Poster Theme Group A: Basic Science and Pathogenesis

A1. Development of New Models and Analysis Methods

1. CROSS-SEEDING CONTROLS Aß FIBRIL POPULATIONS AND RESULTING FUNCTION

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Amyloid peptides nucleate from monomers to aggregate into fibrils through primary nucleation; pre-existing fibrils can then act as seeds for additional monomers to fibrillize through secondary nucleation. Both nucleation processes can occur simultaneously, yielding a distribution of fibril polymorphs that can generate a spectrum of neurodegenerative effects. Understanding the mechanisms driving polymorph structural distribution during both nucleation processes is important for uncovering fibril structure-function relationships, as well creating polymorph distributions in vitro that better match distributions found in vivo. Here, we explore how cross-seeding WT Aβ1-40 with Aβ1-40 mutants E22G (Arctic) and E22Δ (Osaka), as well as with WT Aβ1-42 affects the distribution of fibril structural polymorphs, and how changes in structural distribution impact toxicity. Transmission electron microscopy analysis reveals that fibril seeds derived from mutants of Aβ1-40 impart their structure to WT Aβ1-40 monomer during secondary nucleation, but WT Aβ1-40 fibril seeds do not affect the structure of fibrils assembled from mutant Aβ1-40 monomers, despite kinetics data indicating accelerated aggregation when cross-seeding of any combination of mutants. Additionally, WT Aβ1-40 fibrils seeded with mutant fibrils to produce similar structural distributions to the mutant seeds also produced similar cytotoxicity on neuroblastoma cell lines. This indicates that mutant fibril seeds not only impart their structure to growing WT Aβ1-40 aggregates, but they also impart cytotoxic properties. Our findings provide clear evidence that there is a relationship between fibril structure and phenotype on a polymorph population level, and that these properties can be passed on through secondary nucleation of succeeding generations of fibrils. ***Funding Disclosure:*** *This work was supported in part by Welch Foundation Research Grants F-1722 (to L.J.W.) and F-1929 (to B.K.K.); National Science Foundation CHE-1807215 (to L.J.W.); and the College of Natural Sciences at The University of Texas at Austin (Catalyst Grant to L.J.W., B.K.K., and D.W.T.). Partial support was provided by the National Science Foundation through the Center for Dynamics and Control of Materials: an NSF Materials Research Science and Engineering Center under DMR-1720595. D.W.T. is a CPRIT Scholar supported by the Cancer Prevention and Research Institute of Texas (RR160088) and an Army Young Investigator supported by the Army Research Office (W911NF-19-1-0021).*

2. ANALYSIS OF θ-OSCILLONS IN ALZHEIMER'S DISEASE

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We study the LFP oscillations using a recently developed adaptive technique that may capture the physical architecture of synchronous oscillations in neuronal ensembles. This approach reveals a new level of organization of the brain rhythms-a small number of discrete, phase-modulated waves processes-the oscillons-embedded in a weak noise background. In this study, we focus on the lowest-frequency oscillons that correspond to the traditional hippocampal and cortical θ-waves, and analyze their dynamics during active and quiescent behaviors of male rats. We find that the dynamics of the θ-oscillons are characterized not only by the changes of their amplitudes but also by overt frequency modulations, and moreover, that these dynamics differ in wild type (WT) animals and Alzheimer's disease (AD) models. These results expand and refine a number of previously observed relationships between the traditionally defined θ-wave and the animal's physiological state and provide a number of qualitatively novel observations that pertain specifically to θ-oscillons in WT and AD. Importantly, our results dovetail with several theoretical models that explain the emergence of θ-rhythms from neuronal synchronization, thus providing a direct link between modeling and experiment. ***Funding Disclosure:*** *NIH grants R01NS110806-01A1 and 1R01AG074226-01*

3. PERIPHERAL EXPOSURE OF MISFOLDED Aβ AGGREGATES BY DIFFERENT ROUTES INDUCES CEREBRAL AMYLOID PATHOLOGY IN A MOUSE MODEL OF ALZHEIMER´S DISEASE

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Background: Alzheimer´s disease (AD) is considered a proteinopathy due to the abnormal accumulation of misfolded proteins in the brain, such as amyloid-β (Aβ) and tau. Several reports suggest a prion-like mechanism to explain the progression of pathology throughout different brain regions. To date, intra-peritoneal (i.p.) and intra-venous administrations are the only peripheral routes described to accelerate or "seed" brain Aβ amyloidosis. While understudied, it is suspected that peripheral tissues and fluids may represent additional avenues of Aβ seeding and directly affect pathological changes in the brain. Therefore, in this study we evaluated whether the administration of biologically active Aβ seeds through various peripheral routes, including intra-muscular (i.m.), intra-ocular as well as per os (p.o.), accelerate cerebral amyloid pathology in a mouse model of AD. **Methods:** 50-days-old Tg2576 mice were exposed, by different routes, to brain extracts from 18- to 20-months-old Tg2576 mice harboring large quantities of Aβ deposits. Routes of administration included intra-cerebral (i.c) and i.p, as positive controls, i.m., p.o. and eye drops. Animals were sacrificed at either 285 (i.c.) or 300 (all other routes) days old, and the brain was extracted and assessed by immunohistochemistry. **Results:** As expected, untreated animals displayed low levels of amyloid deposition, while those i.c, and i.p. inoculated with brain extracts from aged Tg2576 mice generated massive deposition of Aβ in the brain. Interestingly, animals i.m. inoculated and those receiving eye drops of brain homogenate laden with Aβ seeds showed amyloid deposition. On the contrary, oral administration of large quantities of brain extracts from aged transgenic mice and AD patients did not have any effect in brain pathology. Importantly, pathological induction by peripheral administration of Aβ seeds generated a large proportion of vascular aggregates, suggesting transport via the bloodstream. **Conclusion:** Several peripheral routes can efficiently induce and accelerate cerebral Aβ pathology in a susceptible animal model of AD suggesting that peripheral tissues and fluids may play a key role in AD-related pathological changes.

4. HUMAN BRAINS WITH ALZHEIMER DISEASES INDUCE DIFFERENT PATHOLOGY IN INOCULATED APP/PS1 MICE

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Alzheimer's disease (AD) affects approximately 10% of the population over 65 years of age, making it one of the main public health challenges in the near future. Amyloid-β (Aβ) misfolding is one of the main pathological hallmarks of AD that has been suggested as a key component for AD pathogenesis. AD can manifest with diverse symptoms that include variable rates of cognitive decline, duration of clinical disease, and other detrimental changes. Several reports suggest that conformational diversity in misfolded Aβ is a major factor for clinical variability in AD, analogous to what has been described for prion strains in prion diseases. In particular, prion strains generate diverse patterns of deposition of misfolded proteins in the brains of affected individuals. We hypothesize that AD includes a spectrum of pathological conditions characterized by the accumulation of misfolded proteins that lead to a differential manifestation of the pathology. In this study, we tested the in vivo prion-like transmission features of four human AD brains displaying different patterns of amyloid pathology as evaluated by immunohistochemical means. Specifically, we evaluated their specific seeding activity, as well as the total amount of Aβ deposited in the surrounding vascular structures and the reactivity of the amyloid pathology to thioflavin S. Our results demonstrate that AD brains with diverse pathology induced different phenotypes in inoculated mice. Interestingly, certain pathological features were shared between the brains of patients with AD and the ones observed in challenged mice, supporting the notion that AD subtypes are encoded in disease-associated Aβ. Additional research exploring whether AD includes a spectrum of different clinical conditions or syndromes can pave the way toward personalized diagnosis and treatments. ***Funding Disclosure:*** *NIH (R56AG061878 and RF1AG059321), the Alzheimer's Association (AARGD-18-566576 and 2018-AARG-591107), ANID/FONDEF ID20I10152 and ANID/FONDECYT 1210622, and PID2019-107090RA-100, 27565 2018 NARSAD and RYC-2017-21879*

5. IN-CELL CONFORMATIONAL ENSEMBLE OF METASTABLE PROTEINS IN NEURODEGENERATIVE DISEASES

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Background: For an organism to survive, its proteins must adopt complex conformations in a challenging environment where macromolecular crowding can derail even robust biological pathways. This situation is

particularly important for metastable proteins like α-synuclein and tau, which have energetic folding landscapes containing multiple local minima. In these cases, the cellular environment can clearly influence the conformation, especially in neurodegenerative diseases, where aggregating proteins often have identical sequences in both healthy and afflicted individuals. Despite the importance of the cellular environment, structural investigations of biomolecules are typically confined to highly purified in-vitro systems. Thus, investigating metastable proteins in their native cellular environment can uncover structural details which might point to the root cause of conformation based neurodegenerative diseases. **Method:** Sensitivity-enhanced DNP solid state NMR has the capability to detect proteins at their endogenous concentration within cellular environment. We have established sample preparation conditions that keeps cells intact and alive during the DNP-NMR process, allowing us for post NMR phenotyping. Our technique detects the entire conformational ensembl of proteins inside cells without any experimental bias through homogenous distribution of polarizing agent, AMUPol. **Results:** Using this technique, we have uncovered that α-synuclein is a mixture of random coils and α-helices inside cells. Currently, we are utilizing the same technique to detect α-synuclein conformations at near physiologic concentrations in neuronal cultures and advancing towards structures at atomic resolution. Overall, this work will provide new structural insights at atomic resolution of metastable proteins like α-synuclein within the biologically relevant context, and has the potential to be extrapolated to any other protein or cell culture models for investigating either physiologic or pathologic conditions. **Conclusion:** Our work established the application of DNP NMR for investigation of in-cell protein structures and uncovers a rare α-helical conformation of α-synuclein which was not reported earlier. ***Funding Disclosure:*** *O'Donnell Brain Institute, NIH (NS-111236), the Welch Foundation, the Kinship Foundation*

6. A SMALL MOLECULE FOR IMPROVED SURVIVAL OF AGING-RELEVANT NEURONS FROM ALZHEIMER'S DISEASE PATIENTS

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Background: Dysfunction of the nucleocytoplasmic transport is associated with Alzheimer's Disease (AD). Pathological TAU directly interacts with components of the nuclear pore complexes (NPCs) and thereby disrupts nucleocytoplasmic transport. However, it is not clear whether such impaired nucleocytoplasmic transport could be improved in aging-relevant human neurons. **Methods:** We generated aging-relevant human induced neurons (hiNs) through direct conversion of skin fibroblasts of normal healthy (NL) adults and sporadic AD patients. Nucleocytoplasmic transport, mRNA transport, and phosphorylated TAU expression were determined in both NL- and AD-hiNs using immunocytochemistry. We then examined the effects of a small chemical compound (Hit3) on neuronal survival, neuronal growth, phosphorylated TAU, and components of the NPCs by using immunocytochemistry. **Results:** We have established a robust protocol for the generation of hiNs from adult human skin fibroblasts. Our preliminary results reveal that AD-hiNs exhibit impaired nucleocytoplasmic transport of proteins and mRNAs and have increased hyperphosphorylated TAU. The small molecule Hit3 can significantly promotes neuronal survival and growth, reduces phosphorylated TAU (AT8, AT100, pS199), and improves NPC components (RanGAP1, RanBP2, and Ran) in AD-hiNs. **Conclusions:** hiNs could serve as an aging-relevant cell model for understanding AD pathology. The small molecule Hit3 or its analogs may constitute a therapeutic candidate for AD. ***Funding Disclosure:*** *TARCC*

A2. Genetics

7. ROLE OF DIFFERENTIAL DNA METHYLATION IN MEXICAN AMERICANS AND THEIR RISK FOR ALZHEIMER'S DISEASE AND TYPE 2 DIABETES

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Background: DNA methylation is an epigenetic mechanism that influences gene expression and has been associated with various age-related diseases. Mexican Americans are the largest ethnic minority group in the US and are consequently predicted to have the largest elderly ethnic population within a few decades. Susceptibility to age-related phenotypes such as Alzheimer's disease (AD), mild cognitive impairment (MCI) and prevalence of type 2 diabetes (T2D), are unique in this cohort. Mexican Americans have an earlier age of onset for cognitive decline (AD/MCI) and have a higher prevalence rate of T2D in comparison to non-Hispanic whites. Mexican Americans also have a metabolic heavy predisposition for AD, compared to non-Hispanic whites who develop predominantly inflammation-based AD. The risk for these phenotypes is multifactorial involving epigenetic factors, such as differential DNA methylation, which is the addition of a methyl group to certain cytosine bases of DNA in the genome. Studies have shown the presence of T2D almost doubles the risk of developing AD/MCI, however an epigenetic link between these phenotypes in the Mexican American cohort remains to be established. We aim to elucidate an epigenetic association between cognitive decline and T2D, specific to the Mexican American population, through analysis of methylation profiles from participants selected from the Texas Alzheimer's Research and Care Consortium (TARCC). **Method:** The TARCC participants consist of Mexican Americans diagnosed with either cognitive impairment alone (either AD/MCI), T2D alone or both cognitive impairment and T2D together and matched for gender and age with a non-Hispanic white counterpart. Peripheral blood samples were drawn from participants and run on the Illumina Infinium MethylationEPIC chip array assessing >850,000 CpG sites to obtain individual methylation profiles. The Chip Analysis Methylation Pipeline (ChAMP) package within R software will be used to assess differential methylation profiles from all 551 TARCC participants. **Result:** The results obtained will be analyzed using pathway and gene set enrichment analysis tools. **Conclusion:** Potential identification of differential methylation specific to the Mexican American population could help provide ethnic specific risk information for T2D and cognitive decline together. This could contribute towards developing ethnic-specific biomarkers, treatments or therapies in the near future. ***Funding Disclosure:*** *This project is supported (in part) by funding provided to the Texas Alzheimer's Research and Care Consortium by the Darrell K Royal Texas Alzheimer's Initiative, directed by the Texas Council on Alzheimer's Disease and Related Disorders, This work was supported by the Office of Vice President for Research and Innovation, the Institute for Healthy Aging, and National Institutes of Health/National Institute on Aging (T32 AG020494) & Half predoctoral international fellowship through VPR and Center for Healthy Aging 2021-2022*

8. IDENTIFYING ALTERATIONS IN THE MITOCHONDRIAL DNA LOAD OF NEURONAL-ENRICHED EXOSOMES ASSOCIATED WITH COGNITIVE DECLINE IN MEXICAN AMERICANS

Courtney Hall, MS, Robert Barber, PhD, Nicole Phillips, PhD *(University of North Texas Health Science Center)*

Background: Alzheimer's disease (AD) is a complex neurodegenerative disorder that disproportionately burdens Mexican Americans (MAs) due to a combination of population-specific environmental exposures and genetic risk factors. In addition to AD, MAs have a higher prevalence of metabolic comorbidities such as type 2 diabetes (T2D) that have been implicated in accelerated age-related cognitive impairment. Tissue-specific mitochondrial dysfunction and oxidative stress are early and prominent features of both AD and T2D that propagate systemic inflammation as these diseases progress. Despite the shared pathophysiology, we do not fully understand the underlying molecular mechanisms linking cognitive decline and metabolic stress, especially in understudied minority populations. Mitochondrial dysfunction may serve as the biological basis of the AD health disparity in MAs who (1) experience earlier onset of symptoms, and (2) have an overrepresentation of T2D compared to non-Hispanic whites (NHWs). This project aims to study T2D-related risk for cognitive impairment by assessing the extracellular vesicles that neurons secrete to communicate with cells in the periphery known as neuronal-enriched exosomes (NEEs). NEEs can cross the blood-brain barrier and are thus capable of mediating systemic inflammation in response to CNS-sourced oxidative and metabolic stress through their mitochondrial DNA (mtDNA) cargo. We hypothesize that plasma NEE mtDNA load will

reflect cognitive status and T2D comorbidity. **Methods:** We enriched for exosomes of neuronal origin using the well-established NEE marker L1CAM (CD171) in plasma samples from 348 TARCC participants stratified by race/ethnicity (MA/NHW), cognitive status (AD/MCI/NC), and T2D comorbidity (+/-). The success of NEE isolation was assessed via nanoparticle tracking analysis (NTA) and immunoblotting with CD171 and CD81 (a canonical exosome surface marker) antibodies. Absolute mtDNA load and deletion ratio were estimated using a real-time qPCR assay targeting sites within both the minor (D-loop) and major (ND4) arcs. **Results:** Herein we demonstrate the ability to isolate NEEs from plasma and quantify their mtDNA cargo. Resultant values were analyzed for group differences and correlation with disease status based on various neuropsychological measures. **Conclusion:** As the first effort to assess mtDNA in NEEs, this project provides novel insight into how T2D confers risk for AD across different populations. ***Funding Disclosure:*** *TARCC (RS00049), NIH/NIA (T32 AG020494)*

9. SEQUENCE-BASED ASSESSMENT OF MITOCHONDRIAL DNA OXIDATIVE DAMAGE IN COGNITIVE IMPAIRMENT: SHEDDING LIGHT ON HEALTH DISPARITIES IN MEXICAN AMERICANS

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Background: Mexican Americans (MAs) are the fastest growing Hispanic population segment in the US, and as this population increases in age, so will the societal burden of age-related diseases such as Alzheimer's disease (AD). Diabetes, stroke, depression, and obesity are common risk factors for developing cognitive impairment in MAs; however, the association between cognitive decline and comorbidities remain unclear. Due to the prevalence of metabolic comorbidities in this group, mitochondrial DNA (mtDNA) damage may be implicated in AD among MAs. Oxidative damage to guanosine (8oxoG) is one of the most prevalent DNA lesions and a putative indicator of mitochondrial dysfunction. Studies have shown correlations between common pathological changes observed in AD and DNA damage. The mitochondrial genome is particularly vulnerable to DNA damage due to its close proximity to reactive oxygen species (ROS). Age-associated decline in mitochondrial function results in accumulation of ROS, which are capable of damaging DNA and other essential biomolecules. We hypothesize that MAs incur oxidative mtDNA damage at an elevated rate due to increased comorbidity burden which impacts the mitochondria. **Methods:** Whole mtDNA was amplified using REPLI-g® Human Mitochondrial DNA Kit and sequenced via Illumina NextSeq from extracted buffy coat DNA of participants enrolled in the TARCC cohort. Somatic variants indicative of oxidative DNA damage were quantified in MAs and compared to NHWs with cognitive impairment (MCI/AD), type-2 diabetes (T2D), and comorbidity (MCI/AD/T2D). **Results:** We found mtDNA 8oxoG mutational load to be significantly higher in MAs compared to NHWs and that MA females are affected to a greater degree. Further, we identified specific mtDNA haplotypes which confer increased risk for oxidative damage and suggestive evidence that cognitive function may be related to 8oxoG mutational load. **Conclusion:** Our findings suggest clinical implications of mitochondrial oxidative DNA damage as a risk factor for cognitive impairment specifically in MA females. These data highlight ethnic/racial differences in oxidative burden which may elucidate sex-specific mechanisms for manifestation of age-related disease etiology (such as AD), and the results may ultimately inform precision-based approaches to therapeutic design for the reduction of AD disparities in the MA population. ***Funding Disclosure:*** *U54, TARCC, IMSD*

10. TRANSCRIPTIONAL ENDOPHENOTYPES PREDICTING GENETIC RISK OF DEMENTIA IN MEXICAN AMERICANS

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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. ADRD is a complex phenotype where both genetic and environmental causal components play significant roles. The identification of early ADRD biomarkers is important and we propose to discover novel non-invasive endophenotypes using high dimensional multiomic data in an existing Mexican American cohort. The 2000 Mexican American participants are members of large families from the GOBS (Genetics of Brain Structure and

Function Study) project from which extensive phenotypic data is available. **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. The estimated heritability is high (h2= 0.75, p = 2.6x10-5) supporting a major role for genes influencing ADRD risk. The ADRD cases have 363 1st, 2nd, 3rd, and 4th degree relatives currently not suffering from dementia. To identify transcriptional endophenotypes that are genetically correlated with ADRD, we contrasted this group of relatives to 839 unaffected individuals without affected relatives. We constructed a genetic risk vector and tested its correlation to the expression level of each gene. **Results:** We tested the validity of our proposal by limiting ourselves to a set of 113 genes previously associated with ADRD. We observed a clear enrichment for significant effects over that expected under the null hypothesis (p=3.3x10-10). Several cytokine genes (TNF, IL1B, and C1QRNF4) exhibited reduced expression in relatives of cases versus controls. Notably, the APBB1 and AOBB2 genes showed increased expression in relatives of ADRD cases. This gene regulates the amyloid precursor protein playing a central role for ADRD development. **Conclusion:** The observed statistical enrichment of previously ADRD associated genes serves as a positive control for our approach. The ERV method is especially powerful for rare diseases when large human families are available. Candidate genes identified will be extensively annotated to aid the detection of relevant early ADRD genes highly correlated with ADRD risk. ***Funding Disclosure:*** *NIDDK, NHLBI, NIMH and STAC*

A3. Human Neuropathology

11. TAU-IMMUNOREACTIVE THORN-SHAPED ASTROCYTES IN BRAIN NEURODEGENERATION AND AGING

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Background: Aggregated tau protein in neurofibrillary tangles is a pathological hallmark of Alzheimer's disease (AD). Evidence suggests astrocytic tau pathology also plays an important role in aging, demonstrated by the classification of thorn-shaped astrocytes (TSA) and granular/fuzzy astrocytes as aging-related tau astrogliopathy (ARTAG). TSA are a prominent feature of chronic traumatic encephalopathy (CTE), a mixed tauopathy linked to repetitive head trauma. Understanding similarities/differences of TSA from traumatic and aging etiologies has important ramifications in elucidating CTE and ARTAG disease pathogenesis. Our goals are two-fold: A) identify differences in astrocytic tau proteoforms between these disorders and B) evaluate astrocytic diversity to understand which pathology-susceptible astrocyte subpopulations [additionally comparing TSA to corticobasal degeneration (CBD) astrocytic plaques (AP) and progressive supranuclear palsy (PSP) tufted astrocytes (TA)]. **Method:** Immunohistochemistry was performed on postmortem human frontal cortex tissue of CTE (N=4), AD/ARTAG (N=4), PSP (N=2) and CBD (N=2) cases with antibodies against phosphorylated tau (AT8, AT180), N-terminal cleaved tau (C3), 3-repeat and 4-repeat tau (RD3, RD4), as well as astrocytic markers glial fibrillary acidic protein (GFAP), vimentin and complement 3. Color deconvolution digital pathology analysis was employed to quantitatively measure differences between AT8, AT180, GFAP and vimentin. **Result:** TSA in CTE and AD/ARTAG were negative for C3 and RD3, but positive with AT8, AT180 and RD4. Quantitative analysis revealed equal AT8:AT180 staining in TA and AP, but higher expression of AT8 vs. AT180 in gray matter TSA for both CTE ($p=0.0023$) and AD/ARTAG ($p=0.0006$) by Mann Whitney tests. While astrocytic lesions across all diseases largely demonstrated GFAP expression, complement 3 was variable between cases. Importantly, vimentin-positive astrocytes were pronounced in CBD and AD/ARTAG but typically absent in PSP and CTE. Gray matter TSA in CTE were rarely immunoreactive for vimentin, yet white matter TSA in ARTAG often exhibited vimentin positivity. **Conclusion:** Overall, results indicate that while tau proteoforms may be broadly comparable between CTE and ARTAG TSA, differences in astrocytic selective vulnerability could differentiate these pathologic entities. Future astrocytic cell profiling studies will provide further insight on these findings. ***Funding Disclosure:*** *JMR Barker Foundation; Reed Center; P30AG066546*

13. TREM2-INDUCED ACTIVATION OF MICROGLIA CONTRIBUTES TO SYNAPTIC RESILIENCE IN NON-DEMENTED INDIVIDUALS WITH ALZHEIMER'S NEUROPATHOLOGY

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The existence of individuals who remain cognitively intact despite the presence of histopathological signs of Alzheimer's disease (AD), here referred to as "Non demented with AD neuropathology" (NDAN), suggests that some unknown mechanisms are triggered to resist cognitive impairment. Synaptic dysfunction has been identified as one of the major AD causes and it is established that microglia, attracted to plaques, phagocyte damaged synapses. In this context, exposed phosphatidylserine (ePS) represents a neuronal "eat-me" signal involved in microglial-mediated phagocytosis of damaged synapses. A possible candidate mediator of this process is represented by TREM2, a microglial surface receptor activated by ligands including PS. Based on TREM2 role in the scavenging function of microglia, we hypothesize that an efficient microglial phagocytosis of damaged synapses underlies synaptic resilience in NDAN, thus protecting from memory deficits. Using immunofluorescence microscopy, a comparative study of human post-mortem frontal cortices of aged-matched individuals, AD and NDAN individuals has been performed. The distribution of activated microglia (IBA1 and IBA1/CD68 positive cells) and the expression of phagocytic microglia-related proteins (TREM2 and DAP12) were evaluated in relation to Aβ plaques. To test the efficacy of microglia in removing debris and damaged synapses, preservation of synapses around plaques was assessed using MAP2 and tubulin βIII as dendritic and axonal markers respectively. As a further confirmation of microglial efficiency, we looked for engulfed damaged synapses inside microglial lysosomes analyzing the colocalization between PSD95 and CD68. Immunofluorescence analyses indicate higher microglial activation and TREM2 expression in NDAN

individuals, as well as preserved axonal and dendritic structure around plaques vs. AD. High levels of PSD95 around NDAN plaques and the colocalization of PSD95 and CD68 may suggest a prompt removal of damaged synapses by hyperactive phagocytic microglia. Furthermore, taking advantage of flow cytometry techniques, a study of the ePS using Annexin V assay has been performed. Annexin V assay on synaptosomes isolated from aged-matched, AD and NDAN individuals indicates changes in the ePS in NDAN individuals, confirming the engulfment of damaged synapses. Our results suggest a higher efficiency of TREM2-induced phagocytic microglia in removing damaged synapses, underlying synaptic resilience in NDAN individuals. ***Funding Disclosure:*** *NIH/NIA R01AG069433, R01AG060718 and R56063405 to GT*

14. INVESTIGATING THE ROLE OF TAU OLIGOMERS IN PRIMARY AGE RELATED TAUOPATHY (PART)
Shrinath Kadamangudi, MPhil, Giulio Taglialatela, PhD *(UT Medical Branch at Galveston)*

Primary Age Related Tauopathy (PART) is a sporadic dementia-related illness of aging, characterized by pathological tau accumulation limited to the hippocampal-entorhinal region (avoiding neocortical infiltration) in the absence of Aβ plaque burden. Studying PART thus presents a unique opportunity to dissect molecular mechanisms underlying regional resilience and vulnerability to toxic tau species, which include hyperphosphorylated (p-tau) and oligomeric (tauO) tau. We compared levels of p-tau and tauO between the hippocampus and superior medial temporal cortex (SMT) of 7 post-mortem PART and age-matched Control patients. Total protein fractions were prepared for Western Blot, using probes for p-tau (AT180 and PHF13.6), total tau (Tau5, validated by Tau13); tauO were ascribed to high molecular weight species identified using total tau probes. The Wilcoxon matched-pairs signed rank test was utilized to compare regional differences. We observed an increased trend for tauO (1°Ab:Tau5) in the hippocampus vs. the SMT in both PART patients ($p=0.11$, $rs=0.11$) and Control ($p=0.99$, $rs=0.07$). No regional differences were found in total tau levels. When probing for p-tau, we observed signal primarily in the high molecular weight region (~75-200kD), thus suggesting phosphorylation of tauO (p-tauO). We found significantly elevated p-tauO (1°Ab:AT180) in the hippocampi vs. SMT, of PART patients ($p=.03$, $rs=-0.09$). When probing for p-tau associated with paired helical filaments (1°Ab:PHF13.6), we also found significantly elevated PHF p-tauO in the hippocampi of PART patients ($p=0.03$, $rs=0.04$). PHF p-tau levels also positively correlated with tauO levels ($p=0.05$, $F=6.81$, $Slope=0.83$). While our findings should be considered within the context of their limitations and warrant further investigation, taken together, this evidence suggests a previously unappreciated association between p-tau, PHFs, and tauO in PART. ***Funding Disclosure:*** *Supported by NIH/NIA R01AG069433, R01AG060718 and R56063405 to GT*

A4. Molecular and Cell Biology

15. CIRCUIT-BASED MECHANISMS OF NEURONAL VULNERABILITY OF THE ADULT EC

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Background: Entorhinal cortex layer II (ECII) neurons are some of the first cells to degenerate in Alzheimer's Disease (AD) and are the major cortical input into the hippocampus. Loss of this input is consistent with the cognitive deficits that present early in AD. To study the cognitive consequences of ECII loss, the Jankowsky lab created a chemogenetic mouse model in which a subset of ECII neurons express an engineered chloride channel (GlyCl) to prevent the generation of action potentials. Unexpectedly, we discovered that adult entorhinal neurons were highly vulnerable to silencing and may require activity for survival. In the present study, we investigated potential mechanisms that may govern cell loss after inactivity. **Methods:** GlyCl expression was localized to ECII neurons using a tetracycline-transactivator driver line (Nop-tTA) that is largely restricted to the superficial entorhinal layer. GlyCl is activated via the ligand ivermectin (IVM) and was co-expressed with a cytosolic yellow fluorescent protein (YFP) to visualize silenced cells. For additional genetic strategies of inactivation, tTA-dependent constructs were packaged with YFP into an AAV expression vector and delivered via stereotaxic injection into adult Nop-tTA mice. Animals were harvested at multiple timepoints after silencing to assess YFP+ cells, relative mRNA levels of target genes, and immunolabeled markers of cell stress, apoptosis, and neuroinflammation. **Results:** Shortly after silencing, many ECII neurons retract their axons from the dentate gyrus, express pro-apoptotic proteins, and are eliminated from the circuit. We discovered this progressive degeneration may act through the MAPK injury signaling cascade. Master regulators of neuronal injury response, ATF3 and phospho-c-Jun, are strongly induced after silencing. We also observed neurodegeneration after eliminating neurotransmitter release with tetanus toxin (TeTX), confirming that neuronal loss is not an artifact of GlyCl activation. To our surprise, TeTX-expressing cells degenerated via a distinct morphological pattern, reminiscent of Wallerian-like disintegration. These data indicate that different means of silencing may trigger different mechanisms of degeneration. **Conclusions:** Our findings suggest that multiple mechanisms of activity-dependent survival are present in the adult EC and likely function through distinct molecular pathways. Our work provides new insights into how activity may support neuronal survival throughout life.

18. MILD-GRADE SEPSIS AT AN EARLY LIFE-STAGE IS SUFFICIENT TO AGGRAVATE AMYLOID PATHOLOGY IN AN ADULT MOUSE MODEL OF ALZHEIMER'S DISEASE

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Background: Sepsis is a severe inflammatory response to the presence of microbial/viral agents in the bloodstream, resulting in dramatic changes to neuro-immune interactions. Septic patient brains exhibit several Alzheimer's disease (AD), including higher levels of amyloid-β (Aβ), a peptide whose aggregation and subsequent accumulation is hypothesized to drive AD pathology. **Methods:** Coecal ligation and puncture (CLP) surgery, the gold standard model of sepsis research, involves variable modes of induction to generate either severe (robust and long-lasting) or mild (attenuated) immune responses. 50 days-old male APP/PS1 mice (n = 8), a commonly used model of AD, were subjected to either mild CLP surgery or a sham procedure. Cognitive performance was queried using novel object recognition analysis at 117 days post-surgery (d.p.s.). At 120 d.p.s., mice brains underwent biochemical and histological examination of amyloid pathology. **Preliminary Results:** Mild sepsis-afflicted AD mice displayed worsened non-spatial memory, relative to the sham-treated group. Moreover, biochemical analysis of frozen brain hemispheres via fluorescent bead-based immunoassay technology revealed that mild sepsis-afflicted AD mice were associated with significantly higher cerebral levels of insoluble, but not soluble, Aβ40/42 species compared to sham-treated AD mice. However, immunohistochemical (IHC) analyses of fixed brain hemispheres revealed similar levels of Aβ-amyloid plaques, microglia activation, and reactive astrocytes between the mild sepsis and sham groups. Interestingly, relative to brains from sham-treated AD mice, mild sepsis-afflicted AD brains showed significantly increased co-localization of Aβ-amyloid plaques and microglia in a brain region-specific fashion. **Summary:** Adult APP/PS1 mice subjected to mild sepsis at an early-life stage exhibited the following: 1) worsened non-spatial

memory; 2) significantly higher levels of insoluble Aβ species; 3) unaltered levels of Aβ-amyloid plaques, suggesting that prior result (2) is due to the presence of non-clustered misfolded Aβ aggregates; 4) unaltered levels of glial activation; and 5) significantly increased co-localization of Aβ-amyloid plaques and activated microglia in a brain region-specific fashion, suggesting that mild sepsis altered the innate immune response in APP/PS1 mice brains. Conclusion: Mild sepsis at an early life-stage appears to be sufficient to aggravate amyloid pathology in adult APP/PS1 mice, suggesting a role for sepsis as a risk factor for AD. ***Funding Disclosure:*** *NIH (National Institute of Aging) and UT Health Science Center at Houston*

19. STRUCTURAL CHARACTERIZATION OF A-SYNUCLEIN STRAINS AMPLIFIED FROM CSF OF PARKINSON'S DISEASE AND MULTIPLE SYSTEM ATROPHY PATIENTS USING CRYO-ELECTRON MICROSCOPY

Victor Banerjee, PhD, Mohammad Shahnawaz, PhD, Corey Hryc, PhD, Nicolas Mendez, Matthew Baker, PhD, Claudio Soto, PhD *(UT Health Science Center Houston)*

Misfolded α-synuclein (αSyn) adopts alternative conformations in different synucleinopathies and becomes able to spread the abnormal structures in a prion-like manner through anatomically connected brain regions. Recently, we developed a seed amplification assay (SAA), also termed PMCA or RT-QuIC for high sensitive detection of αSyn aggregates in patients affected by Parkinson's disease (PD) and related synucleinopathies. Interestingly, we observed different biochemical, biophysical and structural properties of αSyn aggregates amplified from patients affected by PD and a clinically similar synucleinopathy, termed multiple system atrophy (MSA). Here, we elucidated the atomic resolution structure of these amplified aggregates using cryo-electron-microscopy. Our results showed that MSA cases showed the presence of three distinct filament conformations. We were able to obtain high resolution information (3.8 Å) for one of them. Interestingly, the structure of these filaments is strikingly similar to the αSyn structure previously reported in the MSA brain. These results suggest that SAA amplification faithfully replicates the structure of αSyn aggregates. In the case of PD, we found five distinct structures of αSyn filaments. These structures were resolved at resolutions of 3.6 - 5.0 Å, and showed different backbone arrangements of the αSyn subunits in the filament axis. All the PD structures were different from the MSA derived structure. Our findings indicate that αSyn associated to different synucleinopathies correspond to distinct conformational strains. This data may aid in the design of diagnostic and therapeutic strategies for these diseases. ***Funding Disclosure:*** *NIH (National Institute of Aging) and UT Health Science Center at Houston*

20. BIOMECHANICAL CHANGES IN BRAIN ENDOTHELIAL CELLS IN CEREBRAL AMYLOID ANGIOPATHY

Hannah Thompson, BS *(UT Health Science Center Houston)*

Background: While the pathogenesis of cerebral amyloid angiopathy (CAA) is not well understood, it has been thought to be initiated in thickened vascular basement membrane substrate including aggregated amyloid-β (Aβ). The present study investigates how vascular substrate stiffness affects brain endothelial cells (BEC) function in CAA. We further studied the role of endothelial Piezo-1, a mechanosensitive calcium channel, on the cytoskeletal fiber formation in BECs and the brain tissue stiffness. **Methods:** Human primary BECs were cultured on a collagen IV coated dish with the substrate stiffness at 0.2, 2, and 12 kPa. BECs incubated with Aβ (1 μM) underwent OGD for 16 hr. BECs were imaged by immunocytochemistry, super-resolution imaging, and atomic force microscopy (AFM) to determine the tight junction expression, the stress fiber formation, the plasma membrane stiffness changes resulting from OGD, and Aβ stimulations. The role of endothelial Piezo1 on BEC cytoskeletal changes was tested with selective agonist (Yoda1, 5μM) and antagonist (GsMTx4, 0.5μM). To quantitatively determine the biomechanical changes in CAA laden-cerebral blood vessels, an acute brain slice (300 μm) from TgSwDI mice served for AFM force-volume mapping. **Results:** AFM force-volume mapping revealed that the vascular Aβ aggregates showed excessive stiffness (>176kPa). The average brain tissue in TgSwDI mice was 2.01-2.62 fold softer than age-matched WT mice (~2.0 kPa). BEC plasma membrane was proportionally softened by the decreased substrate stiffness. Claudin-5, tight junction marker, expression was also significantly ($p<0.05$) reduced by soft (0.2 kPa) substrate compared to normal condition (2 kPa). BECs under OGD conditions became significantly stiffer (2.1-fold) compared to the normoxic control, but the presence of Aβ blocked this stiffening process in BECs with OGD. BECs incubated with Aβ increased the expression of Piezo1 which regulated the stress fiber formation through retrograde actin flow in BECs. The stimulation of Piezo1 stabilized actin and its flow rate significantly

decreased to 11.6±0.2 nm/sec ($p<0.0001$) compared to control (44.0±0.6 nm/sec). Also, Piezo1 agonism significantly increased the stiffness of brain tissue to the levels seen in WT mice. **Conclusion:** The results suggest the mechanical properties of BECs are altered by the vascular substrate stiffness differences seen in CAA. ***Funding Disclosure:*** *R01AG057576 (to A.U.)*

21. THE BEHAVIORAL AND PATHOLOGICAL EFFECTS OF TAMIFLU IN AN ALZHEIMER'S DISEASE MOUSE MODEL

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Background: Many patients with viral symptoms are treated with the antiviral agent Tamiflu (oseltamivir phosphate) and observational studies have reported acute/delayed adverse neuropsychiatric side effects in patients with age-related neurodegenerative diseases such as Alzheimer's Disease (AD). We have observed a specific form of sialylation, α2-6 sialic acid bonds, near amyloid-βeta (Aβ) plaques in the 5XFAD mouse model of AD and in human AD cases. We hypothesize that Tamiflu's mechanism as a sialidase inhibitor blocks the removal of sialic acid residues and leads to an increase in sialylation levels near Aβ plaques leading to decreased plaque clearance. **Methods:** To test this hypothesis, we investigated the effects of Tamiflu (or vehicle) treatment on aged 5XFAD mice and wild-type (WT) littermates. After initial oral treatment, mice were tested with the Open Field (OF) behavioral task for anxiety-like behaviors. Following drug administration, Novel Object Recognition (NOR) and a second OF test was performed. Mice were euthanized, brain tissue was fixed for paraffin-embedded tissue blocks, and immunostaining for Aβ plaques, microglia, and sialylation was performed. **Results:** A 3-way ANOVA (treatment x genotype x timepoint) revealed no main effect of Tamiflu treatment but 5XFAD mice exhibited greater velocity compared to WT mice in OF and NOR. 5XFAD mice also lacked habituation behavior to the OF test environment as due to no decrease in velocity over time compared to WT mice. Investigation of Aβ plaque pathology with IHC indicated no Tamiflu effect on plaque area or total plaque count in the cortex. We observed greater ratio of cored:diffuse plaques in the vehicle-treated group suggesting that plaque morphology may be altered by Tamiflu treatment. **Conclusions:** Our findings confirm 5XFAD mice are hyperactive and lack normal habituation, but Tamiflu treatment does not alter 5XFAD or WT mouse behavior. We found Tamiflu treatment may lead to morphological differences in Aβ plaques possibly due to microglia activity changes. We have planned additional analyses examining changes in localization of α2-6 sialylation and changes in microglia response to plaques following Tamiflu treatment with double immunofluorescence. Understanding the interaction of antiviral treatment with neurodegenerative pathology is vital for treating aging individuals. ***Funding Disclosure:*** *Biology of Aging T32 AG021890; Reed Precision Medicine Fund, Biggs Institute; NIA R21AG072423 and NIA K01AG066747 to SCH*

22. CALCIUM CHANNEL BLOCKER ALTERS BEHAVIOR AND BRAIN PATHOLOGY IN 5XFAD MICE: A STORY OF RIGOR, REPRODUCIBILITY AND DRUG DELIVERY CHALLENGES

Jessica Wickline, BS, Sabrina Smith, Kristian Odfalk, Riley Shin *(UT Austin)*, Jesse Sanchez, Martin Javors, PhD, Brett Ginsburg, PhD, Sarah Hopp, PhD *(UT Health Science Center San Antonio)*

Background: Epidemiological studies show L-type Ca2+channel (LTCC) blockers reduce the incidence of neurodegenerative diseases, including Alzheimer's disease (AD). Previous studies explored potential mechanisms of the LTCC antagonist isradipine in mouse models of AD, but did not examine the effect on microglia. In AD, microglia take on a neurodegenerative phenotype characterized by toxic gain-of function (e.g., proinflammatory cytokine production) and loss-of-function (e.g., reduced ability to remove aβ). These functions are regulated by intracellular Ca2+. Here, we test the hypothesis that LTCC antagonists act on microglia, modulating their neurodegenerative phenotype in AD. **Method:** We treated 5XFAD and wild type (WT) littermates at 6 or 9 months of age with the LTCC antagonist isradipine (3 mg/kg/day) using three different drug delivery methods: osmotic minipumps, mouse chow, or subcutaneous pellets. Following three weeks of treatment, we tested learning and memory using the Morris water maze (MWM). We used qPCR to measure markers of neurodegenerative microglia and immunohistochemistry (IHC) to examine aβ plaques and microglia or dystrophic neurites. **Result:** We observed a main effect of genotype between 5XFADs and WTs in MWM learning but observed no behavioral effects of treatment by any route, except for a significant change in velocity in the 6-month-old isradipine-treated pellet mice. However, mass spectrometry (HPLC/MS/MS) revealed lower plasma and brain levels of isradipine than expected. In the pellet-treated cohort, analysis of

qPCR revealed genotypic increase in microglia proinflammatory markers and treatment differences in 5XFAD female mice. IHC revealed an increase in the ratio of LAMP1 positive dystrophic neurites to D54D2 stained plaques in isradipine-treated 5XFADs. **Conclusion:** Our studies show that published literature demonstrating therapeutic plasma and brain exposure following isradipine delivery by pumps or pellets is not reproducible. However, our data shows that isradipine delivery by subcutaneous pellet alters non-cognitive behavior and brain pathology. However, this delivery method resulted in inconsistent and low levels of isradipine in blood and brain, suggesting a higher dose or longer-acting formulation may be required. Our future studies will focus on understanding why antagonizing LTCCs leads to an increase in LAMP1 and whether this is due to changes in microglia-mediated neurotoxicity.

23. MICROGLIA INTERNALIZE TAU MONOMERS AND PREFORMED FIBRILS VIA MACROPINOCYTOSIS AND CLATHRIN-MEDIATED ENDOCYTOSIS

Kristian Odfalk, BS, Connor Byrne, BS, Dylan Lim *(high school)*, Sarah Hopp, PhD *(UT Health Science Center San Antonio)*

Background: Aggregation of misfolded tau in neurons is a hallmark of many neurodegenerative diseases including Alzheimer's disease (AD) and is correlated with cognitive decline. Microglia do not express the tau gene. Yet, microglia containing tau are observed in brains of AD patients and mouse models of tauopathy. This suggests that microglia take up neuronal tau, but how this occurs is unclear. Microglia are highly pinocytic and thus efficiently internalize liquid-phase particles in their extracellular milieu. Others have shown that pretreatment with cytochalasin D, an inhibitor of actin polymerization, blocked the uptake of tau by microglia in vitro. Therefore, we hypothesized that microglia employ macropinocytosis (actin-dependent pinocytosis) to internalize free extracellular tau. **Methods:** We treated microglial cells (BV2) in culture with different endocytic pathways inhibitors and probed their uptake of fluorescently conjugated monomer and preformed fibril (PFF) tau. These compounds include: cytochalasin D (CTD), dynasore, chlorpromazine (CPZ), inhibitors of actin polymerization, dynamin, and adaptor protein AP2, respectively. We also co-treated BV2 microglia with fluorescent PFF tau and either pinocytosis marker 10 kDa dextran (Dex10) or macropinocytosis-specific marker 70 kDa dextran (Dex70) and immediately captured images every 30 seconds for 60 minutes. **Results:** Monomer tau uptake was inhibited by all tested compounds and PFF tau uptake was inhibited by CTD and CPZ but not dynasore. PFF tau entered Dex70-positive macropinosomes but also localized to smaller Dex70-negative vesicles. **Discussion:** These results suggests that macropinocytosis (actin-dependent/dynamin-independent) and clathrin-mediated endocytosis (CME) (AP2/dynamin-dependent process) constitute the two potential endocytic pathways of tau monomer uptake in BV2 microglia. Dynasore did not result in significant PFF uptake inhibition, suggesting that the CPZ effect on PFF uptake may be due to an off-target effect. The results of our dextran assay suggest that PFFs can be taken up by macropinocytosis but also other forms of pinocytosis that produce smaller vesicles. Future experiments will include repeating the dextran assay with monomer tau and using complementary inhibitors of macropinocytosis and CME to verify our findings. By determining the tau uptake mechanisms employed by microglia, we hope to aid in the development of therapies aimed at preventing pathological tau progression and cognitive decline. ***Funding Disclosure:*** *NIH T32 NS082145 to KFO; NIH K01 AG066747 to SCH*

24. Aβ AND TAU OLIGOMERS ENGAGE HUMAN SYNAPSES WITH DIFFERENT DYNAMICS SUGGESTING DISTINCT SYNAPTIC TOXICITY ACROSS ALZHEIMER'S DISEASE AND RELATED TAUOPATHIES

Michela Marcatti, PhD, Anna Fracassi, PhD, Mauro Montalbano, PhD, Nisha Puangmalai, PhD, Nemil Bhatt, MS, Chandramouli Natarajan, MS, Balaji Krishnan, PhD, Rakez Kayed, PhD, Giulio Taglialatela, PhD *(UT Medical Branch at Galveston)*

Alzheimer's Disease (AD) is characterized by gradual cognitive decline driven by the targeting of synapses by small oligomers of both Aβ (AO) and tau (TauO), which results in synaptic dysfunction that ultimately underscores disease progression. Recently, failures of clinical trials of Aβ-directed therapeutics redirected the attention onto TauO whose levels increase later in the disease timeline. In support of this view, here we show that recombinant TauO, human brain derived tau oligomers form Alzheimer's disease (BDTO-AD) and Progressive Supranuclear Palsy (BDTO-PSP) as well as AβO target synapses with different dynamics. Using synaptosomes isolated from the hippocampus and frontal cortex of brain mouse slices and postmortem brain specimens from cognitively intact elderly humans, we demonstrated that higher TauO concentrations

effectively oucompete AβO and become the prevailing synaptic-associated species. On the other hand, although lower levels of AβO did not alter TauO binding, higher AβO concentrations resulted in increased TauO binding to human synapses. Immunofluorescence analyses of mouse primary cortical neurons treated with AβO and/or TauO fully supported these data. Consistent with these observations, functional FASS-LTP studies in human synaptosomes revealed that the TauO- induced suppression of chemical long-term potentiation (cLTP) is not affected by the concomitant presence of AβO. Moreover, depletion of synaptosome surface proteins by PK pre-treatment abolished the effect of TauO in reducing AβO synaptic binding; on the other hand, the effect of AβO in increasing TauO synaptic binding was not affected by PK. Taken together, our results provide deeper insight into the interplay between AβO and TauO that contributes to synaptic dysfunction at the basis of the cognitive decline in AD. Furthermore, we observed different synaptic engagement and internalization profiles among the analyzed BDTOs, suggesting different synaptic toxicity of TauO across the tauopathies spectrum. Overall, our results suggest that at the advanced stages of AD, when tau levels increase, TauO become the main synaptotoxic species and likely an effective therapeutic target. Furthermore, subtle disease-specific differences in the dynamic of BDTOs engagement of synapses may underscore different clinical presentations among the tauopathy spectrum. ***Funding Disclosure:*** NIH/NIA R01AG069433, R01AG060718 and R56063405 to GT

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

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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 enhanced genomic instability in neurons. 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 establish new insights into G4-associated molecular mechanisms of 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:** In our studies, we found that stabilizing G4s lead 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. Importantly, in Tg2576 mice, we demonstrated that G4s are stabilized in the brains, well before the deposition of amyloid occurs. **Conclusion:** Our study demonstrates that G4s are dysregulated in AD neurons and AD mouse brains. Our data provide a foundation for investigating G4s, G4-binding proteins and helicases as important molecular mechanisms in AD that warrants further study. This research is being pursued in our laboratory. ***Funding Disclosure:*** *NIH RF1AG068292 to AU, SPM, and AT*

26. NUDT21 DEPLETION IN ALZHEIMER'S DISEASE, LINKS WITH MEMORY LOSS AND CEREBROVASCULAR ACCIDENTS

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Alzheimer's disease (AD) is a severe neurodegenerative disorder and is the most common form of dementia. It is characterized by memory impairment and decline in other cognitive functions. Limited therapies are available for AD, thus there is an urgent need to uncover novel targets. AD is characterized by the accumulation of extracellular plaques composed of amyloid-beta in the brain vasculature that contribute to cerebral amyloid angiopathy (CAA). However, the exact mechanisms that lead to CAA are not fully understood. Recent studies have shown increased accumulation of the extracellular matrix (ECM) product hyaluronan (HA) in CAA. Furthermore, increased levels of hyaluronan synthase 2 (HAS2), a key enzyme that produces HA, correlate with disease severity, suggesting a link between HA accumulation and AD neuropathy. NUDT21, is an important component of the Cleavage Im (CFIm) complex that is responsible for polyadenylation (poly(A)).

Poly(A) is an important biological process required for stability and translation of mature mRNA. The majority of mammalian genes contain more than one poly(A) site, thus polyadenylation results in transcripts with varying 3'UTR lengths. This process is known alternative polyadenylation (APA). The distal polyadenylation site (dPAS) that is located the furthest from the stop codon is generally the most efficient and is more frequently used in normal cells. When NUDT21 is depleted, the CFIm no longer targets the dPAS but instead uses proximal (pPAS) sites, generating transcripts with shorter 3'UTRs. These shorter variants escape mRNA regulation as binding sites for regulatory elements are lost, resulting in increased translation and heightened protein levels for these transcripts. Our research has revealed reduced NUDT21 in brains from patients with AD. Mice with reduced vascular NUDT21 presented with memory deficits. Our data revealed that loss of NUDT21 in vascular smooth muscle cells leads to 3'UTR shortening of HAS2 and increased translation and HA deposits. Furthermore, mice lacking NUDT21 in the vasculature presented with worsened infarct size in a model of stroke compared to NUDT21-competent mice. Taken together, these results point at loss of NUDT21 as a novel pathophysiological mechanism in AD that may aggravate cerebrovascular injury and promote memory loss. ***Funding Disclosure:*** *NIH 1R01HL138510-S1 to HKQ*

Poster Theme Group B: Biomarkers

B2. Neuroimaging

27. IDENTIFICATION OF MULTICOLOR FLUORESCENT PROBES FOR HETEROGENEOUS Aβ DEPOSITS IN ALZHEIMER'S DISEASE

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Background: Accumulation of A□ into amyloid plaques and tau into neurofibrillary tangles are pathological hallmarks of Alzheimer's disease (AD). However, there is a significant intra- and inter-individual variability with respect to coexistence, morphology and conformation of these aggregates, which may account for the extensive clinical heterogeneity observed. Furthermore, A□ can deposit in a spectrum of morphology from diffuse to fibrillar, and dense-cored plaques. The pathological relevance of these varied morphologies in AD is still unknown. In this study, we sought to identfy an array of fluorescent dyes to specifically probe Aβ aggregates, in an effort to address their diversity. **Methods:** Formalin-fixed paraffin-embedded frontal or temporal cortex from pathologically confirmed AD patients and healthy control as well as midbrain specimens from pathologically confirmed LBD patients were used for dyes staining and immunohistochemical staining. APP/PS1 mice brain sections were also used for staining and immunostaining. **Results:** We identified three structurally similar benzothiazole-coumarin fluorescent probes, TC, BC6, and BC15, which intensely stained Aβ plaques in frontal cortex AD brain sections, both parenchymal and vascular, with no apparent staining in healthy control brain. This was confirmed by immunostaining of mirror image sections with 4G8 antibody. Amyloid plaques in APP/PS1 mouse brain were also recognized by these probes. This set of three dyes allowed the visualization of Aβ deposits in three different colors (blue, green and far-red). The triple-stained sections display a staining pattern that suggests binding to different regions of the plaques, and therefore would be valuable to be used for different plaques morphologies. Interestingly, TC also stained NFTs in AD human brain temporal cortex sections and Lewy bodies in LBD human midbrain sections, while BC6 and BC15 did not. **Conclusions:** Aβ aggregate-specific dyes identified in this study have the potential to be developed into Aβ imaging probes for the diagnosis of AD. Additionally, the far-red dye identified here may serve as an imaging probe for small animal imaging of Aβ pathology. The present findings have several implications as they will not only facilitate the development of novel and refined diagnostic tools but also will help us address the clinical heterogeneity observed within AD. ***Funding Disclosure:*** *This work was supported in part by NIH grants AG061069, AG055053 and AG059321 to Claudio Soto*

28. MEG SPECTRAL ACTIVITY WITH CHANGES IN SYSTOLIC BLOOD PRESSURE

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Background: Elevated systolic blood pressure is associated with frontal and temporal brain volume loss. Additionally, midlife hypertension is a known risk factor for Alzheimer's disease (AD). While the structural changes associated with AD are well documented, the functional brain changes that accompany or proceed these clinical changes are not fully understood. Magnetoencephalography (MEG) offers unparalleled spatial and temporal resolution of neural activity. We sought to determine MEG spectral activity with changes in systolic blood pressure (sbp) and grey matter (GM) volume in frontal lobe. **Methods:** 81 adults (median age 63 years, 31/50 males/females) completed six minutes of resting-state MEG and T1 weighted structural brain MRI scan. MEG data underwent standard preprocessing and was source localized to the subject's MRI. Relative mean power of each frequency band (delta, theta, alpha, beta) and GM volume was computed for the frontal lobe. **Results:** Whites/Black <60 years were 21/11 whereas ≥60 years were 36/13 respectively. Multiple linear regression models for age ≥60 showed alpha/theta ratio was associated with the interaction of sbp and race (β = -0.0154; p=0.0251). Additionally, theta was independently associated with sex (β = 0.3206; p=0.0488) and the interaction of GM volume with sex (β = -0.0019; p=0.0363). For age<60, beta was independently associated with age (β = -0.0034139; p=0.0019), sbp (β = 0.0161; p=0.0273), GM volume (β =0.01011; p=0.0185) and the interaction of sbp with GM volume (β = -0.00008; p=0.0259). Theta was also found to be independently associated with age (β = -0.00285; p=0.0027), sbp (β = -0.01347; p=0.0266), GM volume (β = 0.01011; p=0.0185), and the interaction of sbp and GM volume (β = 0.00007; p=0.0278). **Conclusion:** Increase in sbp was found to be associated with decreased alpha/theta ratio in Blacks ≥60 years, while the opposite relationship was observed for Whites. Interestingly, decreased alpha/theta ratio is seen in AD

patients. For adults aged <60, increased sbp was associated with increased beta but decreased mean theta power in the frontal lobe. Further studies are needed to explore the mediating effects of sbp and cortical atrophy on brain aging. ***Funding Disclosure:*** *UTSW Internal Funds for DHMS*

Poster Theme Group C: Clinical Manifestations

C1. Neuropsychiatry and Behavioral Neurology

29. NEUROPSYCHIATRIC INVENTORY QUESTIONNAIRE SCORES ARE PREDICTIVE OF DEMENTIA PROGRESSION

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Background: Alzheimer's Disease (AD) is the most common clinical dementia diagnosis made in older adults. AD pathogenesis involves accumulation of beta-amyloid (Aβ) protein in plaques and tau proteins in neurofibrillary tangles. Consequently, this pathology results in a decreased number of synapses in the brain, altered neuronal function, and cell death via neurotoxicity, as well as learning and memory deficits. Clinically, the presence and severity of neuropsychiatric symptoms that AD patients present with can be reliably measured by the Neuropsychiatric Inventory Questionnaire (NPIQ). This study aims to explore the association between baseline mental health and the severity of AD progression as measured by a latent construct called "D". D is a reliable latent dementia proxy that represents cognitive correlates of functional status and is specific for distinguishing cases with AD from other dementia-related presentations. The D construct used in this study has been adjusted to be equivalent across ethnicities. The association between baseline mental health and changes in D was investigated. **Methods:** Baseline mental health was assessed by NPIQ scores. The latent construct D was used to represent the severity of AD progression within the TARCC cohort. Changes in D overtime were measured using a latent growth curve model (LGM) which yields an estimate of the longitudinal trajectory of changes in D. NPIQ was used to predict the longitudinal changes in D. **Results:** After adjustment for baseline D, NPIQ significantly predicted changes in D, explaining 19% of the variance (p=0.02) for Non-Hispanic Whites. After adjustment for age, sex, and education, NPIQ remained a significant predictor of changes in D. This model explained 25% of the variance in changes in D (p=0.04) for Non-Hispanic Whites. This model was replicated in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort and was consistent with our results TARRC. **Conclusion:** In Non-Hispanic Whites, worse baseline mental health has been shown to predict increased severity and progression of AD. This makes it a clinical therapeutic target with the possible benefit of impacting the course of AD in patients. The interplay between mental health and its relationship to AD should be studied further with an additional focus on ethnicity. ***Funding Disclosure:*** *TARCC supplied the data. SPR was supported by the Graduate School of Biomedical Sciences Medical Student Summer Research Internship.*

30. HOME-BASED tDCS FOR APATHY IN ALZHEIMER'S DISEASE AND RELATED DEMENTIAS: THE FIRST REPORT

Lijin Jose, MD, Lais Bhering Martins, PhD, Robert Suchting, PhD, Hyochol Ahn, PhD, Holly Holmes, MD, Antonio Teixeira, MD, PhD *(University of Texas Health Science Center at Houston)*

Background: Apathy, defined as the loss or reduction of interest and goal-directed behaviors, is the most common neuropsychiatric symptom in Alzheimer's disease (AD). Apathy has been associated with negative outcomes in AD. Transcranial direct current stimulation (tDCS) is a non-pharmacological method that modulates brain activity through low-intensity electrical currents applied over the scalp and has been associated with changes in network connectivity involving the prefrontal cortex and regions implicated in apathy. Given the clinical relevance of apathy, this study aims to test the feasibility, safety, and efficacy of home-based tDCS for the treatment of apathy in AD. **Methods:** This is a randomized, double-blinded clinical trial ongoing at UT Health Geriatric Psychiatry Clinic. We will divide the patients into two groups: one group will receive active tDCS, and another group will receive sham tDCS. We are including only patients diagnosed with AD who present with mild to moderate dementia and apathy for at least four weeks. tDCS will be applied for 30 min a day (from Monday to Friday) at an intensity of 2mA, with 30s ramping up and down using the bilateral Omni-Lateral-Electrode (OLEs) montage. Trained research staff will remotely supervise all sessions. We will assess the participants at baseline, treatment day 14, treatment day 28, treatment day 42, and 6-weeks post-treatment. **Results:** We pre-screened 179 subjects. Forty-three had dementia, of whom 26 had AD. Six of these subjects had clinically significant apathy and went further screening. Four patients were excluded because of other comorbid behavioral problems or very low cognitive performance. One patient was enrolled in

the study. **Conclusions:** Identifying eligible subjects has been challenging, but compliance with the tDCS protocol suggests it is safe for patients. ***Funding Disclosure:*** *TARCC*

31. DEMENTIA SEVERITY IS SIGNIFICANTLY ASSOCIATED WITH A SYNDROME OF GENERAL PSYCHOPATHOLOGY

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Background: The dementia-specific phenotype "δ" is constructed from Spearman's general intelligence factor "g" by Confirmatory Factor Analysis (CFA). It can be reified as a "d-score" and used as a continuous measure of dementia severity. δ's derivation from g suggests that dementia's essential feature is a disruption of intelligence rather than the domain-specific cognitive changes that accompany it. Behavior may also be modulated by g/δ [3]. Others have proposed a general psychopathology factor "p" which may be the behavioral manifestation of g. If so, then δ should adversely impact p. That would imply a dementia-specific syndrome of general psychopathology independent of domain-specific behavioral disturbances arising from regional neuropathology(ies). **Methods:** δ homologs and domain-specific cognitive factors rating memory (MEM) and executive function (EF) were extracted by CFA from cognitive performance data in N = 3,381 TARCC participants, as previously reported [1-2]. p and domain-specific behavior factors were extracted from Neuropsychiatric Inventory (NPI) items in the same sample. δ homologs and domain-specific cognitive factors were related to p and domain-specific behavior factors in a structural model (Figure 1). The δ and p factors were reified as composite scores and submitted to Latent Growth Curve (LGC) analyses over four consecutive TARCC waves (Figure 2). **Results:** Both models fit well (e.g., Figures 1 & 2). δ and Δδ were moderately strongly associated with p ($r = -0.59$, $p < 0.001$) and Δp ($r = -0.29$, $p < 0.001$), respectively. The associations were inverse (adverse). **Conclusions:** δ is significantly associated with p, cross-sectionally and longitudinally and by either the dDx or the dEQ homologs. This confirms the association between two measures of dementia severity and the emergence of a global neurobehavioral syndrome. p is specifically associated with δ and neither with domain-specific factors rating MEM nor EF, when adjusted for g/δ. δ has been shown to be agnostic to a dementia's etiology [5-6]. This suggests the behavioral features of p rather than domain-specific behavioral changes may be the true "Behavior and Psychological Symptoms of Dementia (BPSD)". However, TARCC's sample frame, targeting the dementia of Alzheimer's Disease (AD), is too narrow to test that hypothesis in these data. ***Funding Disclosure:*** *Julia H. and Vann Buren Parr Endowment* ***COI Disclosure:*** *DRR and RFP have formed a company (dNomixTM) to develop clinical applications of "delta" homologs.*

32. THE IMPACT OF TRAUMATIC BRAIN INJURY ON THE COURSE OF NEUROPSYCHIATRIC SYMPTOMS IN AUTOPSY-CONFIRMED ALZHEIMER'S DISEASE

Jeff Schaffert, PhD, William Goette, MS, Nyaz Didehbani, PhD, Christian Lobue, PhD, Laura Lacritz, PhD, John Hart, MD, Heidi Rossetti, PhD, Munro Cullum, PhD *(UT Southwestern Medical Center)*

Objective: Research suggests that history of TBI may alter the course of neuropsychiatric symptoms (NPS) in all-cause dementia, though less is known about specific neuropathological conditions. In this study, we explored the course of NPS in autopsy-confirmed Alzheimer's disease (AD) subjects with and without a history of traumatic brain injury (TBI+ vs. TBI-), expecting that TBI history may be associated with NPS severity over time. **Methods:** Data from 1532 individuals (age 50+) with autopsy-confirmed AD (i.e., high likelihood of AD contributing to their cognitive decline) were obtained from the National Alzheimer's Coordinating Center (Mvisits=3.69). Those with other tau pathology and significant Lewy pathology were removed from the study. TBI history was collected via self-report and included any prior history of TBI with loss of consciousness. Neuropsychiatric Inventory Questionnaire (NPI-Q) and the 15-item Geriatric Depression Scale (GDS) scores were used to examine NPS. Multilevel zero-inflated binomial regression models assessed if NPS severity differed between TBI+ (N=154) and TBI- (N=1378) groups over time. Covariates included: years from baseline visit, demographics, Mini-Mental State Exam scores, Functional Activities Questionnaire score, and whether individuals were currently being treated with psychotropic medication. **Results:** The groups did not differ at baseline in NPI-Q ($p=.36$) or GDS ($p=.07$) scores. NPI-Q scores mildly decreased in the TBI+ group (trend=-0.03), whereas the TBI- group remained stable over time (trend=0.001), 95% CI for the trend [0.01, 0.07]. GDS scores increased more rapidly in the TBI+ group (trend=0.08) than the TBI- group (trend=0.02), 95% CI for the trend [0.02, 0.10]. **Conclusions:** Our findings suggest that NPS course in AD may differ depending on TBI history, though effect sizes were small and are of unclear clinical significance. Over the course of AD, individuals with a history of TBI may experience less NPS overall but may have marginally more depressive

symptoms. The mechanism of this relationship is unknown, but our findings are comparable to recent research suggesting that history of TBI is associated with higher prevalence of apathy in those with all-cause dementia. Future investigations evaluating the relationship between TBI and the course of NPS in neurodegenerative disease are needed. ***Funding Disclosure:*** *The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADRCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI Robert Vassar, PhD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG005131 (PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD).*

C2. Neuropsychology

33. COGNITIVE INTRAINDIVIDUAL VARIABILITY AND ETHNORACIAL DIFFERENCES IN THE 5-YEAR CUMULATIVE INCIDENCE RATE OF MILD COGNITIVE IMPAIRMENT OR DEMENTIA

Bonnie Scott, PhD[1], Donald Royall, MD[2], Robin Hilsabeck, PhD[1] *([1]Dell Medical School at UT Austin, [2] The University of Texas Health Science Center at San Antonio; Glenn Biggs Institute for Alzheimer`s and Neurodegenerative Disorders)*

Background: Intraindividual variability (IIV) across cognitive domains is a promising preclinical biomarker of declines in global cognition and functional independence. Here, we examine ethnoracial differences in the 5-year cumulative incidence of conversion to mild cognitive impairment (MCI) or Alzheimer's dementia (AD) in a sample of cognitively normal older adults and investigate the clinical utility of different types of cognitive IIV. **Methods:** Analyses were based on data from 1369 participants enrolled in the Texas Alzheimer's Research and Care Consortium for 5+ years and were cognitively normal at baseline. IIV metrics were calculated as the SD across tests, domains, etc. and diagnoses were based on clinical judgment by providers at each study site. **Results:** After 5 years of study enrollment, 6.5% of the sample had converted to MCI (n=87) or AD (n=2), and the proportion of converters to non-converters differed significantly across ethnoracial groups (Cramer's V = 0.651): 2.6% non-Hispanic white, 1.7% Hispanic white, 57.1% African American, and 71.2% Asian/Other. Aside from race and ethnicity, there were no differences between converters and non-converters along any demographic or clinical characteristics, but converters demonstrated significantly greater IIV across repeat administrations of a set-shifting task over time. There were significant differences between ethnoracial groups across all cognitive metrics except for mean attention level, IIV-within memory, and IIV-across domains. Within-test IIV for phonemic fluency, within-domain IIV for memory, and IIV-across domains were identified as significant predictors of MCI/AD conversion above and beyond demographics, clinical risk factors, and mean level of cognitive performance. Overall, this model accounted for 62.2% of the variance in MCI/AD conversion and correctly classified 97.7% of the sample. **Conclusions:** Findings suggest that individuals who go on to develop MCI/AD demonstrate greater performance variability across (1) trials within a phonemic fluency task, (2) different tasks assessing memory, (3) different cognitive domains, and (4) repeat administrations of a set-shifting task over time. However, the lack of significant differences between ethnoracial groups on IIV-across and IIV-within the memory domain suggest that these metrics may hold promise for reducing ethnoracial disparities in the evaluation and prediction of cognitive functioning in older adults from diverse populations.
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34. UTILITY OF AN ACTUARIAL NEUROPSYCHOLOGICAL METHOD TO DIAGNOSE MILD COGNITIVE IMPAIRMENT IN A DIVERSE POPULATION

Anne Carlew, PhD, William Goette, MS, Jeffrey Schaffert, PhD, Heidi Rossetti, PhD, Laura Lacritz, PhD *(University of Texas Southwestern Medical Center)*

Background: Use of the Jak/Bondi actuarial neuropsychological method to diagnosis mild cognitive impairment (MCI) has been shown to identify subjects less likely to revert to normal and more likely to have Alzheimer's Disease (AD) biomarkers compared to conventional clinical methods. However, this method generally been applied to datasets of mainly White, highly-educated subjects, limiting generalizability to more diverse cohorts. This project investigated the applicability of the actuarial MCI diagnostic method to the Texas Alzheimer's Research and Care Consortium (TARCC) cohort. **Method:** All subjects from the TARCC cohort with diagnoses of normal control (NC) and MCI at baseline (n = 1911; 65.72% female; 47.11% Hispanic; Mage=67.49; Medu=12.80) were re-classified as NC or MCI using actuarial criteria of 2 impaired tests in a cognitive domain OR at least 1 impaired test in at least 3 cognitive domains. The clinically-diagnosed MCI sample (cMCI; n=655; 58.47% female; 42.44% Hispanic; Mage=71.34; Medu=13.01) and the actuarially-diagnosed MCI sample (aMCI; n=837; 71.21% female; 68.82% Hispanic; Mage=66.30; Medu=10.87) were separately submitted to cluster analysis. Chi Square test was run to investigate frequency of APOE4 allele by diagnostic group. **Result:** Cluster analysis of the aMCI group yielded 3 distinct clusters: a purely amnestic cluster (n=332), a primary language-impaired cluster (n=381), and a multidomain/mixed cluster (n=124). The cMCI group yielded 2 clusters: a multidomain/mixed cluster (n=538), and a cognitively normal cluster (n=117). In chi square analysis, those clinically diagnosed with MCI were more likely to have APOE4 alleles.

Conclusion: Cluster analysis yielded a "cognitively normal" group (~18% of the sample) for participants clinically diagnosed with MCI. Like previous research using the actuarial method, subjects with actuarially-diagnosed MCI fell into 3 distinct cognitively-impaired groups. However, diagnosis using the clinical method was more associated with presence of the AD biomarker APOE4. This finding is of uncertain significance in this heavily Hispanic sample as individuals of Hispanic origin are less likely to carry APOE4 alleles and APOE4 alleles confer less AD risk compared to non-Hispanic Whites. Future research will investigate the prognostic utility of the actuarial method using cognitive and functional longitudinal data and stratified by race/ethnicity.
Funding Disclosure: *TARCC*

35. NEUROPSYCHOLOGICAL FUNCTIONING AND HEAD-INJURY EXPOSURE IN AGING PROFESSIONAL FOOTBALL PLAYERS

Jeff Schaffert, PhD, Nyaz Didehbani, PhD, Christian LoBue, PhD, John Hart, MD, Laura Lacritz, PhD, Heidi Rossetti, PhD, Munro Cullum, PhD *(University of Texas Southwestern Medical Center)*

Objective: In this pilot study, we evaluated whether younger age beginning tackle football (ABTF) and/or more total years of football played (TYFP) were: a) negatively associated with neuropsychological performance, and/or b) related to greater cognitive decline over time in a pilot sample of older (50 and up) retired National Football League (NFL) players. **Method:** Nineteen NFL retirees (age 54-79, Mean=67.1, SD=8.6) underwent clinical interview, neurological exam, neuroimaging, and comprehensive neuropsychological evaluation. Fourteen returned for follow-up evaluation approximately two years later (Mean=23.4 months, SD=8.8). Eleven retirees were cognitively normal, 4 had mild cognitive impairment, and 4 had a clinical diagnosis of Alzheimer's dementia, but all reported some cognitive decline per self/informant report. Retirees were mostly white (2/19 African-American) and had 15-19 years of education (Mean=16.6, SD=1.2). ABTF ranged from 5-14 years-old (Mean=11.0, SD=2.3) and TYFP ranged from 10-26 years (Mean=19.3, SD=4.1). Neuropsychological composite scores for the domains of executive functioning (Mean T=47.0, SD=8.2), language (Mean T=48.2, SD=7.9), and episodic memory (Mean T=45.5, SD=11.3) were entered into mixed-linear models to evaluate the association between ABTF/TYFP and neuropsychological composites (main effect), and neuropsychological functioning over time (time x head-injury exposure interaction). **Results:** TYFP was not significantly associated with executive functioning (F [1,16.3]=0.508, p=.486), executive functioning over time (F [1,7.9=1.997, p=.196), language functioning (F [1,15.4]=1.195, p=.291), language functioning over time (F [1,9.1]=3.657, p=.088), memory functioning (F [1,16.8]=0.161, p=.693), or memory functioning over time (F [1,10.0]=4.704, p=.055). Similarly, ABTF was not significantly associated with executive functioning (F [1,16.8]=0.145, p=.708), executive functioning over time (F [1,8.4=0.959, p=.355), language functioning (F [1,13.9]=0.189, p=.670), language functioning over time (F [1,8.4]=0.520, p=.824), memory functioning (F [1,16.1]=2.958, p=.105), or memory functioning over time (F [1,9.8]=0.074, p=.791). No differences were observed in neuropsychological composite scores between those ABTF<12 and >=12 years old (all p's >=0.475) or between those with TYFP<19 or >=19 years played (all p's >=0.208). **Conclusions:** We did not find any association between ABTF, TYFP, and cognitive functioning or changes in cognitive functioning in this cohort of older NFL retirees. However, our sample was small, and longitudinal research is needed with larger groups to improve confidence in these findings.

Poster Theme Group D: Dementia Care and Psychosocial Factors

D1. Dementia Care Research (nonpharmacological)

36. THE COLLATERAL DAMAGE OF COVID-19 ON PEOPLE LIVING WITH MILD COGNITIVE IMPAIRMENT AND DEMENTIA

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Introduction: Older populations have disproportionately experienced direct effects of the Coronavirus Disease 2019 (COVID-19) pandemic. However, the indirect impact of the pandemic on disruptions in regular healthcare utilization (HCU) among people living with mild cognitive impairment or dementia (MCID) has not been systematically evaluated. **Methods:** Utilizing validated diagnostic criteria in Houston Methodist's electronic medical records, we identified adult (18+) MCID patients. Between 04/2016 and 02/2020 (pre-pandemic phase), patients with ≥2 hospitalizations, one hospitalization and ≥2 outpatient and/or emergency visits, or ≥4 outpatient and/or emergency visits were considered 'established patients' (EP). A propensity-score based non-MCID group was matched for age, sex, race, ethnicity, insurance, geographical deprivation, comorbidities, and COVID-19 infection/severity. Utilizing pre-pandemic data, Autoregressive Integrated Moving Average models for 3 HCU types (inpatient, outpatient, emergency encounters) were fit to predict HCU during the pandemic (03/2020 to 10/2021); disaggregated for lockdown (03/2020 - 05/2020) and post-lockdown (06/2020 to 10/2021) periods. Model-based expected HCU was compared to the observed, proportional difference [confidence intervals] and reported. **Results:** Overall 10,772 (5,386 in each group), MCID (Female - 60.9%, Mean Age - 77.6) and non-MCID (Female - 60.7%, Mean Age - 77.6) EPs were included. Both groups experienced pandemic-related disruptions for all three HCU types (MCID - Inpatient: -19.9% [-25.6%, -14.2%], Outpatient: -33.2% [-39.2%, -27.1%], Emergency: -32,4% [-35.7%, -29.3%]; non-MCID – Inpatient: -12.7% [-17.2%, -8.1%], Outpatient: -17.8% [-24.9%, -10.7%], Emergency: -25.9% [-30.6%, -21.2%]). Disruptions across the entire pandemic period were significantly larger for the MCID (vs. Non-MCID) group (Inpatient: -7.2% [-12.6%, -1.9%], Outpatient: -15.4% [-18.6%, -12.2%], Emergency: -6.5% [-10.8%, -2.2%]). The largest HCU disruptions were in the lockdown period though not significantly different for MCID (vs. non-MCID). However, post-lockdown disruptions were significantly larger for MCID (vs. non-MCID) patients (Inpatient: -9.1% [-14.9%, -3.2%]; Outpatient: -16.3% [-19.6%, -13.1%]; Emergency: -8.7% [-12.9%, -4.5%]). **Conclusion:** At an 8-hospital tertiary healthcare system, MCID patients (vs. matched non-MCID) experienced greater and sustained pandemic-related HCU disruptions underscoring major impacts throughout the care continuum. Mechanisms and clinical / economic consequences of HCU disruptions need to be further evaluated. Furthermore, robust mitigation strategies are needed to sustain essential healthcare for vulnerable populations during pandemic-like catastrophes.

37. PERCEIVED TECHNOLOGY USEFULNESS FOR CAREGIVING AMONG UNPAID CAREGIVERS: A NATIONAL STUDY

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Background: Technological advancements have potential to improve caregiving quality and alleviate burden by providing tools for real-time communication, monitoring, and care coordination. To assist with technology adoption among the 34.1 million unpaid caregivers nationwide, efforts are needed to better understand caregivers' perceptions about the usefulness of technology for caregiving, especially among those caring for others with cognitive impairments. **Methods:** Data were analyzed from a national sample of 483 unpaid caregivers using an internet-delivered questionnaire. All unpaid caregivers were required to provide at least eight hours of weekly care for a care recipient age 50 years or older. The primary dependent variable was the Perceived Technology Usefulness for Caregiving (PTUC) scale, which is a composite score of six items ranging from 0 to 100. PTUC items measured caregivers' perceptions that technology is useful for: (1) easing

caregiving burdens; (2) enabling care recipients to live more independently; (3) enabling better quality of life for care recipients; (4) improving relationships with care recipients; (5) communicating with care recipients' family and friends; and (6) communicating with care recipients' healthcare team. PTUC item responses were summed and averaged, and the overall PTUC scores were transformed into statistical tertiles (higher scores indicating more perceived technology usefulness for caregiving). An ordinal regression model was fitted to identify factors associated with higher PTUC tertiles. **Results:** Across tertiles, unpaid caregivers who were younger (Beta=-0.018, P=0.030), male (Beta=0.422, P=0.048), Hispanic (Beta=0.779, P=0.010), African American (Beta=1.064, P<0.001), and Asian (Beta=0.958, P=0.010) reported higher PTUC scale scores. Unpaid caregivers with lower annual household incomes (Beta=-0.010, P=0.003), higher caregiver strain (Beta=0.149, P<0.001), and more frequent support for caregiving from family/friends/neighbors (Beta=0.009, P=0.002) reported higher PTUC scale scores. Unpaid caregivers whose care recipients had less cognitive impairment reported higher PTUC scale scores (Beta=-0.245, P=0.048). **Conclusion:** Findings indicate caregiver characteristics, caregiving dynamics, and available resources (financial and caregiving support) influence perceptions about the usefulness of technology for caregiving. The utility of technology for caregiving may be higher among informal caregivers with more challenging circumstances or who coordinate care with others. Findings suggest caring for individuals with cognitive impairment may require multi-level support beyond technological solutions.

38. CARE PARTNER ENGAGEMENT IN PROBLEM-SOLVING TRAINING: LESSONS LEARNED FROM THE CADES STUDY TRIAL

Alexandra Holland, LMSW, Susan Herrera, LMSW, Marlene Vega, PsyD, Valeria Silva, BS, Chung Lin (Novelle) Kew, PhD, CRC, Alka Khera, MD, Shannon Juengst, PhD, CRC *(University of Texas Southwestern Medical Center)*

Background: Care partners of persons living with Alzheimer's disease and related dementias (ADRD) often experience feelings of burden and stress. These often stem from the need to balance their caregiving role with other life domains, including managing other relationships and self-care. However, most interventions target only challenges associated with caregiving, and not how to balance caregiving with other life roles. **Method:** Problem-Solving Training (PST) is a remotely delivered metacognitive training strategy that allows care partners to learn a step-by-step approach to manage stressors and achieve goals. PST builds on problem-solving skills care partners already possess by teaching a six-step problem-solving mnemonic learned through iterative supported application. PST is therefore strengths-based and helps care partners identify and overcome challenges they may face. Care partners in CaDeS are randomized to 3 or 6 PST sessions, with or without 6 booster sessions. **Results:** N=15 care partners have participated in CaDeS PST sessions to date. Three care partners did not complete the intervention, with 1 completing only two sessions and two not beginning any sessions. They all indicated the reason for not completing sessions was time constraints and all were randomized to 6 sessions + 6 boosters. Twelve participants completed all assigned sessions. Session lengths ranged from 10 minutes to 121 minutes, with an average time of 52 minutes per session. Participants rescheduled sessions an average of 1.15 times (range: 0-8 times). After completing either 3 or 6 sessions, participant confidence, on a scale of 0 (not at all confident) to 10 (very confident), averaged 8.4 for using the PST strategy and 8.2 for using the PST strategy on other problems that arise post-intervention. **Conclusion:** We share lessons learned so far from our experience implementing remotely delivered PST with this population. It is important to identify retention strategies that work to increase participant engagement in the study, both during and between sessions. Challenges to study participation also need to be identified so research staff can work with the participant to overcome these barriers. By doing this, we hope to illustrate potential strategies that can be used in research with this population in general. ***Funding Disclosure:*** *This work is supported by the Texas Alzheimer's Research and Care Consortium [TARCC 2020, 2020-2023].*

39. CULTURAL ADAPTATION AND MODIFICATION OF "DESCUBRIENDO SOLUCIONES JUNTOS" FOR SPANISH-SPEAKING LATINX CARE PARTNERS OF ADULTS WITH NEUROLOGICAL CONDITIONS

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Background: Care partners of adults with neurological conditions are often tasked with balancing their needs and their care recipient's needs. The lack of support services available outside of traditional psychotherapeutic

services leaves them without a direct supportive approach to manage their lives independently. Furthermore, the gap is greater for Spanish-speaking Latinx care partners in the U.S. due to a lack of bicultural and bilingual support services. As a result, culturally adapted interventions for Latinx care partners are scarce. **Method:** A single group, pre-post-test pilot study using the initial Spanish translation of Problem-Solving Training (PST) into "Descubriendo Soluciones Juntos" (DSJ) was conducted. Participants were assigned to complete six DSJ sessions. Participants completed baseline and one-month follow-up measures to consider DSJ's effects on pertinent behavior outcomes. Three trained bilingual and bicultural interventionists used qualitative feedback from participants and each other to identify further adaptation needs. **Results:** N=4 participants consented to participate in the study; N=3 completed six DSJ sessions. The participant that did not complete sessions did not respond to attempts to contact after baseline. At follow-up, two participants reported less caregiver burden and one reported higher caregiver burden, but also higher positive aspects of caregiving. There was no change in depressive symptoms (N=3) from baseline to follow-up, though 2 participants reported no depressive symptoms at baseline. The participant who did not complete the intervention reported lower life satisfaction and higher caregiver burden at baseline compared to the 3 participants who completed the intervention. One participant reported moderate satisfaction with the intervention and two reported high satisfaction. The interventionists identified further adaptations consisting of cultural, health literacy, and evidence-based aspects. **Conclusion:** Despite accounting for a quarter of the U.S. population, the Latinx community is more likely to face systemic barriers, such as having to navigate resources and support services that are not available or tested in their native language. Our iterative cultural adaptation of DSJ for Spanish-speaking Latinx care partners should provide a culturally appropriate intervention that can help them overcome obstacles and accomplish goals tailored to their values while maintaining the essential and evidence-based components of PST. ***Funding Disclosure:*** *This study was funded by Communities Foundation of Texas.*

40. FEASIBILITY OF COMMUNITY-BASED RECRUITMENT IN THE "CARE PARTNERS IN DEMENTIA PROBLEM-SOLVING TRAINING" (CaDeS) STUDY TRIAL

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Background: We present recruitment feasibility and successful strategies to date in the ongoing CaDeS study. Our participants are English- or Spanish-speaking adults (18 years or older) who care for an individual with dementia. They must have a ≥ 1-year relationship with their care recipient, indicate some level of depression or caregiver burden, and be cognitively able to self-consent. **Method:** We are connecting with organizations serving adults with dementia and their care partners along with the general public. Recruitment has taken place using the following methods: 1) Social Media/General Marketing; 2) In-person event; 3) Flyers in Public Places; 4) Provider Referrals; 5) UTSW Sources (e.g. Study Finder, Research Studies, and Registries); 6) UTRGV Newsletter; 7) Word of Mouth; 8) Aging/Dementia related Organizations (e.g., dementia support groups, senior facilities, etc.); 9) General population organizations (e.g. Primary care physicians, community health workers, etc.); 10) Religious Organizations. **Results:** We approached 51 care partners: 2 were ineligible, 3 refused, and 26 consented. The remaining individuals we were either not able to get a hold of (n=6) or are continuing to approach (n=14). Reasons for refusal were: 1) not interested in research (n=0); 2) feeling overwhelmed (n=2); 3) no time (n=0); and 4) not believing they would benefit (n=1). Of the individuals who consented, they were initially recruited through: 1) Social Media (n=6); 2) In-person event (n=3); 3) Flyers in Public Places (n=0); 4) Provider Referral (n=7); 5) UTSW Sources (n=6); 6) UTRGV Newsletter (n=2); and 7) Word of Mouth (n=2). **Conclusion:** The least successful methods of recruitment have been those without a direct connection to us (e.g., public flyers). Additionally, some organizations (e.g., smaller churches) lack the infrastructure to support opportunities for community outreach. We are actively seeking ways to better connect and build rapport with some of these organizations. The methods of recruitment that have been most successful are those that had a direct connection with a team member or were affiliated with our organization. Moving forward, our recruitment efforts need to be more targeted towards organizations that will allow for direct interaction that will likely lead to an increase in recruitment. ***Funding Disclosure:*** *This work is supported by the Texas Alzheimer's Research and Care Consortium [TARCC 2020, 2020-2023].*

Poster Theme Group E: Dementia Care Practice

E1. Dementia Care Practice (descriptive research)

42. LESSONS LEARNED FROM MONITORING EMERGENCY ALERTING SYSTEM FOR PATIENTS WITH MILD COGNITIVE IMPAIRMENT OR DEMENTIA

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Background: Delirium is a preventable neurological emergency characterized by acute deterioration in cognition and attention that can lead to (1) acceleration of a pre-existing cognitive decline, (2) prolonged hospitalizations, (3) increased need for post-acute care facilities, and (4) excess healthcare costs. Delays in implementing effective delirium prevention protocols can be attributed to a lack of early recognition of delirium, a lack of identification of patients at risk, and gaps in communication with the emergency team. We describe lessons learned and early evaluation of an emergency alerting system for patients known to be at risk for delirium. **Methods:** We implemented two separate alerting mechanisms, one with the regional EMS and one with the regional health information exchange (HIE) in Central Texas. Both alerting mechanisms used distinct patient matching algorithms and both alerts are activated unobtrusively by data entered via routine patient care. We monitored for alert events for patients who were enrolled in the study and conducted quarterly retrospective audits with each organization to identify missed cases and sources of errors. **Results:** EMS and HIE alerts have been operational since August 12, 2020 and March 4, 2021, respectively. We have enrolled 54 participants to date. We have received 1 alert via EMS and 1 alert for a separate patient via the HIE. From retrospective audits after alerting was operational for each organization, we identified 8 emergency events without alerts from EMS and 2 without alerts from the HIE. From 5/1/2021 - 11/1/2021, we identified 8 additional events via the HIE for ED visits or hospitalizations for 5 patients across 5 hospitals where EMS was not involved and thus not within our scope to result in an alert being sent. **Conclusion:** Automated alerts were demonstrated feasible for emergency events and show promise to support communication in care of patients at risk of developing delirium. They also show potential to apply to conditions beyond delirium prevention. We identified multiple factors of complexity in analyses of alerts including timing of information transmission, source, data entry errors, successful matching, and connectivity. We also identified potential for scalability of additional encounter types through the health information exchange. ***Funding Disclosure:*** *TARCC*

43. ASSESSMENT OF BEHAVIORAL AND COGNITIVE DOMAINS IN ELDERLY/OLDER ADULTS LONGITUDINAL STUDY (ABCDE-LS): STUDY RATIONALE AND BASELINE RESULTS

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Background: The current generation of research in geriatric neuropsychiatry is seeking to understand the complex interplay between aging-related processes and the pathophysiology underlying neuropsychiatric disorders, mainly dementia. The Research Domain Criteria (RDoC) is a conceptual framework integrating different levels of pathophysiological processes implicated in neuropsychiatric disorders. This study aims to explore the applicability of RDoC constructs/domains in the clinical practice and to determine which RDoC domains predict cognitive decline in older adults. **Method:** The ABCDE-LS will enroll psychiatric patients 60 years or older who will be followed for three years. Besides assessing cognition using the NIH Toolbox and Montreal Cognitive Assessment (MoCA), and psychopathology using the Geriatric Depression Scale (GDS) and Brief Psychiatric Rating Scale (BPRS), we are also collecting data on medical comorbidities, frailty, and life style (e.g., eating behavior, sleep quality, and drug use). **Results:** We have enrolled 15 (M/F, 8/7) patients so far. The mean age ± SD is 74.8 ± 6.5 years old. Most patients were diagnosed with mood disorders [major depressive disorder (66.7%) and bipolar disorder (5.6%)]. The mean ± SD of NIH Toolbox (raw score), MoCA, BPRS, and GDS scores were, respectively, 86.6 ± 8.3, 23.2 ± 2.9, 21.5 ± 3.2, and 3.9 ± 3.9. There was no association between cognitive and psychopathological measures. **Conclusion:** Patients enrolled in the study have a low level of current psychopathology, but mild cognitive impairment, possibly reflecting their long-standing history of psychiatric disorders. This study might contribute to understanding factors associated with cognitive decline in older adults with behavioral symptoms. ***Funding Disclosure:*** *UTHealth Psychiatry*

44. LINKING PROBLEMS REPORTED BY CARE PARTNERS OF INDIVIDUALS WITH ALZHEIMER'S DISEASE AND LEWY BODY DEMENTIA TO THE ICF

Chung Lin (Novelle) Kew, PhD, CRC, Shannon Juengst, PhD, CRC, Candice Osborne, PhD *(UT Southwestern Medical Center)*

Background: Caring for someone with Alzheimer's disease and related dementias (ADRD) is inherently complex. Oftentimes, such care rests solely on care partners, who are typically family members or close known associates, of the person with ADRD and have little to no experience or guidance in dementia care. Aim: To, classify, describe, and compare the problems reported by care partners of adults with Alzheimer's disease and Lewy body dementia using the International Classification of Functioning Disability and Health (ICF). **Methods:** Problems that care partners experience were collected during a Problem-Solving Training intervention. The meaningful concepts were then extracted and linked to the ICF using a standardized linking technique. **Results:** 402 meaningful concepts were extracted from 128 problems reported by care partners. 79.4% of the concepts were linkable to the ICF. "Body functions' was most frequently addressed followed by "Activities and participation". Care partner of LBD reported more problems (M=23.6±13.4) on average than care partners of AD (M=19.4±12.1). Care partners of LBD reported greater relative proportions of problems in mental function (emotional and sleep functions) than care partners of AD. **Conclusion:** This study suggests that the experience of care partners of adults with LBD may include significantly more challenges and may be more emotionally demanding than the care experience of care partners of adults with AD. Interventions designed to support care partners of adults with dementia may need to be tailored to meet the needs of care partners based on the care receiver's type of dementia.

Poster Theme Group F: Drug Development

F2. Drug Development - Nonhuman

46. SEX DIFFERENCES IN THE IMPACT OF STROKE ON COGNITIVE IMPAIRMENT AND ITS TREATMENT WITH mir20a-3p: A PRECLINICAL STUDY

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Introduction: Stroke is a leading risk factor for dementia. Our previous studies show that the small non-coding RNA, mir20a-3p, is neuroprotective for stroke and reduces sensory motor impairment in the acute phase (Branyan et al., 2021). In this study, we used a battery of tests to assess the integrated functioning of affective and cognitive circuits after stroke in males and females, as well as the impact of mir20a-3p. **Methodology:** Middle-aged (acyclic) females and males were subject to ischemic stroke using endothelin-1 in the left MCA region. Mir20a-3p mimics or scrambled oligo was administered i.v. 4h and 24h after stroke. Long term cognitive changes were assessed by contextual fear conditioning (CFC) and the novel object recognition test (NORT). **Results:** Contextual fear conditioning was evaluated by percent freezing during acquisition, extinction, and retrieval. Sex differences were noted in fear extinction even prior to stroke, with males displaying resistance to extinction. At 30 days post-stroke, % freezing was no different from the pre-stroke extinction in females, while males showed a significant decrease in freezing rates after stroke, irrespective of treatment. In females, retrieval of remote fear memory was impaired as late as 100d post stroke in vehicle-treated females ($p<0.05$) indicating a persistent cognitive impairment, but is preserved in miR20a-3p treatment group, indicating a lasting benefit of microRNA treatment. In contrast, both vehicle and mir20a-3p treated males showed a significant decline in freezing in response to fear memory retrieval (60 days post MCAo). Surprisingly, mir20a-3p treatment improved declarative memory measured with NORT at 100 days post MCAo in both female and male rats ($p<0.05$). Additionally, stroke reduced social interaction among female rats, which was significantly reversed with mir20 treatment. However, among the male rats, stroke did not impair social interaction, although mir20a-3p treatment significantly enhanced the social interaction after stroke. **Conclusion:** While mir20a-3p treatment improved acute stroke outcomes in both sexes, fear related memories were better preserved in females at 30 days, suggesting that neuroprotectants may have similar effects in the short term but may diverge in a sex specific manner in the chronic phase. ***Funding Disclosure:*** *Supported by RFAG042189 to FS; Alzheimer's Association Research Fellowship-21-849749 to DS.*

47. CONTRIBUTIONS OF AGE-RELATED INFLAMMATION AND DECREASED CERVICAL LYMPHATIC FUNCTION ON DIMINISHED AMYLOID BETA CLEARANCE AND PROGRESSION TO ALZHEIMER'S DISEASE

Morgan Jackson, Bsc, Olga Gasheva, PhD, Rebecca Phillips, Andrew Powell, David Zawieja, PhD, Anatoliy Gashev, PhD, Erin van Schaik, PhD, Karienn Souza-Montgomery, PhD *(Texas A&M Health Science Center)*

Background: Accumulation of amyloid beta (Aβ) plaques plays a key role in the development of Alzheimer's disease (AD). Studies have shown that cervical lymphatic vessels are an important element in the elimination of solutes, including Aβ plaques (Pappolla et al., 2014). As aging occurs, the functionality of the cervical lymphatic contractions and flow diminish, thereby decreasing the ability of the lymphatic vessels to eliminate unwanted substances from the brain (Gashev et al. 2002). Chronic inflammation is linked to development of dementia, and we have previously observed that chronic localized inflammation in mesenteric lymphatic compartments contribute to aging-associated deteriorations in immune response (Chatterjee and Gashev 2012). To develop future potential treatments to slow the progression of AD, the mechanisms linking diminished lymphatic function to the development of AD pathology must first be identified and understood. Our hypothesis is that low-grade inflammation induces alterations in lymphatic vessel contractility that decrease the clearance of Aβ plaques from the brain, and accelerates progression of AD-related pathology and phenotype. **Methods:** To test this hypothesis, we inoculated APP/PS1 and aged-matched NTg female and male mice at 3 months of age with Staphylococcus aureus for 4 months, 2x a week, thus producing a low chronic inflammatory state. We then analyzed cervical lymph vessel contraction frequency, ejection fraction, and fractional pump flow. Furthermore, we tested cognition using Barnes Maze, Open field, and Novel Object Recognition, and motor abilities, using rotarod and Digigate. **Results and Conclusion:** We found that the survival rate of APP/PS1 mice was affected by inoculation of bacteria and ongoing analysis suggests that

chronic inflammation alters lymphatic contractility and accelerates age-related decline in motor and cognitive abilities. ***Funding Disclosure:*** *1R56AG061097-01*

48. COGNITIVE OUTCOMES OF CIRCADIAN RHYTHM DISTURBANCES IN AGING

Andrew Powell, William Jackson, Jocelin Reyes, Morgan Jackson, BSc, David Earnest, PhD, Karienn Souza-Montgomery, PhD *(Texas A&M Health Science Center)*

Background: Cognitive changes in aging and Alzheimer's disease (AD) are often accompanied by pronounced disturbances of circadian timekeeping, especially sleep-wake cycle. Normal circadian timekeeping has an important impact on human health and performance by providing the temporal coordination of internal processes to insure their occurrence at the "right time" relative to each other and to the external environment. Aging of the rodent circadian system is characterized by changes comparable to those in human aging and AD. Common disturbances in the sleep-wake rhythms of aged rodents include alterations in the circadian activity. However, not all aged rodents show these changes, demonstrating the variability characteristic of human aging in pre-dementia or mild cognitive impairment (MCI). Because the aging population also shows variability in onset and magnitude of cognitive impairment, we explored the relationship between these cognitive deficits and sleep disturbances during aging in mice. **Methods:** The circadian rhythm of locomotor activity was continuously analyzed for 30-40 days in young (3-5 mo), middle- aged (12-14 mo) and aged (18-24 mo) mice. We then tested the mice in the Barnes maze for learning and memory performance. **Results:** Aged mice exhibited significant impairment of cognitive behavior in conjuction with striking changes in their circadian patterns of activity. Interestingly, we observed a gender-specific relationship between cognitive impairment in the Barnes maze and increased variability in daily onset times of circadian activity in aged female mice (20-24 mo). **Conclusion:** We are currently testing middle aged animals (12-14 mo), to determine if behavioral deficits occur earlier in the lifespan and whether changes in circadian activity occur prior to cognitive impairment. This data will be the foundation of our model to further understand the relationship between circadian synchronization and cognitive impairment, and to probe possible mechanisms of action.

Poster Theme Group G: Public Health

G1. Epidemiology

49. CHEMOTHERAPY AS A RISK FACTOR FOR ALZHEIMER'S DISEASE

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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:*** *NIA: R21AG067204*

G3. Prevention (nonpharmacological)

50. HIPPOCAMPAL ALL-TRANS RETINOIC ACID (ATRA) DEFICIENCY IN ALZHEIMER'S DISEASE: AN INVESTIGATION OF ATRA-DEPENDENT GENE TRANSCRIPTION IN POST-MORTEM HIPPOCAMPAL TISSUE

J. Josh Lawrence, PhD, Kevin Pruitt, PhD, Mosharaf Mahmud Syed, BS, Maria Manczak, PhD, Igor Ponomarev, PhD *(Texas Tech University Health Sciences Center)*

Background: There is accumulating evidence for a role of Vitamin A (VA) deficiency in Alzheimer's disease (AD) pathogenesis and progression. All-trans retinoic acid (ATRA), the bioactive metabolite of VA in the brain, serves diverse roles in the human hippocampus: an exogenous antioxidant (AO), a receptor ligand mediating cytosolic signaling, and a hormone-like nuclear transcription factor. ATRA itself and agonists of retinoic acid receptors (RAR) have been shown to promote activation of the non-amyloidogenic pathway by enhancing expression of α-secretase, thereby providing a mechanistic basis for preventing amyloid beta (Aβ) toxicity. While there is a substantial body of evidence supporting VA deficiency in preclinical AD models and in serum samples of AD patients, it is not known whether ATRA is actually deficient in the human hippocampus of AD individuals. **Methods:** Using a publicly available human transcriptomics dataset (van Rooij et al 2018), we evaluated the extent that ATRA-sensitive genes are dysregulated in the human hippocampus from post-mortem AD tissue (n=20) compared to age-matched controls (n=10). **Results:** ATRA-responsive genes (ADLH1A3, CYP26A1, CYP26B1, RBP1, RBP4, NGRN, GAP43, and CALB1) were generally downregulated. Supporting active transcriptional block, we also found significant upregulation of ATRA receptor co-repressors (NCOR1, PML, ZBTB16, and TNIP1). ROS sensors Nrf1/Nrf2 (NFE2L1/NFE2L2) and NfkB expression was upregulated, indicating oxidative stress and neuroinflammation. We found that Nrf2 targets to be generally impaired, consistent with an age-related increase in histone deacetylase (HDAC) expression. Finally, using 672 ATRA-sensitive genes from the literature, we identified ATRA-responsive 130 genes that were common to two AD data sets (van Rooij et al 2018, Annese et al. 2018). Of these 130 genes, 127 were well correlated between the two AD data sets ($p<0.0001$), sharing the same directionality and approximate fold-change. **Conclusion:** In conclusion, our investigation of ATRA-sensitive genes in the human hippocampus bolsters the scientific premise that ATRA is depleted from the human hippocampus in AD. These observations were generalizable across multiple heterogeneous AD datasets. In light of these observations, dietary VA supplementation as adjunct or prophylactic therapy for AD should be considered, possibly in combination with a class I/II histone deacetylase inhibitor and/or a DNA methyltransferase inhibitor. ***Funding Disclosure:*** *Wylie Foundation (JL), Start-up funds (JL)*

51. DEPRESSION, VITAMIN D, AND HEALTH DISPARITIES AMONG HISPANICS IN OLDER RURAL WEST TEXANS: A PROJECT FRONTIER STUDY

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Background: Accumulating evidence indicates that VD deficiency (VDD; ≤20 ng/ml) and insufficiency (VDI; 21-29 ng/ml) are associated with health disparities among rural populations, particularly depression. **Methods:** Using a cohort of 298 participants recruited in Project FRONTIER (Facing Rural Obstacles to Health Care Now Through Intervention, Education, and Research), we performed descriptive statistics and regression analyses to assess correlations between serum vitamin D levels and subjective measures of depression (Geriatric Depression Scale, a well validated screening tool for depression in the elderly population). **Results:** Of 299 participants, the demographic distribution had a mean age of 62.6 (±11.7), female gender of 70.9% (n=212), and Hispanic/Latino ethnicity (HLE) of 40.5% (n=121). Approximately 61.5% of this population fell into VDD (25.0%) or VDI (36.5%) serum levels categories. We found a significant negative correlation between VD level and GDS total scores ($p=0.022$). The X-intercept at GDS=0 was 116.2 ng/ml, suggesting that a high sufficient VD level is required to achieve a GDS score of zero. The Y-intercept was 7.26, suggesting that VD level accounts for over 2/3 of total GDS score required for a clinical diagnosis of depression (GDS □10). VD level was negatively correlated not only with Dysphoria (Spearman $r = -0.19$; $p=0.001$) but also with Meaninglessness (Spearman $r = -0.15$; $p=0.011$), but not Apathy (Spearman $r = -0.053$; $p = 0.36$) or Cognitive Impairment (Spearman $r = -0.030$; $p=0.60$) subfactors. Interestingly, the GDS question (Q25) "Do you

frequently feel like crying?" was most highly correlated (Spearman r = -0.274, p=1.55e-6). VD levels were associated with HLE (p<0.0001; AUC = 0.755 ± 0.282, p<0.0001). Moreover, HLE (22.93 ng/ml, n=121) was lower than non-HLE (32.36 ng/ml, n=178, U = 5280, p<0.0001). Finally, HLEs/non-HLEs were differentially stratified across VD levels (X2 (3, 299) = 52.09, p<0.0001). The negative significant association between VD status and depression, originally described in a published pilot study (Johnson et al. 2010), was confirmed in a larger sample of Project FRONTIER participants. **Conclusion:** Overall, these data underscore troubling disparities in VD-related health status and depression among HLE and non-HLE populations that need to be addressed while performing a clinical or metabolic evaluation. ***Funding Disclosure:*** *TTUHSC Medical Student Summer Research Program*

52. NEAR-INFRARED LIGHT REDUCES GLIA ACTIVATION AND MODULATES NEUROINFLAMMATION IN THE BRAINS OF DIET-INDUCED OBESE MICE

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Background: Neuroinflammation is a key event in neurodegenerative conditions such as Alzheimer's disease (AD) and characterizes metabolic pathologies like obesity and type 2 diabetes (T2D). Growing evidence in humans shows that obesity increases the risk of developing AD by three-fold. Hippocampal neuroinflammation in rodents correlates with poor memory performance, suggesting that it contributes to cognitive decline. Here we propose that reducing obesity/T2D-driven neuroinflammation may prevent the progression of cognitive decline associated with AD-like neurodegenerative states. Near-infrared light (NIR) has attracted increasing attention as it was shown to improve learning and memory in both humans and animal models. We previously reported that transcranial NIR delivery reduced amyloid beta and Tau pathology and improved memory function in mouse models of AD. Here, we report the effects of NIR in preventing obesity-induced neuroinflammation in a diet-induced obese mouse model. **Methods:** Five-week-old wild-type mice were fed a high-fat diet (HFD) for 13 weeks to induce obesity prior to transcranial delivery of NIR for 4 weeks during 90-s sessions given 5 days a week. After sacrifice, brain slices were subjected to free-floating immunofluorescence for microglia and astrocyte markers to evaluate glial activation, and quantitative real-time PCR to evaluate expression levels of inflammatory cytokines and brain-derived neurotrophic factor (BDNF). **Results:** The hippocampal and cortical regions of the HFD group had increased expression of the activated microglial marker CD68 and the astrocytic marker glial fibrillary acidic protein. NIR-treated HFD groups showed decreased levels of these markers. PCR revealed that hippocampal tissue from the HFD group had significantly increased levels of pro-inflammatory interleukin (IL)-1β and tumor necrosis factor-α. Interestingly, the same samples showed increased levels of the anti-inflammatory IL-10. All these changes were attenuated by NIR treatment. Lastly, hippocampal levels of the neurotrophic factor BDNF were increased in NIR-treated HFD mice, compared to untreated HFD mice. **Conclusions:** The marked reductions in glial activation and pro-inflammatory cytokines along with elevated BDNF provide insights into how NIR could reduce neuroinflammation. These results support the use of NIR as a potential non-invasive and preventive therapeutic approach against chronic obesity-induced deficits that are known to occur with AD neuropathology. ***Funding Disclosure:*** *NIH/NIA R01AG069433, R01AG060718 and R56063405, TARCC*

Poster Theme Group H: Novel Statistical Methods

H1. Novel Statistical Methods

53. CHANGES TO BRAIN RHYTHM PATTERNS IN ALZHEIMERS DISEASE

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Alzheimer's Disease (AD) is a complex, progressive, and devastating neurodegenerative disease. Its detrimental effects span a variety of neurologic and cognitive functions. While AD is classically associated with impaired memory, language skills, and muscle coordination, AD can also induce mood disorders such as dementia and depression. Due to the heterogeneous symptomology, to date, there is neither a cure, nor a definitive antemortem diagnosis for AD. We propose an alternative approach to EEG analysis that focuses on the rhythms' patterns over finite timescales. Specifically, we use two independent methods for quantifying structural regularity and irregularity of the recorded signals and correlate the resulting "stochasticity scores" with behavior. The first method, discovered by A. Kolmogorov in 1933, produces a λ-score that quantifies the pattern's consistency with the underlying mean behavior. The second method, introduced by V. Arnold in the 2000's, yields a β-score that measures how "structured" (e.g., periodic-like or time-clustered) the pattern is. Our work in wild type (WT) mice revealed a curious interrelationship between intracranial EEG morphology in mice and parameters of the animal's activity, such as speed and acceleration. Specifically, we analyzed subcortical EEGs recorded from the CA1 area of the hippocampi of WT mice running a U-shaped track with food wells on either end and studied their θ-waves, γ-waves, and sharp wave-ripple (SWR) events. This is important because these waves coordinate hippocampal spiking activity, and thus play a key role in spatial and episodic memory encoding, consolidation, and retrieval. Moreover, we noticed spatial clustering of waves with different morphology along the animal's trajectory which are reminiscent of hippocampal place fields, as well as interdependencies between θ-wave, γ-waves, and SWR sequences. In contrast, the damaged synaptic circuits in AD brains alter brain wave patterns, compromising information exchange between brain regions. By characterizing the pattern dynamics of brain waves in AD mice, we can distinguish between patterns in AD brains from those in healthy brains. Overall, these results offer a novel perspective on studying the structure, the dynamics, and the functionality of the brain waves. ***Funding Disclosure:*** *NIH R01NS110806-01A1, NSF 1901338, NIH R01NS097764*