjected to either cecal ligation and puncture (CLP) to induce a polymicrobial infection/sepsis or to non-CLP surgery as a control. Using longitudinal timepoints of 3, 30, and 120 days after surgery to inquire about sepsis's short-, intermediate-, and long-term effects on microbiota-gut-brain axis, immune modulation of the brain, cognition, and cerebral amyloid pathology. Additionally, we analyzed the gut microbiome by 16S rRNA sequencing, levels of short-chain fatty acids (SCFAs) in feces, and intestinal morphology to query putative peripheral drivers of AD. The 30- and 120-days groups were subjected to a novel object recognition task (NORT) to assess non-spatial memory. Results: Despite being free from infection, the CLP mice took more time interacting with the new object, reflecting cognitive decline. Peripheral infection profoundly altered the microbiome profile measured by α-diversity and β-diversity at more prolonged periods. Interestingly, we identified an increase in pro-inflammatory gut bacterial taxa at 30 days in the CLP group. At 30 and 120 days after CLP, SCFAs were reduced, and villi length and crypt depth decreased. The chemokine eotaxin and other pro-inflammatory cytokines associated with cognition decline increased, and the IL-13-associated brain homeostasis was decreased in CLP mice brains. The neuroinflammation after infection was verified by measuring the glial cell activation. Compared to the age-matched control, sepsis mice elevated Aβ burden at 120 days after surgery. Prominent microglial accumulation within 15μm near Aβ plaques was increased in mice subjected to CLP. Conclusion: Together, these findings demonstrate that peripheral infection/inflammation modulates gut microbiota, promotes neuroinflammation, and accelerates or exacerbates AD pathology in APP/PS1 mouse model.

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Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #24

SIMVASTATIN MODULATES NEURODEGENERATIVE BIOMARKERS RELATED TO ALZHEIMER'S DISEASE PATHOLOGY IN SEPSIS SURVIVOR ANIMALS

Presenting author: Carlos Henrique Rocha Catalao, PhD (Postdoctoral Fellow, UT Health Science Center Houston)

Sepsis survivors have persistent neurological changes, including cognitive and behavioral dysfunction, which are associated with increased production of neurodegenerative biomarkers and morphological changes in areas with mnemonic functions. Simvastatin has been proposed as a potential therapeutic approach in sepsis, given its anti-inflammatory and antioxidant properties. We hypothesize that treatment with simvastatin, an HMG-CoA reductase inhibitor, interferes with pathways responsible for activating protein kinases that precede amyloidosis in animals surviving sepsis. Here we investigated the possible neuroprotective effect of the simvastatin by analyzing neurodegenerative markers, mitochondrial respiration, and neuronal tracing in the hippocampus, prefrontal cortex, and thalamic nucleus reuniens (RE) of sepsis survivor animals. Adult Wistar rats (280 ± 30 g) were submitted to sepsis by cecal ligation and puncture (CLP, n = 28) or left as non-manipulated (control, n = 24). The animals were treated with simvastatin (20 mg/kg) or vehicle four days before and ten days after surgery. The treatment prevented the increase in the expression of calpain-1 (hippocampus ($F(3, 28) = 16.06$; $P < 0.0001$; prefrontal cortex: $F(3, 28) = 10.54$; $P < 0.05$), BACE-1 (hippocampus: $F(3, 28) = 7.739$; $P < 0.05$; prefrontal cortex: $F(3, 28) = 13.88$; $P < 0.001$) and, GSKβ (hippocampus: $F(3, 28) = 62.79$; $P < 0.0001$; prefrontal cortex: $F(3, 28) = 15.35$; $P < 0.0001$) in the brain structures of the sepsis survivor animals. Septic animals showed mitochondrial dysfunction and a decrease in axon terminals in the RE. Simvastatin seems to restore energy metabolism by improve of the ETS values in the hippocampus ($F(3, 12) = 7.533$; $P < 0.01$) and the P/E ratio in the prefrontal cortex ($F(3, 12) = 5.818$; $P < 0.05$), in addition to preventing the reduction of axon terminals in survivor animals. These results suggest a potential neuroprotective effect of simvastatin and raise the importance of considering HMG-CoA reductase inhibitors as a possible adjuvant therapy in sepsis.

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Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #25

HEPATOTOXICITY IS ASSOCIATED WITH AB-AMYLOIDOSIS IN A MOUSE MODEL OF AMYLOID PATHOLOGY

Presenting author: Celso S. G. Catumbela, MSc (Graduate Student, UT Health Science Center Houston)

BACKGROUND: Alzheimer's disease (AD) is a chronic and fatal neurodegenerative disorder that typically occurs at late-stages of life. Although the cause(s) of AD is (are) unknown, cerebral aggregation and subsequent accumulation of misfolded amyloid-β (Aβ) peptide is hypothesized to trigger the onset of disease. Clinical reports link AD diagnosis with dysregulated Aβ catabolism by peripheral tissues, including the liver, which is the primary site of circulating Aβ clearance. The pathological crosstalk between hepatic dysfunction and AD remains critically understudied. METHODS: Thus, we subjected 90 days-old familial AD (Tg2576) and WT mice, males (5-7 per group), to monthly intraperitoneal (i.p.) injections of either a toxic, but sub-lethal dose of acetaminophen (APAP)-the most reproducible form of experimental liver damage-or PBS as vehicle. Monthly drug-induced acute hepatotoxicity was performed over a groundbreaking period of 12 months. Cognitive performance in these mice was queried using the novel object recognition task and the object location test either 14 or 7 days prior to endpoint, respectively. At endpoint, mice brain hemispheres and peripheral tissues were collected and subjected to biochemical and histological evaluation of amyloid pathology. RESULTS: We found that, independent of genotype, APAP treatment was associated with a bimodal distribution of cognitive scores that heavily skewed towards impaired memory. Thus, supporting the link between hepatotoxicity and cognitive impairment, and revealing that history of acute liver damage does not worsen the memory deficits associated with cerebral Aβ overexpression in these mice. APAP-treated male groups displayed mortality at comparable rates. Biochemical analysis of frozen brain (cortex + hippocampus) homogenates indicated that hepatic AD males showed higher concentrations of insoluble Aβ compared to non-APAP-treated AD mice. Moreover, hepatic AD males exhibited lower cerebral levels of pro-inflammatory cytokines than controls. In agreement, immunofluorescence analysis of mice brains revealed that relative to controls, hepatic AD males showed elevated cortical and hippocampal levels of Aβ-amyloid plaques, but not glia. CONCLUSION: Our findings reveal that history of acute liver damage is sufficient to accelerate the progression of aging-associated cognitive decline as well as Aβ-amyloidosis. Importantly, we link the pathological crosstalk between hepatotoxicity and AD with an Aβ-dependent mechanism of action.

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Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #26

EVIDENCE FOR STABILIZED G-QUADRUPLEXES AS PATHOGENIC DRIVERS IN ALZHEIMER'S DISEASE

Presenting author: Vijay Kumar Marumulla Jagadeshwar Rao, PhD (Postdoctoral Fellow, UT Health Science Center Houston)

Background: Guanine (G)-rich sequences in the human genome can fold into non-canonical structures known as G-quadruplexes (G4s or G4-DNA). These sequences contain at least four G runs, which enable the four Gs to associate via Hoogsteen-type hydrogen bonds to form self-stacking G-quartets, forming a columnar G4 structure. G4s play important roles in DNA recombination, replication, and regulation of transcription. It is now firmly established that stabilized G4s lead to increased genomic instability in neurons. It is also shown that G4s increase with age in AD mouse brains. G4-DNA-binding transcription factors, G4-DNA-associated proteins, and G4 helicases bind to the G4 structures and modulate G4 landscapes in cells. Whether and how G4-DNA and G4-DNA-associated proteins and helicases contribute to Alzheimer's disease (AD) is not clear. Methods: To determine the significance of increased G4 stabilization in AD, we use human wild-type, and AD (PSEN1 M146L) neurons, and Tg2576 mice (a mouse model of AD). We also use antibodies raised against G4s and G4-binding proteins and helicases to detect G4s and G4-binding proteins and helicases in fixed cells and mouse brains. Results: Our studies found that stabilizing G4s led to genomic instability in neurons. We also discovered that PSEN1 M146L neurons contain more G4 structures than wild-type neurons, likely contributing to genomic instability and altered transcription in AD neurons. We demonstrated that stabilized G4s are formed in the brains of Tg2576 mice at a stage well before the deposition of amyloid occurs. We further showed that stabilized G4s cause DNA DSBs and cause genomic instability in aged AD mouse brains. Conclusion: Our study demonstrates that G4s are dysregulated in human AD neurons and in pre-plaque AD mouse brains. These data provide evidence supporting the role of G4s, G4-binding proteins, and helicases in the early molecular mechanisms of AD pathology.

Funding Disclosure: NIA RF1AG068292

Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #27

TYPE I INTERFERON COMPELS MEMORY IMPAIRMENT ASSOCIATED WITH AMYLOID B PLAQUES

Presenting author: Wei Cao, PhD (Professor, UT Health Science Center Houston)

Despite well-documented maladaptive neuroinflammation in Alzheimer's disease (AD), the principal signal that drives memory and cognitive impairment remains elusive. Here, we revealed robust, age-dependent cellular reactions to type I interferon (IFN), an innate immune cytokine aberrantly elicited in murine β amyloid plaque models, and assessed the cumulative importance of IFN in cognition and neuropathology. Long-term blockade of IFN receptor rescued both the memory and synaptic deficits, which was accompanied by reduced microgliosis, inflammation, and neuritic pathology. Interestingly, microglia-specific IFN receptor ablation attenuated the loss at post-synaptic terminals, whereas IFN signaling in other brain cells contributed to pre-synaptic alteration and plaque accumulation. Intriguingly, IFN pathway activation displayed a strong inverse correlation with cognitive performance, promoting selective synapse engulfment by microglia rather than amyloid plaques. Overall, IFN signaling represents a critical module within the neuroinflammatory network of AD and prompts a concerted cellular state that is detrimental to memory and cognition.

Funding Disclosure: NIH grant AG057587; BrightFocus ADR A20183775, and Brown Foundation 2020 Healthy Aging Initiative

Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #28

MICROGLIA INTERNALIZE TAU AGGREGATES OF DIFFERENT SIZES WITH DIFFERING EFFICIENCY AND VIA DISTINCT MECHANISMS

Presenting author: Kristian F. Odfalk, BS (Graduate Student, UT Health Science Center San Antonio)

Tauopathy is class of neurodegenerative disease characterized by aberrant hyperphosphorylation and misfolding of the microtubule-associated protein tau. Tau is thought to drive neurodegeneration via multimerization into neurotoxic aggregates. Neurons are known to release tau aggregates into the extracellular space, which then initiates the spread of tau aggregation to other neurons via a prion-like mechanism. Microglia clear extracellular protein aggregates including tau, but the mechanism by which they take up tau is unknown. Neurons internalize tau via macropinocytosis; thus, we hypothesized that microglia endocytose tau via macropinocytosis. To model extracellular tau in BV2 microglia culture, we used recombinant human P301S mutant Tau preformed fibrils (PFFs), and sonicated PFFs (sPFFs). We measured the tau endocytosis in the presence of absence of validated pharmacological macropinocytosis activators or inhibitors, or clathrin-mediated endocytosis (CME) inhibitors optimized for specificity at the chosen concentrations. Macropinocytosis inhibitors (cytochalasin D, wortmannin, and U73122), a macropinocytosis activator (phorbol 12-myristate 13-acetate, PMA), and CME inhibitor (Dyngo 4a) target different molecular components of endocytic machinery. We found that BV2 microglia internalize tau aggregates in a concentration dependent manner and take up PFFs more efficiently than sPFFs. Macropinocytosis inhibition reduced uptake of both PFFs and sPFFs except in the case of U73122. Macropinocytosis activation increase PFF uptake but decrease sPFF uptake. The inconsistency between effects of pretreatment with macropinocytosis inhibitors could be explained by their distinct targets. Indeed, U73122 and PMA (in the case of sPFFs) may fail to modulate macropinocytosis in the context of tau. We will examine this in future studies and repeat our assay on primary culture microglia. We also observed that CME inhibition blocked uptake of PFFs and sPFFs. Taken together, these results suggests that in BV2s microglia macropinocytosis participates in uptake of both Tau PFFs and sPFFs, and Dyngo 4a inhibition of PFF uptake, suggests CME is also involved. These findings further suggest that the microglial endocytic mechanism for tau differs to that of neurons, as neurons have been shown to more readily endocytose sPFFs over PFFs. Differences between microglial and neuronal endocytosis of Tau could be exploited therapeutically to enhance Tau clearance without promoting neuron-to-neuron spread.

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Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #29

EFFECTS OF ELIMINATING MICROGLIA IN THE CONTEXT OF ALZHEIMER'S DISEASE THROUGH THE LENS OF LIPID METABOLISM

Presenting author: Juan Pablo Palavicini, PhD (Assistant Professor, UT Health Science Center San Antonio)

Microglia are strongly implicated in the development and progression of Alzheimer's disease (AD), yet their impact on pathology and lipid metabolism remains unclear. Here, we assessed the brains of a commonly used mouse model of AD/amyloidosis, i.e. 5xFAD transgenic mice, in the presence or absence of microglia using multidimensional mass spectrometry-based shotgun lipidomics, NanoString gene expression profiling and histological approaches. Microglia were eliminated pharmacologically using an CSF1R inhibitor PLX5622 and genetically using CSF1R hypomorphic mice. Surprisingly, microglial-deficient mice exhibited profound brain lipidome alterations under physiological (non-AD) conditions including increases in major lysophospholipids and remodeling of mitochondrial lipids. Furthermore, microglia elimination under AD conditions did not rescue amyloid beta-induced lipidome alterations, but rather further aggravated them. Finally, we identified a unique lipid species, a polyunsaturated bis(monoacylglycero)phosphate (BMP), that is primarily present in microglia and is increased in AD conditions. BMPs have been reported to be exclusively located in late endosomal and lysosomal compartments. Taken together, our results strongly suggest that microglia act an important role as regulators of brain lipid metabolism, playing protective roles under both physiological and AD conditions. Our data provides further evidence that eliminating microglia may aggravate some aspects of AD pathology.

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Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #30

CYTOPLASMIC TDP-43 AGGREGATES DISASSEMBLE THE P-BODY BY HIJACKING ITS CORE COMPONENTS

Presenting author: Haiyang Yu, PhD (Instructor, UT Southwestern Medical Center)

Introduction: Nuclear clearance and cytoplasmic aggregation of TDP-43 is a pathological hallmark of over 90% of amyotrophic lateral sclerosis (ALS) patients. The mechanism of TDP-43 mislocalization and the consequence of aggregation are poorly understood. Methods: We established an inducible aggregation model for TDP-43 by tagging the C-terminus of TDP-43 with a short peptide (N50) that promotes oligomerization. To discover the binding proteins of TDP-43 cytoplasmic aggregates, we used the proximity labelling approach to identify proteins that co-phase separated with TDP-43 by quantitative mass spectrometry. Results: By tagging TDP-43 with a 50-amino acid weakly self-associating domain (by folding into a beta-solenoid structure), TDP-43 readily de-mixes without added cellular stress. The N50-tagged TDP-43 (TDP-43N50) reliably produces cytoplasmic TDP-43 aggregates that recapitulate pathological features of TDP-43 inclusions observed in postmortem neurons, including phosphorylation, ubiquitination, truncation, and co-localization with p62, an autophagic receptor. Using inducible TDP-43 de-mixing as a model, and APEX2-mediated proximity labeling technology, we have identified unique RNA binding proteins that favor aggregated TDP-43, including P-body components. TDP-43N50 aggregates are first localized to the P-body, a naturally existing cytoplasmic membrane-less organelle in neurons. The P-body regulates RNA metabolism. In cells with large TDP-43N50 aggregates, the number of P-bodies is significantly reduced. Interestingly, DDX6, a core protein component of the P-body, is hijacked by TDP-43N50 aggregates. Knockdown of DDX6 reduces the number of P-bodies in cells, providing a mechanism by which TDP-43N50 aggregates disassemble P-bodies. Additionally, the RNA-binding deficient TDP-43N50 aggregates do not disassemble P-bodes and do not interact with DDX6, indicating that the interaction between P-body and TDP-43N50 aggregates is mediated by RNA. Importantly, TDP-43 aggregates disassemble P-bodies in affected motor neurons of ALS patients. Discussion: Cytosolic TDP-43 aggregates dock on and hijack P-body components and cause P-body disassembly.

Funding Disclosure: NINDS R00NS114162

Poster Theme Group A: Basic Science and Pathogenesis

A4. Molecular and Cell Biology

Poster #31

REGULATION OF TAU SOLUBILITY BY HGK IN AGING-RELEVANT NEURONS FROM ALZHEIMER'S DISEASE PATIENTS

Presenting author: Shuaipeng Ma, PhD (Research Scientist, UT Southwestern Medical Center)

TARCC-Based Project

Background: Hyperphosphorylation of neuronal tau protein is a hallmark of Alzheimer's disease (AD). Our previous work shows that Hit3, an inhibitor of MAP4Ks (including HGK), can suppress hyperphosphorylated TAU in AD-human induced neurons (hiNs). However, the underlying molecular mechanism is not clear. Methods: We used proteomics and immunoprecipitation combined with phos-tag gel technique to identify potential substrates of HGK. In vitro kinase assay was used to confirm the relationship between HGK and its substrate. Mutagenesis was used to identify the potential phosphorylation sites in a kinase substrate. Co-immunoprecipitation and western blotting were used to determine how HGK kinase and its substrate regulate the formation of insoluble tau in HEK cells and hiNs. Results: Hit3 can reduce hyperphosphorylated TAU expression in AD-hiNs. After screening potential interactors of the Hit3 target, HGK, we identified NCK2, an adaptor protein. HGK and its kinase domain interact with NCK2. HGK can directly phosphorylate NCK2 in vitro. Both HGK and NCK2 interact with TAU. Regulation of insoluble TAU by HGK requires its kinase activity. Its substrate, NCK2, may cooperate with HGK in a ratio dependent manner to regulate insoluble TAU. Conclusions: NCK2 is a new substrate of HGK. They co-regulate tau solubility in a ratio dependent manner. Precise modulation of NCK2 and MAP4Ks may be used to reduce insoluble TAU in AD.

Funding Disclosure: TARCC

Poster Theme Group B: Biomarkers

B1. Biomarkers (non-neuroimaging)

Poster #32

IDENTIFICATION OF GENETIC REGIONS ASSOCIATED WITH ALZHEIMER 'S DISEASE BIOMARKERS BLOOD CONCENTRATIONS IN MEXICAN AMERICAN FAMILIES.

Presenting author: Marcio Augusto Afonso de Almeida, PhD (Research Assistant Professor, University of Texas Rio Grande Valley)

Background: Dementias are heterogeneous age-associated neurodegenerative disorders generally included in the broad term, Alzheimer's disease, and related dementias (ADRD). ADRD affects individuals of all ethnicities, but Hispanic individuals show a 1.5-fold higher risk when compared to non-Hispanic whites. Many AD risk biomarkers have been proposed but not much is known about how genetics elements control their expression. We used a set of 2000 completely sequenced Mexican Americans for the identification of genetic regions associated with AD biomarkers blood concentration. Methods: We applied a mean-based endophenotype ranking value (ERV) method tailored for relatively rare diseases and extended pedigrees. A set of 70 GOBS subjects were diagnosed as ADRD cases (h2= 0.75, p = 2.6*10-5). We quantified the blood concentrations, using a Quanterix elisa assay, of four AD candidate biomarkers AB40, AB42, TAU and NFL. We identified genomic regions associated with those four biomarkers using a linear mixed model as implemented in SOLAR on a set of 28 million SNPs. Candidate SNPs identified were extensively annotated and their individual EQTL contribution to the expression of flanking genes defined. Results: The heritability component of each AD biomarker was defined, and the most significant estimate observed for NFL (h2= 0.33, p=6.96*e-17) where the individual's age had a large effect (2.97*e-126). We identified two genome-wide significant associations for markers rs242557 (3.11*e-14) and rs242562 (1.34*e-13) both SNPs are common and located respectively in the first and second introns of the gene MAPT. Both markers are in a conserved region with chromatin accessibility for transcription factors, suggesting regulatory functions. We tested the association between both SNPS and flanking gene expression and identify strong evidence of cis-regulation with the expression of the antisense-RNA (KANSL1_AS1) of the gene KANSL1. Conclusion: The identification of genetic markers associated with AD biomarkers is key to provide a reliable and cost-effective genetic test for AD risk for the Hispanic population. The gene KANSL1 encodes a subunit of histone acetylation enzyme and has been associated with Koolen-de Vries Syndrome and cognitive impairment. The genetic associations are promising, but demand an independent validation to confirm their impact for the AD risk estimation.

Funding Disclosure: NIH P30AG066546; NIH R21AG077501

Poster Theme Group B: Biomarkers

B1. Biomarkers (non-neuroimaging)

Poster #33

FEDEXOSOME: MITOCHONDRIAL DNA & MICRO RNA PROFILING OF NEURONAL-ENRICHED PACKAGES IN ALZHEIMER'S DISEASE

Presenting author: Courtney Hall, PhD (Postdoctoral Fellow, University of North Texas Health Science Center)

TARCC-Based Project

Background: Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by impaired memory, diminished cognitive abilities, and accumulation of amyloid beta plaques and hyperphosphorylated tau tangles in the brain. AD progression is insidious with the earliest clinical symptoms appearing decades after key neuropathological changes have occurred. Accurate diagnosis during the transitional period between disease onset and clinical manifestation could provide critical insight into AD pathogenesis and enable development of effective therapeutic strategies to prevent irreversible neuronal death. Evidence suggests that early alterations in the AD brain (oxidative stress, neuroinflammation, aberrant gene expression) can propagate to local and distal cells through the biological packages secreted by neurons. These neuronal-enriched extracellular vesicles (NEEVs) can cross the blood-brain barrier and are capable of mediating systemic inflammation in response to CNS-sourced stress through their mitochondrial DNA (mtDNA) and microRNA (miRNA) cargo. Circulating NEEVs may therefore serve as an easily accessible, early indicator of the forthcoming neuropathological changes in the AD brain. This study aims to develop a higher throughput workflow for profiling mtDNA and miRNA in plasma NEEVs. Methods: Human plasma samples were processed using a two-step method involving (1) precipitation of total exosomes with ExoQuick (SBI) and (2) immunoprecipitation-based enrichment of NEEVs with a biotinylated antibody against a well-established neuronal surface marker (CD171). Captured NEEVs were stained and analyzed using flow cytometry as well as nanoparticle tracking analysis (NTA). DNA and RNA were then extracted for mtDNA quantification and miRNA sequencing. Result: The protocol modifications implemented in this project were compared based on particle size, distribution, and purity as well as absolute mtDNA load and spike-in normalized miRNA read counts. These data not only demonstrate the feasibility of profiling the mtDNA and miRNA from 500µL of plasma NEEVs but have also resulted in a higher throughput workflow for processing TARCC patient samples. Conclusion: This work represents the first successful attempt to simultaneously quantify mtDNA and sequence miRNA in the relatively small subpopulation of plasma EVs that originate from neurons. Future studies will harness the protocol developed herein to assess the biomarker potential of NEEVs in the TARCC cohort.

Funding Disclosure: TARCC (RS00049)

Poster Theme Group B: Biomarkers

B2. Neuroimaging

Poster #34

EFFECTS OF TRANSCRANIAL INFRARED LASER STIMULATION ON BRAIN RHYTHMIC ELECTRICAL ACTIVITY IN YOUNGER AND OLDER ADULTS

Presenting author: Dariella Fernandez, MA (Graduate Student, University of Texas at Austin)

Background: Transcranial Infrared Laser Stimulation (TILS) is a non-invasive intervention that has been found to modulate mitochondrial respiration and cellular functions in brain neurons. In healthy, young adults, eight minutes of TILS has been shown to improve memory and attention. In older adults, TILS is being investigated as a potential intervention against cognitive decline and dementia. The research on the electrophysiological effects of TILS is in the incipient stage and little is known about what electrophysiological effect TILS has on the aging brain. The objectives of the study are to: 1) Examine the acute electrophysiological effects of TILS during and after TILS administration in younger adults and older adults, 2) Investigate the relationship between baseline cognitive function and electrophysiological effects of TILS in older adults, and 3) Investigate if a single 8-minute administration of TILS in older adults can impact cognitive functioning. Methods: This study will employ a sham-controlled, randomized, single blind experimental design. We will recruit a cohort of younger adults (<45 years old) and older adults (>45 years old) who do not have dementia nor severe cardiovascular disease. All participants will complete a 13-minute electroencephalogram (EEG) that measures before, during and after 8-minutes of TILS (250 mW/cm2, 1064 nm) or sham treatment. Older adults will additionally be asked to complete three quick cognitive tasks before TILS treatment, and will repeat the cognitive tasks 3-4 days later. We will calculate both within-group and between-group changes in EEG power and use non-parametric permutation tests to test for significance. Expected Results: We expect that both younger and older adults will show TILS induced, dose-dependent increases in alpha and beta power and that older adults will have a greater benefit from TILS. We also expect that older adults with lower baseline cognitive scores will show a greater benefit from TILS and that a single administration of TILS will improve performance on the cognitive tasks. Conclusion: The results from this study will help us further understand the mechanistic link between photobiomodulation and the cognitive enhancing benefits from TILS, how TILS affects the aging brain, and can help guide future clinical applications of TILS.

Funding Disclosure: Oskar Fischer Project; Elhapa Foundation

Poster Theme Group B: Biomarkers

B2. Neuroimaging

Poster #35

HEALTHY AGING IMPACTS THE OSCILLATORY DYNAMICS UNDERLYING VERBAL WORKING MEMORY PERFORMANCE

Presenting author: Lin Guo, BA (Medical Student, UT Southwestern Medical Center)

Background: Normal cognitive aging begins in midlife and is associated with decreases in processing speed, working memory capacity, and attention. In contrast to neurodegenerative disorders including Alzheimer's disease and related dementias, age-related cognitive decline does not progress to impair functioning in activities of daily living. Building upon prior work done on a smaller sample of mostly Caucasian males (Proskovec, Human Brain Mapping, 2016), the present study will characterize the impact of healthy aging on the oscillatory dynamics supporting successful verbal working memory (VWM) performance in a more diverse cohort using magnetoencephalographic (MEG) functional brain imaging. Methods: Fifty-four cognitively normal (CN) adults without subjective cognitive complaints (15 Black, 30 female, 59 mean age, 38-81 age range) performed a modified Sternberg VWM task during MEG. 6 letters were simultaneously presented in a 2x3 grid for 2.0 s (encoding), followed by an empty grid for 3.0 s (maintenance), and a test letter for 0.9 s (retrieval). Subjects responded via button pad whether the test letter had been in the original 6-letter set. MEG data underwent standard pre-processing and co-registration to the subject's anatomic MRI. Artifact-free, correct trials will be transformed into the time-frequency domain to identify significant, sensor-level oscillatory responses, which will then be reconstructed in brain space using a beamformer approach. The resulting whole-brain maps of oscillatory activity will be entered into regression analyses to assess the effects of age, while controlling for race, sex, and education level. Hierarchical regression was also performed to model the effect of age on VWM task performance with race, sex, and education level as covariates. Results: Average reaction time increased with age after adjusting for race, sex, and education level ($p=0.003$); however, age was not predictive of task accuracy ($p>0.05$). The oscillatory dynamics underlying this well-preserved VWM task performance in older adults despite age-related decrement in processing speed will be investigated. We expect to observe stronger, more generalized recruitment of predominantly left-lateralized VWM brain areas with advancing age. Conclusion: Understanding neural changes in cognitively healthy, older adults will help delineate pathological alterations and differentiate abnormal from expected cognitive aging during early, clinically indistinguishable stages.

Funding Disclosure: None

Poster Theme Group C: Clinical Manifestations

C2. Neuropsychology

Poster #36

THE ROLE OF AGE AND EDUCATION ON NEUROCOGNITIVE FUNCTIONING IN HISPANIC AND NON-HISPANIC INDIVIDUALS IN RURAL WEST TEXAS

Presenting author: Lauren Elliott, BA (Graduate Student, Texas Tech University)

Background: Research indicates education and age influence neurocognitive functioning; however, little is known about education and age affecting Hispanic and non-Hispanic populations, specifically, within underserved rural individuals in West Texas. Methods: 1864 participants (752 non-Hispanic, 1053 Hispanic; Mage = 59.68 years, SDage =12.21) in Project FRONTIER (Facing Rural Obstacles to Healthcare Now Through Intervention, Education, & Research) completed five Neuropsychological tests: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Trails Making Test A and B, and Clock Drawing 1 and 2. Age was dichotomized at 65 to assess older (65+) vs younger adults (<65). Education was grouped by completed years of schooling: elementary school (0-5 years), middle school (6-8), high school (9-12), and higher education (13-20). Results: The MANOVA identified significant main effects for age (Roy's Largest Root = 12.52, $F(5, 1,363)$, $p < .001$, $\eta 2p = 0.044$) and ethnicity (Roy's Largest Root = 61.29, $F(5, 1,363)$, $p < .001$, $\eta 2p = 0.184$) on indicators of neurocognitive functioning. Post-hoc analysis revealed older participants had lower overall neurocognitive functioning on RBANS (M=82.52, SD=16.75) than younger participants (M=85.24, SD=14.95). Post-hoc analysis revealed Hispanic participants had lower overall neurocognitive functioning (M=78.49, SD=14.26) than non-Hispanic participants (M=92.11, SD=15.07). The second MANOVA identified a significant interaction between ethnicity and education on neurocognitive functioning (Roy's Largest Root = 5.11, $F(5, 1,548)$, $p < 0.001$, $\eta 2p = 0.016$). Non-Hispanic individuals who reported less education had worse neurocognitive functioning compared to participants with more education. However, Hispanic participants did not have as significant increase between low education compared to higher education. Conclusions: Lower age and higher education were linked to greater neurocognitive functioning. However, educational attainment had a disproportionate lower impact on neurocognitive functioning for Hispanic individuals compared to non-Hispanic individuals. These results are consistent with the theory of Minorities' Diminished Returns, which posits educational attainment has weaker protective effects for ethnic minority groups. It could be hypothesized the education system is structured to provide greater benefits for non-Hispanic individuals, compared to Hispanic individuals. Due to potential systematic biases, education status may only serve as a protective factor for those it was developed: non-Hispanic, white individuals.

Funding Disclosure: None

Poster Theme Group C: Clinical Manifestations

C2. Neuropsychology

Poster #37

INTRAINDIVIDUAL VARIABILITY ACROSS NEUROPSYCHOLOGICAL TESTS AND BETWEEN COGNITIVE DOMAINS: WHAT ARE WE REALLY MEASURING?

Presenting author: Bonnie M. Scott, PhD (Assistant Professor, The University of Texas at Austin Dell Medical School)

TARCC-Based Project

Background: Intraindividual variability (IIV) in cognitive performance is a non-specific finding associated with cognitive and functional decline, morbidity and death in a number of neurodegenerative conditions, which raises the question as to what exactly it is that these IIV metrics are measuring. In the current study, we sought to address this question by examining the construct validity and clinical correlates of cognitive IIV in the Texas Alzheimer's Research and Care Consortium (TARCC) Hispanic Longitudinal Cohort (HLC). Methods: The sample included baseline data from 1790 older adults, including 1002 older adult controls (OAC), 287 individuals with subjective cognitive decline (SCD), and 501 individuals with a diagnosis of mild cognitive impairment (MCI). IIV was calculated as the standard deviation of tests across all cognitive tasks (IIV-Across) and between the mean scores of tests within each of four cognitive domains (IIV-Between: attention, language, memory, and executive domains). These IIV metrics were compared between groups and examined in relation to clinical characteristics, biological risk factors, and blood-based biomarkers representing microvascular dysfunction (VEGFR-1: vascular endothelial growth factor receptor-1), neuroinflammation (C-reactive protein), and thrombin generation (FVII: coagulation factor VII). Results: The OAC group demonstrated significantly lower IIV-Across than SCD ($p<0.01$) and MCI ($p<0.001$) groups but there were no significant between-group differences for IIV-Between. In the combined sample, greater IIV was found in Hispanic vs. non-Hispanic individuals and in those with anxiety, apathy, and dysphoria, but these effects were stronger for IIV-Across than IIV-Between. Both IIV metrics were related to lower cognitive status and higher CRP values, but only IIV-Across was associated with higher pulse pressure and IIV-Between with higher FVII levels ($p<0.001$). The two IIV metrics shared a relatively modest correlation with each other ($R2=0.56$) and with mean performance level in different cognitive domains ($R2=0.01$-0.03), thereby suggesting that they may be measuring somewhat distinct neuropsychological processes. Conclusion: Findings suggest that different pathophysiological processes hypothesized to occur in the prodromal phase of AD may be reflected in different IIV metrics which appear to have their own strengths and weaknesses, depending on their intended use.

Funding Disclosure: TARCC

Poster Theme Group C: Clinical Manifestations

C2. Neuropsychology

Poster #38

COMPARISON OF GENDER DIFFERENCES ON THE QUICK MILD COGNITIVE IMPAIRMENT (QMCI) SCREEN IN COGNITIVELY NORMAL AND MILD COGNITIVE IMPAIRMENT GROUPS

Presenting author: Robin C Hilsabeck, PhD (Associate Professor, The University of Texas at Austin Dell Medical School)

Background: The quick mild cognitive impairment (QMCI) is a relatively new cognitive screening measure that prior research suggests is equal to or better than other screening measures at differentiating individuals who are cognitively normal (CN) from those with mild cognitive impairment (MCI). However, limited research to date has explored the role of demographic factors such as gender on interpreting performance. The aim of our current study was to examine gender differences on the QMCI total and subtest scores in diagnostic groups. It was hypothesized that CN women would perform better than CN men on verbal memory and fluency tasks and that CN men would perform better on the clock drawing task. In contrast, it was also hypothesized that women with MCI would perform worse than men with MCI on verbal memory measures because prior research has shown this performance advantage is no longer apparent once a cognitive disorder is present. Methods: The sample included data from 123 (75 CN, 48 MCI) older adults, 56 men and 67 women. One-way and multivariate analyses of variance using covariates as appropriate were used to investigate group differences in the QMCI total score and six subtest scores. Results: No significant demographic differences between CN and MCI groups were found, but women had significantly less education than men. As expected, CN participants obtained significantly higher QMCI total scores than MCI participants across total and subscales except Word Registration and Clock Drawing ($p < .001$). There were no statistically significant gender differences on QMCI total or any subtest score in either diagnostic group. While CN women obtained higher scores on Verbal Fluency, Delayed Recall, and Logical Memory and CN men obtained higher scores on Clock Drawing, none of these differences were statistically significant. In the MCI group, women obtained higher Delayed Recall and Logical Memory scores but not Verbal Fluency scores; none of the differences were statistically significant.Conclusion: Findings suggest that gender differences in CN and MCI groups are not statistically significant on the QMCI. However, replication of these findings in larger and more diverse samples are needed before firm conclusions can be drawn.

Funding Disclosure: NIH/NIA R61AG069780

Poster Theme Group C: Clinical Manifestations

C2. Neuropsychology

Poster #39

ANALYZING DIRECT EFFECTS OF VARIOUS DEMOGRAPHIC FACTORS BETWEEN HISPANICS AND NON-HISPANIC WHITES ON BOSTON NAMING TEST PERFORMANCE

Presenting author: Paulina Devora, BA (Graduate Student, The University of Texas at Dallas)

TARCC-Based Project

The assessment of picture naming is commonly used in both clinical and research settings for diagnosing neurodegenerative disorders such as Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). The most widely used measure of confrontation naming is the Boston Naming Test (BNT), but performance can be affected by several demographic factors including age, level and quality of education, gender, and ethnicity. Prior studies have established that healthy Non-Hispanic Whites perform better on the BNT when compared to members of minority groups. However, factors underlying score discrepancies between different ethnic groups have not been fully explored. The current study examines data from cognitively normal Hispanic and Non-Hispanic White adults from the Longitudinal Continuation of Texas Alzheimer's Research and Care Consortium (TARCC) Hispanic Cohort project. Hierarchical regressions to test for ethnic differences between education and estimated VIQ as predictors of BNT were conducted. The modeling involved hierarchically entering sex, age, ethnicity, VIQ, and education, sequentially followed by Ethnicity X Education and Ethnicity X VIQ interaction terms. Ethnicity was observed to be differentially associated with BNT for the two ethnic groups. BNT was more strongly associated with education for Hispanics (R^2= 0.04) compared to Non-Hispanic Whites (R^2 = 0.01). Furthermore, BNT also was more strongly associated with VIQ for Hispanics (R^2 = 0.15) than for Non-Hispanic Whites (R^2 = 0.12). Thus, it can be concluded that education and estimated VIQ are both more strongly associated with BNT performance in Hispanics than in Non-Hispanic Whites, highlighting the importance of properly controlling for these factors when assessing for impairments in cognition.

Funding Disclosure: TARCC

Poster Theme Group C: Clinical Manifestations

C2. Neuropsychology

Poster #40

NEUROPSYCHOLOGICAL PROFILE OF AGE-RELATED CHANGES IN MILD INTELLECTUAL DISABILITY: CASE REPORT

Presenting author: Lubnaa Abdullah, PsyD, ABPP (Assistant Professor, University of Texas Rio Grande Valley)

BACKGROUND: There is available research that highlights the neuropsychological pattern of aging in severe and highly debilitating forms of intellectual disability (ID), such as Down's Syndrome. However, less is known about the neuropsychology of aging and memory in mild or acquired forms of ID. METHOD: The following case illustrates a neurocognitive profile in a 67 year-old, cis-gender, Caucasian male with a previous diagnosis of Major Depressive Disorder (MDD). He complains of lonliness, chronic suicidal ideation and plan with one previous suicide attempt, recent memory changes, confusion, and exploitation by others requiring intervention by Adult Protective Services (APS). RESULT: Results of his neuropsychological evaluation demonstrate an RIAS-2 IQ of 64, and variable performance in verbal, memory and executive functioning. He is diagnosed with mild ID and age-related memory changes. Assessment reveals a complex psychiatric profile associated with severe psychosocial trauma. He is treated with sertraline injections and recommended for social services and milieu therapy. This case will discuss the implications for assessment of abnormal aging in the ID population and the psychiatric functioning of individuals with ID in later life. Recommendations regarding diagnostic considerations will be discussed. CONCLUSION: The assessment of aging in geriatrics with mild forms of ID requires the consideration of many factors that remain sensitive to pre-existing deficits and functioning.

Funding Disclosure: None

Poster Theme Group C: Clinical Manifestations

C2. Neuropsychology

Poster #41

EXECUTIVE FUNCTIONING IS AN IMPORTANT PREDICTOR OF LIFE EXPECTANCY IN THOSE WITH ALL-CAUSE DEMENTIA

Presenting author: Jeff Schaffert, PhD (Assistant Professor, UT Southwestern Medical Center)

Background: Neuropsychiatric, functional, motor, and demographic factors have been associated with life expectancy (LE) in those with dementia. Recent findings suggested cognition (assessed by the Mini-Mental State Exam [MMSE]) to be the strongest predictor of LE in Alzheimer's disease (AD; Schaffert et al., 2022). We evaluated if more detailed neuropsychological scores predict LE in a larger sample of individuals with all-cause dementia. Method: Participants were 4,090 deceased individuals (Mean age=74.5, Mean education=14.8, Male=44%, White=90%, Non-Hispanic=96%) with all-cause dementia (at visit 1, AD=78%) from the National Alzheimer's Coordinating Center. Three index scores [executive function/speed/attention (EFAS), language, memory] were calculated from the NACC neuropsychological batteries. Variables (from visit 1) were entered into a forward regression model ($p<.001$ as point-of-entry) to predict days of LE, and included: age, gender, race (white/non-white), ethnicity (Hispanic/Non-Hispanic), diagnosis (AD/non-AD), abnormal neurological exam (yes/no), Functional Activities Questionnaire (FAQ, total score), Neuropsychiatric Inventory Questionnaire (NPI-Q, total score), MMSE, and EFAS, language, and memory composite Z-scores. Results: Performance on the EFAS composite explained the most variance in LE ($R2=.065$), followed by age ($R2=.044$), diagnosis ($R2=.023$), FAQ ($R2=.016$), gender ($R2=.012$), abnormal neurological exam ($R2=.006$), NPI-Q ($R2=.004$), language abilities ($R2=.003$), and Hispanic ethnicity ($R2=.003$). Plus/minus one Z-score on the EFAS composite predicted 158 days of LE, and each year of age predicted 27 days of LE. Conclusions: EFAS performance and age explained >10% of LE variance. The MMSE failed to predict LE in this model that included more detailed neuropsychological data. EFAS impairment may be a more important predictor of LE compared to other neurocognitive domains and cognitive screeners.

Funding Disclosure: None

Poster Theme Group C: Clinical Manifestations

C2. Neuropsychology

Poster #42

THE ASSOCIATION OF NEIGHBORHOOD TRUST AND VIOLENCE WITH WHITE MATTER INTEGRITY IN A DIVERSE SAMPLE

Presenting author: Anthony Joseph Longoria, MS (Graduate Student, UT Southwestern Medical Center)

Objective: Hispanic and non-Hispanic Black older adults are at increased risk of dementia compared with non-Hispanic Whites. Cerebral white matter disease may contribute to this disparity, though little is known about how factors such as neighborhood disadvantage and perceived economic status may relate to white matter integrity in diverse groups. Method: Participants from a population-based, multiethnic cohort (N=2766; Female=58%; Black=48%; Hispanic=14%) completed a measure of neighborhood perceptions ("resources," "trust," "violence") and perceived SES ("access to food," "access to healthcare") and underwent 3T brain MRI with 2D FLAIR and 3D T1-weighted sequences to assess white matter hyperintensity (WMH) burden and white matter volume (WMV), respectively. Linear regression models examined associations among these variables controlling for demographic and traditional SES variables (income, education), followed by post-hoc analyses by race/ethnicity and sex. Results: Reported income, education, ethnoracial group, and sex were associated with WMH in the overall sample (ps<.05), and "trust," "access to healthcare," income, education, race/ethnicity, and sex were significantly associated with cerebral WMV. Post-hoc analyses revealed "violence" was associated with more WMH in Black women ($p<.05, \beta=-0.12$), lower "trust" was associated with lower WMV in Hispanic men ($p<.05, \beta=0.22$), and lower "access to medical care" was associated with lower WMV in White women ($p<.05, \beta=-0.18$). Conclusions: Neighborhood disadvantage and perceived SES were significantly associated with indicators of white matter pathology, with differential relationships across race and sex. Findings may reflect disproportionate environmental and social stressors encountered by some groups. Future analyses will examine whether these sociocultural factors relate to white matter burden and cognitive function later in life.

Funding Disclosure: Moss Heart Trust

Poster Theme Group C: Clinical Manifestations

C2. Neuropsychology

Poster #43

ASSESSING THE EXTERNAL VALIDITY OF A MAGNETOENCEPHALOGRAPHY-BASED VERBAL WORKING MEMORY TASK IN COGNITIVELY HEALTHY ADULTS

Presenting author: Sahil Chilukuri, BS (Research Intern, UT Southwestern Medical Center)

Introduction: Verbal working memory (VWM) encompasses the temporary maintenance and/or manipulation of verbal information to be used towards concurrent processing, and in prior studies we have developed and validated a Sternberg- type VWM task to be performed during magnetoencephalographic (MEG) neuroimaging. However, how performance on the VWM task relates to performance on other well-established neuropsychological instruments, that are commonly administered in both clinical and research settings, is unknown. The goal of the present investigation was to assess the external validity of the MEG-based VWM task. Methods: Fifty cognitively healthy adults (29 Female, M age = 59.04) performed the VWM task during MEG. During the task, participants were presented with sets of 6 letters (encoding) and, following a brief delay (maintenance), responded as to whether a test letter was in the previous 6 letters (retrieval). 128 trials were collected and average reaction time across correct trials (ms) and accuracy (% correct) were computed per participant. Participants also completed an animal fluency task (AF), the Weschler test for adult reading (WTAR), and the Montreal Cognitive Assessment (MoCA) outside of the scanner. Partial correlations were computed to assess the relationships between VWM performance (accuracy, reaction time) and neuropsychological performance (AF, WTAR, MoCA), while controlling for age, and a Bonferroni correction was applied. Results: There was a significant relationship found between VWM accuracy and performance on the WTAR ($pr = 0.487$, $p<0.001$) and MoCA ($pr= 0.455$, $p= 0.001$). VWM reaction time was not significantly related to neuropsychological task performance. Conclusion: The external validity of the VWM task (the extent to which task results are generalizable to real world situations) has been demonstrated to a certain degree, but further analysis which incorporates a broader range of neuropsychological metrics is necessary. In future analyses, the MEG-derived neural oscillatory dynamics underlying VWM-task performance should also be utilized to investigate neurobehavioral relationships.

Funding Disclosure: None

Poster Theme Group C: Clinical Manifestations

C2. Neuropsychology

Poster #44

PRELIMINARY EXPLORATION OF A NOVEL SPEECH ANALYSIS ALGORITHM TO DETECT COGNITIVE IMPAIRMENT IN A SPANISH POPULATION

Presenting author: Alyssa Kaser, BA (Graduate Student, UT Southwestern Medical Center)

Background: Early detection of mild cognitive impairment (MCI) and dementia is crucial for initiation of treatment and access to appropriate care. While comprehensive neuropsychological assessment is often an intrinsic part of the diagnostic process, access to services may be limited and cannot be utilized effectively on a large scale. For these reasons, novel technologies to screen for cognitive changes in older individuals are evolving as new avenues for early detection. The present study presents preliminary data on a new technology that uses automated linguistic analysis software to screen for MCI and dementia. Methods: Data were collected from 148 Spanish-speaking individuals recruited in Spain (MAge=74.4, MEducation=12.93, 56.7% females) of whom 78 were diagnosed as cognitively normal [CN; MMMSE = 28.51 (1.39)], 49 as MCI [MMMSE = 25.65 (2.94)], and 21 as all-cause dementia [MMMSE = 22.52 (2.06)]. Participants were recorded performing various verbal tasks [Animal fluency, phonemic (F) fluency, Cookie Theft Description, and CERAD list learning task]. Recordings were processed via text-transcription and sound signal processing techniques. Receiver Operating Characteristic (ROC) analysis was conducted to determine sensitivity and specificity of predicted algorithm performance [CN vs. impaired (MCI or dementia)] against clinical diagnoses. General linear modeling was used to test whether age, sex, education, and multilingualism significantly predicted logistically transformed weighted algorithm scores. Results: Scores were transformed to logit scores, with significant differences in mean logit scores between all groups ($p<.001$). Logit-inverse transformation of mean logit scores (possible range 0 -1) resulted in values of 0.06 for CN, 0.90 for MCI, and 0.99 for all-cause dementia groups. ROC curve analyses revealed the algorithm obtained a total area under the curve of 0.92, with an overall accuracy of 86.8%, a sensitivity of 0.92, and specificity of 0.82. Age was identified as a significant predictor (beta = 0.22; $p <0.01$) of algorithm output. Conclusions: Findings provide initial support for the utility of an automated speech analysis algorithm to detect cognitive impairment quickly and efficiently in a Spanish-speaking population. Additional research is needed to validate this novel methodology in other languages, as this may represent a promising cross-cultural screening method for MCI and dementia detection.

Funding Disclosure: AcceXible Impacto, Sociedad Limitada

Poster Theme Group C: Clinical Manifestations

C2. Neuropsychology

Poster #45

NOT NORMAL BUT NOT MCI: COURSE OF MEMORY OVER TIME

Presenting author: Michael Conley, MCRC (Graduate Student, UT Southwestern Medical Center)

TARCC-Based Project

Objective: A diagnosis of mild cognitive impairment (MCI) requires memory complaint and objective memory impairment. This study aimed to compare memory performances over time in individuals who do not meet traditional MCI criteria to those with normal cognition (NC) and those who converted to MCI. Participants and Methods: 827 participants from a longitudinal sample of the Texas Alzheimer's Research and Care Consortium were classified by retrospective diagnosis: 1) NC over 5 visits (n=511, 71% female; 42% Latinx/Hispanic), 2) baseline NC to amnestic MCI (n=62; 63% female; 57% Latinx/Hispanic), 3) subjective memory complaint (SMC) at last visit (n=133; 58% female; 70% Latinx/Hispanic), and 4) impaired but not MCI (i.e., no complaint) at last visit (n=121; 71% female; 60% Latinx/Hispanic). A memory composite (z-score) was created from the CERAD list-learning task (immediate, delayed, and recognition-discrimination) and Wechsler Memory Scale (Immediate and Delayed Logical Memory and Visual Reproduction) to evaluate memory performance over time. Linear mixed-models adjusting for age, education, sex, ethnicity, and number of APOE e4 alleles evaluated memory performance and depression over time. Results: At baseline, groups differed by age ($F=22.82$; $p<.001$), education ($F=8.60$; $p<.001$), MMSE scores ($F=9.38$; $p<.001$), depression (GDS-30) ($F=3.56$; $p=.015$), and memory performance ($F=24.29$; $p<.001$). A significant group X time interaction was observed ($F=4.83$, $p<.001$). Memory improved in both the SMC and NC groups, remained stable in the impaired but not MCI group, and declined in those who converted to amnestic MCI. Depression scores also showed a significant group X time interaction ($F=2.43$; $p=.004$), in which the NC to MCI group endorsed slightly more depression symptoms over time, while other groups declined or remained stable. Conclusions: Memory trajectories in this diverse sample differed across groups. Individuals with SMC but without objective memory impairment and normal controls showed some improvement in memory over time, presumably due to practice effects. Those with subtle memory impairments but no complaint (i.e., did not meet MCI criteria) remained stable and those who converted to amnestic MCI had worse memory across time. The stability of memory performances in the impaired not MCI group suggests these subtle memory inefficiencies may be longstanding or unperceived.

Funding Disclosure: TARCC

Poster Theme Group D: Dementia Care and Psychosocial Factors

D1. Dementia Care Research (nonpharmacological)

Poster #46

ASSESSING CHALLENGES OF CAREGIVERS OF ELDERLY PEOPLE WITH DEMENTIA IN TEXAS TO ESTABLISH A DIGITAL PLATFORM: A QUALITATIVE STUDY

Presenting author: Jeswin Vennatt, MBA (Medical Student, Texas A&M University Health Science Center)

Background: The caregivers of people living with Alzheimer's disease and dementia face a high degree of psychological, physical, and financial stress. However, the needs of caregivers of people with dementia are poorly understood. The objectives of the study are to identify the living, financial, and legal challenges faced by caregivers of people living with dementia, and to understand their expected features and needs in order to develop a digital platform. Method: A qualitative study was conducted among unpaid caregivers for people with dementia in Texas. Caregivers who were 1) non-paid caregivers for dementia patients, 2) actively involved in the care recipient's living, legal or financial decisions, and 3) adults (18 years and older) were included in the study. A one-on-one semi-structured interview was conducted via Zoom with each participant. The interviews are transcribed and analyzed using NVivo (Version 12.0) for thematic analysis. Results: The pre-screening survey was completed by 323 respondents, and 28 of them met the eligibility criteria for the interview. According to survey responses, 64.6% of respondents reported challenges in making financial or legal decisions for their loved ones. The main challenges reported by caregivers included balancing other family obligations and work, financial burdens, finding reliable providers and services, providing transportation, tension with family members, navigating the legal process, coping with catastrophic events, and lack of mental health support. The digital platform is expected to include support groups, education materials, communication with doctors, psychologists, psychiatrists, or licensed professional counselors to assist caregivers, peer-reviewed research evidence about dementia, task-based reminders (such as taking medication), and a comprehensive database to locate reliable services. Conclusion: Caregivers of people with dementia face a variety of living, financial, and legal challenges. Innovative digital platforms and community participatory initiatives need to be developed in order to provide caregivers with support. These innovations can empower caregivers and result in the successful aging of their loved ones.

Funding Disclosure: NIA Small Business Innovation Research Grant (SBIR) Grant

Poster Theme Group D: Dementia Care and Psychosocial Factors

D1. Dementia Care Research (nonpharmacological)

Poster #47

CAREGIVER-REPORTED DECLINES IN ACTIVITIES OF DAILY LIVING AMONG PERSONS WITH MILD DEMENTIA DURING THE COVID-19 PANDEMIC

Presenting author: Matthew Lee Smith, PhD, MPH, CHES (Professor, Texas A&M University)

Background. Although cognitive and physical functioning are expected to decline over time among persons living with dementia, the COVID-19 pandemic may have accelerated these declines because of required shut-downs, stay-at-home orders, and service disruptions. This study examines the naturally occurring declines in activities of daily living (ADL) among persons with mild dementia during the early stages of the COVID-19 pandemic. Methods. As part of an NIH-funded study, caregivers (CG) were asked to manually assess their care recipients (CR) each month using the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL). Assessments took place from October 2020 to August 2022, and the maximum study duration was 18 months. The ADCS-ADL consists of 23 items, with 6 basic ADL (BADL) items and 17 instrumental ADL (IADL) items. Analyses included 110 CR. Cox regression models were fitted to time to 25% score decreases in the total ADCS-ADL, BADL, and IADL over the study period. Each regression model controlled for the CR's age, sex, and baseline Mini-Mental State Examination (MMSE) score. Sensitivity analyses were performed based on if the CR lived with their CG. Results: The majority of CR was female (57.3%) and lived with their CG (56.4%). On average, CR were age 78.7 (±8.5) years, had a baseline MMSE of 22.6 (±2.7), and had a baseline ADCS-ADL of 56.0 (±16.3). On average, a one unit decrease in baseline ADCS-ADL corresponded to a 3% hazard rate increase for a 25% decline in ADCS-ADL over time (HR=0.973, P=0.006). For BADL and IADL, a one unit decrease in baseline MMSE corresponded to a 14% (HR=0.876, P=0.021) and 13% (HR=0.883, P=0.027) hazard rate increase for a 25% decline over time, respectively. In sensitivity analyses, CR living with their CG reported more dramatic declines in total ADCS-ADL, BADL, and IADL scores compared to CR not living with their CG, respectively. Conclusions: This study investigates factors associated with rates of ADL decline among persons with mild dementia during the COVID-19 pandemic. Findings suggest that CG residing with CR and baseline MMSE are useful for the timely initiation of additional care-related supports and services.

Funding Disclosure: This study was funded by the National Institute on Aging (NIA) as part of an SBIR (#R44AG065118-03)..

Poster Theme Group D: Dementia Care and Psychosocial Factors

D1. Dementia Care Research (nonpharmacological)

Poster #48

UTILIZATION AND PERCEIVED USEFULNESS OF MONITORING TECHNOLOGY FOR FAMILY CAREGIVERS OF PEOPLE LIVING WITH DEMENTIA

Presenting author: Matthew Lee Smith, PhD, MPH, CHES (Professor, Texas A&M University)

TARCC-Based Project

Despite the proliferation of technology-based solutions for caregiving, less is known about their utilization and perceived value among caregivers of persons living with dementia (PLWD). In collaboration with three TARCC sites (Texas A&M, University of North Texas, and University of Texas at Austin), PLWD and family caregiver dyads were recruited from clinical and community sites. PLWDs were asked to wear a GPS-based wearable device, which were paired with caregivers' smartphone application that enabled location monitoring. The wearable device was equipped with an accelerometer and call functions. After three months, researchers called caregivers to ask about their utilization of the system (i.e., wearable device paired with smartphone application) and the perceived value of this caregiving technology. Forty-one caregivers completed follow-up telephone interviews. About 70% of caregivers reported their care recipient wore the wearable device daily, and 39.1% of caregivers used the smartphone application daily. Approximately 31% of caregivers reported daily use of the tracking feature, 30.8% reported daily use of the "safe zone" feature (i.e., geo-fencing), and 17.1% reported daily use of the two-way calling feature. About 39% of caregivers were extremely satisfied with the system, 43.6% found the system extremely easy to use, and 46.2% found the system extremely useful for caregiving. On average, caregivers with higher baseline Zarit Burden Interview scores were more satisfied with the system ($f=3.75$, $P=0.034$) and found the system to be more useful with their caregiving ($f=5.97$, $P=0.006$). Findings suggest that caregiver burden may drive the perceived usefulness of, and satisfaction with, technology-based solutions.

Funding Disclosure: TARCC

Poster Theme Group D: Dementia Care and Psychosocial Factors

D1. Dementia Care Research (nonpharmacological)

Poster #49

GENDER DIFFERENCES IN CARE NETWORKS OF OLDER ADULTS WITH DEMENTIA

Presenting author: Phillip A. Cantu, PhD (Assistant Professor, University of Texas Medical Branch at Galveston)

Background: Gender differences in care networks, the use of paid and informal caregivers, and the need for care among older adults with dementia remain unclear. Objective: To evaluate gender differences in care networks of community dwelling older adults with dementia in the United States. Methods: We used data from the 2018 wave of the Health and Retirement Survey, a nationally representative sample of older adults in the United States. We included individuals aged 70 and older with dementia. We estimated the total annual care hours received from paid and unpaid informal caregivers. Paid care was categorized as formal institutional care, paid care from family and friends, and care paid by insurance. Informal care was categorized as from a spouse, children, or other sources. We used OLS regression to predict gender differences in types of care controlling for demographic characteristics, wealth, and level of disability. Results: Our sample was 61.3% women, with a mean age of 85.1. Women received on average 1,384 total hours of care a year compared to 1,015 hours for men, with a greater proportion of women's care coming from paid sources. Differences in hours of care from all sources were explained by higher levels of disability for women, except for differences in hours of care from spouses and children. Conclusions: There were more women than men with dementia and, as a result, they had higher levels of disability. The greater cost of care for older women is reflected by more hours of formal and informal care.

Funding Disclosure: K12HD052023 P30AG059300 P30AG059301

Poster Theme Group D: Dementia Care and Psychosocial Factors

D1. Dementia Care Research (nonpharmacological)

Poster #50

FEASIBILITY OF THE CART IN-HOME TECHNOLOGY PLATFORM IN A PILOT STUDY OF HISPANIC OLDER ADULTS RESIDING IN SOUTH TEXAS

Presenting author: Julia Mathews, BS (Graduate Student, UT Health Science Center San Antonio)

Background: As the prevalence of Alzheimer's disease (AD) rises, the development of effective screening tools are needed to aid in earlier AD diagnosis. Early identification is important to help maintain patient and caregiver quality of life, as well as to improve patient care. In the USA, Hispanic and Non-Hispanic Black adults are at a disproportionately higher risk of developing dementia than non-Hispanic whites, but are poorly represented in AD research. Researchers at OHSU developed the Collaborative Aging Research using Technology (CART) platform, which has the potential to remotely and continuously detect early declines in cognition by analyzing changes in everyday activity levels. Although the platform is promising, installing digital technology in a home can cause concerns about privacy and user friendliness, especially in older adults. In our CART pilot study at UTHSCSA, we sought to determine the feasibility of the CART platform in an underrepresented, mostly Hispanic population and to gain insight from their experiences. Method: A total of seven participants were enrolled in our year-long pilot study. The CART technology platform consisted of a wearable watch, digital scale, electronic pillbox, bed mat (to measure sleep), and wall-mounted movement sensors, as well as a small computer to upload device data to secure servers. Participants completed the UDS3 neuropsychological battery at baseline and the one-year end of study. Participants also completed an end of study user experiences survey. Result: Our cohort consisted of five Hispanic, one non-Hispanic Black, and one non-Hispanic white participant, ages 65-80. There were no significant changes in cognition over the course of the study (all $p>0.05$); however, self-reported depressive symptoms reduced ($p=0.034$). The responses to the user experience survey demonstrated that our participants found the technology installation satisfactory (43%) or very satisfactory (57%) and perceived that their privacy concerns were addressed satisfactorily (43%) or very satisfactorily (57%). Conclusion: Our results suggest that the CART platform was widely accepted by our mostly Hispanic older adult participants and that they were comfortable with the study devices. The findings support the feasibility of increasing representation of diverse older adults in dementia prevention research using digital devices.

Funding Disclosure: NIH P30AG066546

Poster Theme Group D: Dementia Care and Psychosocial Factors

D1. Dementia Care Research (nonpharmacological)

Poster #51

VALIDATION OF THE MULTIDIMENSIONAL HEALTH PERCEPTIONS QUESTIONNAIRE IN CARE PARTNERS OF INDIVIDUALS WITH ALZHEIMER'S DISEASE AND RELATED DEMENTIAS (ADRD)

Presenting author: Alexandra B Holland, LMSW (Psychological Associate, UT Southwestern Medical Center)

TARCC-Based Project

Background: Health beliefs affect healthcare engagement, treatment adherence and uptake, and clinical outcomes. Understanding these beliefs is a critical component of person- and family-centered care. We developed the Multidimensional Health Perceptions Questionnaire (MHPQ) as an all-encompassing measure of health perceptions. The MHPQ has seven health perceptions subscales validated among both English and Spanish-speakers in the general population (content validity index of 98.1%; Cronbach's alphas >.70 for all subscales). Our aim is to describe the health perceptions of care partners of individuals with Alzheimer's Disease and Related Dementias (ADRD) participating in our Care Partners in Dementia Problem Solving (CaDeS) trial, a TARCC collaborative project. Method: Care partners of individuals with ADRD participating in CaDeS completed the MHPQ. It includes 65 items rated on a 1-to-5 agreement scale with items and instructions at a modified SMOG reading level of 6th grade in English and 8th grade in Spanish. It has 7 subscales yielding average scores (1-5): (1) anticipated discrimination and judgment, (2) spiritual health beliefs, (3) social and emotional wellbeing beliefs, (4) confidence and trust in healthcare providers and medicine, (5) health self-efficacy/internal locus of control, (6) trust in social health advice, and (7) health literacy. Results: N=71 care partners are included in this analysis. Internal consistency reliabilities were acceptable to good for all but 2 subscales (Cronbach's alphas= .748-.856; .584-.682). Means and standard deviations for all subscales were as follows: (1) 1.9155 (SD .5259); (2) 2.685 (SD .63093); (3) 3.518 (SD .41274); (4) 3.5813 (SD .37023); (5) 3.9525 (SD .44036); (6) 2.6268 (SD .53264); (7) 4.2394 (SD .43254). We will further present differences in health perceptions by race, ethnicity, language, age, and relationship (e.g., spouse, child, etc.) Conclusion: By understanding care partner health perceptions and how this affects their health outcomes, healthcare providers can adapt their intervention approaches for an increasingly diverse population and implement patient/family-centered care. We plan to examine how differences in health perceptions affect engagement, uptake, and outcomes after Problem-Solving Training (PST), at the completion of the CaDeS trial. These data will inform important adaptations to PST that may be required based on care partners' health perceptions.

Funding Disclosure: TARCC

Poster Theme Group D: Dementia Care and Psychosocial Factors

D1. Dementia Care Research (nonpharmacological)

Poster #52

MACHINE LEARNING ALGORITHM TO PREDICT DURATION TO FULL TIME CARE AFTER ALZHEIMER'S DISEASE DIAGNOSIS

Presenting author: Jessica Helphrey (Graduate Student, UT Southwestern Medical Center)

Background: Patients and their families often ask clinicians to estimate when full-time care (FTC) will be needed after Alzheimer's Disease (AD) is diagnosed. Our objective was to develop a clinically relevant, data-driven predictive model, that provides precision and user-friendliness, using machine learning to estimate time to FTC in AD based on information gathered from clinical interview plus neuropsychological data. Method: The National Alzheimer's Coordinating Center dataset was used to examine 3,809 participants (M age at AD diagnosis = 76.05, SD = 9.76; 47.10% male; 87.20% Caucasian) with AD dementia aged ≥50 years, had no history of stroke, and not dependent on others for basic activities of daily living at time of diagnosis. To develop a predictive model for time until FTC, supervised machine learning algorithms were implemented. In Model 1, 29 variables captured at the time of AD diagnosis were included. In Model 2, additional neuropsychological variables were added. Algorithms were trained and tested, cross validation was conducted using bootstrapping, and accuracy and precision calculations were performed. Result: The average time to requiring FTC after AD diagnosis was 3.32 years. For the clinical interview model (Model 1), younger age of onset, use of cholinesterase inhibitor medication, incontinence, apathy, living alone, a positive family history of dementia, and lower MMSE score significantly predicted duration to FTC. In the clinical interview + neuropsychological variables model (Model 2), the clinical predictors remained significant, and lower Boston Naming Test and Digit-Symbol Coding scores showed the largest effects in predicting duration to FTC. After testing prediction models, the average estimated time to FTC using the clinical interview model was within an average of 5.2 months of the recorded event and within an average of 5.8 months for the model with neuropsychological data. Conclusion: Predicting when individuals diagnosed with AD will need FTC is important as the transition often carries significant financial costs related to caregiving. Duration to FTC was predicted by clinical and neuropsychological variables that are easily obtained during standard dementia evaluations. Implementation of the model for prediction of FTC in cases showed encouraging prognostic accuracy.

Funding Disclosure: AWARE foundation

Poster Theme Group D: Dementia Care and Psychosocial Factors

D2. Psychosocial Factors and Environmental Design

Poster #53

A PUBLIC HEALTH CRISIS IN RURAL WEST TEXAS: NEUROCOGNITIVE DISPARITIES BETWEEN HISPANIC AND NON-HISPANIC COMMUNITIES MODERATED BY DEPRESSION

Presenting author: Carol Fadalla, BA (Graduate Student, Texas Tech University)

Background: Hispanic adults are at increased risk for neurocognitive decline compared to other racial-ethnic minorities. Few studies have examined the prevalence of neurocognitive decline among Hispanics living in rural West Texas-a population deeply underserved. The study explored whether depression moderated prevalence utilizing data from Project FRONTIER (Facing Rural Obstacles to Healthcare Now Through Intervention, Education, & Research). Methods: 1,842 participants (Mage = 59.68 years, SDage = 12.21) 1,053 Hispanics and 752 non-Hispanics, from multiple rural counties in West Texas between June 2006 and January 2022. We evaluated neuropsychological testing using five measures: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), The Trails Making Test A and B, and Clock Drawing 1 and 2. Geriatric Depression Scale was used to assess depression and we dichotomized using a validated cutoff of "no depression" (0-10) and "mild/severe depression" (11-30). Results: The MANOVA identified a significant interaction between ethnicity and depression on neurocognitive functioning (Roy's Largest Root = 3.56, $F(5, 1{,}548)$, $p = 0.003$, $\eta 2p = 0.01$). More specifically, non-Hispanic individuals who reported mild/severe depression had worse neurocognitive functioning compared to participants with no depression. However, there was no difference for Hispanic participants who reported mild/severe depression compared to no depression. A post-hoc ANOVA revealed a significant main effect on neurocognitive functioning (RBANDS) for ethnicity ($F(5, 1{,}549)$, $p < .001$, $\eta 2p = 0.06$), as participants who identified as Hispanic ($M = 79.41$ and $SD = 0.57$) had lower overall neurocognitive functioning than non-Hispanic ($M = 88.38$; $SD = 0.78$) participants. On indicators of neurocognitive functioning, a significant main effect for depression was found ($F(5, 1{,}549) = 13.62$, $p < 0.001$, $\eta 2p = 0.04$). Conclusion: Results are consistent with the minority stress model, which states racial-ethnic minorities are exposed to chronic stressors, which negatively influences functioning. Non-Hispanic individuals encounter fewer chronic stressors than minorities and, the introduction of stressors, like depression, may impact neurocognitive functioning-unlike Hispanic individuals. Previous studies suggest chronic life stressors are equally detrimental to cognitive functioning in individuals with and without depression. Results support the need for culturally tailored interventions because underlying factors related to cognitive function differ, such as depression in non-minority individuals.

Funding Disclosure: None

Poster Theme Group D: Dementia Care and Psychosocial Factors

D2. Psychosocial Factors and Environmental Design

Poster #54

NEIGHBORHOOD PHYSICAL DISORDER AND ARCHITECTURAL FEATURES OF STREETSCAPES OF PARTICIPANTS OF THE LONGITUDINAL HISPANIC COHORT IN CAMERON COUNTY: PRELIMINARY RESULTS

Presenting author: Cristian Maestre-Nunez, BArch (Graduate Student, University of Texas Rio Grande Valley)

Background: An estimated 23% of global deaths are due to the environments in which people live. We aim to characterize the level and characteristic of neighborhood physical disorder in areas where participants of the Longitudinal Hispanic Cohort reside in the Rio Grande Valley, Texas. In addition we will characterize prevalent architectural features in streetscapes of one of the counties, Cameron, Texas. Methods: We used Google Street View Imagery to rate elements of the neighborhood physical disorder score in the Rio Grande Valley. In addition we studied different architectural attributes of the streetscape in Cameron County. Elements analyzed included: site connectivity with context, pedestrian quality, scale of buildings, architectural elements, landscaping, and signage. Results: We generated a map to visualize the distribution and intensity of neighborhood physical disorder in the Rio Grande Valley. Results indicate that the distribution is heterogeneous within each of the cities and between cities. Some of the most frequent architectural features in streetscapes are: -There is little interrelationship between open spaces and buildings. Parking lots are usually in front of buildings. -Urban streetscapes are mostly designed for motorists and not for pedestrians. -Most buildings are at human scale, with few buildings over 5 floors. -The most common residential architectural style is Ranch-Style house characterized by single-story, open space concept, almost non-existent ornaments, and low-pitch rooflines. -The tall palms characteristic of the region add scale to street edges; however, their canopies are high and small, and few provide shade. -Blank walls are common, with few exhibiting architectural features that enhance streetscapes. -Most signage is commercial and does not enhance building character or the pedestrian experience. Discussion: Neighborhood physical disorder is high and heterogenous in the area. We identified the most frequent typologies of architectural design in Cameron County. This information will be particularly relevant for community advocates and city planners as well as to residents and researchers interested in understanding influences on urban health.

Funding Disclosure: NIH DP1AG069870, P30AG059305 and P30AG066546

Poster Theme Group D: Dementia Care Practice

E1. Dementia Care Practice (descriptive research)

Poster #55

SERVICE USAGE AMONG CARE PARTNERS OF ADULTS WITH DEMENTIA IN THE CADES TRIAL

Presenting author: Jill Morales, MS (Research Study Coordinator, UT Southwestern Medical Center)

TARCC-Based Project

Background: Participants in the Care Partners in Dementia Problem-Training (CaDeS) study are care partners who are involved in the care of a loved one with Alzheimer's Disease or related dementias (ADRD). Care partners include parents, adult children, other family members, or close friends. They perform many jobs to assist their loved ones; however, they may need the assistance of community resources (e.g., home care, adult daycare, etc.). Here, we examine whether the care partner's relationship type (e.g., spouse, adult child, etc.) was associated with the types of community resources and services they used. Method: Care partners completed an initial evaluation that included information about their demographics and other personal information. They were asked to report their relationship with the person with ADRD and rate the quality of that relationship on a 10-point scale; higher ratings indicate higher relationship quality. They were also asked about community resources and services used as a care partner. Result: Eighty-two care partners were included in analyses. Care partner relationships with the care recipient were as follows: n=44 spouses, n=19 parents, n=13 adult children, n=4 other family member, and n=2 siblings. Over 90% of care partners indicated that they used adult daycare, caregiving education programs, written resource materials, respite care, support groups, and/or help from their family or friends. All children (n=13) used these community resources. Spouses, parents, and children reported that they also used community resources such as Meals on Wheels, counseling, care managers, and other community programs available to them. Conclusion: Care partners perform many services for their loved ones, and can benefit from various community resources. While almost all care partners in the CaDeS trial used community resources, adult children care partners seemed to especially rely on these resources. This is consistent with other studies indicating that adult children care partners may experience more feelings of burden and distress than other family caregivers. Unfortunately, not everyone has resources available to them; therefore, future efforts are needed to identify what resources are most beneficial to care partners so that service access can be prioritized.

Funding Disclosure: TARCC

Poster Theme Group F: Drug Development

F1. Human

Poster #56

REDUCED PREVALENCE OF DEMENTIA IN PATIENTS TREATED WITH BRAIN-PENETRANT CALCINEURIN INHIBITION

Presenting author: Jacqueline Silva, BS (Graduate Student, University of Texas Medical Branch at Galveston)

Background: Evidence suggests that patients treated with calcineurin inhibitors (CNIs) have a lower prevalence of dementia, including Alzheimer's disease (AD), compared to the general population. While plausible, whether the observed effects are related to brain penetrance remains unresolved. To address this question, we interrogated electronic medical records comparing dementia prevalence in patients treated with the brain penetrant CNI tacrolimus to patients treated with the non-brain penetrant CNI cyclosporine. Methods: We conducted a retrospective cohort study using the TriNetX global health research network. Patients currently over age 65 were included based on prescription of tacrolimus or cyclosporine. Patients who were prescribed both drugs were excluded. Cohorts were propensity-score matched by age, race, sex, and a range of other covariates. The outcomes examined were diagnosis of dementia, including AD, at least thirty days following earliest recorded drug treatment. Results: Of the 65,599 patients in each cohort, 2,587 (4.05%) of those prescribed tacrolimus and 2,929 (4.62%) of those prescribed cyclosporine were later diagnosed with dementia. Tacrolimus treatment was associated with a 12% risk reduction of developing dementia (relative risk of 0.88 of dementia in tacrolimus vs. cyclosporine, $p<0.0001$). Similar results were achieved when examining AD diagnoses separately (relative risk of 0.71 of AD in tacrolimus vs. cyclosporine, $p<0.0001$). Conclusion: The results suggest the brain penetrant CNI is associated with a lower prevalence of dementia, including AD, relative to the non-brain penetrant CNI. These data encourage clinical evaluation of localized delivery of tacrolimus to the brain as a viable therapeutic for prevention and treatment of dementia, including AD, with localized delivery potentially reducing systemic side effects.

Funding Disclosure: NIH R01AG060718

Poster Theme Group F: Drug Development

F2. Nonhuman

Poster #57

GAIT AND MOTOR CHANGES AS PREDICTORS OF ALZHEIMER 'S DISEASE IN INFECTED APP/PS1 MICE

Presenting author: Jocelin Reyes (Undergraduate Student, Texas A&M University)

Background: Aβ plaques and neuronal loss in regions of the brain responsible for cognition, such as the hippocampus and prefrontal cortex, characterize Alzheimer 's Disease (AD). Cognitive symptoms are commonly used to diagnose clinical AD, though recent studies show that changes in motor abilities may occur early in the disease, as AD pathology also develops in the motor cortices, striatum and substantia nigra. Understanding the projection of development of early deficits and determining if motor impairments are part of this early phenotype can aid in prediction of further decline in AD patients who do not yet present detectable cognitive impairment. Further, external insults such as minor chronic infection may be necessary to initiate the disease cascade, and may shed light into the mechanism of disease origination. We hypothesize that a low-grade nonpathological staph infection accelerates the disease process in the APP/PS1 mouse AD model. Methods: Male and female APP/PS1 and non transgenic mice were infected with Staphylococcus aureus (or PBS for control) via nasal inoculation starting at 12 weeks of age twice a week for 3 months. At 6 months of age, mice were tested for motor performance in the rotarod and DigiGait. Results: We observed no differences between vehicle groups of both genotypes. However, Staph infection impaired gait measures in APP/PS1 male mice. The same cohort was also impaired in the rotarod measures. Conclusion: Bacterial infection resulted in lower motor performance in the APP/PS1 mouse model, suggesting that added external insults may be necessary for development of disease-related early deficits.

Funding Disclosure: None

Poster Theme Group F: Drug Development

F2. Nonhuman

Poster #58

CONTINUOUS WAVE 670NM LED LIGHT THERAPY IMPROVES SHORT- AND LONG-TERM OBJECT RECOGNITION, LOCOMOTION, AND REDUCES PHOSPHORYLATED TAU BURDEN IN 3XTGAD

Presenting author: Kevin Johnson, BS (Graduate Student, University of Texas Medical Branch at Galveston)

Non-invasive therapeutic alternatives for Alzheimer's Disease (AD) are highly sought after due to their accessible nature and sustainability of use. Photobiomodulation (PBM) therapy uses 620-1100nm red to near-infrared light to modulate a variety of biological processes including neuroinflammation, amyloid and tau oligomerization, and apoptosis. 670nm red light has been shown to reduce synaptic vulnerability to amyloid-β oligomers in wild-type (WT) mice and reduce tau oligomerization in multiple mouse models of tauopathy. The 3xTgAD mouse model of AD neuropathology, expressing human APP, PS1, and tau mutations, develops an abundance of amyloid plaques and neurofibrillary tangles causing progressive cognitive dysfunction starting around 12 months of age. Here we sought to determine if 670nm light therapy could rescue cognitive and motor dysfunction and reduce tau hyperphosphorylation in 14-to-18-month-old 3xTgAD mice. METHODS: 14-to-18-month-old 3xTgAD mice were treated with continuous-wave 670nm LED light applied directly to the head for 90s per day, 5 days per week for 4 weeks. 3xTgAD sham and WT control animals were held under the LED device with the light turned off for the same amount of time. During the fourth week of treatment, spontaneous locomotor behavior was measured by placing animals in an empty chamber for 10 minutes and using ANY-maze software to track distance traveled, mobile time, mobile episodes, and latency to mobile episodes. Animals were then tested for working memory in the Y maze spontaneous alternation task and short-and long-term memory in the novel object recognition task during the last 2 days of treatment. At the completion of behavioral testing on treatment day 20, brains were collected for western blot analysis of total tau using the Tau5 antibody (Abcam) and phospho-tau (pTau) using the paired helical filament (PHF13.6) antibody (ThermoFisher). RESULTS: Light-treated 3xTgAD mice showed increased distance traveled compared to sham (17.43 ± 3.46 vs. 9.97 ± 3.03, one-way ANOVA $p=0.03$), and decreased immobile episodes (4.50 ± 1.92 vs 10.00 ± 1.83, one-way ANOVA $p=0.02$) in the spontaneous locomotor activity test. Light-treated animals also showed significant object recognition at 2 hours (DI 32.75 ± 7.71, one sample t-test $p<0.001$) and 24 hours (DI 44.14 ± 15.73, one sample t-test $p=0.001$) post-training.

Funding Disclosure: NIH R01AG06943302

Poster Theme Group F: Drug Development

F2. Nonhuman

Poster #59

SELECTIVE UPREGULATION OF THE MASTER REGULATOR E2F1 IN THE CEREBRAL VASCULATURE IMPROVES MEMORY IN AGED MICE

Presenting author: Jose Felix Moruno Manchon, PhD (Instructor, UT Health Science Center Houston)

TARCC-Based Project

Background: Brain aging is a major risk factor for the progression of Alzheimer's disease (AD) and Vascular contribution to cognitive impairment and dementia (VCID). VCID is identified by cognitive deficits caused by dysfunction of the cerebral endothelium and disruption of the blood brain barrier (BBB). With aging, cerebral endothelial cells (CEC) enter into a non-proliferative state of senescence characterized by DNA damage and a pro-inflammatory secretory phenotype that negatively affects the cerebral vasculature and central nervous system function. The mechanisms underlying endothelial senescence and their contribution to VCID are poorly understood. Inefficient DNA damage repair has been linked to vascular aging and senescence. Thus, targeting master regulators of DNA repair may increase genome stability and prevent senescence in the aged brain. E2F1 is a critical transcription factor that positively regulates the expression of genes involved in DNA repair pathways. From the existing literature, E2F1 prevents senescence in endothelial cells. We hypothesize that selective expression of E2F1 in brain endothelium can prevent endothelial senescence and improve cognitive function in aged mice. Methods: We used aged (18-months old) mice and cultured CEC derived from aged mice. We analyzed the transcriptome of cultured CEC transfected with an E2F1-encoding plasmid or an empty plasmid as control. We used an adenovirus construct to overexpress E2F1 specifically in the cerebral vasculature of aged mice, and evaluated isolated brain microvessels by immunostaining and evaluated spatial memory by behavioral tests. Results: We found that E2F1-overexpressing CEC derived from aged mice showed a reduced senescence-associated transcriptional profile, higher expression of DNA repair genes, and upregulation of tight junction gene expression, compared with control aged CEC. Micro-vessels isolated from aged mice showed hypo-phosphorylated E2F1 (reduced transcriptional activity) and enhanced p16INK4a (a tumor suppressor associated to senescence), compared with micro-vessels from young mice. Importantly, we found that selective upregulation of E2F1 in the cerebral vasculature improved spatial memory in aged mice. Conclusions: Our data suggest that selective upregulation of E2F1 in the cerebral vasculature can improve endothelial function and enhance spatial memory in aged mice.

Funding Disclosure: TARCC, American Heart Association, NIA

Poster Theme Group G: Public Health

G1. Epidemiology

Poster #60

ANALYZING RELATIONSHIPS BETWEEN FATTY LIVER DISEASE, VITAMIN D, ALCOHOL CONSUMPTION, AND COGNITIVE IMPAIRMENT IN A RURAL WEST TEXAS ELDERLY COHORT

Presenting author: Nicholas Vojtkofsky, BS (Graduate Student, Texas Tech University Health Sciences Center)

Background: As the proportion of the elderly population in the U.S. continues to grow, our understanding of cognitive dysfunction becomes increasingly important. One aspect of age-dependent cognitive decline that remains relatively understudied relates to the liver-brain axis. In a preclinical model, age-dependent changes in liver function have been demonstrated hepatic trapping of vitamin A (VA) accompanied by age-dependent cognitive decline and hippocampal deficiency of the bioactive metabolite of VA, retinoic acid, in the brain. In addition, human studies have shown that non-alcoholic fatty liver disease (NAFLD) disrupts hepatic retinoid homeostasis. However, the relationship between fatty liver disease and cognition is not clear. This study aims to investigate the relationship between cognitive impairment and biomarkers of liver function as well as Vitamin D (VD) status and alcohol consumption. Methods: Cognitive function was compared to a battery of blood-based biomarkers for liver dysfunction and disease available in 299 Project FRONTIER participants (ages 62±12, 71% female, and 41% Hispanic) using Pearson correlations and linear regression analysis. Our approach examined the Repeatable Battery for Assessment of Neuropsychological Status total score (rbttlsc), serum biomarkers of liver dysfunction used in a liver function panel (ggt, ast, alt, alkp, bw_tprot, bw_tbili, trigy), serum VD (bw_vitd), and responses to an alcohol use questionnaire (aau_1). In addition, using available variables, we calculated four diagnostic indexes for NAFLD: fatty liver index (FLI), NAFLD fibrosis score (NFS), hepatic steatosis index (HSI), and the fibrosis-4 (FIB-4) index. Results: First, among individual liver biomarkers, we discovered significant negative correlations between serum bilirubin ($p=0.0294$) and total serum protein ($p=0.0028$) and RBANS total score. Second, we found significant negative correlations between FIB-4 ($p=0.0108$) and NFS ($p=0.001$) and RBANS total score. Third, we found a significant positive correlation between aau_1 and RBANS total score ($p=0.0025$). Finally, we discovered significant negative correlations between HSI ($p<0.0001$), FLI ($p<0.0001$), and serum alkaline phosphatase ($p=0.0001$) and RBANS total score. Conclusion In conclusion, our comprehensive analyses support the conclusion that liver disease is associated with a:e-related cognitive dysfunction. We identify potential diagnostic measures that could improve future protocols for identification and treatment of cognitive dysfunction in elderly populations.

Funding Disclosure: Supported by the TTUHSC Medical Student Summer Research Program (NV), TTUHSC Garrison Institute of Aging (JJL), and NIH R01 AG071859-01A1 (JJL)

Poster Theme Group G: Public Health

G1. Epidemiology

Poster #61

DUAL-LANGUAGE USE AND COGNITIVE FUNCTIONING AMONG MEXICAN AMERICANS AGED 65 AND OLDER

Presenting author: Brian Downer PhD (Associate Profesor, University of Texas Medical Branch at Galveston)

Background: Bilingualism has been associated with lower dementia risk and delayed dementia onset. However, there is limited work investigating the association between individual, family, and community factors that underly differences in dual-language use and cognitive aging.This is particularly true in Hispanics, the largest population of bilingual speakers in the US. We build on prior research by investigating if bilinguals who use English and Spanish to a similar degree demonstrate better cognitive function, relative to those who use one language more than the other. Methods: We used data from waves one (1992/93) to eight (2012/13) of the Hispanic Established Population for the Epidemiological Study of the Elderly. At wave one, participants were asked what language they usually use across communicative contexts (i.e., spouse, children, family gatherings, friends, and neighbors). Degree of dual-language was based upon reported use of Spanish and English within and across contexts. Participants were categorized as low (n=1068), medium (n=696), and high (n=688) dual-language users. Cognitive functioning was measured at each observation wave with the Mini-Mental State Examination. Linear mixed models were used to estimate the association between dual-language use category, cognitive function at wave one, and change in cognition while adjusting for baseline demographic factors. Results: Participants in the medium and high dual-language use categories scored 1.47 points and 2.38 points higher at wave one compared to the low dual-language use category. Findings were stable after adjusting for language of interview. The association between dual-language use and cognition at wave one was reduced when adjusting for education (medium B=0.58 SE=0.17 $p<0.01$; high B=0.80 SE=0.19 $p<0.01$). The association between dual-language use and cognitive decline was not statistically significant in any model. Conclusion: We found that greater dual-language use is associated with higher baseline cognition but not cognitive decline among older Mexican Americans, even when accounting for differences in education level. This finding is consistent with evidence of bilingualism-induced effects on executive control, memory recall, working memory, and semantic memory. Future work should characterize bilingualism with greater nuance in order to identify the components of the bilingual experience that may serve to protect against cognitive decline in aging bilinguals.

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Poster Theme Group G: Public Health

G1. Epidemiology

Poster #62

CHEMOTHERAPY AND RISK FOR ALZHEIMER'S DISEASE

Presenting author: Rocio Diaz Escarcega, PhD (Postdoctoral Fellow, UT Health Science Center Houston)

Background: Cognitive impairments may occur in cancer patients and survivors during or after chemotherapy. Cognitive deficits associated with neurotoxicity (chemobrain) can be subtle or disabling and frequently include disturbances in memory, attention, executive function, and processing speed. Cognitive impairments may go away soon after chemotherapy is over or may persist for years and yet, there is a paucity of effective treatments. Research has shown that chemotherapy drugs such as doxorubicin promote neurotoxicity and cognitive disturbances. Critically, some studies demonstrated that dementia occurs more commonly in cancer patients who had chemotherapy treatment compared to individuals never exposed to chemotherapy. Understanding whether and how chemotherapy may promote dementia later in life is needed. Methods: To establish new insights into chemotherapy-induced cognitive impairments, we use wild-type and Tg2576 mice (a model of Alzheimer's disease (AD)) treated with Doxil, a liposomal form of doxorubicin. Mice are injected intraperitoneally with saline or Doxil for six weeks. These conditions recapitulate a dosing schedule used in human patients and are the same as those used in similar studies in mice. Mice are then tested with cognitive and behavior assays, and their brains are analyzed for aging and AD phenotypes. Results: In our studies, we discovered that Doxil promotes cognitive impairment in wild-type mice. We also found that the brains of young mice exposed to Doxil contain lipofuscin-a mixture of oxidized proteins and lipids that is usually found only in the aged or diseased brains. DNA damage occurred with Doxil treatment in mice, confirming Doxil accelerated features of brain aging. Critically, Doxil enhances the deposition of amyloid in Tg2576 mice. Conclusion: Our study demonstrates evidence of accelerated brain aging in wild-type mice and amyloid deposition in AD mice due to Doxil treatment. Our data provide a foundation for investigating chemotherapy as a potential risk factor for AD that warrants further study. This research is being pursued in our laboratory.

Funding Disclosure: NIH R21AG067204

Poster Theme Group G: Public Health

G1. Epidemiology

Poster #63

THE RELATIONSHIP BETWEEN TBI AND DEPRESSION IN MEXICAN AMERICANS WITH MILD COGNITIVE IMPAIRMENT

Presenting author: Haydee Izurieta Munoz, MS (Research Specialist, University of North Texas Health Science Center)

Background: The outcomes of Traumatic Brain Injuries (TBI) have been shown to vary depending on race and ethnicity. Studies suggest TBI as a potential risk factor for the development of dementia. The link between TBI, cognition and depression is not well understood in older Mexican Americans (MA). Our research showed that MAs with MCI and history of TBI had higher depression scores than those without. The purpose of this study is to assess depression and TBI in Mexican American elders with either amnestic or non-amnestic Mild Cognitive Impairment (MCI). Method: Participant data was obtained from the Health and Aging Brain Study: Health Disparities, a community-based research study of cognitive aging in diverse communities. Data were analyzed from 164 MAs with MCI (n=89 Non-amnestic, n=75 amnestic) and cognitive diagnosis was determined by consensus review. TBI status (obtained via self-report from Ohio State University TBI Identification method- interview form) divided participants into groups: TBI+ (at least 1 head or neck injury with loss of consciousness) and TBI- (no loss of consciousness). The Geriatric Depression Scale 30-item (GDS) was used to assess depression. Independent sample T-tests were used to determine significant differences in GDS total and subscale scores, age, education, between TBI groups (TBI + and -) split by MCI status (amnestic/non-amnestic). Results: Of n=164 MA participants with MCI, 10.4% were TBI+ for both non-amnestic and amnestic. In the non-amnestic group, there were no significant differences in age, education, total GDS or GDS subscales between TBI+ and TBI-. Amnestic MCI TBI+ participants had significantly higher total GDS scores (p=0.019) and Apathy subscale scores (p=0.019) compared to the TBI- group. There was also a trend towards significance for the subscales of Dysphoria (p=0.079) and Meaninglessness (p=0.070). There were no significant differences in age or education within the amnestic MCI participants. Conclusion: Older MAs with amnestic MCI with TBI+ had significantly increased total depression, as well as Apathy. Although the role of TBI in mood disorders is not fully understood, additional research in this area could provide insight into the importance of cognitive status when evaluating depression.

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Poster Theme Group G: Public Health

G2. Health Services Research

Poster #64

IMPROVING CARE TRANSITIONS FOR CAREGIVERS OF HOSPITALIZED VETERANS LIVING WITH DEMENTIA: A QUALITATIVE STUDY OF HEALTH PROFESSIONALS

Presenting author: Molly Horstman, MD, MS (Assistant Professor, Baylor College of Medicine)

Background: Hospital admissions are stressful for adults with dementia and their caregivers. During care transitions from hospital to home, outcomes for adults with dementia depend, in part, on the caregiver's health and well-being. We aimed to identify the resources and training needs of dementia caregivers during care transitions. Methods: We conducted semi-structured interviews with licensed health professionals. Eligible health professionals were those who provide care for Veterans with Alzheimer's Disease and Related Dementias (ADRD) at the Michael E. DeBakey Veterans Affairs (VA) Medical Center in Houston, TX. Interviews were recorded and transcribed verbatim. We conducted a rapid qualitative analysis with structured summaries and matrices. Results: Fifteen health professionals completed a semi-structured interview (4 Social Workers, 4 Hospitalists, 2 Inpatient Nurse Case Managers, 2 Geriatrics Providers, 1 Primary Care Provider, and 2 Geriatric Psychiatrists). Health professionals identified opportunities to improve the information provided to dementia caregivers in the hospital with an emphasis on supporting caregivers to set "realistic expectations" for dementia progression and the availability of VA and community-based services and supports. Although training is determined on a "case-by-case basis", six health professionals recommended that caregiver training on behavioral interventions to address dementia behaviors should be available in the hospital. Interviewees perceived that services that provided an "extra pair of hands" were most beneficial to caregivers after discharge, such as home health aides. Across health professions, interviewees recommended that caregivers receive clear instructions on who to contact following discharge if problems arise. Interviewees recommended a dementia "navigator for the caregivers" who would meet the caregiver in the hospital and follow up with the caregiver after discharge to assist with post-discharge problem-solving, provide dementia-specific education, and connect the caregiver to VA and non-VA services and supports. Conclusions: Health professionals identified several opportunities to improve the hospital and care transition experience for caregivers of hospitalized veterans with dementia. Adding a caregiver navigator who can follow the caregiver from the hospital to home was recommended across health professions and is supported by evidence-based care transitions interventions.

Funding Disclosure: VA HSR&D CDA, National Institute on Aging

Poster Theme Group G: Public Health

G3. Prevention (nonpharmacological)

Poster #65

THE INTERPLAY BETWEEN ALL-TRANS RETINOIC ACID, THE GUT-BRAIN AXIS, AND THE PATHOGENESIS OF ALZHEIMER'S DISEASE: A POTENTIAL MECHANISM

Presenting author: Matthew Buxton, BS (Medical Student, Texas Tech University Health Sciences Center)

Background: Alzheimer's disease (AD) is a debilitating disease affecting 6.5 million people in the United States (US) presently, anticipating to impact approximately 12.7 million people in the US by 2050. Recent studies demonstrating bacterial lipopolysaccharide (LPS) is present in the hippocampus of AD patients has warranted a closer examination of the role of the gastrointestinal (GI) tract integrity and the gut-brain axis (GBA) in AD. There is growing evidence that microbiota composition of the GI tract influences the cascade of signals sent throughout the complex system of the GBA. In relation to AD, the appearance of LPS in the post-mortem hippocampus could signify a compromised mucosal barrier and tight junction coupling between GI endothelial cells, which subsequently alters the GBA. The breakdown of mucosal and epithelial barrier integrity, combined with immune system activation, results in a pro-pathologic state that creates gut microbial dysbiosis. We propose tight junction deficiencies found in pathologic states arise primarily through preventable environmental causes. Methods: A standard literature search including PubMed was used to identify knowledge gaps and molecular interrelationships between VA and AD. Results: There is evidence of Vitamin A (VA) dysregulation in AD pathogenesis and progression. Our currently funded NIH R01 grant addresses how brain transcriptomic, metabolomic and lipidomic profiles are altered by VA deficiency. All-trans retinoic acid (ATRA) is essential for normal expression of the tight junction proteins ZO-1, occludin, and claudin-1. VA deficiency leads to decreased expression of these proteins and subsequently compromises tight junctions. VA is also required for the differentiation of Treg cells. We propose VA deficiency compromises tight junctions, which results in pathologic metabolites like LPS penetrating the epithelium and entering the bloodstream. The loss of Treg cells cannot counteract the proinflammatory response, beginning an escalating cycle of inflammation. In addition, butyrate, a short-chain fatty acid (SCFA) produced from Firmicutes through fiber fermentation, produces retinoic acid in gut epithelial cells by inhibiting histone deacetylases. Conclusion: The proposed mechanism attempts to explain the complex interrelationship between VA, butyrate, AD, and the GBA. Pharmacologic treatments targeted at such a mechanism could ameliorate and decrease the risk of developing Alzheimer's Disease.

Funding Disclosure: Supported by the Medical Student Summer Research Program (MB) and NIH R01AG071859.

Poster Theme Group G: Public Health

G3. Prevention (nonpharmacological)

Poster #66

COGNITIVE AND SLEEP DIFFERENCES IN INDIVIDUALS WITH PARKINSON'S DISEASE AND RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

Presenting author: Vanessa M. Young, MS (Clinical Research Coordinator, UT Health Science Center San Antonio)

Background: Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by dream reenactment and simple or complex abnormal motor behaviors during the REM sleep stage. RBD can be an early predictor of Parkinson's disease (PD) and dementia; however, the relationship between dementia, RBD, and broader sleep disturbance in PD remains unclear. The aim of this pilot study was to objectively assess sleep differences among individuals with PD with and without RBD using polysomnography. Method: Twenty adults with PD were enrolled in the study. The presence of RBD was assessed with the validated Mayo Sleep Questionnaire. Participants completed neuropsychological evaluations, physical functioning assessments, questionnaires, digital device sleep monitoring, and an overnight in-clinic polysomnography. Demographic and objective sleep differences between the RBD and non-RBD groups were evaluated using independent sample t-tests for continuous variables and chi-square tests for categorical variables. Results: The RBD group (n=12) and the non-RBD group (n=8) showed no statistically significant differences in educational level, age, and sex distribution (all $p>0.05$). However, the RBD group displayed poorer global cognition as assessed by the Montreal Cognitive Assessment (RBD mean = 23.73 ± 4.29, non-RBD mean = 26.88 ± 2.23, $t(17)= -3.11$, $p=0.006$). On polysomnography, the RBD group trended towards a lower average sleep duration ($t(18)=-2.0$, $p=0.06$), and displayed significantly lower percentage of REM sleep (3.40 ± 1.68; $t(18)=-2.6$, $p=0.02$). There were no group differences in percentages of Stage 1 and 2 sleep and the number of periodic limb movements (all $p>0.05$). Conclusion: Individuals with PD and RBD displayed poorer global cognition relative to individuals with PD without RBD. On the polysomnography, individuals with PD and RBD also trended towards lower total sleep time and less time spent in REM sleep. The results suggest broad sleep differences in RBD and non-RBD groups, which have been associated with increased dementia risk in other samples. However, the study was underpowered to fully explore these differences and the one-night sleep assessment may not be representative of typical sleep at home hindering generalization. Future studies incorporating digital sleep monitoring devices are underway.

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TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER
UNT HEALTH SCIENCE CENTER
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Dell Medical School
UTRGV
UT Health
Rio Grande Valley
UT Southwestern
Medical Center
UTHealth
The University of Texas
Health Science Center at Houston
McGovern
Medical School
UT Health
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Baylor
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Medicine
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