Theme A. Development of New Models and Analysis Method
Clinical Science

(1) **Prediction of Biomarker Profiles by Cognitive Assessment**

Presenting Author: Donald R. Royall, MD
Professor and Chief: Division of Aging and Geriatric Psychiatry
The University of Texas Health Science Center at San Antonio

Donald Royall and Raymond Palmer

Background: We've developed a latent biomarker panel ("INFLAMMATION") that predicts dementia severity as measured by the latent dementia-specific cognitive phenotype "δ". INFLAMMATION is indicated by pro- and anti- inflammatory proteins including alpha 2 macroglobulin (a2M), interleukins 3 (IL-3), 10 (IL-10), and 13 (IL-13), pancreatic polypeptide (PPP), prolactin (PRL), serum amyloid peptide (SAP), tumor necrosis factor alpha (TNFa), thrombopoietin (THPO), and von Willebrand factor (vWF). We have replicated INFLAMMATION's association with δ in two cohorts [the Texas Alzheimer's Research and Care Consortium (TARCC) and the Alzheimer's Neuroimaging Initiative (ADNI)] and in two biofluids; serum (TARCC) and plasma (ADNI)[1]. We want to recognize individuals with INFLAMMATION-related cognitive declines and triage them for INFLAMMATION-specific interventions. Method: We correlated INFLAMMATION-adjusted and unadjusted factor scores and analyzed cases presenting above and below their line of identity (LOI). Cases presenting above the LOI are predicted to be adversely impacted by INFLAMMATION. Result: In TARCC, 1179 /2215 (53.2%) of Non-Hispanic White (NHW) subjects present above the LOI (i.e., their δ-scores are adversely impacted by INFLAMMATION). 46.6% of ADNI's cohort does so. These groups differ from those below the LOI on the INFLAMMATION construct and multiple observed biomarkers:

TARCC (Serum)			**ADNI (Plasma)**		
Biomarker	**F**	**p**	**Biomarker**	**F**	**p**
INFLAMMATION Construct	3820.23	<.0001	**INFLAMMATION Construct**	1255.57	<.0001
Differences in Observed Biomarker Concentrations (by ANOVA, df = 1)					
A2M	1284.17	<.0001	**A2M**	18.91	<.0001
IL-3	3226.76	<.0001	**IL-3**	771.62	<.0001
IL-10	162.39	<.0001	**IL-10**	Not Available	
IL13	3630.72	<.0001	**IL13**	74.34	<.0001
PPP	296.49	<.0001	**PPP**	Not significant (NS)	
PRL	2281.81	<.0001	**PRL**	NS	
SAP	484.84	<.0001	**SAP**	79.65	<.0001
TNFa	1259.77	<.0001	**TNFa**	NS	
THPO	2552.46	<.0001	**THPO**	9.06	0.003
vWF	144.16	0.002	**vWF**	7.93	0.005

Conclusion: We can select cases with pre-specified dementia-relevant biomarker profiles by cognitive screening alone and have replicated this across two cohorts /biofluids. Our approach can be easily adapted to telephone and on-line assessment and can be used to prescreen cases for study recruitment. 1. Royall, Bishnoi, & Palmer. Blood-based protein predictors of dementia

severity as measured by δ: Replication across biofluids and cohorts. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2019;11:763-774.

Funding Disclosure: Julia H. and Vann Buren Parr Endowment

Conflict of Interest Disclosure: DRR and RFP have formed a company (dNomixTM) to develop clinical applications of "delta" homologs.

Theme A. Development of New Models and Analysis Method
Basic Science

(2) **Optogenetic function is maintained across aging in neurons from ChR2-eYFP VGAT and Vglut2 ChR2-eYFP BAC transgenic mice**

Presenting Author: Karienn Montgomery, PhD
Research Assistant Professor
Texas A&M Health Science Center

Karienn Montgomery, Eunyoung Bang, Dustin Dubois, David Murchison, Eric Bancroft, Annette Fincher, Ursula Winzer-Serhan, Amanda Mahnke, and William Griffith

Background: Disruption of synaptic function is believed to be the final common pathway for age-related impairment; however, questions remain because of our inability to study specific neurotransmitter systems in detail. To overcome these limitations we developed an aging model utilizing bacterial artificial chromosome (BAC) transgenic mouse lines with stable expression of the channelrhodopsin-2 (ChR2) variant H134R in two cell-type specific populations, including ChR2(H134R)-EYFP VGAT cells from mice of three ages, young (2-8 mo), middle (10-14 mo) and aged (17-25 mo). Methods: Patch-clamp recording, 470nm light stimulation, fura-2 microfluorimetry were used in basal forebrain (BF) neurons to assess a wide array of physiological functions known to decline during aging. Cognition, circadian activity and overall behavior were also assessed across aging and genotype (Barnes maze, open field and rotarod). Results: We found ChR2 expression is functionally maintained across aging and BF inhibitory synaptic transmission was reduced in aged cohorts. Age-related impairment observed in a battery of behavioral assessments demonstrated no effect of genotype. Conclusions: These results demonstrate that optogenetic vGAT BAC mice are excellent models for investigating age-related changes in calcium signaling, synaptic transmission and behavior.

Funding Disclosure: NIH grant AG047652, AARFD-16-440750

Conflict of Interest Disclosure: None

Theme A. Development of New Models and Analysis Method
Clinical Science

(3) **Aging-relevant human basal forebrain cholinergic neurons as a cell model for Alzheimer's disease**

Presenting Author: Shuaipeng Ma, PhD
Postdoctoral Researcher
The University of Texas Southwestern Medical Center

Shuaipeng Ma, Tong Zang, Meng-Lu Liu, and Chun-Li Zhang

Background: Alzheimer's disease (AD) is an adult-onset mental disorder with aging as a major risk factor. Early and progressive degeneration of basal forebrain cholinergic neurons (BFCNs) contributes substantially to cognitive impairments of AD. An aging-relevant cell model of BFCNs will critically help understand AD and identify potential therapeutics. Recent studies demonstrate that induced neurons directly reprogrammed from adult human skin fibroblasts retain aging-associated features. However, human induced BFCNs (hiBFCNs) have yet to be achieved. Methods: We examined a reprogramming procedure for the generation of aging-relevant hiBFCNs through virus-mediated expression of fate-determining transcription factors. Skin fibroblasts were obtained from healthy young persons, healthy adults and sporadic AD patients. Properties of the induced neurons were examined by immunocytochemistry, qRT-PCR, western blotting, and electrophysiology. Results: We established a protocol for efficient generation of hiBFCNs from adult human skin fibroblasts. They show electrophysiological properties of mature neurons and express BFCN-specific markers, such as CHAT, p75NTR, ISL1, and VACHT. As a proof-of-concept, our preliminary results further reveal that hiBFCNs from sporadic AD patients exhibit time-dependent TAU hyperphosphorylation in the soma and dysfunctional nucleocytoplasmic transport activities. Conclusions: Aging-relevant BFCNs can be directly reprogrammed from human skin fibroblasts of healthy adults and sporadic AD patients. They show promises as an aging-relevant cell model for understanding AD pathology and may be employed for therapeutics identification for AD.

Funding Disclosure: the Welch Foundation (I-1724), the Decherd Foundation, Kent Waldrep Foundation Center for Basic Research on Nerve Growth and Regeneration, and NIH Grants (NS099073, NS092616, NS111776, NS117065 and NS088095)

Conflict of Interest Disclosure: None

Theme A. Development of New Models and Analysis Method
Clinical Science
Work in Progress

TARCC-Based Project

(4) **Characterization of Mitochondrial DNA Damage in Complex Disease Using Two Different NGS Platforms**

Presenting Author: Danielle Reid, BS
Graduate Research Student
The University of North Texas Health Science Center

Danielle Reid, Alexandra Blessing, Robert Barber, and Nicole Phillips

Background: The aging population (65+) is rapidly expanding leading to increases in age-related diseases (e.g., cardiovascular disease, metabolic disorders, cancer, and neurodegenerative diseases). Alzheimer's Disease (AD) is the 3rd and 6th leading cause of death in aging adults and in the U.S., respectively, and age is the greatest risk factor for AD. The U.S. Hispanic/Latinx population is expected to substantially increase through the year 2060 compared to their non-Hispanic/Latinx white (NHW) counterparts, and as a result it is projected that the number of AD cases in the Hispanic/Latinx population to approximately quadruple. In the Mexican American (MA) population specifically, diabetes, depression, stroke, and obesity are common risk factors for developing cognitive impairment; however, reasons for the association between cognitive decline and comorbidities remain unclear. Studies have shown correlations between common pathological changes observed in AD and those that are a result of 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. Lifestyle and/or metabolic health may contribute directly to age-related neurodegeneration. Developing an improved method to assess mitochondrial oxidative damage may help resolve the potential association between abnormal mitochondrial function as indicated by oxidative DNA damage in cognitively impaired MAs. Oxidative damage to guanine (G) forming 8oxoG, is one of the most prevalent DNA lesions. Currently, methods for detection of 8oxoG are limited and lack reproducibility due to several reasons. Method: We aim to investigate the mutational load indicative of oxidative DNA damage in MAs compared to NHWs with AD, type-2 diabetes (T2D), and comorbidity (AD/T2D) using Illumina-bases NGS. Additionally, we propose nanopore sequencing technology as an improved alternative to current detection and quantification methods. Results: Here we describe preliminary proof of concept results and discuss future applications of this method for analysis of mtDNA damage in participants of the TARCC cohort. Conclusion: Investigation of oxidative DNA damage may aid our understanding of the differences in manifestation of age-related cognitive decline in MAs as compared to NHWs.

Funding Disclosure: TARCC, U54 admin supplement, NBAAD, IMSD, Pre-MiHero

Conflict of Interest Disclosure: None

Theme A. Development of New Models and Analysis Method
Basic Science

(5) **Functionalized Mesoporous Silicas Direct Structural Polymorphism of Amyloid-β Fibrils**

Presenting Author: Henry Pan, BS
Graduate Student
The University of Texas at Austin

Henry Pan, Michael Lucas, Eric Verbeke, Lauren Webb, David Taylor, and Benjamin Keitz

The aggregation of amyloid-β (Aβ) is associated with the onset of Alzheimer's disease (AD) and involves a complex kinetic pathway as monomers self-assemble into fibrils. A central feature of amyloid fibrils is the existence of multiple structural polymorphs, which complicates the development of disease-relevant structure−function relationships. Developing these relationships requires new methods to control fibril structure. In this work, we evaluated the effect that mesoporous silicas (SBA-15) functionalized with hydrophobic (SBA-PFDTS) and hydrophilic groups (SBA- kinetics, while as-synthesized and hydrophobic SBA-PFDTS accelerated aggregation kinetics. Subsequently, we quantified the PEG) have on the aggregation kinetics and resulting structure of Aβ1−40 fibrils. The hydrophilic SBA-PEG had little effect on amyloid relative population of fibril structures formed in the presence of each material using electron microscopy. Fibrils formed from Aβ1−40 fibrils with shorter crossover distances that were more structurally representative of fibrils found in AD patient derived samples. exposed to SBA-PEG were structurally similar to control fibrils. In contrast, Aβ1−40 incubated with SBA-15 or SBA-PFDTS formed Overall, our results suggest that mesoporous silicas and other exogenous materials are promising scaffolds for the de novo production of specific fibril polymorphs of Aβ1−40 and other amyloidogenic proteins.

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Conflict of Interest Disclosure: None

Theme B. Genetics
Basic Science

TARCC-Based Project

(6) **Probing the Mechanism of ROS-induced Lipid Droplet formation and Implications for Alzheimer's disease**

Presenting Author: Matthew Moulton, PhD
Postdoctoral Fellow
Baylor College of Medicine

Matthew Moulton, Scott Barish, Jake Harland, Lucy Liu, Paul Marcogliese, and Hugo Bellen

Background: We have generated an animal model of reactive oxygen species (ROS) induced lipid droplet (LD) formation and age-dependent, progressive neurodegeneration to probe roles for lipid regulation in neuronal health and disease. We have shown that elevated ROS in neurons triggers the production and peroxidation of lipids. Neuronal peroxidated lipids are transferred to glia where they accumulate in LDs, which is neuroprotective. Glial LD formation requires the apolipoprotein, Glial Lazarillo (GLaz), and the expression of human ApoE4 in fly retinal glia reduces glial LD formation and promotes neuronal demise while ApoE3 and ApoE2 both facilitate LD formation and offer protection against neurodegeneration. These data implicate lipid transport in Alzheimer's disease (AD) pathogenesis. Lipid dysregulation may also affect Aβ42-induced neurotoxicity. APOE4 carriers have higher rates of amyloid deposition and lower rates of amyloid clearance than individuals harboring APOE3 or APOE2, suggesting an interplay between lipid transport and Aβ42 clearance. Method: We seek to understand the mechanism of lipid transport between neurons and glia using our fly model of ROS-mediated age-progressive neurodegeneration that induces LD formation in glia. We screened for genes required for LD formation in neurons and glia using RNAi strategies and assayed age-dependent neurodegeneration using electroretinograms (ERGs). We also tested whether lipid uptake in glia may contribute to neuronal maintenance and the clearance of Aβ42 by promoting its uptake, along with lipids, in glia. We induced ROS in a fly and mouse model of Aβ42 expression to assess for combinatorial effects of these cellular stressors. Results: We identified several genes required for LD formation that also overlap with AD risk associated alleles identified in genome wide association studies (GWAS). Reduced expression of these genes leads to LD loss and age-dependent neurodegeneration, suggesting a critical role for lipid homeostasis in the development and pathogenesis of AD. We have also demonstrate that elevated ROS exacerbates Aβ42-induced neurodegeneration in both fly and mouse models suggesting that these two insults may synergize to exacerbate disease phenotypes. Conclusion: Our data implicate a link between lipid uptake, ROS, Aβ production, and neurodegeneration and suggest that ROS mitigation could be an important therapeutic strategy for AD.

Funding Disclosure: TARCC, NIH

Conflict of Interest Disclosure: None

Theme B. Genetics
Clinical Science

(7) **Assessment of DNA methylation-based biological age in diverse human populations**

Presenting Author: Talisa Silzer, PhD, MS
Postdoctoral Research Fellow
The University of North Texas Health Science Center

Talisa Silzer, Courtney Hall, Jie Sun, Zhengyang Zhou, Nicole Phillips, and Robert Barber

Background. The global aging population (> 65 years of age) is growing rapidly. Advanced age has long been associated with increased risk for chronic conditions like hypertension, metabolic dysfunction, cancer and Alzheimer's disease. Other risk factors such as genetics, environment and familial history also play a role, therefore age-related disease risk and prevalence vary considerably across individuals and populations. A more meaningful measurement of aging may be 'biological age' (BA), which captures the state of an individual's biological/physiological well-being. In line with this, individuals with an older BA in comparison to their chronological age, may hypothetically be at higher risk for different age-related conditions. Though several methodologies for estimating BA have emerged in recent years, utilization of DNA methylation (DNAm) data has become popular and led to the creation of various DNAm-based BA clocks. While a growing number of studies have focused on the link between BA and disease among Caucasians, a knowledge gap currently exists for racially and ethnically diverse populations. Investigating how these BA clocks perform on diverse populations will enhance our understanding of age-related disease risk across ancestral groups and will bring equity to personalized science and medicine. Purpose. The goal of the study was to identify 1) differences in BA across ancestral groups and, 2) whether BA is predictive of cognition. Methods. Phenotypic and genome-wide methylation data generated on the Illumina MethylationEPIC array were obtained for 578 Non-Hispanic Whites (NHWs) and Mexican Americans (MAs) enrolled in the Texas Alzheimer's Research Care and Consortium (TARCC). BA was derived from DNAm data using two different clock calculations: Horvath and Hannum. Results. Linear regression revealed differences in the predictability of BA on cognition (using two different calculations) when comparing MAs to NHWs. Future Directions. Future studies will investigate the performance of BA calculations in diverse populations. Feature selection-based methods in a larger, diverse DNAm dataset would be ideal for discerning which CpGs are most important for estimating BA. Further, relationships between BA and existing proteomic biomarkers for cognitive impairment will be informative for understanding disease pathophysiology and may be used to guide personalized medicine in the future.

Funding Disclosure: None

Conflict of Interest Disclosure: None

Theme B. Genetics
Clinical Science
Work in Progress

TARCC-Based Project

(8) **Longitudinal mitochondrial DNA and microRNA profiling of neuron-enriched exosomes associated with cognitive decline in Mexican Americans**

Presenting Author: Nicole Phillips, MS, PhD
Assistant Professor
The University of North Texas Health Science Center

Nicole Phillips, Zhengyang Zhou, and Robert Barber

Mexican Americans experience earlier onset of disease than their Non-Hispanic White counterparts, and the origins of this disparity are not understood. We aim to study neuronal enriched exosomes (NEEs), biological packets that originate from neurons and travel throughout the body carrying critical signaling molecules. The exosomal profiles will shed light on potential mechanisms by which cognitive changes manifest in Mexican Americans as part of Alzheimer's disease pathogenesis. We will focus on microRNAs (miRNAs) and mitochondrial DNA (mtDNA) which are released within exosomes by neurons for communication both within the brain and to the peripheral body. In neurons, mitochondria-the primary engines of our cells-are critically important for neuronal health and are greatly influenced by environment/lifestyle. Metabolic diseases, such as type 2 diabetes (T2D), increase risk for Alzheimer's disease (AD), and interestingly, both T2D and AD feature mitochondrial dysfunction as a prominent, early event in disease progression. This fact indicates that neuronal mitochondrial dysfunction may be critical for understanding the AD health disparity in the Mexican American population who (1) have earlier onset of symptoms compared to non-Hispanic whites, and (2) have an over-representation of metabolic diseases such as T2D. The biological basis of the health disparity in Mexican Americans is poorly understood and represents a significant and meaningful gap in our understanding of disease pathogenesis and progression. Our long-term goal is to identify epigenetic-based risk factors and longitudinal modulators of mitochondrial function that originate in the brain and are detectable in the peripheral blood of Mexican Americans. Using TARCC biorepository samples, the following specific aims are underway. Specific Aim 1: To detect and quantify damaged mitochondrial DNA (mtDNA) in plasma NEEs which correlate with disease progression (e.g., by testing plasma samples at two time points, 5 years apart) in Mexican Americans and Non-Hispanic Whites. Specific Aim 2: To identify the aberrant miRNAs profiles that correlate with disease progression (e.g., by testing plasma samples at two time points, 5 years apart) in NEEs from Mexican Americans and Non-Hispanic Whites that correlate with disease progression and are associated with oxidation status of mtDNA. We hypothesize that altered NEE profiles will be

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme C. Human Neuropathology
Basic Science

(9) **Inflammatory Response in Cerebral Amyloid Angiopathy**

Presenting Author: Carson Finger BS
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The University of Texas Health Science Center at Houston

Carson Finger, Juneyoung Lee, Diego Morales, Michael Maniskas, Louise Mcullough, Aki Urayama, and Bharti Manwani

Introduction: Cerebral amyloid angiopathy (CAA) is one of the common causes of intracerebral hemorrhage in the elderly. It is caused by the deposition of amyloid-beta1-40 (Aβ1-40) deposition within cerebral blood vessels, especially the smooth muscle layer, that can cause cerebral microbleeds (CMBs) and cognitive impairment. We hypothesize Aβ deposition causes an innate inflammatory response characterized by an increase and activation of microglia and macrophages. This inflammation might cause CMBs, neuronal damage and cognitive decline CAA. Methods: C57BL6 Tg-SwDI male and female mice (18 months) were used as mouse model for CAA. Age-matched wild-type (WT) mice were used as controls. Brain samples from these mice were fractionated and 23-plex cytokine multiplex was performed on the 0.1g/ml brain lysates. Data was analyzed using two sample t-test or GraphPad PRISM. Results: Our data showed that CAA increased levels of pro-inflammatory cytokines in the brain, as compared with WT mice. Multiplex analysis showed that TgSwDI mice had significantly higher levels of cytokines/chemokines; tumor necrosis factor-α (TNF-α; 54.38 vs. 17.03 pg/ml, , p=0.00207), IL-12 (70.81 vs. 53.95, p= 0.014), macrophage inflammatory protein-1α (MIP-1α, 113.92 vs. 16.81, p=3.85E-10), MIP-1β (86.15 vs. 53.43, p= 3.51E-09) and monocyte chemoattractant protein (MCP-1, 109.46 vs. 118.53, p= 0.00033). Conclusion: This study highlights a monocyte/macrophage driven pro-inflammatory milieu in CAA. Recent studies using in vivo two-photon imaging and histology have found recruitment of microglia and monocytes/macrophages around induced 100 μm sized hemorrhage. The increase in these microglia is only found in AD patients who also had CAA and was not seen in patients with no CAA, suggesting the role of microglia in causing vascular frailty in CAA. Our study suggests that pro-inflammatory cytokines like TNF-a, IL-12, MIP-1α, MIP-1β and MCP-1 can be therapeutic targets for CAA.

Funding Disclosure: None

Conflict of Interest Disclosure: None

Theme C. Human Neuropathology
Clinical Science
Work in Progress

TARCC-Based Project

(10) **Characterization of white matter pathology in tauopathies using machine learning**

Presenting Author: Anthony Vega PhD
Postdoctoral Research Fellow
The University of Texas Southwestern Medical Center

Anthony Vega, Rati Chkheidze, Vipul Jarmale, Charles White, and Satwik Rajaram

Background: Neurodegenerative disorders are characterized by the accumulation of aggregated proteins within different cell types and cell compartments in the central nervous system (CNS). As most of these disorders are associated with cognitive impairment, most neuropathological investigations to date have focused on gray matter, where neuronal cell bodies reside. In contrast, despite knowledge that significant alterations are present in white matter on both neuroimaging and neuropathological evaluations, these white matter changes in neurodegeneration have been less well characterized. Method: We will investigate the role of white matter lesions in tauopathies, a large and heterogeneous group of neurodegenerative disorders that include Alzheimer disease (AD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). White matter abnormalities in these diseases are variable and complex, making it impractical to manually quantify these changes and integrate them over slides that may contains tens of thousands of cells. Here, we aim to leverage recent computer-based machine learning approaches that have been shown to outperform human recognition for such large-scale tasks involving subtle, complex visual patterns. Specifically, we first will build a computational framework to measure the location, shape, and other properties of aggregates and cell types in the white matter using virtual slides prepared from differentially stained microscope slides of human autopsy brain cases. Next, through a series of controlled comparisons, we will quantify which aspects of white matter neuropathology are most impacted by specific diseases. Result: Our preliminary analyses indicate that the magnitude of tau aggregation in the white matter is strongly correlated with that in the gray matter, but this relationship is highly disease specific. Moreover, despite the lack of some of the better known canonical aggregate types in the white matter, the morphologies of these white matter tau aggregates are just as disease specific as those in the gray matter. Conclusion: Our results suggest that white matter tau aggregation is informative from a disease-recognition standpoint, and amenable to characterization by machine learning. Going forward, we aim to better understand several aspects of white matter pathology including the cellular compartments where tau pathology is occurring, the structural impact of the individual diseases (possibly tau independent)

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme C. Human Neuropathology
Clinical Science
Work in Progress

TARCC-Based Project

(11) **The Texas Statewide Brain Bank Initiative**

Presenting Author: Charles L. White, III, MD
Professor of Pathology
The University of Texas Southwestern Medical Center

Charles White, Jamie Walker, Venkat Malladi, Bret Evers, and Kevin Bieniek

Background The Texas Alzheimer's Research and Care Consortium (TARCC) was established and funded by the Texas Legislature in 1999. The research cohort has since grown to a total of 3670 subjects, about 40% of whom are of Hispanic heritage. While the database, derived from studies of the original clinical cohort, contains rich longitudinal clinical data as well as genetic and blood biomarker data, to date, no efforts have been made to establish a human brain tissue resource ("brain bank") to supplement the antemortem studies of the original cohort or of newly recruited subject cohorts. Method In the Fall of 2020, TARCC provided 2 years of initial funding to establish the Texas Statewide Brain Bank Initiative, whose goal is to establish a human Brain Bank derived from autopsies of TARCC subjects from the large clinical cohorts that have been assembled and followed or will be developed at the various TARCC member institutions. Result Two University of Texas System academic medical centers, UT Southwestern and UT Health San Antonio, have neuropathology faculty who are actively involved in neurodegenerative disease diagnosis and research. These centers will serve as the hubs for the statewide network, leveraging their facility resources, experience and expertise to develop and operate this extended resource. Additional expertise and experience in data management for TARCC will facilitate the development and integration of a web-based database of research data and resources that can be queried by authorized investigators to facilitate broad sharing throughout the TARCC network. Conclusion This resource will provide important neuropathologic data for correlation with antemortem clinical and research findings. In addition, tissue resources will provide an invaluable tool for supporting ongoing and new basic and translational research projects at academic institutions statewide by TARCC-funded investigators whose studies may depend upon, or be enhanced by, access to well-characterized human autopsy brain tissue. Providing diagnostic and research data as well as research specimens from this minority-enriched pool of subjects will allow investigators to conduct important research into the potentially unique biological features of neurodegeneration in these subject groups.

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme C. Human Neuropathology
Clinical Science

TARCC-Based Project

(12) **Tau seeding and strain identification across the spectrum of Alzheimer's disease and Lewy body pathology**

Presenting Author: Trung P. Nguyen, MD, PhD
Assistant Professor
The University of Texas Southwestern Medical Center

Trung Nguyen, Jaime Vaquer-Alicea, and Charles White, III

Background: Alzheimer's disease (AD) pathology of neurofibrillary tangles composed of hyperphosphorylated tau and Lewy body (LB) pathology of alpha-synuclein occur often in the same subject. These proteinopathies are hypothesized to spread like prions, where different pathogenic protein conformations, or strains, seed subsequent protein conformational change and aggregation in interconnected brain regions. This project explores whether tau seeding activity (TSA) and strain types associated with AD differ with disease presentation and LB pathology. Method: 39 autopsy cases were grouped by extent of pathology: 1) AD-only; 2) AD/low LB; 3) AD/high LB; 4) LB/low or no AD. Older cases were reevaluated according to contemporary neuropathological diagnostic criteria. TSA was determined using cell-based biosensors expressing the tau repeat domain with a P301S mutation fused to cyan and yellow fluorescent protein (CYP, YFP). Cells were transfected with middle frontal gyri frozen brain tissue homogenates and harvested after 48 hours. Fluorescence resonance energy transfer (FRET) between the CFP/YFP pair was measured via flow cytometry and used as proxy for aggregation. TSA was determined by percent of FRET-positive cells. Kinetic profiles of TSA using automated confocal live-cell imaging were compared to distinguish tau strains. Result: TSA was lower in the group with predominant LB and low or no AD pathology (Group 4) compared to cases with high AD pathology (Groups 1-3, $p < 0.005$). No TSA differences were detected between AD groups with differing LB pathology (Groups 1-3). Within groups, TSA did not differ by clinical diagnoses. Lower TSA was associated with reported cognitive fluctuations and AD pathology (Groups 1-3, $p < 0.05$), though no associations with other dementia symptoms were found. TSA kinetics were similar across all samples, indicating a lack of tau strain diversity. Conclusion: Frontal lobe TSA is associated with tau pathology, but does not differ in the presence of LB pathology nor with clinical presentation, suggesting a lack of interaction and less evident role in disease heterogeneity. Tau strain diversity was not detected across the AD and LB pathology spectrum. Further efforts will continue to explore differences in TSA and strain types across different brain regions.

Funding Disclosure: TARCC; NIH/NIA 1R21AG063081

Conflict of Interest Disclosure: None

Theme D. Molecular and Cell Biology
Clinical Science
Work in Progress

TARCC-Based Project

(13) **Characterization of a New Risk Cell Type in Alzheimer's Disease**

Presenting Author: Yihe Zhang, BS
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The University of Texas Southwestern Medical Center

Yihe Zhang and Lu Sun

The long-term objective of this project is to address cell complexity of Alzheimer's disease (AD), with a focus on a newly identified risk cell type. In the United States, more than 5 million patients have been diagnosed with Alzheimer's disease. In Texas alone, nearly 500,000 people are projected to have AD by 2025. Despite decades of research, the cellular and molecular complexity for this devastating neurogenerative disease still remains poorly understood. Previous studies primarily focused on the pathology of neurons and synapses. Recent work from many laboratories, however, demonstrated that the dysfunctions of glial cells, the supporter cells in the brain, play critical roles in the occurrence and progression of AD and other forms of brain dementia. In particular, several recent studies suggest that the myelinating glial cells in the central nervous system, called oligodendrocytes, are mysteriously linked with AD. Nevertheless, whether there are inheritable genetic variations in this newly identified risk cell type, and how oligodendrocyte and myelination deficiencies contribute to AD remain unanswered. Based on previous findings, we hypothesize that oligodendrocyte genetic alterations are linked with AD etiology, and that oligodendrocyte-axon decoupling drives AD pathology. In this proposal, we will utilize bioinformatic approach to systematically analyze genomic variations in AD oligodendrocytes, and further employ glial cell biology and genetic methods to determine the roles of this newly identified risk cell type in AD etiology. Specifically, we will utilize the TARCC Genetic I and Genetic II datasets to determine single nucleotide polymorphism (SNP) features and copy number variations among oligodendrocyte specific genes (Aim 1). We will perform comprehensive analysis on oligodendrocyte lineage cells and myelination in several AD mouse models across entire disease progression (Aim 2). Finally, we will address the autonomous function of oligodendrocytes and oligodendrocyte-axon coupling at the onset of AD (Aim 3). The proposed work will characterize a new risk cell type in Alzheimer's disease, and will provide better understanding about how individual brain cell types communicate with each other and contribute to this complex neurodegenerative disease.

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme D. Molecular and Cell Biology
Basic Science

(14) **Neuronal ablation of GHS-R mitigates diet-induced neuro-inflammation showing improved memory**

Presenting Author: Hongying Wang, PhD
Postdoctoral Research Associate
Texas A&M Health Science Center

Hongying Wang, Chia-Shan Wu, Pengfei Ji, Ji Yeon Noh, Da Mi Kim, Alexandra Trott, David Threadgill, Hui Zheng, Xiaoqiu Xiao, and Yuxiang Sun

The ghrelin receptor, growth hormone secretagogue receptor (GHS-R), is highly expressed in the brain. Obesity is highly associated with changes in central nervous system (CNS). Our previous study showed neuronal GHS-R deletion almost completely prevents diet-induced obesity, here we investigate whether neuronal deletion of GHS-R mitigates mood and cognitive dysfunctions in diet- induced obesity (DIO). Age-matched male Ghsr f/f (control) and Syn1-Cre; Ghsr f/f (neuronal specific KO) mice were fed with either regular diet (RD) or high-fat diet (HFD). Forced swimming test (FST) was performed to determine depressive-like behavior. Novel Object Recognition Test (NORT) and Morris Water Maze (MWM) were conducted to assess learning and memory. Metabolic signaling pathways and inflammatory regulators have in the cortex and hippocampus were investigated to determine the metabolic and inflammatory state of the neural GHS-R deficient mice under DIO. The neuron-specific GHS-R deficient mice exhibited reduced depressant-like states and enhanced spatial memory under DIO. Moreover, neuronal specific deletion of GHS-R showed stronger short-memory under RD, but not DIO. In the cortex and hippocampus, GFAP-labeled astrocytes increased in Syn1-Cre; Ghsr f/f mice; In addition, neuronal deletion of GHS-R altered AMPK - mTOR - autophagy signaling pathway in the cortex and hippocampus; The inflammatory cytokines significantly decreased under DIO in Syn1-Cre; Ghsr f/f mice. In conclusion, neuron-specific GHS-R deletion under DIO improved depressive like state and enhanced cognitive function mainly by attenuating neuro-inflammation.

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Conflict of Interest Disclosure: None

Theme D. Molecular and Cell Biology
Clinical Science

TARCC-Based Project

(15) **TREM2-induced activation of microglia contributes to synaptic resilience in non-demented individuals with Alzheimer's neuropathology**

Presenting Author: Anna Fracassi, PhD
Postdoctoral Fellow
The University of Texas Medical Branch at Galveston

Anna Fracassi, Michela Marcatti, Randall Woltjer, and Giulio Taglialatela

Objective: 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. A possible candidate mediator of this process is represented by TREM2, a recently identified AD risk factor. Based on TREM2 role in the scavenging function of microglia, we hypothesize that an efficient microglial phagocytosis underlies synaptic resilience in NDAN, thus protecting from memory deficits. Methods: 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 microglia-related proteins (TREM2 and DAP12) were evaluated. Furthermore, 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, and PSD95 as a post synaptic marker. Results: NDAN individuals show higher microglial activation and TREM2 expression, as well as preserved axonal and dendritic structure around plaques vs. AD. High levels of PSD95 around NDAN plaques may suggest a prompt removal of damaged synapses by efficient microglia. Conclusions: 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, TARCC grant to GT

Conflict of Interest Disclosure: None

Theme D. Molecular and Cell Biology
Basic Science

(16) **Sepsis-Induced Dysbiosis Accelerates Cognitive Impairment in Alzheimer's Disease Mouse Model**

Presenting Author: Vijayasree V Giridharan, M Pharm, PhD
Postdoctoral Fellow
The University of Texas Health Science Center at Houston

Vijayasree Vayalanellore Giridharan, Jaqueline Generoso, Juneyoung Lee, Fabricia Petronilho, Felipe Dal-Pizzol, Rodrigo Morales, and Tatiana Barichello

Background: Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to microbial infection that accounts for high mortality and morbidity worldwide. More than 50% of sepsis survivors suffer from severe and long-term cognitive deficits. Recent studies affirmed the disruption of gut microbiota at both compositional and functional levels in sepsis patients. In this context, we aimed to explore if experimental sepsis-induced dysbiosis accelerates or exacerbates Alzheimer's disease pathology. Methods: Male, 50-day-old APP/PS1 mice (overexpress the human APP harboring Swedish double mutation and presenilin-1 with delta-E9 mutation) were subjected to a gold standard sepsis model by cecal ligation and perforation (CLP) surgery to sepsis or sham surgery as a control group. Assessment of cognition was performed using novel object recognition (NOR) task at 30 and 120 days after sepsis. Longitudinally, at 3, 30, and 120 days after sepsis or sham surgery, feces were collected for 16S ribosomal RNA sequencing. The brain was harvested to measure amyloid beta expression (Aβ) and inflammatory cytokines levels in the prefrontal cortex (PFC) and hippocampus region. Results: Alpha and beta diversity analyses revealed higher disruption of intestinal communities at 30 and 120 days after sepsis compared to control. At 30 days, inflammatory cytokines IFN-γ and IL1-α increased and IL-6, IL-13, and IL-17A decreased in PFC; IFN-γ, IL1-α, IL-12 (p40), eotaxin, and TNF- α in the hippocampus were increased. At 120 days, eotaxin, KC, MIP-1, and RANTES in PFC were increased; anti-inflammatory cytokines IL-6, IL-10, and IL-13 were decreased in both PFC and the hippocampus. Further, at 30 and 120 days, the sepsis group demonstrated significant memory decline in the NOR task and elevated Aβ expression compared to the sham group. Conclusion: Sepsis-induced dysbiosis precedes overt cognitive impairment in APP/PS1 mice. Therefore gut microbiota can be modified to impact outcomes from sepsis-related long-term cognitive decline positively.

Funding Disclosure: Faillace Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston (UTHealth), USA; The Graduate Program in Health Sciences, University of Southern Santa Catarina (UNESC), Brazil. AARGDNTF-19-619645

Conflict of Interest Disclosure: None

Theme D. Molecular and Cell Biology
Basic Science

TARCC-Based Project

(17) **Amelioration of cognitive impairment in mouse models of Alzheimer's disease after intravascular delivery of Neural Precursors**

Presenting Author: Nazaret Gamez Ruiz, MSc, PhD
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The University of Texas Health Science Center at Houston

Nazaret Gamez-Ruiz, Enrique Armijo, Ruben Gomez-Gutierrez, Claudio Soto, Rodrigo Morales, and Ines Moreno-Gonzalez

Background: Alzheimer's disease (AD) is considered a serious global health problem with the increase of the elderly population and the absence of disease-modifying treatments. This disease is clinically characterized by progressive memory impairment and cognitive dysfunction. The neuropathological hallmarks of AD are the accumulation of extracellular β-amyloid (Aβ) peptide in senile plaques, intracellular deposition of hyper-phosphorylated tau as neurofibrillary tangles (TNF), neurodegeneration, synaptic loss the brain, and a neuroinflammatory process governed by the activation of glial cells. Recently, throughout stem cell therapy has provided great potential in treating AD patients. However, there is an urgent need to replace the conventional intracerebral stem cell therapy for a less invasive method to avoid some of the technical challenges. Our recently published results indicated that peripheral treatment with neural precursors (NPs) ameliorates clinical symptoms by reducing the disease-associated neuroinflammation in a mouse model of Parkinson's disease. Therefore, we hypothesize that intravenous administration of NPs and their released neurotrophic factors can be used as a non-invasive therapy to ameliorate memory impairment in mouse models of AD. Methods: In this pre-clinical study, NPs derived from mesenchymal stem cells (MSC-NPs) and induced pluripotent stem cells (iPSC-NPs) were intravenously injected into APP/PS1 and P301S mice at 3 and 6 months old (before and after brain pathology is stablished). Before treatment and at the age of 7 months old, experimental and control (PBS) animals were subjected to Barnes maze task, novel object recognition and rotarod test. Results: NPs treated mice displayed an amelioration in memory dysfunction compare to the PBS-injected animals. In addition, P301S mice injected with NPs showed improved motor function to rotarod coordination test in comparison to the control group. Conclusion: Peripheral inoculation using NPs can be used as a treatment to reduce AD-related clinical signs.

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme D. Molecular and Cell Biology
Basic Science

(18) **Pathogenic soluble tau aggregates impair neurovascular coupling and cognitive outcomes**

Presenting Author: Candice E. Van Skike, PhD
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The University of Texas Health Science Center at San Antonio

Candice Van Skike, Andy Banh, Stephen Hernandez, Rakez Kayed, and Veronica Galvan

Background: The brain consumes large amounts of energy but lacks energy reservoirs. The coupling between neuronal activity and increased blood flow (neurovascular coupling, NVC), which ensures the delivery of energy substrates 'on demand' to active neurons, is essential to brain function. Cerebrovascular dysfunction occurs early in Alzheimer's disease (AD), leading to chronic brain injury and neurodegeneration. Pathogenic forms of tau protein are causally implicated in AD and other dementias. We recently reported accumulation of pathogenic soluble tau aggregates (tau oligomers) in human AD brain microvasculature. The functional consequences of brain microvascular tau accumulation in AD, however, are not yet understood. Methods: To define the impact of microvascular soluble tau aggregate accumulation on NVC and define mediation by this tau species, we used tau oligomer-specific monoclonal antibody (TOMA) immunotherapy to specifically remove soluble tau aggregates from brains of hTau mice expressing non-mutant human tau that models tauopathy in AD. Male and female hTau mice were given 6 monthly i.v. infusions of TOMA immunotherapy or vehicle starting in mid-life (12 mo.). Vehicle-treated C57BL/6J were used as controls. Morris water maze was performed at 18 months of age, and NVC was subsequently measured with laser Doppler flowmetry. Results: Soluble tau aggregates inhibit activation of neuronal nitric oxide synthase (nNOS), which drives NVC dysfunction and cognitive impairment in the hTau model of AD tauopathy. Removal of pathogenic tau with TOMA immunotherapy beginning in midlife, however, negates nNOS dysfunction at late stages of AD-like disease in hTau mice, and restores NVC. Restoration of NVC by TOMA immunotherapy was associated with reinstatement of spatial memory in hTau mice. Conclusions: Taken together, our data indicate that soluble tau aggregates impair nNOS activation and thus drive NVC dysfunction and cognitive impairment in a model of AD tauopathy. Tau immunotherapy may thus have potential to treat AD and other tauopathies.

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Conflict of Interest Disclosure: None

Theme D. Molecular and Cell Biology
Basic Science

(19) **Competitive synaptic binding of Tau versus Aβ oligomers may underscore shifting targets for an effective AD therapy**

Presenting Author: Michela Marcatti, PhD
Postdoctoral Fellow
The University of Texas Medical Branch at Galveston

Michela Marcatti, Anna Fracassi, Nemil Bhatt, Chandramouli Natarajan, Balaji Krishnan, Rakez Kayed, and Giulio Taglialatela

Medical Branch at Galveston Background. Alzheimer's Disease (AD) is characterized by gradual cognitive decline driven by the targeting of synapses by small oligomers of both Aβ (AβO) and tau (TauO), which results in synaptic dysfunction that ultimately underscores disease progression. Indeed, there is ample consensus that targeting oligomer binding to synapses would be an effective therapeutic concept for AD. However, recent failures of clinical trials of Aβ-directed therapeutics suggest reduced effectiveness of targeting Aβ in clinically-manifest AD, redirecting attention onto tau oligomers that are known to increase later in the disease timeline. In support of this vision, here we show that TauO and Aβ target synapses with different dynamics affecting each other binding. Methods. Binding of labeled, pre-formed Aβ and tau oligomers onto synaptosomes isolated from human and rodent hippocampus and cortex was evaluated using flow-cytometry, western blot techniques. Binding of labeled, pre-formed Aβ and tau oligomers onto mouse primary neurons was assessed using immunofluorescence assay. The synaptic dysfunction was measured by FASS-LTP assay. Results. We found that TauO competes AβO off synaptosomes in a dose-dependent fashion, thus becoming the prevailing species associated with the synapses. On the other hand, not only Aβ oligomers are ineffective in competing tau oligomers off the synapse, but at higher concentration Aβ oligomers appear to recruit TauO to the synapses. Consistent with these observations, analyses of FASS-LTP show that the suppression of long-term potentiation driven by TauO is exacerbated when in the presence of AβO. Furthermore, pre-digestion of synaptosomes with proteinase K abolishes the ability of TauO to compete off AβO without affecting the increased synaptic recruitment of TauO by high levels of AβO, suggesting that the former phenomenon necessitates of a proteic substrate whereas the latter does not. Conclusions. Our results support the concept of tau oligomers becoming the main synaptototoxic species in later AD stages when tau oligomer levels increase dramatically, thus making them an effective therapeutic target.

Funding Disclosure: NIH/NIA R01AG069433, R01AG060718 and R56063405 to GT

Conflict of Interest Disclosure: None

Theme D. Molecular and Cell Biology
Basic Science

(20) **Mechanistic Role of High-Fat Diet in Obesity Associated Cognitive Impairment**

Presenting Author: Narendra Kumar, PhD
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Texas A&M Health Science Center

Premranjan Kumar, Jayshree Mishra, and Narendra Kumar

Compromise in intestinal mucosal functions is associated with several chronic inflammatory diseases. Previously we reported that obese humans have reduced intestinal Janus kinase-3 (Jak3), a non-receptor tyrosine kinase, and reconstitution of these conditions using loss of Jak3 in mouse led to predisposition to obesity associated metabolic syndrome. Using diet induced obesity (DIO) model, in this report we demonstrate the molecular basis of high-fat diet (HDF) in gut-dysbiosis associated cognitive impairment. Our data show that HFD suppresses Jak3 expression both in intestinal mucosa and in brain where global (Jak3-KO) and intestinal epithelial cell-specific conditional (IEC-Jak3-KO) Jak3 knock-out mouse recapitulated these conditions. Using cognitive testing, western analysis, flow-cytometry, and immunofluorescence microscopy we demonstrate that HFD-induced loss of Jak3 is responsible for cognitive impairments in mouse and these were in-part, due to intestinal epithelial loss of Jak3. Our data show that HFD and/or loss of Jak3 leads to gut-dysbiosis associated compromised TREM-2 functions and increased microglial activation. We demonstrate that microglial activation were due to increased TLR-4 expression and HIF1-alpha-mediated inflammation in the brain. These led to increased M1 polarization and compromised microglial functions-led increased deposition of beta-amyloid (Abeta) and hyperphosphorylated Tau (pTau) which were responsible for cognitive impairments. Hence, we not only illustrate cognitive impairment during obesity but also demonstrate the underlying molecular mechanism where HFD-mediated impact on Jak3-expression was responsible for microglial activation and compromised clearance of Abeta and pTau as the mechanism during obesity associated cognitive impairments.

Funding Disclosure: Global Institute of Hispanic Health (GIHH)

Conflict of Interest Disclosure: None

Theme D. Molecular and Cell Biology
Basic Science

TARCC-Based Project

(21) **Modulating APP levels as a therapeutic strategy for Alzheimer's disease**

Presenting Author: Jennifer Leigh Johnson, PhD
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Baylor College of Medicine

Jennifer Johnson, Ji-Yoen Kim, Ismael Al-Ramahi, Maria de Haro, Lorena Garaicoechea, Jean Pierre Revelli, Stephen J. Elledge, Kandice Levental, Ilya Levental, Juan Botas, and Huda Zoghbi

Background Dysregulation of lipid pathways has been implicated in a growing number of neurodegenerative disorders, including AD. Although much attention has been given to the link between cholesterol and AD pathogenesis, growing evidence suggests that fatty acids, the building blocks of membrane phospholipids, are altered in the AD brain, and genes involved in the transport of lipids such as ABCA1 have been genetically linked to AD. Nevertheless, the mechanism by which aberrant lipid metabolism could be involved in AD pathology is still unclear. Method We performed parallel shRNA screens in human cells and flies, targeting the druggable human genome to identify genes that regulate APP levels. From the genetic screens, I identified two genes involved in fatty acid metabolism that, when inhibited, lowered APP levels in a transgenic cell line expressing fluorescently labeled APP and mitigated toxicity in flies overexpressing APP. These candidates were then tested for their ability to regulate endogenous APP levels and processing in human cells. Result We found that inhibition of these genes lowers full-length APP levels via increased α-secretase-mediated nonamyloidogenic processing of APP in human embryonic stem cell-derived neurons and neurons expressing familial AD mutations in APP and PSEN1. We performed lipidomics and discovered that levels of several lipids previously implicated in AD were altered upon candidate inhibition. Conclusion Ongoing work aims to understand how these changes in the lipid milieu affect membrane composition and the localization of APP, β-secretase, and/or α-secretase. The proposed studies will improve our current understanding of APP biology, including how lipid pathways regulate the composition and structure of the neuronal membrane leading to altered APP steady-state levels and processing. Further mechanistic and translational studies may identify potential therapeutic targets acting through these pathways to offer new and effective options for the treatment of AD.

Funding Disclosure: TARCC, NIA, JPB Foundation

Conflict of Interest Disclosure: None

Theme D. Molecular and Cell Biology
Basic Science

(22) **PPARγ for Memory in Aging and Neurological Disease: Role of ERK Phosphorylation**

Presenting Author: Egide Ishimwe, MS
Research Associate
The University of Texas Medical Branch at Galveston

Egide Ishimwe, IbDanelo Cortez, Larry Denner, and Kelly Dineley

ERK MAPK (extracellular-signal regulated kinase) forms a central node in multiprotein complexes that execute cellular processes as ubiquitous, yet diverse, as cell proliferation, differentiation, transformation, and death. Dysfunctional ERK multiprotein complexes contribute to neurological diseases such as Huntington's, Parkinson's, and Alzheimer's disease and it is clearly established many forms of memory consolidation require ERK-dependent gene transcription. We recently discovered that, in animal models of aging and disease, PPARγ (peroxisome proliferator activated receptor-γ) establishes a nuclear multiprotein complex with ERK that is necessary for hippocampal memory consolidation. In this study, we established an in vitro model system to recapitulate ERK-PPARγ multiprotein complexes for transcriptional competency. We found that: 1) PPARγ transcriptional activity is ERK-dependent, 2) nuclear co-localization of ERK-PPARγ complexes requires ERK activity (pERK), 3) PPARγ phosphorylation occurs during this process. This model system forms the launching point for subsequent studies interrogating ERK-PPARγ multiprotein complexes in plasticity and memory formation.

Funding Disclosure: None

Conflict of Interest Disclosure: None

Theme E. Biomarkers Non-Neuroimaging
Clinical Science

TARCC-Based Project

(23) **Blood Biomarkers of Neuronal/Axonal & Glial Injury for MCI and Dementia in TARCC**

Presenting Author: Mitzi Gonzales, PhD
Assistant Professor
The University of Texas Health Science Center at San Antonio

Mitzi Gonzales, Meghan Short, Claudia Satizabal, Sid O'Bryant, Habil Zare, and Sudha Seshadri

INTRODUCTION: This study evaluated if blood markers reflecting diverse biological pathways differentiate clinical diagnostic groups among Hispanic and non-Hispanic white adults. METHODS: Within Hispanic (n=1193) and non-Hispanic white (n=650) participants, serum total tau (t-tau), neurofilament light (NFL), ubiquitin carboxyl-terminal hydrolase LI, glial fibrillary acidic protein (GFAP), soluble clusterin of differentiation-14, and chitinase-3-like protein 1 (YKL-40) were quantified. Mixed effects partial proportional ordinal logistic regression and generalized mixed effects models were used to evaluate the association of serum biomarkers with diagnostic group and cognition, adjusting for age, sex, ethnicity, APOE ε4, education, and site. RESULTS: Serum T-tau, NFL, GFAP, and YKL-40 discriminated between diagnostic groups (Receiver Operating Curve: 0.647 - 0.873). Higher levels of t-tau (odds ratio=1.671, 95% CI=1.457 - 1.917, p<0.001), NFL (odds ratio=2.150, 95% CI=1.819 - 2.542, p<0.001), GFAP (odds ratio=2.283, 95% CI= 1.915 - 2.722, p<0.001), and YKL-40 (odds ratio=1.288, 95% CI= 1.125 - 1.475, p<0.001) were associated with increased likelihood of dementia relative to cognitively unimpaired and MCI groups. Higher levels of NFL were associated with poorer global cognition (beta=-0.455, SE=0.083, p<0.001), semantic fluency (beta=-0.410, SE=0.133, p=0.002), attention/processing speed (beta=2.880, SE=0.801, p<0.001), and executive function (beta=5.965, SE=2.037, p=0.003). GFAP levels were associated with poorer cognition across the domains of global cognition (beta=-0.345, SE=0.092, p<0.001), learning (beta=-1.426, SE=0.359, p<0.001), and memory (beta=-0.980, SE=0.266, p<0.001). Additionally, higher YKL-40 (beta=-0.537, SE=0.186, p<0.001) levels were associated with lower memory scores. Significant interactions with ethnicity for cognition were observed for learning, memory, and semantic fluency (all interaction terms p<0.008), indicating weaker associations in Hispanics. DISCUSSION: Blood biomarkers of neuronal/axonal and glial injury differentiated between cognitively unimpaired, MCI, and dementia groups in a bi-ethnic cohort of Hispanic and non-Hispanic whites. Our results add to the growing literature indicating that blood biomarkers may be viable tools for detecting neurodegenerative conditions and highlight the importance of validation in diverse cohorts.

Funding Disclosure: TARCC, National Institute of Aging grants AG054076 and AG059421 and National Institute of Neurological Disorders and Stroke NS100605.

Conflict of Interest Disclosure: None

Theme E. Biomarkers Non-Neuroimaging
Clinical Science

TARCC-Based Project

(24) **Diagnosing Alzheimer's and Parkinson's using Blood Plasma and Machine Learning**

Presenting Author: Alex Treacher, BS
Graduate Student
The University of Texas Southwestern Medical Center

Alex Treacher, Krishna Kanth Chitta, Julia Kozlitina, Jeffrey McDonald, Dwight German, and Albert Montillo

Background: Definitive diagnosis of most neurodegenerative diseases currently does not occur until postmortem analysis via autopsy. Additionally, how disease processes manifest in blood is not well understood. Recent lipidomic studies have identified multiple lipid classes and species linked with Alzheimer's disease (AD). These studies indicate that phospholipids, ceramide and sulfatide metabolism may be involved. Method: To address these knowledge gaps, blood plasma lipidomics, clinical and demographic data were used to train predictive models to distinguish neurodegenerative disease from cognitive normal healthy control (HC) and those with the second most common neurodegenerative disease, Parkinson's disease (PD). We began the analysis with plasma samples from 100 subjects with AD and 100 age- and sex-matched HCs, both from the TARCC consortium. We also used plasma samples from 100 PD subjects from the Parkinson's Disease Biomarker Program. Result: Analysis of the fitted models distinguishing PD from controls demonstrate an accuracy of 75.6% and a sensitivity of 75%. Several novel lipids had high predictive value. Our models for predicting AD yielded an accuracy of 58.5% with a sensitivity of 72.9%. Conclusion: While the studies are ongoing to improve the diagnostic accuracy for both AD and PD, we have shown the predictive power of lipidomics to build diagnostic models for AD and PD. Additionally, we have reveled potential lipid biomarkers that help to distinguish PD from HC.

Funding Disclosure: TARCC and NIH

Conflict of Interest Disclosure: None

Theme E. Biomarkers Non-Neuroimaging
Clinical Science

TARCC-Based Project

(25) **Metabolomic and Lipidomic Analysis in Alzheimer's Disease Plasma and Brain Cortex Reveals Altered Profiles Including Abnormal Microbial Metabolites**

Presenting Author: Karel Kalecky, MSc
Graduate Student
Baylor University

Karel Kalecky, Dwight German, and Teodoro Bottiglieri

Background: Alzheimer's disease (AD) is multifactorial in origin, leading to progressively impaired neuronal function and cellular death. Understanding metabolic changes in people with AD can provide insight into processes affecting the cellular environment in the central nervous system and disease etiology. We performed a metabolomic and lipidomic analysis in AD plasma and brain tissue and compared their alterations. Methods: Plasma samples were obtained from the Texas Alzheimer's Research and Care Consortium (95 AD, 68 controls). Frontal cortex samples were acquired from Banner Sun Health Research Institute (35 AD, 38 controls). Analysis of plasma and brain tissue was performed on a Sciex QTrap 5500 UHPLC-MS/MS platform using the Biocrates MxP Quant 500 kit, which potentially detects 630 metabolites, including 523 lipid species in a flow-injection mode, and calculates 232 metabolic indictors. Results: We found 67 compounds and 41 indicators altered in AD plasma, and 59 compounds and 41 indicators altered in AD cortex (FDR≤0.05). The differences detected in both types of tissue are often related. Multiple metabolites and metabolic indicators suggest existence of altered microbiome composition (indole derivatives, 5-aminovaleric acid, p-cresol sulfate, in plasma also bile acids and TMAO) in the direction of increased neurotoxicity and decreased neuroprotection. Other significant differences include changes in methylation cycle and polyamines, cortisol metabolism and in cortex also in amino acid metabolism. Lipids of several classes are increased in plasma and cortex (acylcarnitines, ceramides, acyl-alkyl phosphatidylcholines, triglycerides), although the exact lipid species are mostly non-overlapping. Sphingomyelins are increased in brain tissue only whereas lysophosphatidylcholines and diacyl phosphatidylcholines are increased in plasma. Conclusion: AD is associated with altered metabolic and lipid profiles in both plasma and cortex. While the results implicate specific pathways, the changes are not large enough to be useful diagnostic biomarkers. This is in line with the view that AD does not have a single cause but rather stems from synergistic effect of various factors impairing neuronal homeostasis. Our results revealed several alterations with pathological impact on neuronal and vascular health, likely contributing to the etiology of the disease. Some of these factors could be modulated, for example by targeted microbiome remodeling.

Funding Disclosure: Work in this study was supported by research grants awarded to DW from TARCC, and to TB from Aging Mind Foundation and Baylor Scott & White Foundation, Dallas, Texas

Conflict of Interest Disclosure: None

Theme E. Biomarkers Non-Neuroimaging
Clinical Science

TARCC-Based Project

(26) **Evidence of elevated neurofilament light chains (NfL) in recently diagnosed AD patients with abnormal innate and adaptive immune profiling**

Presenting Author: Chaitanya R. Joshi, PhD
Postdoctoral Researcher
The University of Texas Southwestern Medical Center

Chaitanya Joshi, Karthigayini Sivaprakasam, Scott Christley, Wei Zhang, Rebecca Logan, Doris Lambracht-Washington, Roger Rosenberg, Munro Cullum, Brian Hitt, Robert Barber, Benjamin Greenberg, Lindsay Cowell, Rong Zhang, Ann Stowe, Ryan Huebinger, Brendon Kelley, and Nancy Monson

Recent reports suggest immune system dysregulation in Alzheimer's disease (AD). However, changes in immune cells and their relationship to AD pathology remains unknown. To address this, we collected cerebrospinal fluid (CSF) from recently diagnosed AD patients and examined the immune profile in combination with b-amyloid (Ab)42 and neurofilament light chain (NfL) levels to infer CNS damage. CSF from similar-age healthy controls (HC) and clinically diagnosed amnestic mild cognitive impairment patients were used as comparator cohorts. Immune profiles were obtained using multiparameter flow cytometry on blood and CSF cells. Ab42 and NfL concentrations in the CSF were obtained by ELISA. Results indicated that innate cells are expanded in the CSF of recently diagnosed AD patients in comparison to similar-age healthy controls and this expansion correlated with advancing age. The frequency of CD4+ T cells reduced with advancing age and T cell diversity was compromised in these AD patients in comparison to similar-age healthy controls. Finally, recently diagnosed AD patients that displayed abnormal innate and adaptive immune profiles also displayed advancing neurodegeneration as evidenced by reduced concentrations of Ab42 and increased concentrations of NfL in the CSF. The combination of immune profiling data with features of neurodegeneration in the CSF from these recently diagnosed AD patients could facilitate earlier diagnosis of AD.

Funding Disclosure: TARCC to Ryan Huebinger, NIH R21NS104509 and R01NS102417 to Nancy Monson

Conflict of Interest Disclosure: None

Theme E. Biomarkers Non-Neuroimaging
Clincal Science

TARCC-Based Project

(27) **Prediction of Biomarker Profiles by Cognitive Assessment (Second Demonstration)**

Presenting Author: Raymond F. Palmer, PhD
Professor
The University of Texas Health Science Center at San Antonio

Donald Royall and Raymond Palmer

Background: We've developed a latent biomarker panel ("Adipokines") that predicts dementia severity as measured by the latent dementia-specific cognitive phenotype "δ". Adipokines is indicated by proteins known to be secreted by adipose tissues, including Adiponectin (APN), Alpha_1_Antitrypsin (A1AT), complement H, interleukin 1 receptor antigen (IL1ra), leptin, monocyte chemotactic protein 1 (MCP1), resistin, tumor necrosis factor alpha (TNFa), and vascular endothelial growth factor (VEGF). We have replicated Adipokines' association with δ in two cohorts [the Texas Alzheimer's Research and Care Consortium (TARCC) and the Alzheimer's Neuroimaging Initiative (ADNI)] and in two biofluids; serum (TARCC) and plasma (ADNI) (DRR unpublished). We want to recognize individuals with Adipokine-related cognitive declines and triage them for Adipokine-specific interventions. Methods: We correlated Adipokine-adjusted and unadjusted factor scores and analyzed cases presenting above and below their line of identity (LOI). Cases presenting above the LOI are predicted to be adversely impacted by Adipokines. Results: In TARCC, 1087 /2215 (49.1%) of Non-Hispanic White (NHW) subjects present above the LOI (i.e., their δ-scores are adversely impacted by Adipokines). 60.8% of ADNI's cohort does so. These groups differ from those below the LOI on the Adipokines construct and multiple observed biomarkers:

TARCC (Serum)			**ADNI (Plasma)**		
Biomarker	**F**	**p**	**Biomarker**	**F**	**p**
Adipokine Construct	3037.63	<.0001	**Adipokine Construct**	1518.54	<.0001
Differences in Observed Biomarker Concentrations (by ANOVA, df = 1)					
APN	13.21	<.001	**APN**	1.34	0.25
A1AT	146.12	<.0001	**A1AT**	178.59	<.0001
complement H	Not available (NA)		**complement H**	257.63	<.0001
IL-1ra	81.16	<.0001	**IL-1ra**	NA	
leptin	4.50	0.03	**leptin**	140.35	<.0001
MCP1	279.67	<.0001	**MCP1**	31.50	<.0001
resistin	583.70	<.0001	**resistin**	207.48	<.0001
TNFa	36.61	<.0001	**TNFa**	54.14	<.0001
VEGF	186.94	<.0001	**VEGF**	266.29	<.0001

Conclusion: We can select cases with pre-specified dementia-relevant biomarker profiles by cognitive screening alone and have replicated this across two cohorts /biofluids. Our approach can be easily adapted to telephone and on-line assessment and can be used to prescreen cases for study recruitment.

Funding Disclosure: Julia H and Vann Buren Parr endowment

Conflict of Interest Disclosure: DRR and RFP have started a company (dNomixTM) to develop clinical applications of delta homologs.

Theme E. Biomarkers Non-Neuroimaging
Clinical Science

TARCC-Based Project

(28) **Sex Differences in plasma markers of gut permeability in control and probable Alzheimer's Disease cases and Aberrant Astrocyte Function.**

Presenting Author: Yumna El-Hakim, BS
Graduate Student
Texas A&M Health Science Center

Taylor Branyan & Yumna El-Hakim, Kathiresh Mani, Courtney Stewart, Sivani Pandey, Robert Barber, and Farida Sohrabji

Background: Sex differences have been well-documented in AD, with a higher prevalence and higher rates of disease progression in women as compared to men, although the precise mechanism underlying these sex differences is not known. Recent evidence indicates that the gut microbiome is altered under AD conditions, such changes are associated with increased gut permeability and systemic inflammation, increasing the potential for blood brain barrier dysregulation and promoting a senescent phenotype in the brain. We tested the hypothesis that AD may be associated with sex differences in gut permeability and astrocyte function. Methods: Plasma samples from the TARCC cohort were assayed by ELISA for surrogate markers of gut permeability: lipopolysaccharide (LPS; a product of gram negative bacteria), LPS binding protein (LBP), mucin-2, and zonulin. Control and probable pAD male and female samples were balanced for race/ethnicity and Type 2 diabetes diagnosis. In addition, human astrocyte cultures were incubated with male and female plasma samples and tested for mitochondrial function. Results: LPS and muc-2 were elevated in control males as compared to control females, however, pAD females showed a 2-fold increase in both markers as compared to sex-matched controls while male pAD patients did not. Multiple linear regression showed that biological sex, and gut permeability markers were predictive for the outcome variable (pAD). When analyzed for each sex separately, zonulin/muc-2 were predictive for pAD in females ($p=0.0096$). Treatment of human astrocytes in vitro with control and pAD plasma significantly altered mitochondrial respiration, with greater levels of oxygen consumption in pAD plasma treated groups relative to control and vehicle groups. Furthermore, treatment with indole-3-carbinol, a gut metabolite known for inducing cellular senescence, evoked similar changes in mitochondrial respiration. Conclusion: These data indicate sex specific changes in gut permeability, with female pAD patients showing a deterioration of the mucin barrier. Exposure to pAD plasma constituents triggers a senescent phenotype in astrocytes, although further analysis is necessary to determine if this is due to gut metabolites. Collectively, these studies indicate that disease-based alterations in the brain-gut axis may contribute to sex differences in the prevalence and/or progression of AD.

Funding Disclosure: None

Conflict of Interest Disclosure: None

Theme E. Biomarkers Non-Neuroimaging
Clinical Science

(29) **Discriminating Alpha-synuclein strains and sub-strains in Synucleinopathies**

Presenting Author: Mohammad Shahnawaz, PhD
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BACKGROUND: Synucleinopathies are a diverse group of neurodegenerative diseases characterized by misfolding aggregation and accumulation of misfolded alpha-synuclein (αSyn) in neurons or glial cells, which include Parkinson's disease (PD) multiple system atrophy (MSA), and dementia with Lewy bodies (DLB). Although they share the same pathological protein, different synucleinopathies present distinct clinical and pathological phenotypes. Clinically, it is very challenging to differentiate particularly PD from MSA, especially at the early stage of the disease. Accumulating evidence suggests that αSyn aggregates associated with different synucleinopathies adopt distinct conformational strains. Our results also suggest the existence of distinct αSyn strains with the same disease (here called sub-strains to avoid confusion). αSyn strains and sub-strains faithfully self-propagate and spread between cells. We propose that discrimination of these conformational αSyn strains and sub-strains hold promise for differential diagnosis and understanding the relationship between structures of αSyn strains and sub-strains and their pathologic functions. METHODS: We used protein misfolding cyclic amplification (PMCA) assay to detect αSyn oligomers in (cerebrospinal fluid) CSF referred to as αSyn-PMCA, which exploits the functional properties of these oligomers to seed soluble monomers used as substrates thus facilitating their detection. Further, we used a combination of biochemical, structural, and biological methods to characterize the amplified products of αSyn-PMCA. RESULTS: αSyn-PMCA assay could readily discriminate between CSF samples from PD and MSA patients with high sensitivity. Moreover, the characteristics of amplified aggregates from the CSF of PD patients differed from aggregates amplified from CSF of MSA patients. We also found that the properties of aggregates that were amplified from CSF samples were similar to those amplified from the brain samples. Most importantly, we were able to subgroup PD and MSA patients based on αSyn-PMCA parameters and characteristics of amplified aggregates from CSF samples. CONCLUSION: The findings obtained here will not only help to understand the relationship between the structure of αSyn strains and sub-strains and their pathologic function but may also help to discriminate diverse synucleinopathies, which will help in patients' stratification, target enrollment for a clinical trial, and personalized treatment.

Funding Disclosure: This study was funded in part by grants from MJFF and NIH to Claudio Soto.

Conflict of Interest Disclosure: Claudio Soto and Mohammad Shahnawaz are inventors on patent applications for the use of PMCA technology for high sensitive detection of alpha-synuclein aggregates in patients affected by synucleinopathies.

Theme F. Biomarkers Neuroimaging
Clinical Science

TARCC-Based Project

(30) **A Novel MRI Biomarker for Brain Tau Deposition**

Presenting Author: Fang Frank Yu, MD
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Fang Frank Yu, Elena Vinogradov, James Ratnakar, Brian Hitt, and Dean Sherry

Introduction: Alzheimer's disease (AD) is the leading cause of dementia, incurring substantial financial and social costs. Neurofibrillary tangles (NFT) of tau have received increasing attention for their strong association with clinical disability and cerebral atrophy. Tau burden can be assessed with tau-PET imaging, which utilizes ionizing radiation, or invasive CSF sampling. A non-invasive MRI-based approach leveraging endogenous contrasts would address these shortcomings while offering widespread availability and high spatial-resolution, making it particularly well-suited for longitudinal disease monitoring. Chemical exchange saturation transfer (CEST) MRI has emerged as a tool to detect low concentration molecules. Amide proton transfer (APT), a specific type of CEST experiment, has shown promising results but may lack specificity for NFT formation. We hypothesize that interrogation of other chemical species using CEST may reveal a unique z-spectral signature that would confer increased specificity for pathologic tau aggregation. Methods: Recombinant full-length (4R) monomeric and fibrillated tau were expressed and purified as previously described, and dissolved in HEPES buffer. All CEST experiments were performed using a 9.4 T vertical bore Varian NMR spectrometer. Three sets of RF pulse intensities were utilized (1, 1.3 and 2 uT) and applied over a 2-second saturation pulse duration. These were performed at three separate temperatures: 25, 37, and 420 C. Z-spectra were acquired in the ±10ppm range, using 0.25 ppm step (total of 82 points). Results: Z-spectra of the tau monomers showed signal peaks at 1, 2, and 3.5 ppm downstream of the water resonance. On the other hand, Z-spectra of the tau fibrils demonstrated a singular peak at an offset frequency of 3.5 ppm. Discussion: We delineated the CEST Z-spectra of full-length (4R) monomeric and fibrillated tau, and found that the Z-spectrum of aggregated tau fibrils differed from tau monomers at 1 and 2 ppm. We believe that this finding could serve as a non-invasive imaging biomarker for monitoring disease progression in AD patients, corresponding to increased NFT deposition. Additional in vivo work is needed to validate these findings and determine if they can be applied clinically.

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme F. Biomarkers Neuroimaging
Basic Science

TARCC-Based Project

(31) **Early alterations of neurovascular unit in the retina in mouse models of tauopathy**

Presenting Author: Hua Liu, PhD
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Hua Liu, Fan Xia, Yonju Ha, Shuizhen Shi, Yi Li, Shengguo Li, Jonathan Luisi, Rakez Kayed, Massoud Motamedi, and Wenbo Zhang

Background: The retina, as the only visually accessible tissue in the central nervous system, has attracted significant attention of using it as a biomarker for neurodegenerative diseases. Yet, most of studies focus on the loss of retinal ganglion cells (RGCs) and degeneration of their axons. There is no integrated analysis to address temporal alterations of different retinal cells in the neurovascular unit (NVU) in particular retinal vessels. Here we assessed NVU changes in two mouse models of tauopathy and evaluated the therapeutic effects of a tau oligomer monoclonal antibody (TOMA). Method: Studies were performed in P301S and P301L transgenic mice which overexpress the human tau mutated gene. Vascular leakage was determined by analyzing FITC-BSA extravasation into the retina. Leukocyte adhesion was assessed by Concanavalin A labeling. Alterations of adhesion junction, microglia, leukocytes and RGCs were assessed by immunostaining in retinal flatmounts. Optical coherence tomography, scanning laser ophthalmoscopy and electroretinography were applied to non-invasively analyze retinal structural and functional changes. TOMA was utilized to treat tauopathy. Result: Retinal edema and breakdown of blood-retina barrier were observed at the very early stage of tauopathy. Leukocyte adhesion/infiltration, and microglial recruitment/activation were constantly increased in the retinal ganglion cell layer of tau transgenic mice at different ages, while Müller cell gliosis was only detected in relative older tau mice. Concomitantly, the number and function of RGCs progressively decreased during aging although they were not obviously altered in the very early stage of tauopathy. Moreover, intrinsically photosensitive RGCs appeared more sensitive to tauopathy. Remarkably, TOMA treatment in young tau transgenic mice significantly attenuated vascular leakage, inflammation and RGC loss. Conclusion: Our data provide compelling evidence that abnormal tau accumulation can lead to pathology in the retinal neurovascular unit, and vascular alterations occur more manifest and earlier than neurodegeneration in the retina. Oligomeric tau-targeted immunotherapy has the potential to treat tau-induced retinopathies. Retinal NVU may serve as a potential biomarker for tauopathy and a platform to study the molecular mechanisms of neurodegeneration.

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Conflict of Interest Disclosure: None

Theme F. Biomarkers Neuroimaging
Clinical Science

(32) **Relationship of phosphate brain energy metabolism (BEM) and cognition using volume-coil 31P MRS at 7Tesla in Alzheimer's disease**

Presenting Author: Namrata Das MD, PhD, MPH
Research Neuroscientist in Alzheimer's Disease
The University of Texas at Dallas

Namrata Das, Jimin Ren, Jeff Spence, and Sandra Chapman

Introduction: Mitochondrial dysfunction is a neurometabolic hallmark signaling abnormal brain energy metabolism (BEM) targeted as a potential early marker of Alzheimer's disease (AD). Advanced imaging technologies, such as 31phosphorus magnetic resonance spectroscopy (31P MRS) at ultra-high-field (UHF) magnetic strength 7-T, provides sensitive BEM data measurement with precision. The study's first goal was to replicate a methodology to measure energy phosphate and membrane phospholipid metabolites simultaneously across the whole-brain using volume-coil 31P MRS at 7-T with precision to characterize BEM markers in three groups-cognitively normal (CN), amnestic mild cognitive impairment (aMCI), and AD. The second aim was to investigate whether BEM markers in the four brain regions-frontal, temporal, parietal, and occipital were significantly different across the three groups. The final goal was to investigate the BEM markers and cognition correspondence across the three groups. Methods: A total of 41 participants (CN=15, aMCI=15, AD=11) were enrolled to complete cognitive assessment and scan. The cognitive domains included executive function, memory, attention, visuospatial skills, and language. BEM markers were measured using energy reserve index (PCr/t-ATP), energy consumption index (intracellular_Pi/tATP), metabolic state indicator (intracellular_Pi/PCr), and regulatory co-factors [magnesium (Mg2+) and intracellular pH]. Results: A well-resolved spectral peaks with an improved signal-to-noise ratio of the 13 metabolites were acquired simultaneously from the whole-brain across the three cohorts using31P MRS at 7-T. ANOVA-between group BEM markers-energy reserve and energy consumption indices were reduced in aMCI with further reduction in AD than CN except for metabolic state indicator and Mg2+ in the temporal region, a vulnerable area of AD pathophysiological changes. Finally, using a linear mixed model, we found a significant positive correlation between Mg2+ and cognitive performance of memory, EF, and attention measures in the CN group only in contrast to aMCI and mild AD groups, respectively. Results suggest that in healthy brains, Mg2+ supports the BEM mechanism, neuronal function, and cognition. Whereas, in aMCI and AD, the Mg2+ co-factor fails to support these systems. Conclusion: The preliminary results across the three groups suggest that BEM alterations may be early neuropathophysiological markers of AD. Still, the sequence and impact of energy metabolism should be further explored.

Funding Disclosure: UT Dallas

Conflict of Interest Disclosure: None

Theme F. Biomarkers Neuroimaging
Clinical Science

(33) **Electrophysiological Effects of Transcranial Infrared Laser Stimulation**

Presenting Author: Dariella Fernandez, MA
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Dariella Fernandez, Xinlong Wang, Zachary Wade, Laura Gamboa, Hanli Liu, and Francisco Gonzalez-Lima

Background: Transcranial Infrared Laser Stimulation (TILS) is a novel non-invasive brain intervention that has been found to modulate mitochondrial respiration and cellular functions in cortical neurons. In healthy adults, eight minutes of TILS to the right prefrontal cortex has been shown to improve memory and attention. This technology is also being tested as a possible intervention against cognitive decline in dementia, including Alzheimer's disease. However, little is known about what electrophysiological effect TILS has on the human brain. Objective: Our objective was to map and image the electrophysiological effects in the cerebral cortex during and after TILS to the right prefrontal cortex. Method: To investigate this question, we used electroencephalographic (EEG) recordings from the entire human scalp before, during and after the administration of a 1064 nm wavelength laser with a power density of 0.25 W per cm2 delivered to the right forehead using a randomized between-subjects, sham-controlled design with subjects unaware of sham or active laser. Results: Here we show that 8 minutes of TILS significantly increased the EEG power density of alpha and beta waves as compared to sham controls, with the largest increases seen in the alpha waves. These electrophysiological changes were dose-dependent and did not continue after the TILS intervention ended. Conclusion: Eight minutes of TILS increases the power density of alpha and beta waves in the brain of healthy adults. The results from this study help us to further understand the mechanistic link between cerebral electrophysiological effects and the cognitive enhancing benefits from TILS and can help guide future applications of TILS.

Funding Disclosure: NIH grant RF1MH114285; Oskar Fischer Project Fund

Conflict of Interest Disclosure: None

Theme F. Biomarkers Neuroimaging
Basic Science

(34) **Comparison of [11C]MPC-6827, a microtubule targeted PET tracer and amyloid tracer [11C]PiB in J20 mice**

Presenting Author: Ramesh Neelamegam, PhD
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The University of Texas Health Science Center at San Antonio

Ramesh Neelamegam, Wei Zhang, Michael O'Boyle, Veronica Galvan, Peter Fox, Sudha Seshadri, and Dileep Kumar

Objective: The existing PET tracers used in Alzheimer's Disease (AD) have limited utility in prognosis and in revealing reliable clinicopathologic correlations of disease. Therefore, identifying novel biomarkers for neurodegeneration through PET imaging is a top priority in biomedical research. We proposed to target microtubules (MTs) as an imaging target for neurodegeneration owing to established preclinical, postmortem and clinical studies that support the implication of altered regulation of MTs AD. Blood brain barrier-penetrating PET tracer, [11C]MPC-6827 is the one of the validated PET tracers available for in vivo imaging of MTs in brain.1,2 In this presentation, we report the head-to-head comparison [11C]MPC-6827 and [11C]PiB, in Aβ over expressing APP mutated transgenic J20 mice and controls. Methods: [11C]MPC-6827 and [11C]PiB were synthesized by reacting corresponding O-desmethyl precursor with [11C]CH3I and [11C]CH3OTf in a GE Tracerlab FX2 MEI module. microPET imaging were performed in 6-month-old J20 mice and littermates (n=4) using a Siemens Focus Scanner. Image analyses were performed with vendor-provided software on reconstructed data. Results: Automated synthesis of [11C]MPC-6827 and [11C]PiB were achieved in 40+5% yield. Dynamic PET images show ~25% of reduced whole brain uptake of [11C]MPC-6827 in J20 mice compared to control. Whereas, [11C]PiB exhibited <10% higher binding. [11C]MPC-6827 show higher standardized uptake value (SUV) than [11C]PiB. The effect size of [11C]MPC-6827 is significantly higher than [11C]PiB in whole brain, prefrontal cortex and hippocampus J20 mice, compared to control mice. Conclusion: Our preliminary studies show that in J20 transgenic mice, binding of the MT PET ligand [11C]MPC-6827 exhibit higher effect size and SUV than the amyloid PET tracer [11C]PiB. Therefore, [11C]MPC-6827 could be used as a potential PET tracer for human brain imaging of AD and related neurodegenerative diseases.

Funding Disclosure: Center for Biomedical Neuroscience (CBN-2020), UT Health San Antonio

Conflict of Interest Disclosure: None

Theme G: Clinical Manifestations
Clinical Science

(35) **Validation of a Second δ Homolog for Telephone Assessment of Dementia Severity**

Presenting Author: Donald R. Royall, MD
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The University of Texas Health Science Center at San Antonio

Donald Royall and Raymond Palmer

Background: We have developed the latent dementia-specific cognitive phenotype "δ". δ is constructed from Spearman's general intelligence factor "g" by Confirmatory Factor Analysis (CFA) in a Structural Equation Framework. It can be reified as a composite factor "d-score" and used to predict dementia severity or to identify dementia-specific biomarkers. δ's derivation from g suggests that it can be constructed from almost any cognitive battery. It would be convenient to construct δ homologs adapted to telephone administration. The test of Every Day Cognition (ECog) is ideally suited to that application. CFA supports a seven-factor ECog structure including six domain-specific factors (i.e., Memory, Language, Visuospatial Abilities, Planning, Organization, and Divided Attention) and one global factor. The ECog's global factor may be a proxy for g itself. If so, then it becomes possible to extract δ from ECog items. Method: We constructed two δ homologs from ECog data obtained by the Alzheimer's Disease Neuroimaging Initiative (ADNI). "dECog" was indicated by either patient- or caregiver-rated ECog items (Figure 1) and targeted instrumental activities of daily living (IADL) as measured by the Functional Abilities Questionnaire (FAQ). Result: dECog's Area Under the Receiver Operating Characteristic Curve (AUC) for the discrimination between Alzheimer's Disease (AD) v. normal controls (NC) was 0.93 (CI: 0.91 - 0.95; N = 1737). dECog correlated strongly with Clinical Dementia Rating Scale Sum of Boxes (CDRSOB) regardless of which informant was used (caregiver-rated $r = 0.85$, $p < 0.001$; patient-rated $r = 0.83$, $p < 0.001$). Both dECog homologs (informant and self-rated) correlated strongly with the "dT2A" δ homolog (caregiver-rated $r = 0.85$, $p < 0.001$; patient-rated $r = 0.82$, $p < 0.001$). dT2A had no advantage over dECog in predicting CDRSOB even though dT2A is indicated by formal measures. Conclusion: δ homologs can be constructed from ECog items. Unlike dT2A or the CDR, dECog can be administered by phone. TARCC is now collecting the ECog and can be used to replicate this analysis.

Funding Disclosure: Julia H. and Vann Buren Parr Endowment

Conflict of Interest Disclosure: DRR and RFP have formed a company (dNomixTM) to develop clinical applications of "delta" homologs.

Theme G: Clinical Manifestations
Clinical Science

TARCC-Based Project

(36) **Neurocognitive effects of Immune Checkpoint Inhibitors: A Literature Review**

Presenting Author: Neveen Mostafa, MD
TARCC Fellow
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Neveen Mostafa, and Mukaila Raji

Background: Immune checkpoint inhibitors (ICI) are novel but rapidly growing class of cancer treatments. They have pleotropic effects on several cancer-specific targets that underlie their therapeutic properties. These targets include programmed cell death 1, programmed cell death ligand 1, and cytotoxic T lymphocyte antigen 4 pathways. ICI have been approved in treatment guidelines of several cancers like melanoma and lung cancers and are being routinely used in clinical practice due to its proven efficacy. The mechanism of ICI primarily targets the immune system, which also serves important roles in the structure and function of the central and peripheral nervous system. The reported associated adverse effects are essentially immune mediated due to T-cell activity upregulation that causes disrupted immune tolerance. The same mechanism leading to cancer death might be driving the neurocognitive sequalae. Several specific neurological adverse events were described due to the role of inflammatory pathways in mediating behavioral and cognitive functions. ICI have clear proven responses, leading to increase in the overall survival such that patients are now living longer with its side effects. Thus, it is essential to understand and assess the long-term side effects and quality of life outcome among the growing population of cancer survivors previously treated with ICI.
Methods: This review discusses the reported cognitive changes associated with immune checkpoint inhibitors. We employed a systematic search of literature in PubMed database, up to November 2020, mentioning neurological and cognitive side effects in patients treated with ICIs. Eligible studies included clinical trials, observational studies and case reports. Results: The clinical spectrum of neurological disorders is highly heterogeneous. Most of the reported neurological adverse events consist of non-specific symptoms such as headache and fatigue, with the more functionally devastating ones being myasthenia gravis, demyelinating polyradiculopathy, meningitis and limbic encephalitis. Cognitive decline and memory problems were infrequently reported in the reviewed studies. Conclusion: Although few clinical studies have targeted ICI immunotherapy for associated neurological sequelae, it appears that cognitive decline is not a common adverse effect for ICI. However, over time and with longer use of ICI, there will be a need for more rigorous studies

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme G: Clinical Manifestations
Clinical Science
Work in Progress

TARCC-Based Project

(37) **Utility of Neuropsychological Methods to Improve Diagnostic Accuracy of Mild Cognitive Impairment in a Hispanic Population: A TARCC-Funded Study**

Presenting Author: Anne R. Carlew, PhD
Assistant Professor
The University of Texas Southwestern Medical Center

Anne Carlew, William Goette, Jeffrey Schaffert, Heidi Rossetti, Laura Lacritz

Background: Conventional diagnostic criteria for mild cognitive impairment (MCI) in many large-scale studies requires only 1 impaired neuropsychological test score combined with subjective complaint and/or clinical judgment, which can lead to a high rate of false positive diagnoses (>30% in some cases). This can dilute results of clinical drug trials, overestimate the prevalence of MCI, and decrease the stability of MCI diagnoses over time. In a series of studies, Jak and Bondi developed a neuropsychological actuarial method of MCI diagnosis that when retrospectively applied to large Alzheimer's datasets identified subjects who were less likely to revert to normal and who were more likely to have AD biomarkers. This method has so far been applied to datasets composed of mostly White, highly educated subjects, which may limit generalizability to a rapidly growing elderly minority population in the U.S., 20% of which will be of Hispanic origin by 2050. The Texas Alzheimer's Research and Care Consortium (TARCC) is one of the few comprehensive longitudinal studies with a large sample of aging Hispanic Mexican Americans, creating a unique opportunity to investigate diagnostic strategies in this rapidly growing population. Method: This study will analyze existing TARCC data using the actuarial neuropsychological method to reclassify MCI participants compared to conventional diagnostic methods in both Hispanic and non-Hispanic subjects. MCI subjects identified by conventional and actuarial methods will be separately submitted to cluster analysis to identify latent groups based on cognitive phenotype. A second step will analyze participants diagnosed with MCI at subsequent visits to investigate which method is most likely to capture true underlying neurodegenerative disease at the first visit, and which is more likely to produce false positive diagnoses (individuals who later revert to normal). Results of this study have the potential to inform and improve the diagnostic method used by TARCC and other research and clinical settings to minimize misdiagnosis, which is of particular concern in Hispanics who are more likely to be clinically misdiagnosed.

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme G: Clinical Manifestations
Clincal Science

TARCC-Based Project

(38) **Correlates of apathy in Alzheimer's disease: a cross-sectional analysis of the Texas Alzheimer's Research and Care Consortium (TARCC) cohort**

Presenting Author: Antonio L Teixeira, MD, PhD
Professor
The University of Texas Health Science Center at Houston

Antonio Teixeira, Haitham Salem, Lais Martins, and Robert Suchting

Background: Apathy, clinically defined by a marked reduction in motivation, is among the most frequent behavioral and psychological symptoms in Alzheimer's disease (AD) and related dementias. Importantly, apathy has been associated with functional impairment, caregiver burden, and increased risk of institutionalization. Because of its prevalence and clinical meaning, apathy is an important therapeutic target in AD. Objective: The aim of this study was to determine the prevalence of apathy and its predictors in patients with clinical diagnosis of AD enrolled at the Texas Alzheimer's Research and Care Consortium (TARCC) cohort. Methods: The TARCC is a longitudinal cohort of individuals with AD, mild cognitive impairment and cognitively intact controls. The diagnosis of AD was based on clinical consensus according to the NINCDS-ADRDA criteria. The diagnosis of apathy was determined by a positive response to the item 'apathy' of the Neuropsychiatric Inventory - Questionnaire (NPI-Q) applied to family members or caregivers. Serum levels of biomarkers were determined by HumanMap multiplex immunoassay. Data were analyzed using t-tests and logistic regression analysis, with a significance level set at 0.05. Results: From 1,322 subjects with AD (M/F: 581/741, mean age ± SD: 75.3 ± 8.4), 374 (28.3%) exhibited apathy. The apathy group had more male (48.7% vs. 42.1%), history of alcohol, tobacco and other drugs use, not differing from the non-apathy group regarding age, education, and cardiovascular comorbidities. The apathy group also had worse cognitive (MMSE) and functioning performance (PSMS, IADL) than the non-apathy group. Subjects with apathy exhibited higher levels of inflammatory molecules, including CRP, IL-6, TNF, IFN-y, among others. In the multivariate analysis, apathy was associated male sex, tobacco use, worse cognition and functioning, increased IFN-y and sICAM-1 levels. Conclusions: As previously reported in the literature, the prevalence of apathy in subjects with AD is high and associated with cognitive and functioning performance. The association between apathy and inflammatory mediators needs to be better explored in AD.

Funding Disclosure: TARCC and UTHealth Department of Psychiatry

Conflict of Interest Disclosure: None

Theme G: Clinical Manifestations
Clincal Science

TARCC-Based Project

(39) **Diastolic Dysfunction and Cognitive Impairment**

Presenting Author: Alicia S. Parker, MD
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Alicia Parker, Jayandra Himali, Alexa Beiser, Vinutha Ganapathy, Leila Saadatpour, Jonathan Donnelly, Ramachandran Vasan, and Sudha Seshadri

Background Numerous studies have shown an association between cardiac health and brain health. The relationship between diastolic dysfunction and cognition is undefined at present. If diastolic dysfunction is found to be associated with cognitive impairment, that would suggest diastolic dysfunction is a novel modifiable risk factor for the development of dementia. Method In this cohort study, data from 1438 participants from the Offspring Cohort of Framingham Heart Study was evaluated for Exam 8, which was of roughly eight years duration. Echocardiographic, MR brain imaging and neuropsychological data were analyzed. Result Analyses of data from 1438 participants showed that increasing E/E' ratio was associated with increased executive function impairment in the Similarities (β±SE:-0.29±0.09,p<0.002) and Phonemic Fluency (-1.27±0.33,p<0.001) tasks. Using Model 1, participants with mild diastolic dysfunction had improvements in their phonemic fluency scores as compared to those with intact diastolic dysfunction (β±SE:-2.00±0.8,p<0.013). Executive function was more impaired on the Phonemic Fluency task in those with moderate-to-severe diastolic dysfunction (-2.75±1.11,p<0.014). Executive function trended towards being more impaired in those with moderate-to-severe diastolic dysfunction (-0.59±0.30,p<0.052). The global cognitive score PC1 trended towards being more impaired with moderate-to-severe diastolic dysfunction (-0.16±0.08,p<0.055). Logical memory was significantly more impaired in those with moderate-to-severe diastolic dysfunction (-0.70±0.34,p<0.036). While increasing diastolic dysfunction was found with increasing numbers of incident dementia, this association was not statistically significant. Data from 1438 participants showed that increasing E/E' ratio, indicating increasing diastolic dysfunction, was associated with increased incident mild cognitive impairment (HR 1.29 [95%CI: 1.01, 1.66], p<0.043). Data from 1217 participants showed that those with mild diastolic dysfunction trended towards increased white matter hyperintensities (0.11±0.07, p<0.088); participants with moderate-to-severe diastolic dysfunction had increased white matter hyperintensities (0.28±0.09,p<0.002). Conclusion Increasing severity of diastolic dysfunction was found to be associated with increased white matter hyperintensities on brain MRI, which is indicative of cerebral small vessel disease, and with increased executive dysfunction on neuropsychological testing. Additionally, patients with moderate to severe diastolic dysfunction were found to have more impaired verbal memory on a cognitive task. This study suggests that diastolic dysfunction is a reversible risk for the development of cognitive impairment and dementia.

Funding Disclosure: None for the FHS project; the accompanying prospective study is funded by TARCC

Conflict of Interest Disclosure: None

Theme G: Clinical Manifestations
Clinical Science

TARCC-Based Project

(40) **Predictive utility of cognitive intraindividual variability in the Texas Alzheimer's Research and Care Consortium (TARCC) cohort**

Presenting Author: Bonnie M. Scott, PhD
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The University of Texas at Austin Dell Medical School

Bonnie Scott, Don Royall, John Hart, Parunyou Julayanont, and Robin Hilsabeck

Background: Intraindividual variability (IIV) in cognitive performance has shown promise as a sign of early cognitive change in neurodegenerative conditions. Although accumulating research suggests that IIV both within and between neuropsychological domains may be a more sensitive indicator of future cognitive and functional decline than mean performance level, there have been no studies to date comparing the predictive utility of within- versus between-domain IIV. Thus, the overall goal of the current study was to determine if IIV within and between cognitive domains differentially influences functional independence over time. Methods: The present study included annual data from 1080 participants (Controls=651, MCI=211, AD=218) over 5 years. Mixed linear modeling was used to analyze the longitudinal relationship between cognitive IIV and functional independence (IADLS). Raw scores from each neuropsychological test were z-transformed and IIV-within scores were calculated as the difference between tests in five cognitive domains: attention, language, immediate memory, delayed memory, and executive functioning (EF). Mean scores were also computed for each domain and an IIV-between domain score was calculated as the standard deviation of these mean scores. Results: There was a significant random effect of linear time, indicating that the rate of change in IADLS was not uniform across the sample. There were significant fixed effects for ethnicity and baseline MMSE, which interacted with age and education, suggesting these variables moderated baseline level and rates of change in functional status. IIV within the EF domain and between domains were the only significant predictors of individual IADLS. There was a significant random effect of IIV between and IIV within all domains, indicating that the effect of these variables on IADLS varies from person-to-person. However, IIV between domains showed the greatest effect on functional status over time. Conclusions: Findings highlight the importance of cognitive IIV, especially between cognitive domains, for identifying individuals at greatest risk for future cognitive and functional decline. In turn, such findings may facilitate future investigations into the mechanisms underlying preclinical declines in global cerebral integrity and the development of clinical trials aimed at early prevention and treatment.

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme G: Clinical Manifestations
Clinical Science

TARCC-Based Project

(41) **Latent Item Response Theory Regression Using Neuropsychological Tests to Predict Functional Ability**

Presenting Author: William Goette, MS
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The University of Texas Southwestern Medical Center

William Goette, Anne Carlew, Jeffrey Schaffert, Heidi Rossetti, and Laura Lacritz

Objective: Examine prediction of functional ability with neuropsychological tests using latent item response theory. Method: The sample included 3155 individuals (Mage=69.72, SD=9.41; Meducation=13.15, SD=4.40; white=92.81%; female=62.03%; MCI=25.13%; Dementia=28.87%) from the Texas Alzheimer's Research and Care Consortium who completed functional and cognitive assessments [Mini Mental State Examination (MMSE), Logical Memory (LM), Visual Reproduction (VR), Controlled Oral Word Association Test (COWAT), Trail Making Test (TMT), Boston Naming Test, and Digit Span]. Functional measures [Clinical Dementia Rating Scale, Physical Self Maintenance Scale, and Instrumental Activities of Daily Living)] were combined into a single outcome variable using confirmatory factor analysis. Item response theory (IRT) was used to fit the data, and latent regression to predict the latent trait score using neuropsychological data. Results: All three functional scales loaded onto a single factor and demonstrated good construct coverage and measurement reliability (Supporting Figure). A graded response IRT model best fit the functional ability composite measure. MMSE (b=-1.08, p<.001), LM II (b=-0.58, p<.001), VR I and II (b=-0.09, p=.02 and b=-0.43, p<.001, respectively), COWAT (b=-0.10, p=.003), and TMT-B (b=-0.30, p<.001) all significantly predicted functional abilities, as did age (b=0.61, p<.001) and education (b=0.31, p<.001). Conclusions: Global cognition, memory and executive function tests predicted functional abilities while attention and language tasks did not. These results suggest that certain neuropsychological tests meaningfully predict functional abilities in elderly cognitively normal and cognitively impaired individuals. Further research is needed to determine whether these cognitive domains are predictive of functional abilities in other clinical disorders.

Funding Disclosure: BVB Dallas Foundation Alzheimer's Disease Neuropsychology Fellowship; UT Southwestern Medical Center O'Donnell Brain Institute Cognition and Memory Center

Conflict of Interest Disclosure: None

Theme G: Clinical Manifestations
Clinical Science

TARCC-Based Project

(42) **Characterizing Memory Measurement in Cognitively Normal Individuals Using Latent State Trait Modeling of Neuropsychological Tests**

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The University of Texas Southwestern Medical Center

William Goette, Jeffrey Schaffert, Anne Carlew, Heidi Rossetti, Laura Lacritz

Objective: Characterize trait and state measurement of memory in a longitudinal, cognitively normal (CN) sample. Method: Data were taken from 515 participants (81.17% white; Mage=64.78, SD=8.20; Medu= 13.04, SD = 4.39; 73.40% female) deemed CN for 5 consecutive visits in the Texas Alzheimer's Research and Care Consortium. The memory trait was measured by the CERAD (total learning and delayed recall) and WMS-III Logical Memory (LM) and Visual Reproduction (VR) I and II subtests. Multiple-indicator growth models were used as the primary analysis. Results: Assumption screening revealed the memory trait was characterized by three domain factors: list learning (CERAD learning and recall), story memory (LM I and II), and visual memory (VR I and II). Generalized second-order growth models demonstrated best overall fit. Scores demonstrated a positive latent growth process such that trait memory scores actually increased over time. Consistency and specificity coefficients suggest less situation-specific error occurs as individuals are tested over time with the first evaluation having the largest portion of situation-specific measurement error. Conclusions: Measurement accuracy of memory in CN individuals improved over repeated administrations. Accurate identification of cases with normal memory in memory disorders research may require serial assessments to account for (a) improved measurement accuracy of the trait after multiple assessments and (b) reducing the influence of state-specific sources of error that are greatest at the first assessment time. Further research is needed to determine whether the observed positive growth in trait scores is unique to CN samples and whether measurement accuracy changes in cognitive domains other than memory.

Funding Disclosure: BVB Dallas Foundation Alzheimer's Disease Neuropsychology Fellowship; UT Southwestern Medical Center O'Donnell Brain Institute Cognition and Memory Center

Conflict of Interest Disclosure: None

Theme G: Clinical Manifestations
Clinical Science

TARCC-Based Project

(43) **Latent Classes of Cognitively Normal Individuals have Unique Relationships between Demographic and Neuropsychological Variables**

Presenting Author: William Goette, MS
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The University of Texas Southwestern Medical Center

William Goette, Jeffrey Schaffert, Anne Carlew, Heidi Rossetti, Laura Lacritz

Objective: Determine whether clinically normal (CN) individuals represent a single homogeneous group prior to normative adjustment. Method: Data from 1,055 CN participants (Mage=68.0, SD=8.68; Meducation=14.9, SD=2.90; white=92.7%) from the Texas Alzheimer's Research and Care Consortium were used. Participants had no recorded neurological, cognitive, or psychiatric diagnoses. Raw scores from the AMNART, Animal Fluency, Boston Naming Test (BNT), CERAD verbal learning test, CLOX1 and CLOX2, MMSE, and Trail Making Test (TMTA and B) were examined with finite mixtures of general linear regression models using age, education, race, and gender as predictors. Each test was modeled with up to 10 latent classes with the Bayesian Information Criterion used to select best fit. Results: Animal Fluency, CLOX2, and TMT A errors were best fit by 1 underlying group. The remaining tests required 2 (CERAD, CLOX1, MMSE, and TMT-B errors), 3 (BNT and TMT-A), and 5 (AMNART and TMT-B) latent classes. Generally, latent classes for tests differed in coefficients for race, gender, and intercepts, though results differed from test-to-test. Conclusions: Latent classes of CN individuals were identified for which the predictive power of certain demographic variables differed depending on the latent class. Further research is needed to identify who may belong to distinct latent classes so the appropriate regression-based norms are used. Different latent class coefficients for race and gender suggest heterogeneity within these variables that can be addressed to produce more accurate models. These findings suggest that regression-based norms could be improved by identifying these latent classes and finding ways of predicting who belongs to which latent class.

Funding Disclosure: BVB Dallas Foundation Alzheimer's Disease Neuropsychology Fellowship; UT Southwestern Medical Center O'Donnell Brain Institute Cognition and Memory Center

Conflict of Interest Disclosure: None

Theme G: Clinical Manifestations
Clinical Science

TARCC-Based Project

(44) **Examination of Three Functional Living Scales Using Item Response Theory Modeling in a Mixed Sample**

Presenting Author: William Goette, MS
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The University of Texas Southwestern Medical Center

William Goette, Anne Carlew, Jeffrey Schaffert, Heidi Rossetti, and Laura Lacritz

Objective: Characterize three functional living scales under item response theory and examine these scales for evidence of differential item functioning (DIF) by participant and/or informant ethnicity and education. Method: Baseline data from 3155 participants [Mage=70.59(9.55); Medu=13.3(4.26); 61.72%female] enrolled in the Texas Alzheimer's Research and Care Consortium with data from the Clinical Dementia Rating Scale (CDR; functional items), Physical Self-Maintenance Scale (PSMS), and Instrumental Activities of Daily Living Scale (IADL) were used. The sample was predominately white (93.94%) and 35.97% identified as Hispanic. Graded response models fit all three tests best. DIF was examined by iteratively dropping item-by-item constraints and then testing model fit. Results: The CDR demonstrated overall good item functioning with clear separation between all of the rating categories for each item, while the PSMS and IADL did not, suggesting the item ratings should be reconsidered. DIF was observed by ethnicity (Hispanic v. non-Hispanic) and education (separated into low, average, high) for every item on all three scales (all ps $\leq$ .01 after adjustment for multiple observations). Hispanic ethnicity and higher education subjects were more likely to be rated as more impaired. Conclusions: Results suggest these three commonly used functional scales have DIF depending on the ethnicity and education of the patient. This finding has implications for understanding functional change in certain populations, particularly the potential for mischaracterization of impairment in minority samples. The finding that individuals with higher education tended to be rated as more functionally impaired warrants further investigation.

Funding Disclosure: BVB Dallas Foundation Alzheimer's Disease Neuropsychology Fellowship; UT Southwestern Medical Center O'Donnell Brain Institute Cognition and Memory Center

Conflict of Interest Disclosure: None

Theme G: Clinical Manifestations
Clinical Science

TARCC-Based Project

(45) **Neuropsychiatric symptoms over time in autopsy-confirmed Alzheimer's, Lewy body disease, and mixed pathology**

Presenting Author: Jeff Schaffert, PhD
TARCC Neuropsychology Fellow
The University of Texas Southwestern Medical Center

Jeff Schaffert, Will Goette, Allison Parker, Anne Carlew, Laura Lacritz, Heidi Rossetti, and Munro Cullum

Objective: Neuropsychiatric symptoms (NPS) are common in neurodegenerative disease, and are associated with caregiver burden, functional status, and survival time. Research shows NPS differ among neurodegenerative conditions such as Alzheimer's disease (AD) and Lewy body disease (LBD), but studies investigating the progression of these symptoms over time is limited. Furthermore, clinical diagnoses of AD and LBD frequently do not match post-mortem pathological diagnoses, limiting inferences that can be made when using only clinical diagnoses. As such, longitudinal studies of NPS in those with autopsy-confirmed LBD, AD, and mixed pathology (AD+LBD) are needed, which was the primary aim of this study. Methods: Data on individuals 50+ years of age with autopsy-confirmed AD (N=1568), AD+LBD (N=349), or LBD (N=142) were obtained from the National Alzheimer's Coordinating Center (Mean visits = 2.61). Total Neuropsychiatric Inventory Questionnaire (NPI-Q) and 15-item Geriatric Depression Scale (GDS) scores were used to examine NPS. Multilevel zero-inflated binomial regression models were used to assess if NPI-Q and GDS scores differed between AD, AD+LBD, and LBD over time. Covariates included: years from baseline visit to last visit, baseline cognitive diagnosis (dementia vs. MCI/normal cognition), demographic characteristics, MMSE, Functional Activities Questionnaire score, and psychotropic treatment. Results: Higher NPI-Q and GDS scores were observed at baseline for the LBD group, compared to AD (p's<.001). NPI-Q scores increased more over time in the LBD group compared to the AD/LBD and AD groups at a 90% CI. Differences between all the group's baseline GDS marginal means scores were observed at the 95% CI and increased more rapidly in the LBD group compared to the AD and AD/LBD groups. R2 values were 0.67 (95% CI:0.66-0.68) for the NPI-Q and 0.61 (95% CI:0.59-0.62) for the GDS. Conclusions: Overall, those with LBD pathology appear to have more NPS over time compared to those with AD and AD+LBD pathology. Depressive symptoms increased more in those with LBD and AD+LBD compared to AD over time. As such, the course of NPS appear to differ based on disease pathology. However, the clinical impact of NPS progression for patients and caregivers remains unclear, and future prospective investigations are needed.

Funding Disclosure: TARCC; NACC is funded by the National Institute on Aging (UO1 AG016976);

Conflict of Interest Disclosure: None

Theme H: Dementia Care and Psychosocial Factors
Clinical Science

TARCC-Based Project

(46) **Assessing the Utility of Monitoring Technology for Family Caregivers of People Living with Dementia**

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Texas A&M Health Science Center

Marcia Ory, Shinduk Lee, Ashley Wilson, Robin Hilsabeck, Paulina Devora, Alyssa Aguirre, Kristen Reuter, Barbara Harty, Janice Knebl, and Matthew Smith

Background: Wandering among people living with dementia (PLWD) can be common, which poses risk to their safety and independence. This study examined the use and feasibility of monitoring technology for PLWD. Method: As part of an ongoing TARCC-funded study, PLWD and their family caregivers are being recruited from clinical and community sites. PLWDs were asked to wear a GPS-based wearable device (i.e., watch) that was tied to a smartphone application enabling their caregivers to monitor the PLWD's location. The wearable device was also equipped with an accelerometer and call functions. After three months of using the wearable device, the caregivers were asked about the usability of the system (PLWD's wearable device and caregiver's smartphone application). A total of 39 caregiver-PLWD care recipient dyads have been recruited, and 23 caregivers have completed the 3-month post-test survey. Results: Average age was 66.6 and 76.2 years old for caregivers and PWLD, respectively. At baseline, all participating caregivers reported using at least a little bit of computer, smartphone, and email. About 70% of caregivers found the system easy to use, and over 65% found the system useful in performing the caregiver role. The most frequently reported challenges were related to the watch's short battery life and difficulties charging it (10 out of 18 caregivers reported challenges). Conclusion: Despite its exploratory nature, this ongoing study demonstrates the feasibility of a digital solution among PLWD and their caregivers. Future analyses will document the characteristics of caregiver-PLWD dyads and explore technology-induced changes in caregiving for PLWD.

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme H: Dementia Care and Psychosocial Factors
Clinical Science

(47) **Technology Use among People Living with and Without Dementia: Results from a Nationwide Study**

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Shinduk Lee, Marcia Ory, Deborah Vollmer Dahlke, and Matthew Smith

Background: Information and communication technology can be sources of knowledge, social interaction, and virtual care that facilitate autonomy and improve care quality for people living with dementia (PLWD). Despite the recent advancement and increase in the availability of digital applications to support dementia care, little is known about technology use among PLWD from different settings and backgrounds. This study described and compared the use of various devices and features among older adults living with and without dementia and other cognitive impairments. Method: A cross-sectional survey was collected from an online panel of paid or unpaid primary caregivers of older adults (n=626). The caregivers reported whether their care-recipients had dementia or mild cognitive impairment diagnosis and the types of devices and functions their care-recipients used. Among 561 caregivers aware of their care recipient's chronic conditions, 46.5% (n=261) reported their care-recipients had dementia or mild cognitive impairment. Result: Average care-recipient age was 74.6 years old. Overall, care-recipients living with dementia or cognitive impairment were significantly less likely to use devices (e.g., smartphone, tablet, or computer) and functions (e.g., technology for communication, shopping, banking, navigation, or entertainment) than those without dementia or cognitive impairment. Conclusion: Findings suggest that there is potentially a missed opportunity for caregivers to benefit from technology-based dementia care solutions. PLWD's ability to use or access to technology vary depending on multiple factors (e.g., cognitive functions, self-efficacy, dependence to caregivers, and caregivers' perception of caregivers' ability to use technology), and further research is needed to enhance feasibility and efficacy of technology-based dementia care.

Funding Disclosure: None

Conflict of Interest Disclosure: None

Theme H: Dementia Care and Psychosocial Factors
Clinical Science

(48) **Care partner outcomes associated with perceived relationship closeness between care partners and care recipients**

Presenting Author: Chung Lin (Novelle) Kew, CRC
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The University of Texas Southwestern Medical Center

Chung Lin (Novelle) Kew, Charlene Supnet, Alka Khera, Brendan Kelley, and Shannon Juengst

Background: Caregiver burden is a multidimensional response to social, physical, psychological, and financial stressors that contribute negatively to caregiver outcomes. Numerous psychosocial interventions target reducing caregiver burden, yet few address dyadic caregiver-recipient relationships and their impact on caregiver burden. There is limited research relating relationship closeness with care partner outcomes in patients with dementia diagnoses. Research Objectives: Determine the relationships between care partners' perceived relationship closeness with their care recipients and care partners' depressive symptoms, general anxiety symptoms, caregiver burden, and positive aspects of caregiving. Methods: 26 community-dwelling informal care partners of individuals with Alzheimer's disease(n=5), Lewy body dementia(n=3), Parkinson's Disease(n=7), Multiple System Atrophy(n=7), or other dementias(n=4). Main Outcome Measure(s): Unidimensional Relationship Closeness Scale(URCS; closeness of social and personal relationships), Patient Health Questionnaire(PHQ-8; depressive symptoms), General Anxiety Disorder(GAD-7; general anxiety symptoms), Alcohol Use Disorders Identification Test (AUDIT; maladaptive alcohol use), Zarit Burden Interview(ZBI; perceived caregiver burden), and Positive Aspects of Caregiving scale(PAC; positive aspects of caregiving). Results: Perceived relationship closeness (URCS) was negatively correlated with depression(r=-0.39), anxiety(r=-0.37), maladaptive alcohol use(r=-0.31) and caregiver burden(r=-.41), but not correlated with positive aspects of caregiving(r=0.16). The 26 care partners included 22 spouses, 2 parents, and 2 children of care recipients. Adult children care partners reported the lowest perceived relationship closeness(median of 5.96[range:3.42-6.92]) compared to care partners who are spouses(median of 5.17[range:4.67-5.67]) or parents(median of 2.92[2.08-3.75]). Relationship closeness may be dependent on the relationship of care partners to their care recipients. Conclusions: In this study, the closer the care partners viewed their relationship with their care recipient to be, the lower the depressive symptoms, general anxiety symptoms, maladaptive alcohol use, and caregiver burden they endorsed. Of the different types of relationships, children of care recipients reported the lowest relationship closeness. This may be the result of being "sandwiched" between the demands of caring for their older parents and their own children. Future work should explore care partners' feelings of obligation versus choice in their caregiving role and care partners' ability to balance other life roles demands with caregiving responsibilities.

Funding Disclosure: None

Conflict of Interest Disclosure: None

Theme H: Dementia Care and Psychosocial Factors
Clinical Science
Work in Progress

TARCC-Based Project

(49) **Bilingual Problem-Solving Training for Care Partners of Adults with Dementia: Randomized Factorial-Design Trial Protocol**

Presenting Author: Shannon B. Juengst, PhD, CRC
Assistant Professor
The University of Texas Southwestern Medical Center

Shannon Juengst, Charlene Supnet, Novelle Kew, Matthew Smith, and Glady Maestre

Background: Care partners - informal caregivers - of individuals with Alzheimer's disease and related dementias (AD/ADRD) are essential, but often underserved, members of the healthcare team, particularly among those with fewer resources and the large and rapidly growing Hispanic population. They often experience debilitating caregiver burden and emotional distress. To address these negative emotional consequences of caregiving, we will test and refine a strategy training intervention - Problem-Solving Training (PST) - that promotes self-management and self-efficacy and reduces caregiver burden and depressive symptoms. Previous research supports efficacy of PST, but we do not know exactly how many PST sessions are needed or if post-training "boosters" are needed to maintain PST benefits. We also previously translated and culturally-adapted PST to our novel Descubriendo Soluciones Juntos (DSJ) for Spanish-speaking care partners. Method: In this factorial design randomized controlled trial, we will test remotely-delivered PST/DSJ sessions for both English- and Spanish-speaking care partners of those with AD and ADRD, to determine the optimal number of sessions needed and the need for ongoing "booster" sessions to best help care partners navigate current and future needs that change and progress over time. Aims: 1) Compare the efficacy and feasibility of 3 vs. 6 PST/DSJ sessions + booster sessions for enhancing care partner self-efficacy and decreasing caregiver burden; 2) Identify key factors associated with efficacy of PST/DSJ, including age, gender, primary language, relationship to care recipient, and disease severity or disability of the care recipient. Result: These results will establish guidelines needed for an evidence-based, culturally adapted, and implementable self-management intervention to reduce care partner stress and burden and improve care partner health and well-being. Conclusion: Providing such training to both English- and Spanish-speaking care partners promotes inclusion of diverse and underserved populations and contributes to advancement in therapeutic behavioral interventions that improve the lives of care partners of individuals with chronic conditions.

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme I: Dementia Care Practice and Public Health
Clinical Science

TARCC-Based Project

(50) **Predictors of life expectancy in autopsy-confirmed Alzheimer's disease**

Presenting Author: Jeff Schaffert, PhD
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The University of Texas Southwestern Medical Center

Jeff Schaffert, Christian LoBue, Linda Hynan, John Hart, Heidi Rossetti, Anne Carlew, Laura Lacritz, Charles White, and Munro Cullum

Objective: Life expectancy (LE) varies widely (between 3 and 12 years) following a diagnosis of Alzheimer's disease (AD). We sought to comprehensively evaluate predictors of LE following AD diagnosis in a large autopsy-confirmed AD sample. Methods: Review of the literature identified 21 variables available in the National Alzheimer's Coordinating Center (NACC) dataset previously associated with LE, which included demographic, medical/health, disease severity, and psychiatric variables. Data from individuals 50 years and older, and clinically and neuropathologically diagnosed with AD (N=764) were obtained from NACC. LE was calculated in months from the visit of AD diagnosis to death. 21 variables were first evaluated in univariate analyses. Fourteen variables had significant univariate associations with life expectancy, which were then entered into a forward multiple regression. Results: Seven predictors in the model explained 27% of the variance in life expectancy (F= 40.7, R-squared= 0.267). Lower MMSE scores (β= 0.339, p<.001), male sex (β= -0.144, p<.001), older age (β= -0.130, p<.001), non-Hispanic Caucasian race/ethnicity (β= 0.115, p<.001), greater impairment on the Functional Activities Questionnaire (β= -0.091, p=.042), abnormal neurological/physical exam (β= -0.083, p=.011), and higher Neuropsychiatric Inventory Questionnaire total scores (β= -0.079, p=.016) predicted shorter life expectancy. Post-hoc analyses revealed stratified MMSE scores (i.e., 0 to 12, 13 to 20, and 20 to 30) differed significantly in average life expectancy (F=86.5, p<.001), but only the lowest range of MMSE scores (i.e., MMSE ≤ 12) was significantly associated with LE (R= .265, p<.001). MMSE scores ranging from 13 to 20 (R=.088, p=.086) and >20 (R=.066, p=.132) were not significantly associated with LE. The correlation between LE and MMSE items were similar for both orientation (R=.413, p< .001) and non-orientation (R =.428, p< .001) items. Conclusions: Global cognitive impairment, sex, age, race/ethnicity, functional impairment, psychiatric symptoms, and abnormal neurological exam findings explained a significant proportion of life expectancy following an AD diagnosis, and severe global cognitive impairment was the strongest predictor. Currently, this model cannot predict LE following AD diagnosis on an individual basis, though our current results suggest several factors, especially cognitive ability, that may be particularly important for future investigations in this area.

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Conflict of Interest Disclosure: None

Theme I: Dementia Care Practice and Public Health
Clinical Science

TARCC-Based Project

(51) **Neurocognitive Effects of Acupuncture in Dementia: A brief literature review.**

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Ernst Nicanord

Background: Dementia, including Alzheimer's disease, is one of the biggest global public health challenges that stretches through generations. Given the limitations of current pharmacologic interventions, acupuncture has been proposed as a potential alternative to dementia therapy. We review the literature to find studies that illustrate the effects of acupuncture on mild cognitive impairment (MCI), post-stroke cognitive impairment (PSCI), Vascular dementia (VD), and Alzheimer's disease (AD). Methods: Five databases, including PubMed, Cochrane database, Google Scholar, CINAHL, and Trip database were searched for Keywords: acupuncture OR acupuncture treatment OR acupuncture therapy and mild cognitive impairment OR dementia OR vascular dementia OR poststroke dementia. Articles' titles and abstracts were reviewed and selected according to their relevance for this review. Most of the selected papers were systematic reviews (SR) and meta-analysis dated to 2020 publication. Only randomized controlled trials (RCTs) that are not included in the selected systematic reviews are selected for this review. Results: Of the selected articles, two studies found acupuncture could offer an alternative to conventional treatment of MCI. Three studies showed some cognitive benefits including, improving functional communication and language function in PSCI. One study found that acupuncture might stimulate neurogenesis after a stroke. One RCT revealed acupuncture with routine care may improve cognitive status and activities of daily living (ADLs) but has limited effects on quality of life in those with VD. Four studied showed mixed results of acupuncture in AD. No major adverse reactions from acupuncture were reported. Conclusion: Acupuncture may improve cognitive function in those with MCI and PSCI. For VD and AD, the evidence is still lacking. More well-structured, large scale double-blinded RCTs are needed with more focus on the different stages of AD.

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme I: Dementia Care Practice and Public Health
Clinical Science

TARCC-Based Project

(52) **COVID-19 and cognitive impairment in the elderly: A Literature Review**

Presenting Author: Seshagiri Rao Veerapaneni, MD
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Seshagiri Veerapaneni

Abstract Background and importance: COVID-19 was declared a pandemic by the World Health Organization on the 11th of March 2020,and it represents an unprecedented immediate but also persistent threat to our health care systems .Emerging data reveals neurological symptoms and subclinical cognitive dysfunction and the development of dementia or worsening of it coming to light in the elderly . Objective: To conduct a literature review on the neurologic characteristics and potential for causation of dementia in the elderly patients with COVID-19. Methods: An exhaustive search of scientific publications, which included original articles(Randomized controlled trials studies, cohort studies, case control studies, cross sectional studies, case reports common case series , on relevant experimental and observational studies, case series) and reports was conducted using the following online databases /online search engines like Pub Med, with search terms used being neurologic manifestations of COVID-19, neurological complications of novel coronavirus 2019, with relevant articles analyzed for a possible neurological syndrome related to COVID-19. Based on specific selection criteria the relationship between COVID-19 and the nervous system was established and a brief narrative literature review performed. Results: There has been convincing evidence that SARS-CoV-2,the etiologic agent of COVID-19 can affect the nervous system with consequent damage and neurologic alterations .These neurologic disorders are grouped into several categories ranging from nonspecific and moderate symptoms such as headaches, myalgias, hypoxemia, to severe symptomology of cerebrovascular disease and intracranial infections with often poor outcomes, with the prospective of cognitive decline and worsening of dementia in the elderly survivors Conclusions: Based on evidence gathered from scientific literature, this review raises a possibility of nervous system involvement in COVID-19 with progression to dementia or worsening of existing Dementia especially in the elderly patients. Longitudinal neurological assessments of patients after recovery will be crucial in understanding the natural History of COVID-19 in the CNS and monitoring for potential neurologic sequalae and long-term effects on causation and worsening of dementia. The literature review also states the need to start investigating the mechanistic link between Alzheimer's disease and COVID-19 for further follow up. Keywords: Dementia, Covid-19, neurodegenerative disease, cognitive decline, neuroinflammation

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme I: Dementia Care Practice and Public Health
Clinical Science

TARCC-Based Project

(53) **Dementia as a poor prognostic factor for severe COVID-19 infection**

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Yousaf Ajam, Prashant Rai, Bhanu Gogia, Tamer Ghanayem, Ayush Singh, Neeharika Thottempudi, Kyra Curtis, Alok Dabi, and Xiang Fang

Background: The coronavirus 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Heath Organization (WHO) in March 2020. Since then the virus has infected millions of people, and hospitalized hundreds of thousands around the world. Patients with dementia are at a higher risk of developing severe infections when infected with viruses. The study was conducted to assess the effect of having a prior diagnosis of dementia on mortality in patients with SARS-coV-2 infection. Method: A retrospective analysis was done on patients admitted to the University of Texas Medical Branch Hospitals between 4/1/2020 - 7/1/2020. Patients were included in the study who tested positive for COVID-19 at admission. A survey tool was developed with using "google forms". The patient's electronic medical records were reviewed by dedicated medical professionals and data was put into the form. Result: A total of 250 patients were screened who tested positive for COVID-19 on admission. 36 patients carried a diagnosis of dementia prior to admission. Unfortunately, there was no documentation of the subtype of dementia, and none of the patients had prior neuropsychological testing. Out of the total number of patients (n=250) 99 needed to be transferred to the intensive care unit, 17 patients with dementia and 82 who did not have dementia OR: 1.44 95% CI 0.71 - 2.93, P-value 0.15). From the total patient group (n=250) a total of 23 patients died, 10 patients from the dementia sub-group and 13 from the non-dementia group (OR: 5.95, 95% CI: 2.37 - 14.92, P-value < 0.05). Conclusion: The results of the study showed that both dementia and non-dementia patients required intensive care monitoring at an approximate equal proportion. However, patients with dementia were at an approximate 6 times higher risk of dying compared to the patients who did not have dementia. The results of the study show that once patients with dementia are admitted to the intensive care unit, they find it harder to be transferred out of the ICU and most patients die compared to non-demented patients.

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme I: Dementia Care Practice and Public Health
Clinical Science

(54) **COVID-19 required modifications to door-to-door recruitment and assessment of cognitive health in a bi-ethnic community: The Brain Attack Surveillance in Corpus Christi (BASIC)-Cognitive project**

Presenting Author: Nelda Garcia BS
Research Intermediate
The University of Michigan

Nelda Garcia, Emily Briceno, Roshanak Mehdipanah, Xavier Gonzales, Steven Heeringa, Daniel Zahs, Deborah Levine, Kenneth Langa, Ruth Longoria, and Lewis Morgenstern

Introduction: At its onset, the NIH funded Brain Attack Surveillance in Corpus Christi (BASIC)-Cognitive community-based study utilized a probability sample door-to-door ascertainment method to examine the prevalence of cognitive impairment among Mexican Americans (MA) and non-Hispanic Whites (NHW) aged 65 or older in Nueces County, TX. Due to the COVID-19 pandemic, protocol adjustments were necessary resulting in a change to a telephone-based sample method. Methods: Prior to COVID-19, households were identified from a two-stage area probability sample of housing units, with use of Census data and ethnicity indicators to aim for an equal balance of MA and NHW sampled households. In-person cognitive screenings were conducted utilizing the Montreal Cognitive Assessment (MoCA). MoCA score eligible (score <26) participants completed further neuropsychological assessment utilizing the Harmonized Cognitive Assessment Protocol (HCAP). Beginning in Mar 2020, in-person research was suspended due to COVID-19. A new phone sample set was selected by matching a sample of addresses against a commercially available database to append telephone numbers (cell or landline) where available. MoCA screenings were modified to the 22-item telephone MoCA (T-MoCA). Individuals with T-MoCA scores of 18 or less completed a Health and Retirement Survey (HRS) version of the Telephone Interview of Cognitive Status (TICS), in addition to selected subtests from the HCAP that are amenable to telephone administration (T-HCAP). HCAP Informant interviews required minimal modification for telephone administration. Results: Original protocol methods (5/1/18 thru 3/13/20) resulted in 10,842 residences visited and the identification of 1856 age-eligible households. 1232 MoCAs were conducted and 351 HCAP respondent/informant study pairs completed. Since telephone recruitment initiation on 4/20/20 and as of 11/30/20, 6535 unique telephone numbers were dialed and 515 age-eligible households were identified. 269 individuals completed T-MoCAs. T-HCAPs began on 10/26/2020 and as of 11/30/20, 31 study pairs have been completed. The phone recruitment method is expected to add an additional 252 study pairs to meet project goals. Conclusions: This large project was able to pivot to a telephone-based recruitment and assessment of community members and demonstrates the feasibility and usefulness for studies of cognitive impairment.

Funding Disclosure: NIH R01NS100687

Conflict of Interest Disclosure: None

Theme I: Dementia Care Practice and Public Health
Clinical Science

TARCC-Based Project

(55) **Developing and evaluating emergency alerts to support data-driven delirium prevention platform for patients with mild cognitive impairment or dementia**

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Justin Rousseau, Daniel Harrell, Eliel Oliveira, Paulina Devora, Janelle Geltman, Robin Hilsabeck, and David Paydarfar

Background: Delirium is a preventable condition 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. Communication gaps often delay implementation of delirium prevention protocols when emergency medical services (EMS) and the receiving hospital are unaware that a patient is at high risk. We sought to design and implement an emergency alerting system for a population of patients known to be at risk for delirium. Methods: Dell Medical School's (DMS) Comprehensive Memory Center collaborated with Austin EMS, and Integrated Care Collaborative (ICC), a regional health information exchange (HIE) in Central Texas, for this project. Following informed consent, we provided identifying patient information with Austin EMS and ICC. Austin EMS's electronic patient care record (ePCR) transmits automated email alerts to our research team if information entered into their ePCR in the field matches the participant information. Austin-EMS also transmits patient information to ICC daily, providing a second alert that identifies an emergency event for a participant by its matching algorithms. Both alerting mechanisms are activated by data entered via routine patient care by EMS. We plan to compare the accuracy of identification of participants receiving care by EMS via the two methods, Austin EMS's ePCR vs ICC. Results: We have established bidirectional data sharing agreements between DMS and both ICC and Austin EMS, and have enrolled 26 participants from the CMC and from the community. Austin EMS's alerts have been operational since August 12, 2020. A feasibility test confirmed that the Austin EMS method automatically alerted the investigators for one emergency event that occurred prior to the start date. We have not received any subsequent alerts. The alerting mechanism from ICC is currently under development. Conclusion: Automated alerts at the time of the initial evaluation by Emergency Medical Services are feasible using a patient matching algorithm and rapid notification either directly via ePCR or via a regional Health Information Exchange. This EMS communication platform can be used for early identification and treatment of patients at risk for delirium.

Funding Disclosure: TARCC

Conflict of Interest Disclosure: None

Theme I: Dementia Care Practice and Public Health
Clinical Science

TARCC-Based Project

(56) **Ambiguity with the diagnosis of Vascular dementia in clinical practice**

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Background: Vascular dementia (VaD) includes a wide spectrum of clinical phenotypes ranging from vascular cognitive impairment to dementia. It is typically defined as a step-like pattern of decline in memory with each vascular insult. It is a type of subcortical dementia with modifiable risk factors and therefore requires critical thinking. Due to its overlapping features and co-existence with Alzheimer's disease (AD) and it is commonly misdiagnosed. However, it is imperative to distinguish the two as the pathophysiology is different and so is the management. Currently, there exist neuroimaging modalities such as MRI (Magnetic Resonance Imaging) brain, PET (positron emission tomography) scan, and DTI (Diffusion Tensor Imaging) which can help distinguish VaD from AD. Methods: We ran a search for "vascular dementia" on our electronic medical record database that is used in our university. A retrospectively chart review of these patients was performed and the data was collected in a Microsoft Excel sheet. Results: A total of 297 patients resulted from the EMR search of "vascular dementia". At the time of this writing this abstract, only 20 charts were reviewed. The age range of the reviewed patients was 63-97 years with 8 males and 12 females. Eleven patients were seen and evaluated by a neurologist in an outpatient setting while the remaining were managed by geriatric/primary care physicians. Ten patients (50%) carried a diagnosis of AD as well. About 5 patients had MMSE (mini-mental status examination) score during a clinic visit at some point and 7 patients underwent formal neuropsychological testing. Of the 20 patients, three had moderate to severe microvascular ischemic changes on MRI brain, 6 had mild microvascular ischemic changes with cortical atrophy and 11 patients did not have MRI brain. None of the patients had PET or DTI scan done. Conclusions: VaD often co-exists with AD; however; misdiagnosis of VaD is a common occurrence in clinical practice. Despite the advancement of neuroimaging techniques and neuropsychological testing, patients with possible vascular dementia do not undergo a thorough workup and are often mislabeled. A timely referral to a behavioral neurologist is strongly recommended for further comprehensive work-up and management for those.

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Conflict of Interest Disclosure:

Theme J: New Treatment Development
Basic Science

(57) **Near-Infrared Light Reduces Neuroinflammation in Hippocampus and Cortex of Diet-Induced Obese Mice**

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Background: Obesity and type 2 diabetes (T2D) are major risk factors for Alzheimer's Disease (AD), which are characterized by neuroinflammation, a key event in neurodegeneration. Hippocampal neuroinflammation, in rodents, correlates with poor memory performance, while in humans, growing evidence shows that obesity increases three times the risk of developing AD. The overall objective of our work is to reduce the impact of obesity/T2D-driven neuroinflammation, which in turn may lead to dementia. Recently, near-infrared light (NIR) has gained growing interest, showing improvement of learning and memory in both humans and animal models. We previously reported that a transcranial delivery of NIR reduced Aβ and Tau pathology and improved memory function in mouse models of AD. Here, we tested whether NIR light may prevent obesity-induced neuroinflammation, in a diet-induced obese (DIO) mouse model. Methods: 5-weeks old wild-type mice were fed a high-fat diet (HFD) for 12 weeks to induce obesity prior the beginning of treatment, which consisted of a transcranial delivery of NIR light for 4 weeks throughout daily sessions of 90 seconds each. After sacrifice, we performed free-floating immunofluorescence of brain slices stained for microglia and astrocytes markers to evaluate glial activation, and quantitative real-time PCR to evaluate the expression levels of inflammatory cytokines and neurotrophic factor BDNF. Results: Immunofluorescence showed that, in both hippocampus and cortex, HFD caused increased expression of CD68 (activated microglia) and GFAP (astrocytic marker), which were reversed by NIR light treatment. Also, PCR analyses showed that HFD caused a significant increase of pro-inflammatory IL-1β and TNF-α, which was reversed by NIR; likewise, the anti-inflammatory IL-10 was increased in HFD mice, likely due to a compensatory mechanism, and returned to basal levels after NIR light treatment. Also, the neurotrophic factor BDNF is increased in HFD mice treated with NIR light, compared to HFD not-treated mice. Conclusions: Our results show a reduction of glial activation and pro-inflammatory cytokines, in both hippocampus and cortex, after NIR light treatment, perhaps driven by a BDNF-dependent mechanism. This evidence poses NIR light as a potential preventive therapeutic approach against obesity-induced CNS deficits that are known to concur to AD neuropathology.

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Theme J: New Treatment Development
Basic Science

(58) **Gene therapy using Aβ variants for amyloid reduction**

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Background: The tortuous path of aducanumab has on one hand reinvigorated the therapeutic potential for targeting amyloid beta (Aβ) and caused well-justified consternation among its critics on the other. If antibody-based therapies like aducanumab are ultimately successful, they come with notable side effects and would require repeated delivery for effective treatment. Alternative strategies can and should be pursued. Peptide-based aggregation inhibitors have been studied for several decades but suffer from poor brain penetrance and rapid proteolysis. Viral expression may offer a means to overcome these limitations by allowing continuous peptide delivery into the brain. In the present study, we investigated whether peptide aggregation inhibitors based on Aβ sequence variants could be effectively vectorized for viral delivery to impact pathology in the APP/PS1 mouse model. Methods: Peptide inhibitors were designed using sequence variants targeting the central hydrophobic region of endogenous Aβ. We built a novel minigene construct to express these variants at the cell surface where peptide release into the extracellular space was dependent on endogenous γ-secretase cleavage. The minigene was placed under control of the CAG promoter and packaged into AAV8 for intraventricular injection into neonatal APP/PS1 and wild-type mice. Animals were harvested 7.5 mo later to assess amyloid load, Aβ levels, and neuroinflammation. Results: We identified two variants, F20P and F19D/L34P, that satisfy four essential features for therapeutic use in vitro: neither variant self-aggregates, while both peptides inhibit aggregation of WT Aβ, promote the disassembly of pre-formed fibrils, and reduce cytotoxicity after Aβ exposure. Intracranial AAV injection at birth resulted in prolonged CNS delivery of variant peptides. When evaluated 7.5 mo later, F20P, but not F19D/L34P, diminished Aβ levels, plaque burden, and neuroinflammation. Conclusions: Our findings suggest that viral delivery of peptide aggregation inhibitors may offer a novel therapeutic strategy for Alzheimer's disease. More broadly our work offers a structure for identifying and delivering peptide variants targeting other proteinopathies.

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Theme J: New Treatment Development
Clinical Science

(59) **Quantifying bilateral prefrontal photoneuromodulation via broadband near-infrared spectroscopy**

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Background and Objectives Transcranial infrared laser stimulation (TILS) is a novel, non-invasive method to neuromodulate metabolic and hemodynamic responses that enhance cognitive function. The objectives of this study were to independently replicate the metabolic and hemodynamic effects of TILS on the ipsilateral prefrontal cortex (stimulated by laser) and to investigate the effects of the laser on the contralateral prefrontal cortex (opposite of stimulation). Materials and Methods Broadband near-infrared spectroscopy (bbNIRS), a safe and non-invasive imaging modality, monitored prefrontal cortex (BA10) changes in oxidized cytochrome c oxidase (CCO), oxygenated hemoglobin (HbO), deoxygenated hemoglobin (HHb), differential hemoglobin (HbD) and total hemoglobin (HbT) during a two-minute baseline, eight-minute TILS (1064 nm, 250 mW/cm2) or sham treatment, and five-minute post-treatment. Data were analyzed on 33 subjects (60.6% female; M = 19.58 years old, SD = 1.08), with 16 receiving sham and 17 receiving TILS. Repeated measures ANOVA evaluated overall effects of treatment and t-tests evaluated temporal effects of treatment. Results TILS caused significant ($p<0.05$) dose-dependent increases in HbO, HbD, and HbT in the ipsilateral prefrontal cortex, which continued to increase through the post-stimulation period. HHb did not significantly decrease relative to the sham condition. Ipsilateral oxidized CCO significantly increased during stimulation at approximately one tenth the magnitude of the hemoglobin concentrations. This increase was significant during the stimulation period and the first minute post-stimulation. No significant hemodynamic or metabolic effects of TILS were found in the contralateral prefrontal cortex. Conclusions These findings support the hypothesized neuromodulation mechanism by which TILS results in cognitive enhancement: dose-dependent photo-oxidation of cytochrome c oxidase that induces a robust hemodynamic oxygenation response, thereby promoting cognitive functioning in the prefrontal cortex. Furthermore, there was ipsilateral vs. contralateral specificity for the metabolic and hemodynamic effects. This study may advance bbNIRS as a novel brain mapping modality and guide research into future neuromodulation applications of TILS.

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Theme J: New Treatment Development
Basic Science

(60) **Immunotherapy for Synucleinopathy**

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Background: Parkinson's disease (PD) is a progressive disorder that manifests clinically through motor and nonmotor symptoms. The principal motor manifestations of PD include bradykinesia, resting tremor, rigidity, and postural instability. There are also non-motor PD signs that can manifest 20 years or more prior to the onset of motor symptoms. PD belongs to a cluster of neurodegenerative diseases called synucleinopathies because brain pathology is predominated by aggregated α-synuclein protein. PD can also be classified as a tauopathy; a class of disorders with intracellular inclusions composed of hyperphosphorylated and aggregated tau protein. An emerging concept in neurodegenerative disease research and diagnosis is that disease pathologies overlap or even form a disease continuum. In this continuum theory, two proteins are central: tau and αsyn. Both form abnormal intracellular inclusions, and mutations in either are sufficient to cause disease and neurodegeneration. Methods: Previously, it has been shown that mice harboring the A53T Asyn mutation exhibit motor, memory, and innate behavioral impairments at 7 months old (MO) that can be reversed by targeting tau oligomers. In this study, we extend this work by studying older animals (9MO) and asking whether dual therapy targeting both tau and Asyn oligomers perform more effectively in ameliorating neurobehavioral deficits. Thus, 9MO homozygous A53T mice were given intravenous tail vein injections of one of the following monoclonal antibodies: control IgG, TOMA, F8H7, or a combination of TOMA + F8H7. Experimental groups were then subjected to a battery of neurobehavioral tests to target exploratory and anxiety-like behavior, muscle strength, motor learning and coordination, and depression-like behavior followed by post mortem evaluation of Asyn and tau pathology. Results: While 9MO homozygous A53T mice displayed exploratory locomotor behavior similar to WT littermates, we found differential efficacy of the immunotherapies on strength and motor coordination. Grip strength and motor deficits (rotarod, gait) were relieved with monotherapy targeting Asyn oligomers and combination immunotherapy, respectively. A depression-like phenotype was revealed with tail suspension yet was unaffected by any of the immunotherapies. Conclusion: These findings indicate that Asyn oligomers underlie motor insufficiencies whereas downstream pathology likely contributes to emotional ill-health that also plagues PD patients.

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