The Wisconsin Alzheimer's Disease Research Center presents

Alzheimer's Disease & Related Disorders Research Day

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POSTER ABSTRACTS

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Wisconsin Alzheimer's Disease Research Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

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1

Association between Cerebrovascular Reactivity and Intravascular Cellular Activation in Postmenopausal Women Following Use of Menopausal Hormone Treatments

Andrew G. Pearson, Muthuvel Jayachandran, Brian D. Lahr, Michael J. Joyner, Virginia M. Miller, Jill N. Barnes

Background: Cerebrovascular reactivity to hypercapnia increases during menopausal hormone treatment (MHT) in postmenopausal women. It is unclear whether the effects of MHT are continued beyond the years of MHT. Cerebrovascular reactivity is associated with vascular activation in postmenopausal women with elevated cardiovascular risk. We hypothesized that prior MHT use would not affect cerebrovascular reactivity 3 years after treatment. We hypothesized that cerebrovascular reactivity would not be associated with markers of intravascular cellular activation in postmenopausal women with low cardiovascular risk who were within 10 years of menopause.

Methods: Cerebrovascular reactivity to hypercapnia was measured in 58 postmenopausal women from the Kronos Early Estrogen Prevention Study at Mayo Clinic 3 years after the cessation of MHT [oral conjugated equine estrogen (oCEE, n=15); transdermal 17β - estradiol (tE2, n=22); or placebo (PLA, n=23)]. Fasting blood was analyzed for a set of 14 activation markers of platelet and endothelial cells, inflammation and thrombogenicity. Principal components analysis was used to reduce these measures to fewer dimensions on which the associations of intravascular cellular activation with cerebrovascular reactivity could be based.

Results: Women were 60±3 years of age. The hemodynamic response was not different among groups. Cerebrovascular reactivity did not differ among women based on previous MHT randomization. The 14 markers of intravascular cellular activation did not differ based on prior MHT assignment. There was no overall association of cellular activation with cerebrovascular reactivity.

Conclusion: The effects of MHT on cerebral microvascular reactivity do not extend beyond the time of menopausal hormone treatment. ◇

2

Association between Resting Cerebral Perfusion and Cerebrovascular Reactivity to Hypercapnia in Healthy Adults

Kathleen B. Miller, Anna J. Howery, Sterling C. Johnson, Jennifer M. Oh, Howard A. Rowley, Jill N. Barnes

Background: Individuals with Alzheimer's disease (AD) and other dementias demonstrate reduced cerebral perfusion and a reduced vasoactivity of the cerebral vessels. It is unclear if cerebral perfusion at rest is directly related to the function of the cerebral vessels. Therefore, the purpose of this study is to determine if cerebral perfusion at rest is related to cerebrovascular reactivity to a vasoactive stimulus in healthy adults.

Methods: 41 cognitively normal, healthy adults (age=37±19 years) participated in this study. Cerebrovascular reactivity to hypercapnia was accessed by administering stepwise elevations of CO_2 while middle cerebral artery velocity (MCAv) was recorded with a transcranial-Doppler ultrasound. Mean arterial pressure (MAP) and end-tidal carbon dioxide ($ETCO_2$) were measured continuously. Cerebrovascular conductance index (CVCi) was calculated as MCAv/MAP. Reactivity was calculated as the linear relationship between $ETCO_2$, MCAv, and CVCi. Global cerebral perfusion was assessed at rest with a pseudo-continuous arterial spin labeling (ASL) sequence on a 3 Tesla MRI scanner.

Results: There was no significant relationship between MCAv reactivity and resting global cerebral perfusion ($r = 0.20$, $p = 0.21$); however, there was a positive relationship between CVCi reactivity and resting global cerebral perfusion ($r = 0.31$, $p = 0.05$).

Conclusion: These results indicate that when blood pressure is considered, individuals with higher cerebral perfusion at rest demonstrate a more robust response to a vasoactive stimulus. Future studies are planned to evaluate the role of cerebral perfusion and cerebral vessel function in the development of AD. ◇

Biology/Physiology

3

Molecular Basis for Chirality-regulated Aβ Self-Assembly and Receptor Recognition Revealed by Mass Spectrometry

Gongyu Li, Lingjun Li

As chiral Aβ peptides with partial amino acid D-isomerization have been detected in AD brains, there is a possibility that D-isomerized Aβ play a vital role in early AD pathogenesis and development. However, since Aβ D-isomerization is age-dependent and is present at low stoichiometry (e.g. less than 10%), the role of chiral Aβ has long been ignored and largely underexplored, in part due to lack of effective tools. In this study, we develop and establish an innovative analytical platform based on ion mobility mass spectrometry (IM-MS) (Figure C1), we discover and characterize the important role of chirality in regulating AD-related Aβ self-assembly and receptor recognition. Benefiting from these rational designs targeting Aβ chiral chemistry, distinct structural and molecular differences have been revealed between wild type and D-isomerized Aβ, including its monomer structure, oligomerization behavior and its receptor-recognition and binding characteristics. In addition to the crosstalking effects among those epimeric Aβ during oligomerization, the differential contributions of the chirality of Aβ N-terminal and C-terminal fragments were also interrogated, suggesting cooperative effects. The current results could facilitate future investigations of novel therapeutic treatments for AD as new insights can be obtained via elucidation of the roles of D-isomerized Aβ in early AD development, diagnosis, and prognosis. ◇

Clinical Practices

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An investigation of various cardiovascular risk factors and their effects on intra-individual cognitive variability

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Background: We sought to examine how lipid pathology and other risk factors influence a sensitive marker of cognitive function previously shown to predict incident cognitive impairment: intra-individual cognitive variability (IICV).

Method: Cross-sectional data has been obtained from 796 participants; 568 cognitively healthy middle-aged; and 207 cognitively impaired older adults. In order to dissociate the effects of cholesterol pathology from the co-morbidities associated with vascular and metabolic diseases, we conducted hierarchical regression models including age, education, and race with fasting lipid values (total cholesterol, triglycerides, HDL), predicting IICV. Next, chronic co-morbidities (Systolic and Diastolic blood pressures, fasting glucose, waist-to-hip ratio (WHR), tobacco use and diabetes) were used to assess for an additive effect on IICV.

Results: Demographic factors were associated with IICV, but lipid values did not have an association with IICV. Unexpectedly, elevated WHR and fasting glucose levels were associated with lower IICV in cognitively healthy middle-aged adults, but a diagnosis of diabetes was associated with increased IICV.

Conclusion: Education and white race had reduced IICV scores in cognitively healthy individuals and 9% of variance in IICV could be explained by those demographic covariates. Lipid values did not statistically explain any variance in IICV. Fasting glucose, WHR, and non-diabetic status were negatively associated with IICV. For the cognitively impaired individuals, increased age and reduced education were significantly associated with increased IICV scores. Contrary to expectations, lipid pathology was not associated with IICV but markers of metabolic health & demographic factors were associated with cognitive variability. ◇

5

A Qualitative Analysis of Coordinator Perceptions of the Consent Process: Lessons Guiding the Development of an Electronic Consent Platform

Erin Chin, Christine Suver, Jennifer Hamann, Amy Truong, Megan Doerr, Dayne Legreid, James Lah, Felicia Goldstein, Cecelia Manzanares, Hanna Blazel, Dorothy Edwards

Background: The informed consent process is vital to performing ethical human subject research. Typically, consent forms are too long, burdensome and do not necessarily meet the needs of participants from groups underrepresented in research. Study coordinators have a unique role in facilitating the consent process, and they report difficulties retaining participant attention and addressing misinformation. To prepare for the development of an electronic consent we examined the current paper consent from the perspective of research study coordinators at the University of Wisconsin-Madison and Emory University Alzheimer's Disease Research Centers (ADRC). Each institution enrolls healthy adults and those with mild cognitive impairment and Alzheimer's disease.

Methods: Interviews were completed with ADRC study coordinators in a private setting, following an interview guide to allow a semi-structured approach that encouraged open conversation. Coordinators reviewed their respective consent document in order to elicit feedback on past experiences while consenting study participants. Interviews with twelve coordinators, two participant screeners and one outreach specialist were recorded, transcribed and coded.

Results: Key themes were detected upon the analysis of the coordinator interviews. Comments such as the following were positive, "For the most part, they all go well… people seem very receptive to everything I'm saying." However, barriers and coordinator adaptations were also uncovered. Data shows that 93% of the coordinators were asked follow up questions about the biomarker procedures, 80% on study logistics and duration and 67% were asked about physical pain. Common barriers include participant inattention, study complexity and therapeutic misconceptions. Due to these obstacles coordinators adapt the process to the perceived needs of the participant. Adaptations may include cadence, vocabulary, use of supplemental materials, order of topics and amount of information presented. However well intentioned, coordinator adaptations may not address participant needs.

Conclusion: Study coordinators report consent forms are too long, complex, and contain unnecessary medical terminology. These findings reflect the consent process is not taking into consideration the needs and literacy of the participants. In exploring an electronic approach, we hope to improve comprehension by allowing participants to have control over the order and level of detail of information presented to them. ◇

6

Caregiver Kits from the Library

Melissa Roelli, Librarian

The Mount Horeb Public Library created resources for caregivers of people with memory loss. These kits, filled with a variety of books, pictures, videos, music and other items, were created to help inspire connections, spark memories and offer activities to do with people experiencing memory loss. ◇

7

Perspectives of VA Mental Health Providers on Working with Older Adults with Dementia and their Caregivers

Wyman, M.F., Voils, C.I., Trivedi, R., Goldman, D., Boyle, L., Umucu, E., Zuelsdorff, M., Johnson, A.L., & Gleason, C.E.

Background: Mental health (MH) providers hold professional competencies relevant to dementia care and may help address geriatric workforce shortages. However, most do not have dementia-specific training. To inform the development of continuing education curricula, we surveyed MH providers about working with persons with dementia (PwD) and their caregivers.

Method: N=65 MH providers (response rate 82%) in a Veterans Affairs (VA) outpatient clinic completed a questionnaire on beliefs, experience, and perceived barriers to serving PwD and caregivers, and competence to manage risk of harm to self/others in PwD. Respondents with caseloads comprising >50% versus <50% older adults were compared.

Results: Most providers served PwD but had minimal experience in caregiver engagement. Respondents rated relevant skills as highly important, but one-third reported no or minimal confidence in providing services to this population. Half (50.7%) reported low competence for managing risk of harm in PwD. System inadequacies and training deficits were identified as key barriers, and interest in dementia training was high. Providers serving >50% older adults endorsed greater competence to manage risk ($\chi 2=6.25(1)$, $p=.012$), but endorsed similar confidence in and barriers to service provision as those serving <50%.

Conclusion: MH providers represent an underutilized resource in dementia care Providers report modest self-confidence in providing MH services to PwD and caregivers and note multiple barriers to providing care. However, they place high importance on having skills to provide services and receiving further training. Our findings highlight the need to develop provider trainings and to address system-level barriers in MH settings. ◇

8

The Construct Validity of a New Screening Measure of Functional Cognitive Ability

Muhammad O. Al-Heizan, MS; Gordon Muir Giles, PhD; Timothy J. Wolf, OTD, PhD; and Dorothy Farrar Edwards, PhD

This study evaluated the construct validity of the Menu Task (MT): a new performance-based screening measure of functional cognition. We enrolled 114 community dwelling adults (55 years or older) in the study: all participants completed the MT and four other neuropsychological screening measures. Construct validity was evaluated using a three-step hierarchical regression model with the MT as the dependent variable. Demographic control variables were entered at step 1, followed by the Brief Interview of Mental Status (BIMS), and the Trail Making Test A (TMT A) at step 2, and finally TMT B and the Montreal Cognitive Assessment (MoCA) at step 3. It was hypothesized that measures sensitive to executive functioning (TMT B and MoCA) would significantly explain MT performance after controlling for demographic variables and adding measures of cognitive function to the model, providing additional evidence for construct validity of the MT. All three steps of the model were statistically significant ($p < 0.01$). Inclusion of measures sensitive to executive function in step 3 explained 30% of variability in MT score (adjusted $R2 = 0.30$). Our findings provide further empirical support for the construct validity of the MT, and offer implications for the use of the MT in acute and post-acute care settings. ◇

9

Documentation of Dementia Diagnoses in the Emergency Department Among Patients Presenting with Chest Pain

Sarah A Keller, BA, Timothy R. Holden, MD, MS, Manish N. Shah, MD, MPH, Laura M Block, BS, and Amy J. Kind, MD, PhD

Background: Patients with dementia present more frequently to the emergency department (ED) than their non-cognitively impaired counterparts. Failure to recognize dementia in the ED could set patients on non-goal concordant diagnostic pathways. Our objectives were to determine how often dementia is recognized and documented in the ED for patients with known dementia diagnoses, and to identify whether the presence of a caregiver or an activated health care power of attorney (AHCPOA) influences dementia documentation.

Method: We retrospectively assessed records of patients 65 and older presenting to the ED with chest pain between 2012 and 2015 for prior dementia diagnoses identified through medical records and billing claims. Abstractors reviewed ED documentation created by clinicians to determine if the dementia diagnosis was recognized and documented by ED providers, the physical presence of a caregiver, and AHCPOA status.

Result: The sample included 241 patients with dementia (median age of 82; 57% female). Twenty-five percent had an AHCPOA, and 42% had a caregiver present. Dementia diagnoses were documented by providers for 51% of patients. Having an AHCPOA ($p<0.0001$) was a predictor of dementia documentation but having a caregiver present was not associated with such documentation ($p=0.29$).

Conclusion: Half of all patients with dementia presenting to the ED with chest pain do not have a dementia diagnosis documented by providers. AHCPOA documents may be helpful in promoting documentation. Additional study is needed to assess whether lack of documentation is associated with a lack of clinician awareness of the dementia diagnosis or with non-goal concordant care. ◇

10

Screening for Functional Cognition Using a Simple to Score Performance-Based Test of Cognition and Medication Management

Timothy Marks, OTR, Vanessa Everson, Meaghan Leighton, Shelby Manor, Lionel Palomer, Guadalupe Rivas, Muhammad Al-Heizan, OT, Gordon Giles, PhD, Dorothy Farrar Edwards, PhD

Objectives: Occupational therapists assess functional cognition which is defined as the integration of thinking and performance skills needed for independence in instrumental activities of daily living (IADL). This study compares performance on three functional cognition screening measures to performance on cognitive screening measures and on a functional cognition assessment known to predict community living skills.

Methods: Community dwelling adults age 55 and older (n = 185) were administered the Brief Interview of Mental Status (BIMS), Trail-Making Tests (TMT) A and B, Montreal Cognitive Assessment (MoCa), the Mini-Cog, the Medication Transfer Screen-Revised, the PASS Medication Management, Shopping and Checkbook Balancing tasks (PSCT), and the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory Scale (ADCS), a measure of basic and IADL. ROC analyses were computed for each screening measure using the PASS shopping and checkbook balancing tasks (PSCT) combined cues as the index measure. Area under the curve (AuC), sensitivity, and specificity were computed for each measure.

Results: The Medi-Cog most accurately identified individuals impaired on the PSCT. The Medi-Cog demonstrated an AUC (area under the curve statistic) of .82, higher than the Mini-Cog (.75) or the MTS-Revised (.73). A sensitivity of .71 and a specificity of .78 was obtained for classification as impaired on the PSCT task, using a cut score of 9 on the Medi-Cog.

Conclusion: The Medi-Cog demonstrated predictive and discriminant validity in addition to the best combination of sensitivity and specificity than the other screening measures in identifying impairment on the PSCT subtasks. ◇

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Beta-amyloid status is associated with longitudinal connected speech and language in cognitively unimpaired adults

Kimberly D Mueller, Rebecca Koscik, Erin Jonaitis, Elizabeth Dunn, Erin Hackett, Bruce Hermann, Tobey Betthauser, Brad Christian, Sterling Johnson

Objective: Although there is a body of evidence showing changes to discourse in Alzheimer's disease (AD) dementia, little is known about discourse changes in preclinical AD. Our objective was to determine if beta-amyloid status was associated with longitudinal discourse patterns in cognitively unimpaired (CU) adults.

Participants/Methods: 178 CU participants from the Wisconsin Registry for Alzheimer's Prevention (WRAP) with longitudinal connected speech-language (CSL) and [11C]Pittsburgh Compound B (PiB) imaging. We extracted CSL measures and determined amyloid+/- using a previously established cutoff of >=1.19 from global PiB-DVR. Method: Linear mixed-effects models with CSL measures as outcomes and AB as predictor.

Results: Participants had a mean(sd) age of 64(6) at 1st speech sample, 17(3) years of education, 121 (68%) were female, and 25 (14%) were AB+. Significant interactions between AB and age estimated that MLU was 0.85 lower with each year older in the AB+ group vs 0.11 higher in the AB-group ($p < .001$); similar results were seen for usage of unique words ($p = .02$) and total words ($p = .003$). At centered age of 63, Aβ+ was associated with higher mean length of utterance (MLU) ($p<.001$) and total words ($p<.001$) and lower open/closed class ratio ($p=.03$).

Conclusion: In this CU group, discourse measures worsened more rapidly in the AB+ vs AB- group. The speech samples were quick and inexpensive to administer. If we achieve future replication of findings, this suggests that CSL may be a practical and sensitive tool to add in clinical and research settings investigating preclinical AD. ◇

12

Difference Analysis of DWI and Cortical Thickness in the Alzheimer's Disease Connectome Project

Nagesh Adluru, Veena A. Nair, Jennifer M. Oh, Gyujoon Hwang, Vivek Prabhakaran, Shi-Jiang Li, Andrew L Alexander, and Barbara B. Bendlin

Background: We conducted analysis of diffusion weighted (DW) and T1-weighted MRI data from the Alzheimer's Disease Connectome Project (ADCP) to examine microstructural and cortical thickness differences among three diagnostic groups: cognitively unimpaired (CU), mild cognitive impairment (MCI), and Alzheimer's disease dementia (AD) in two age categories for both the sexes.

Methods: Participants (N=73) underwent connectome quality MRI. Diffusion tensor imaging measures in regions from JHU atlas were estimated from the DWI data. FreeSurfer based processing of T1-weighted data was used to estimate the cortical thickness in regions from Destrieux atlas. A difference analysis approach was applied to test for pairwise mean differences between the three diagnostic groups for each age category, and sex across all regions. Instead of performing the analysis directly on the distributions of mean measures in the regions, the analysis is performed on the distributions of these pairwise mean differences in all the regions jointly. Intuitively, such pairwise differences can take advantage of the inherent dependencies among the data to better estimate the effects of interest.

Results: White matter microstructural differences among the three groups were observed among younger participants (55-72.5 years), while gray matter cortical thickness differences were observed among the older adults (72.5-90 years). Differences were also more pronounced in the males compared to females. The difference analysis approach showed greater sensitivity compared to traditional mean analysis approach.

Conclusion: We identified diagnostic group differences in the bivariate space of white matter and gray matter imaging features (derived using pairwise differences) of AD. Longitudinal data collection is needed to further examine the temporal trajectories of white matter and gray matter change across the development of AD. ◇

13

Neurofibrillary tangles and beta-amyloid plaques measured by [F-18]MK-6240 and [C-11]PiB are associated with retrospective cognitive decline in WRAP participants

Tobey J Betthauser, Erin M Jonaitis, Rebecca L Koscik, Samantha L Allison, Karly A Cody, Claire M Erickson, Alexander K Converse, Dhanabalan Murali, Todd E Barnhart, Charles K Stone, Lindsay R Clark, Bradley T Christian, Sterling C. Johnson

Background: This work investigates the association between PET measured NFTs, AB plaques and retrospective cognitive trajectories, and associations between these biomarkers and other biological, demographic and cognitive factors in persons cognitively unimpaired at their baseline WRAP visit.

Methods: Individuals (N=159; 59±6 years at baseline composite) recruited from WRAP underwent T1-weighted MR, [F-18]MK-6240 and [C-11]PiB PET imaging, and longitudinal cognitive assessments. Four biomarker groups (A+/-, T+/-) were established based on PiB (Global DVR>1.19) and MK-6240 (entorhinal cortex SUVR>1.27) PET. A preclinical Alzheimer's cognitive composite (PACC-3: mean of z-scored RAVLT Total, WMS-R Delayed Recall, WAIS-R Digit Symbol) for each assessment was used with a linear mixed effects model (random person-level slopes and intercept) to test for differences in cognitive trajectories by group. Group differences in demographics, select neuropsychological tests, and biomarkers were also investigated.

Results: The group×time interaction was significant wherein the A+/T+ group had steeper cognitive decline than all other groups (Tukey-adjuset post-hoc). Groups did not differ by sex, race, or dementia family history, but did differ in frequency of APOE-e4 carriers. Systolic blood pressure and hippocampal volume did not differ by group at baseline or last assessments. RAVLT Total, WMS-R Delayed Recall, self-reported severity of memory problems, PACC-3 and the frequency of MCI differed by group at last assessment, but MMSE, self- and informant-reported memory problems, and WAIS-R Digit Symbol did not.

Conclusion: Concurrent NFT and AB pathophysiologies appear to contribute to cognitive decline prior to clinical impairment. The PACC-3 may be sensitive to early pathophysiological processes during preclinical AD. ◇

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Cerebral glucose uptake in the context of peripheral insulin

Gilda E. Ennis, Jennifer M. Oh, Nancy Davenport-Sis, Chase Taylor, Bradley T. Christian, Nathaniel Chin, Sanjay Asthana, Sterling C. Johnson, and Barbara B. Bendlin

Background: Insulin resistance (IR) has been related to cerebral glucose hypometabolism in cross-sectional research but longitudinal studies are lacking. A consequence of IR is increased insulin secretion (IS), but its relationship to cerebral metabolism is unknown. We hypothesized that higher baseline IR and IS in healthy adults would be associated with lower average cerebral glucose uptake and greater decline over time.

Methods: Participants were enrolled at the Wisconsin ADRC (P50AG033514). Insulin and glucose from a 2-hour OGTT at baseline were used to calculate measures of IR and IS. A subsample of participants underwent fluorodeoxyglucose PET at baseline and 2 years later. Regions of interest (ROIs) (scaled to cerebellum-pons) vulnerable to AD were examined. Repeated measures ANOVAs were used to determine group and within-person differences in FDG uptake (N = 28).

Results: There was a significant within-person decrease in cerebral FDG uptake in the lateral temporal lobe and supramarginal gyrus (ps < .01). Within-person FDG uptake across time did not significantly differ by IR or IS group; however, average regional FDG uptake did. The higher IR and higher IS group had, respectively, less FDG uptake in the angular gyrus and posterior cingulate (ps < .05).

Conclusions: Higher IR and IS groups had significantly lower average regional cerebral glucose uptake but did not differ from lower IR and IS groups in within-person cerebral glucose uptake. Lower cerebral glucose uptake may be an indicator of synaptic dysfunction. Additional research is needed to determine mechanisms linking IR and IS to cerebral glucose metabolism. ◇

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Modeling PiB PET trajectory groups identifies a subgroup with PiB beta-amyloid accumulation near age 50 and predicts MK-6240 SUVR

Rebecca L. Koscik; Tobey J. Betthauser; Erin M. Jonaitis ; Lindsay R. Clark; Samantha Allison; Kimberly D. Mueller; Bruce P. Hermann; Jennifer D. Poetter, Leah Sanson, Heather Shouel, Nathaniel A. Chin; Bradley T. Christian; Sterling C. Johnson

Background: The timing of detectable beta-amyloid plaque and neurofibrillary tangle (NFT) accumulation is unknown. This study identified PiB PET-based beta-amyloid trajectory groups in late middle-aged persons, estimated PiB(+) age, and related these to MK-6240 SUVR.

Methods: Participants from the Wisconsin Registry for Alzheimer's Prevention (WRAP) with longitudinal [C-11] PiB PET scans were included in pattern mixture modeling to identify age-based PiB trajectory groups (n=167; modeling mean PiB DVR in 8 cortical regions ("global PiB", cerebellum GM reference, Logan graphical analysis). Trajectory model outputs were used to calculate individualized estimated PiB(+) ages ("est_PiB(+) age", global PiB≥1.2). MK-6240 SUVR (70-90min, inferior cerebellum GM reference) was compared across PiB trajectory groups in a subset (n=130); est_PiB(+) age was investigated as a predictor of MK-6240 SUVR (entorhinal cortex, hippocampus).

Results: Four PiB trajectory groups were identified: the largest (72%) having no predicted PiB-accumulation and three with differing est_PiB(+) ages and accumulation rates. Groups with younger est_PiB(+) ages had more APOE-ε4 carriers and worse cognitive status. MK-6240 SUVR differed between PiB trajectory groups and began increasing after est_PiB(+) age. The difference between est_PiB(+) age and MK-6240 scan age was 10.4 years earlier in individuals with elevated hippocampal MK-6240 SUVR (p=.002, 95% CI=4.1-16.7).

Conclusions: Beta-amyloid accumulation potentially begins in the early 50's, particularly among APOE-ε4 carriers. Years PiB(+) predicted MK-6240 SUVR in Braak-associated regions and suggested that PET-measureable amyloid plaques precede measurable NFTs by ≥4 years. PiB trajectory models may allow earlier identification of persons at-risk of developing further AD pathophysiology or AD-dementia. ◇

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Neighborhood Disadvantage is Associated with Neuropathologically Confirmed Alzheimer's Disease

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Background: Social determinants of health, such as neighborhood disadvantage, have been linked to an increased risk of clinical dementia syndrome; however, their association with neuropathologically confirmed Alzheimer's disease (NPC-AD) remains unknown.

Objective: To investigate the association between neighborhood disadvantage and NPC-AD cases in two Alzheimer's Disease Research Center (ADRC) brain banks.

Method: The study included all brain bank participants with an available non-institutional address at the time of death (N=434). Addresses were geocoded and linked to the Area Deprivation Index (ADI) state ranking, a validated measure of US neighborhood disadvantage. All neuropathological data were collected via NACC methodologies, using neuritic and diffuse plaque presence on neuropathological exam to determine NPC-AD.

Result: There was no significant difference in mean age or proportion of male participants between the two groups. However, significant differences were found in amyloid plaque burden, whereby the more disadvantaged group had a higher proportion of both neuritic and diffuse plaques. As compared to those from the least disadvantaged 80% of neighborhoods, participants from the most disadvantaged 20% of neighborhoods had higher adjusted odds of NPC- AD (Adjusted OR=5.24, [95%CI: 1.12, 20.09], p=0.034).

Conclusion: Living in a highly disadvantaged neighborhood at the time of death is associated with NPC-AD for participants within two ADRC brain banks. This study adds to the growing literature that neighborhood disadvantage, a potentially modifiable and directly targetable social determinant of health, may be associated with an increased risk of AD. ◇

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A mediation analysis of the relationship between white matter hyperintensities, CSF biomarkers, and cognition in cognitively unimpaired and impaired adults

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Background: White matter hyperintensities (WMH) of presumed vascular origin are indicators of small vessel disease and ischemia, and appear to contribute to cognitive decline and dementia. This study evaluated how WMH are linked with AD pathology using a statistical mediation analysis of the relationship between WMH, CSF biomarkers of AD, and cognition.

Method: 215 participants (mean age of 64 yrs, 27% dementia or MCI due to AD, 73% cognitively unimpaired) from the Wisconsin ADRC underwent MRI (WMH measurement), lumbar puncture, and cognition assessment including MMSE (global cognition) and WAIS-R Digit Symbol (executive function). CSF biomarkers included Aβ42/40 ratio, p-tau, and t-tau, i.e., markers for β-amyloid clearance, hyperphosphorylation of tau, and neurodegeneration, respectively. Structural equation modeling of path models tested the effect of WMH on cognition that is mediated through CSF biomarkers.

Result: In the single mediator models, higher WMH significantly predicted lower CSF Aβ42/40 ratio, higher p-tau, but did not reach significance for t-tau. Lower CSF Aβ42/40 ratio, higher p-tau and t-tau predicted lower MMSE. Significant mediation paths through CSF Aβ42/40 ratio and p-tau were identified. The predictions and mediations remained significant in the subsequent model that included both CSF Aβ42/40 ratio and p-tau as mediators. CSF Aβ42/40 ratio showed larger mediation effect than p-tau. WAIS-R Digit Symbol had similar findings.

Conclusion: The findings supported the effects of WMH on cognition through β-amyloid clearance and hyperphosphorylation of tau, with the former being a stronger pathway. Future studies including longitudinal data would allow further evaluation and refinement of the theory. ◇

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Sleep, cognition, and beta-amyloid in adults with Down syndrome

Karly Cody, Brianna Piro-Gambetti, Matthew Zammit, Iulia Mihaila, Shahid Zaman, Dana Tudorascu, Annie Cohen, William Klunk, Barbara Bendlin, Sterling Johnson, Ben Handen, Brad Christian, and Sigan Hartley

Background: Poor sleep has been associated with increased AD-related pathology and cognitive impairment in the general population; however, the relationship between beta-amyloid accumulation, cognition and sleep in the DS population remains unknown.

Methods: Forty-eight adults with DS wore an actigraph accelerometer continuously over a seven-night period. Actigraph variables of interest were averaged over the number of nights of wear and included: total sleep time, wake after sleep onset, sleep fragmentation index, sleep efficiency, and number of awakenings. Prior to wearing the actigraph (5.8±0.9 months), participants underwent MRI and [11C]PiB PET imaging (SUVR; cerebellar GM reference region). Participant cognitive status (mild cognitive impairment (MCI), dementia, no MCI/dementia) was assessed using a case consensus process and direct cognitive assessment.

Results: On average, participants had poor sleep-including sleeping less than seven hours a night and spending nearly two hours awake after sleep onset. While the cognitively impaired group showed generally worse sleep health, no significant differences were observed between diagnostic groups in the actigraph sleep variables. Similarly, partial correlations, showed no significant associations between the actigraph sleep measures and striatal or global PiB SUVRs.

Conclusion: These adults with DS showed severely disordered sleep; however, the measured actigraph sleep features were not related to PiB PET beta-amyloid burden and did not differ between cognitive diagnostic groups. With the ubiquity of beta-amyloid and disordered sleep in adults with DS, the discrimination of the effects of poor sleep on amyloid and cognition may require a larger sample size or a more quantitative measure of sleep. ◇

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Aging-Related Protein Misfolding and Neurodegenerative Diseases

Tsao FHC, Barnes JN, Amessoudji A, Li ZH, Meyer KC

Background: Aging-related misfolded proteins appear to play critical roles in neurodegenerative diseases including Alzheimer's disease (AD).

Methods: A secretory phospholipase A2 (sPLA2)-liposome assay was used to determine the albumin-fatty acid binding activity (Alb-FA-BA) in the sera of young control volunteers (YC) (average age 24), older control subjects (OC), and individuals with mild cognitive impairment (MCI) or patients with AD (average age 74). All components were mixed either at 0oC (Assay-1) or 24oC (Assay-2) prior to being assayed.

Results: Denatured albumin increased its Alb-FA-BA due to hydrophobic effect. The specific activity of Alb-FA-BA (per µg albumin) of OC, MCI and AD was 50% higher than that of YC in Assay-2 ($p = 2.4 \times 10^{-9}$), perhaps because of the presence of misfolded albumin in the sera of older subjects. Also, Alb-FA-BA in the sera of all subjects determined by Assay-2 was 2-3-times higher than that determined by Assay-1, likely due to increasing liposomal membrane fluidity in Assay-2. The specific activity of Alb-FA-BA of OC, MCI and AD in cerebrospinal fluid (CSF) was nearly twice as high as the values determined by either Assay-1 or Assay-2 for serum, suggesting a higher proportion of misfolded albumin in CSF versus serum.

Conclusion: The results of this study suggest that aging-related misfolding of albumin or protein (i.e. oligomers) may elicit membrane degradation in the presence of an inflammatory response and active sPLA2 combined with high membrane fluidity. We suggest that such interactions may represent an important mechanism in the pathogenesis of aging-related dementia and AD. ◇

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The ATN framework and polygenic scores of AD endophenotypes

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Background: GWAS of endophenotypes are a powerful tool for understanding disease biology. Polygenic scores (PGS) combine the effects of multiple variants from GWAS and can uncover pleiotropic effects as well as be highly predictive. Recent NIA-AA guidelines for AD research reflect growing trends in the field to better understand biological factors of disease, by utilizing a biomarker-based framework (A=amyloid, T=tau, N=neurodegeneration) to classify individuals. The goal of this study was to construct PGS from AD-endophenotypes and test them against AT(N) biomarkers. Although currently the guidelines incorporate imaging and CSF biomarkers, blood or saliva may be leveraged (via genotyping) with PGS constructed from endophenotype GWAS to help identify individuals at risk and uncover genetic overlap between biomarkers.

Methods: Summary results obtained from large GWAS of CSF Aβ42, tau, ptau181 (N=3146), and hippocampal volume (HV; N=33,536) were used to calculate weighted-PGS for participants enrolled in the Wisconsin Registry for Alzheimer's Prevention (WRAP) who had undergone structural T1-weighted MRI scans (N=429). PGS were then regressed against intracranial volume-normalized HV, correcting for age, sex, scanner, and head coil.

Results: Preliminary best-fit PGS analyses revealed that PGS calculated from the HV GWAS (clumping r2=0.1, Pthreshold=1) accounted for ~3.0% of the HV variance in WRAP participants ($P=1.53\times10^{-4}$). Additionally, best-fit PGS from the top SNPs for CSF ptau181 explained 0.9% of the HV variance observed in WRAP (P=0.041); two of these loci were associated with HV in WRAP (rs35055419[C]:β=161.4, P=0.002; rs9527039[C]: β=-352.6, $P=6.35\times10^{-4}$). There was no association between HV and APOE genotype.

Conclusions: PGS calculated from a large HV GWAS predicted ~3% of the variance of HV in a much smaller sample enriched for AD risk. Interestingly, PGS calculated from top SNPs for CSF ptau181 accounted for almost 1%of HV variance. Two of the lociassociated with ptau181 were also associated with HV, suggesting that biological pathways underlying neurodegeneration observed in AD may be related to tau hyperphosphorylation. We are testing PGS against CSF and imaging biomarkers in additional cohorts including the Wisconsin ADRC. Future work will determine the predictive power of different biomarker PGS in classifying individuals within the AT(N) framework. ◇

21 Socioeconomic Status and Brain Health: The CARDIA Study

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Background: Low socioeconomic status (SES) has been linked to a variety of poor lifestyle factors and greater risk of developing Alzheimer's dementia (AD). Recent research suggests SES may be related to alterations in brain health, however, extant studies have not investigated modifiable risk factors that may contribute to the observed associations. The aims of this study were to i) investigate whether SES is related to brain volume in AD relate regions, and if so, ii) determine whether this relationship is mediated by modifiable factors that are known to associate with risk of AD.

Methods: We studied 645 biracial (41% black) participants (mean age 55.3±3.5) from the Coronary Artery Risk Development in Young Adults (CARDIA). SES was operationalized as a composite measure of annual income and years of education. Grey matter volume was estimated within the insular cortex, thalamus, cingulate, frontal, inferior parietal and lateral temporal cortex. Risk factors of interest included hypertension, obesity, depression, cognitive activity, physical activity, smoking, diet, alcohol consumption and diabetes. Multiple linear regression tested the association between SES and brain volume. Sobel mediation analyses determined if this association was mediated by modifiable risk factors. All models were age, sex, and race adjusted.

Results: Aim i) regression analysis revealed SES was positively associated with brain volume (Figure 1; β=.118 SE=.039; p=.002). Aim ii) from the nine risk factors investigated, smoking and depression were identified as two potential mediators due to their significant relationships with SES and brain volume (all p<.05). A Sobel mediation analysis determined smoking significantly mediated the relationship between SES and brain volume (Figure 2; p=.016). With respect to brain volume, smoking accounted for a significant amount of variance (β=-.116 SE=.065; p=.01) that was previously attributed to SES.

Conclusion: Targeting SES disparities could be a promising means to improve brain health and may decrease vulnerability for AD. Notably, smoking appears to partly explain the adverse effects of low SES on brain volume. ◇

22 Disclosing beta-amyloid status to cognitively unimpaired late-middle aged adults

Claire Erickson, Nathaniel Chin, Lindsay Clark, Sterling Johnson

Biomarkers of Alzheimer's disease (AD) appear years, perhaps decades, before clinical manifestation of AD. By utilizing positron emission tomography (PET) and CSF analysis, we can identify amyloid and tau, two of the main proteins implicated in Alzheimer's disease, in the earliest stages of AD. While the role of these proteins in disease is still not fully understood, more protein accumulation is associated with advanced stages of AD dementia. With the new NIA-AA guidelines for defining AD, elevated markers of both proteins are defined as preclinical AD. Recently, studies have begun disclosing amyloid status to cognitively unimpaired participants so that individuals can partake in prevention and clinical drug trials. Despite initial rises in anxiety and other distress measures among amyloid elevated individuals, these negative effects of amyloid disclosure are mild and subside after a few months. Thus far, disclosing amyloid status to participants has been a safe and well-tolerated process in cognitively unimpaired participants. Here, I will present our planned disclosure process for the Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort. We are interested in disclosing amyloid status to cognitively unimpaired research participants who express a desire to know this information. Our study is novel in its personal AD risk assessment health education visit and follow-up to assess if people modify their behaviors after learning their amyloid status. Ultimately, disclosing amyloid status to these participants will provide empowering information that may lead to improved future planning and health lifestyle changes that may enhance brain health and possibly alter disease trajectory. ◇

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Gut microbial metabolites in cerebrospinal fluid are associated with biomarkers of Alzheimer's disease pathology

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Background: Cognitively unimpaired (CU) and Alzheimer's Disease (AD) dementia patients harbor divergent fecal bacterial communities, and several bacterial abundances covary with AD pathology, as measured via cerebrospinal fluid (CSF) (Vogt et al. 2017). Here we tested whether gut flora-associated metabolites are 1) measurable in CSF, 2) differentially present across the AD spectrum, and 3) associated with AD biomarkers.

Methods: The Wisconsin Registry for Alzheimer's Prevention and the Wisconsin Alzheimer's Disease Research Center collected CSF from patients via lumbar puncture [CU (N=334); AD mild cognitive impairment (MCI) (N=35); AD dementia (N=40)]. CSF metabolites were quantified using Metabolon's UHPLC/MS metabolomics platform, and Spearman's partial correlations examined the relationship between metabolites associated with gut microbiota and AD biomarkers, controlling for age, sex and assay batch.

Results: Twenty-five gut flora-regulated metabolites were identified in CSF. Sixteen were more abundant in AD-dementia patients compared to controls (Kruskal-Wallis, $p<.05$; Wilcoxon, $p<.05$). More significant metabolite/AD-biomarker associations were present in the CU group compared to AD-dementia patients (fifteen and nine, respectively; all unadjusted $p<.05$).

Conclusions: This exploratory analysis is the first demonstration that numerous gut bacteria-modulated metabolites are detectable within CSF. Several abundances differ across diagnoses and correlate with AD CSF biomarkers, even before dementia development. Nevertheless, these results should be interpreted cautiously. Metabolite abundances expressed here are raw m/z ratios; absolute measurements would refine observed associations. Additionally, since microbial metabolites have only recently been discovered in CSF (Del Rio et al 2017), their impact on AD is unknown. Mechanistic studies are needed to clarify gut microbes' roles in AD. ◇

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CSF Markers of Neurodegeneration Are Associated with Quantitative T1

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Background: Quantitative T1 mapping can be useful in measuring subtle neural injury potentially undetectable with conventional MRI. MPnRAGE facilitates the generation of hundreds of T1-weighted contrast images for the precise estimation of T1 (Kecskemeti et al., 2016). Here, we investigate whether CSF biomarkers of neurodegeneration and AD are associated with quantitative T1 to determine the potential utility of T1 mapping for tracking neurodegeneration.

Methods: Cognitively unimpaired participants (n=45, age = 66.56 ± 5.82 years) from the Wisconsin Registry for Alzheimer's Prevention underwent MPnRAGE MR. Average gray and white matter T1 (in ms) was extracted from processed quantitative T1 maps. Multiple regression models were estimated to determine relationships between T1 and CSF biomarkers of neurodegeneration and AD including total tau, neurogranin, neurofilament light protein (NFL), phosphorylated tau, and Aß42/Aß40 ratio, while controlling for age, sex, APOE status, and time between MRI and CSF sample collection.

Results: Higher total tau was associated with higher T1 in gray matter ($b = 62.735$ [4.22, 121.25], $F(1, 39) = 4.703$, $p = 0.036$). There were no significant relationships between phosphorylated tau, NFL, and Aß42/40 ratio and quantitative T1 in gray and white matter, although higher neurogranin was unexpectedly associated with higher T1 in white matter ($b = 94.346$ [9.503, 179.188], $F(1, 37) = 5.077$, $p = 0.03$).

Conclusions: CSF tau was associated with higher quantitative T1, potentially suggesting myelin loss and/or increased water content due to neurodegeneration. Additional studies with larger samples will determine whether quantitative T1 may be useful for mapping neurodegeneration in the context of Alzheimer's, and the NIA-AA research framework. ◇

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Distinguishing Executive Function from Processing Speed in a Parkinson's Disease Cohort

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Background: Parkinson's Disease (PD) affects both cognitive processing and movement speed. Executive function is an umbrella term that broadly describes higher-order complex cognitive processes necessary for accomplishing complex goals. Pinpointing a precise definition and operationalization of executive function is a topic of much nuanced debate. However, many commonly used assessments of executive function involve a timing or a speed component. The goal of our analysis was to isolate a group of PD patients who showed consistent slowness on measures of movement speed, and determine to what extent speed deficits were correlated with measures of executive function — both measures that explicitly included a timing component and those that did not.

Methods: 40 PD patients and 44 controls were recruited through the William S. Middleton V.A. Hospital and Wisconsin Alzheimer's Disease Research Center to participate in a longitudinal MRI study which also involved a targeted neuropsychological battery, which included a motor sequence task, Trail-Making Tests A & B, Stroop Task, Category Fluency, Digit Span and the Wisconsin Card Sort. Scores were standardized relative to the control group at baseline.

Results: We selected a sub-group of PD subjects who showed impairment on three predominantly speed-dependent tasks. These subjects also performed poorly on timed measures used to assess executive function, but had variable results on other measures of executive function that were more independent of speed.

Conclusions: Caution should be used in interpreting commonly-used measures of executive function, as results are often confounded by speed deficits. ◇

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Cardiac workload is associated with CSF biomarkers in cognitively normal late-middle-aged adults at risk for Alzheimer's disease

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Background: A relationship between cardiovascular disease and dementia is fairly well-established. However, the pathophysiological mechanisms underlying this relationship remains unknown. Rate pressure product (RPP) is a simple, indirect assessment of myocardial oxygen consumption that can indicate risk for heart disease and may provide additional information about the mechanisms of this relationship. Therefore, the goal of this study was to assess the relationship between RPP and biomarkers of Alzheimer's disease (AD) in a cohort at risk for AD.

Methods: Two hundred seventy-one cognitively normal late-middle-aged adults (mean age=61.3, 70.8% female) from the Wisconsin Alzheimer's Disease Research Center and the Wisconsin Registry for Alzheimer's Prevention underwent lumbar puncture (LP) to collect CSF. RPP was calculated from resting vitals taken prior to the LP. CSF levels of A42, t-tau and p-tau were measured by ELISA. Linear regression was used to determine the effect of RPP on CSF biomarkers, controlling for age, gender, APOE ε4, and immunoassay batch.

Results: RPP was positively associated with t-tau (B=.009, p=.009) and p-tau (B=.008, p=.037), but not with A42 (B=.005, p=.183). Posthoc analyses revealed that the observed relationships were more marked in older participants (≥61 years of age; t-tau: B=.018, p=.001; p-tau: B=.014, p=.007) compared with younger participants (<61 years of age; ps > .05).

Conclusion: Our findings suggest that high myocardial oxygen demand at rest — especially within the context of advancing age — either promotes or co-occurs with alterations in tau, but not with brain amyloidosis. Longitudinal studies would be needed for further establishing causality in these associations. ◇

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Sedentary Behavior Associates with Vessel Pulsatility in the Brains of Adults at Risk for Alzheimer's Disease

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Objective: There is increasing evidence of a vascular component in the pathogenesis of Alzheimer's disease (AD). One important measure of cerebrovascular health is pulsatility index (PI). Increased PI indicates greater vessel stiffness and has been associated with reduced mean blood flow in the intracranial vasculature. Sedentary behavior (SB) has emerged as an independent risk factor for vascular conditions, such as cardiovascular disease. However, its relation to cerebral vascular indices, like PI, has not yet been fully explored. Therefore, the aim of this study was to examine the association between SB and pulsatility characteristics of cerebral vessels of the Circle of Willis.

Methods: Thirty-six cognitively healthy, late-middle-aged adults (age=64.03±4.80, 50%female) from the Wisconsin Registry for Alzheimer's Prevention participated in this study. Participants underwent 4D flow MRI brain imaging to measure PI in multiple cerebral vessels. Participants also wore an accelerometer (ActiGraph GT3X+) for one week to record free-living physical activity, which yielded a measure of SB. Multiple linear regression, adjusted for age and sex, was used to analyze the relationship between SB and PI.

Results: There was a trend for a positive association between SB and mean PI in the inferior ICA (p=.052). When examined hemispherically, there was a significant association between SB and PI in the right inferior ICA (p=.044) but not the left (p=.241).

Conclusions: Findings show that as SB increases, PI increases in the ICA, indicating increased vessel stiffness. Because increased vessel stiffness has been reported in persons with AD, this suggests reductions in SB may promote vessel compliance, thereby protecting against cerebrovascular changes related to AD. ◇

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AT-1/SLC33A1 in aging and age-associated disease vulnerability

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Background: The acetyl-CoA transporter, AT-1, is a key member of the endoplasmic reticulum (ER) acetylation machinery; it transports acetyl-CoA from the cytosol into the ER lumen where it serves as a donor of the acetyl group for Nε-lysine acetylation. Dysfunctional ER acetylation has been linked to both developmental and degenerative diseases. Importantly, (i) overexpression of AT-1 in the mouse causes a progeria-like phenotype that mimics an accelerated form of aging and (ii) AT-1 levels are upregulated in the brain of Alzheimer's disease (AD) patients.

Methods: A) Human fibroblasts from neonates through 94 years of age were used to determine the expression levels of AT-1 as a function of age. (B-C) A systemic AT-1 Tg mouse model that ubiquitously overexpresses human AT-1 and demonstrates a progeria-like phenotype was used to determine translational potential of four novel compounds (Compound 9, A, B, and C) that are able to inhibit the ER acetylation machinery.

Results: A) The expression of the ER acetylation machinery increases with age, as demonstrated in human fibroblasts. B) Late treatment with Compound 9 can rescue the progeria-like phenotype of AT-1 sTg mice. C) Compound A, B and C show similar translational potential.

Conclusions: Dysfunctional ER acetylation is an intrinsic feature of normal aging. Compounds that inhibit the ER-resident acetyltransferases (ATase1 and ATase2) down-stream of AT-1, normalize dysfunctional ER acetylation and rescue the accelerated aging phenotype of AT-1 sTg mice. Studies in AD-relevant mouse models are underway. ◇

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Targeting the Endoplasmic Reticulum-based Nε-Lysine Acetyltransferases for Therapeutic Benefit in Alzheimer's disease

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Background: Nε-lysine acetylation in the lumen of the endoplasmic reticulum (ER) has emerged as a novel mechanism for the regulation of protein homeostasis by regulating the selection of correctly folded glycoproteins and autophagy-mediated disposal of unfolded/misfolded protein aggregates. Acetyltransferase 1 (ATase1/NAT8B) and acetyltransferase 2 (ATase2/NAT8) are ER-resident enzymes responsible for Nε-lysine acetylation; pharmacologic inhibition of both ATase1 and ATase2 results in activation of reticulophagy (ER-specific autophagy), enhanced clearance of protein aggregates within the secretory pathway, and rescue of a mouse model of Alzheimer's disease (AD). The physiologic and pathologic differences between ATase1 and ATase2 remain uncharacterized, which prevents more targeted therapeutic approaches for diseases like AD where the pathogenic event resides in accumulation of toxic protein aggregates within the secretory pathway.

Methods: Purified wild type and mutant ATase1 and ATase2 were assayed for acetyltransferase activity in vitro. ATase1-/- and ATase2-/- mice were generated and their phenotype assessed via behavioral testing, pathologic examination, and biochemical analysis. The AD model mice APPswe/PSEN1dE9 (APP/PS1) were crossed to generate APP/PS1;ATase1-/- and APP/PS1;ATase2-/-mice, and the AD phenotype was assessed via survival assessment, biochemical analysis, and pathologic examination.

Results: ATase1 but not ATase2 is autoacetylated, which serves as an allosteric regulatory switch. The ATase1-/- and ATase2-/- mice exhibit normal development, behavior, and lifespan with widespread, mild to moderate tissue inflammation. Biochemical analysis reveals activation of reticulophagy in both ATase1-/- and ATase2-/-mice. The APP/PS1;ATase1-/- but not the APP/PS1;ATase2-/- exhibits improved lifespan compared to the APP/PS1 mice.

Conclusion: ATase1 is the preferred target for translational medicine. ◇

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Unexpected Findings from 14,721 Brain Magnetic Resonance Imaging Exams in Research Volunteers

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Background: Our neuroradiology group has reviewed 14,721 consecutive research brain MRIs as part of an IRB directive intended to discover clinically relevant unexpected findings. Herein we describe the incidence and characteristics of the unexpected findings for which clinical referral was recommended.

Methods: N=14,721 consecutive scans were prospectively collected from 2002-04-12 to 2018-09-30. The study population included 'typical' normal volunteers and those with known diagnoses (e.g. trisomy 21). Neuroradiologists reviewed scans on a clinical PACS and reported findings using a structured reporting form. A forced final interpretation placed each scan into one of three categories: normal, abnormal but no follow-up recommended, or abnormal with follow-up recommended.

Results: Among the 14,721 exams, 12,240 (83%) were normal, 1949 (13%) were abnormal but for which follow-up was not recommended (e.g. known disorder or common minor changes, such as sinus inflammation), and 532 (4%) were categorized as abnormal with follow-up recommended. The most common abnormalities prompting follow-up were. categorized as vascular (22%), white matter (34%), tumors (12%), and congenital lesions (9%). Females had a significantly greater number of abnormal scans (1,299) compared to men (1,182). When grouped by age (e.g. 40-49), clinically significant abnormalities increased dramatically between the 5th and 6th decades of life and declined beyond the age of 70.

Conclusion: Four percent of research volunteers have a clinically significant appearing MRI finding prompting medical referral. These findings are more common in women and peak in the 5th and 6th decades of life. A well developed MRI review and follow-up process is recommended for all aging studies. ◇

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Amyloid accumulation in the striatum is more rapid than in the cortex early in Down syndrome and can serve as a marker for early intervention

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Background: Individuals with Down syndrome (DS) show increased production of the amyloid precursor protein with earliest amyloid-beta (Aβ) deposition in the striatum. This study assesses whether striatal Aβ deposition occurs more rapidly than cortical deposition in DS by evaluating longitudinal PiB SUVR change.

Method: N=34 adults with DS underwent three [11C]PiB scans (2-3 years apart) in addition to structural T1w-MRI. ROIs were defined using FreeSurfer (v5.3.0). SUVR images were generated from summed 50-70 minute PET frames using cerebellar gray matter as the reference region. Mean SUVRs were extracted for the striatum and target cortical ROIs (anterior cingulate, superior frontal gyrus, orbitofrontal gyrus, insula, lateral temporal gyrus, parietal cortex, posterior cingulate, precuneus). Longitudinal change in SUVR were compared across participants based on their PiB status (PiB(-), PiB converter, or PiB(+)).

Results: Between all cycles, PiB converters displayed significantly greater SUVR change in the striatum than in the cortex (two-sample paired t-test; Cycle 1-2: p=0.008, Cycle 2-3: p=0.001). Participants that remained either PiB(-) or PiB(+) between cycles showed no significant difference between striatal and cortical accumulation (all p>0.05).

Conclusion: These results suggest that in DS, changes in Aβ accumulates are greater in the striatum during the early stages of amyloid accumulation compared to cortical regions. Once the transition from PiB-converter to PiB(+) occurs, no difference between striatal and cortical Aβ change is noticed. This analysis reveals that the striatum may be more vulnerable to Aβ plaque formation and identifies the striatum as a potential marker for early intervention in DS. ◇

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Vagal Nerve Stimulation Modulates CSF Penetrance

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Background: Vagus nerve stimulation (VNS) is a currently FDA-approved therapeutic method for conditions such as epilepsy and depression with a growing list of clinical indications. Despite its growing application the therapeutic mechanisms behind VNS are poorly understood. Two recently described systems, the meningeal lymphatic and glymphatic, have been described to explain how the brain is cleared of misfolded proteins, cellular, and metabolic waste and impairment of the glymphatic system can significantly reduce clearance of amyloid- β. It has been postulated that cerebral arterial pulsations are one of the main driving forces behind this system. Given the reported effects of VNS on systemic and cerebral hemodynamics we tested whether VNS could alter brain waste clearance.

Methods: We applied VNS to mice using clinically derived stimulation parameters for 1 hour. Mid-way through stimulation a fixable fluorescent dye was injected into the cisterna magna (CM). After stimulation, the mice were perfusion-fixed, and the degree of CSF penetrance was measured in whole ex vivo slices.

Results: We found that VNS significantly increased the degree of CSF dye penetrance (18.60% ± 1.98%) relative to naïve controls (10.75% ± 1.26%) and sham (13.05% ± 2.29%) and that there was no difference between the naïve controls and sham VNS groups.

Conclusions: Our results demonstrate a novel, and potentially therapeutic, effect of VNS on the brain's waste clearance systems. The ability to alter this system could have implications for the treatment of Alzheimer's Disease in which the build-up of misfolded proteins, such as Aβ, contribute to disease progression. ◇

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Effects of Dysregulated Cortisol on Predicting Pulsatility for Cerebrovascular Health

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Background: As the U.S. population ages, the prevalence of Alzheimer's Disease and Related Dementia (ADRD) and other age-related cognitive impairment increases. Socio-behavioral and biological stress pathways are potentially modifiable, and implicated in many chronic diseases, including ADRD, but their link to cognitive and brain health is unclear. The dysregulation of cortisol, a stress hormone, may impact ADRD risk through cerebrovascular mechanisms. We explored associations between cortisol dysregulation and novel markers cerebrovascular health, pulsatility and pulsatile flow.

Methods: Key cortisol predictors included cortisol awakening response (CAR) and bedtime cortisol level. Our outcomes, pulsatility and mean blood flow were determined for brain arteries from MRI images (N=97) of WRAP and ADRC participants. Dysregulated cortisol was expected to predict greater pulsatility and lower mean blood flow.

Results: In bivariate models, there was a marginal positive association between bedtime cortisol level and ICA pulsatility. However, this association was attenuated by the inclusion of demographic covariates. Neither CAR nor bedtime cortisol was found to be associated with pulsatile flow in the MCA or ICA regions. Age was the only significant predictor of flow for both MCA and ICA regions.

Conclusion: In this small sample, we did not see associations between cortisol dysregulation and cerebrovascular health after controlling for the strong influence of age. Future analyses in larger samples should focus on additional cerebrovascular and AD-specific outcomes. Ultimately, our findings should improve our understanding of stress on the brain, which ultimately may influence cognition and preclinical ADRD in aging populations. ◇

Social and Behavioral Sciences

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Feasibility of Residential History Construction Methodology for Decedents at two Alzheimer's Disease Research Center Brain Banks

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Background: Geographically-linked exposures, such as neighborhood disadvantage or environmental toxins, have been suggested as possible factors in AD neuropathological change. Our objective was to test the feasibility of a novel method to create residential histories for decedents from two ADRC brain banks, which could facilitate examination of links between life-course exposures and neuropathological data.

Method: We used standard genealogical research methods to create lifetime residential histories for a sample of 23 decedents at the University of Wisconsin (n=12) and the University of California-San Diego (n=11) ADRC brain banks. We located residences using searches of targeted public records. Two trained researchers independently verified each record using the Standard for Genealogical Proof, which involves locating multiple records, then testing and validating evidence through its agreement with other records.

Results: Sample decedents were born between 1920 and 1950 and died in 2015. We located between 3 and 41 public records per decedent (mean =16), including city directories (78%) and census records (6%). We found county of residence for 34% to 100% of the years within each decedent's life (median: 80%, IQR= 64%-85%). Early-childhood and later life residential information was more complete than for middle ages Overall, a sizable majority of person-years (1357 of 1828 (74.2%)) within the sample were assigned to a county.

Conclusion: This novel method is feasible and promising for recreating lifetime residences for decedents, but requires additional validation in future studies and across more locations. This work facilitates research to clarify pathways linking life-course contextual exposures to AD-related brain changes. ◇

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Association of cardiovascular risk and subjective memory complaints in healthy middle aged adults

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Background: Cardiovascular risk (CR) and subjective memory complaints (SMC) are associated with cognitive decline dementia due to Alzheimer's disease (AD). Yet it is unclear if there is a direct link between cardiovascular risk and SMC. Prior research, which has not found an association between CR and SMC, is potentially hampered by a reliance on a single global memory rating. The goal of this study was to examine the association between CR and SMC using a validated measure of self-reported memory function in a sample of healthy, middle-aged adults.

Methods: N=1,666 participants from the WRAP and the Wisconsin ADRC completed the Memory Functioning Questionnaire (MFQ) and a Depression questionnaire (CESD). 10-year risk of heart disease or stroke was calculated using the Atherosclerotic Cardiovascular Disease (ASCVD) algorithm. We examined two subscales, Frequency of Forgetting (FF) and Seriousness of Forgetting (SF). Low scores indicate more severe complaints. Participants were divided into high (ASCVD >= 7.5%) and low risk (ASCVD <7.5%) groups. We controlled for gender, age, years of education, APOE4 carrier status, and CESD score in all models. We also tested for moderation of the association between cardiovascular risk and SMC by gender and APOE4 carrier status.

Results: High cardiovascular risk was modestly associated with more frequent forgetting ($b = -.11$, $p = .06$), but not with seriousness of forgetting ($b = -0.06$, $p = .44$). We found evidence for moderation by APOE4; the association between cardiovascular risk and frequency of forgetting was stronger among APOE4 carriers than non-carriers ($p = .05$).

Conclusions: We found evidence for a weak association between cardiovascular risk and subjective memory complaints. Future analyses will look at whether cardiovascular risk predicts change in SMC over time. ◇

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Visceral Adiposity and Cognitive Function in Midlife

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Background: Obesity at midlife is associated with over a threefold increased risk for Alzheimer's disease, while being overweight is associated with a two-fold increased risk. Visceral obesity may be more harmful than overall body weight, but remains understudied with regard to cognitive function. Given that midlife may be a critical period when trajectories of cognitive decline begin, we sought to test the relationship between visceral adiposity and cognitive function among middle-aged adults. We hypothesized that higher visceral adiposity would be associated with poorer performance on cognitive testing.

Methods: Cognitively unimpaired adults were recruited to participate in studies on glucoregulatory function and cognition. Visceral adiposity was assessed using waist circumference at umbilicus. Secondarily, we examined and waist-hip ratio, body mass index (BMI), and measures of body fat, muscle mass, and visceral fat rating determined via bioelectric impendence analysis. Participants underwent a comprehensive neuropsychological battery. Domains included were: Executive Function (Trail Making Test B, Animal Fluency) and Episodic Memory (RAVLT, Craft Story). Multiple regression models conducted in R version 3.4.2 were used to test the relationship between visceral adiposity and cognitive scores, controlling for age, sex, and education where appropriate.

Results: Employing corrections for multiple comparisons, neither visceral adiposity nor related measures were associated with cognitive function in middle-aged adults.

Conclusions: The results suggest that measures of visceral adiposity do not contribute to cognitive function in middle-aged adults. Given that participants enrolled into this study are cognitively unimpaired, it may be that there is insufficient variability in cognitive performance to detect an effect. Longitudinal studies are needed to elucidate the temporal relationship between visceral adiposity and cognitive decline and to test whether the effects of obesity on cognition are observed at older ages. ◇

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Baseline Dispersion Intra-Individual Cognitive Variability in a Young Pre-Clinical Cohort

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Background: Intra-Individual Cognitive Variability (IICV) has been identified as a cost-effective and non-invasive cognitive marker of Mild Cognitive Impairment (MCI) and Dementia due to Alzheimer's Disease (AD). Several methods of estimating IICV have been proposed. Dispersion IICV can be calculated to detect the magnitude of variability in neuropsychological test performance varies across cognitive domains. IICV has the potential to assist clinicians with reaching a greater number of individuals, including those who may not have access to treatments at major medical centers. Enhanced understanding of the relationship between biopsychosocial factors and IICV will elucidate attributes of this tool, which will be of use in the development of a "smarter" IICV.

Methods: Participants were from the Wisconsin Alzheimer's Disease Research Center (ADRC) and included 368 participants with ≥2 study visits. Baseline Dispersion IICV was calculated using our previous methods (Holtzer et al, Koscik et al 2017). Tests included in IICV estimate included Rey Auditory Verbal Learning Test (Learning and Delayed Recall Trials), the Trail Making Test (Forms A and B), and either the Boston Naming Test (BNT) or the Multilingual Naming Test (MINT). Scores from the MINT were converted to BNT scores using the NACC Crosswalk Study (Monsell, et al., 2016). Associations between IICV and education, sex, and relative hippocampal volume (RHV) were analyzed.

Results: Female RHV was slightly larger than male RHV at baseline. Female RHV demonstrated a very weak positive correlation with baseline dispersion IICV. Within this group, significant differences were seen between male and female levels of education. The age of female participants during baseline neuropsychological testing and MRI were slight lower than that of male participants. Fewer women met criteria for MCI due to AD at baseline. There was no significant correlation between baseline IICV and years of education.

Conclusions: A non-invasive cognitive biomarker of pre-clinical AD would be an easily-disseminated and cost-beneficial tool that would enable clinicians to reach a greater number of persons from differing ethnic and socioeconomic backgrounds. Elucidation of additional dimensions of this metric will be helpful in the development of a "smarter" and clinically useful IICV. This is the first attempt at exploring this in a younger pre-clinical cohort. Overall, female participants were younger at baseline, and had a larger RHV. Additionally, baseline dispersion IICV and RHV were weakly correlated in females. It is unclear as to why this same phenomenon is not seen in male participants. ◇

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Subjective Memory Complaints Associated with Discrimination in Healthcare Settings Among Transgender and Gender Non-conforming Older Adults

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Background: Emerging data suggest that social factors influence cognitive decline. Marginalized communities, including transgender and gender non-conforming (TGNC) individuals, encounter higher levels of stress and health disparities. Recent data indicate an association between social stress and subjective cognitive complaints (SCCs) — a marker of risk for Alzheimer's disease and related dementias (ADRD) in TGNC elders. We propose there are unique factors influencing cognitive aging in TGNC older adults, including increased risk for discrimination and violence, justifying study of this population alone. This study examines psychosocial factors associated with SCC, and the relationship between discrimination in healthcare settings and memory complaints in a sample of TGNC older adults.

Method: We utilized cross-sectional data from The PRIDE Study - Rainbows of Aging Survey for TGNC adults aged 50+ (n=115), a national, online, cohort study focused on the health of LGBTQ people including questions on memory complaints, health experiences and discrimination. Associations between discrimination in healthcare settings and memory complaints were examined using chi-squared and t-tests, and multivariable logistic regression.

Results: Participant median age was 58.2 (SD=6.5), range: 50-76. Participants were well-educated (>95% attended some college or higher), and predominantly white (90%). Nearly 16% of participants rated their memory as poor to fair and 17% reported that their memory was worse than a year ago. TGNC participants with memory complaints were more likely to report food insecurity (44%), poor-to-fair health status (50%), and physical violence (71%, all $p < 0.01$). Discrimination in medical settings was associated with memory complaints and worsening memory in the past year (all p-values <0.01). After accounting for demographics, TGNC older adults experiencing discrimination in medical settings were >5 times more likely to report recent worsening memory (OR: 5.3; 95%-CI: 1.8-16.0; p=.003) and >10 times more likely to report poor to fair memory (OR: 10.0; 95%-CI: 2.6-38.3; p=0.001).

Conclusions: TGNC older adults reported both higher frequencies of memory complaints (SCC) and higher rates of discrimination in healthcare settings. Implications for training healthcare professionals in affirmative cognitive screening and dementia-related care in various fields of practice will be discussed. ◊

Other: Biostatistics

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Conditional standards: Identifying cutoffs for predicting AD surrogates using traditional and machine learning methods

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Background: Interpreting cognitive test scores requires a reference standard, whether based on a patient's demographics (unconditional) or their prior performance (conditional), along with thresholds. We developed reference standards for several cognitive measures and compared the classification performance of numerous thresholds for differentiating subsequently normal and impaired participants.

Method: Using a cognitively-unimpaired subsample from WADRC and WRAP (N=1404), conditional and unconditional standards were developed for thirteen cognitive outcomes using restricted regression quantiles with semi-automated model selection. Selected models were applied to the larger sample to estimate the best-fit conditional and unconditional percentiles. These percentiles were used as features for training several classifiers, including traditional multi-test methods, ROCs, and random forest. The primary target was clinical progression (N=37/1041 with complete data); a secondary target was amyloid positivity (N=77/298). Classification performance was estimated using repeated, stratified five-fold cross-validation. Thresholds were selected to maximize Youden's index on the training sets and evaluated in the test sets.

Results: A strong specificity-sensitivity tradeoff was evident, with no measures exceeding 0.8 on both. Conditional Trails A percentile emerged as a sensitive, but not specific, marker for both targets. Accuracy metrics tended to favor memory over non-memory measures. No clear advantage for unconditional or conditional measures emerged.

Conclusion: The low discriminability of progressors/non-progressors and amyloid positive/negative individuals may reflect class imbalance, or it may indicate misspecification of our implicit temporal model linking poor test performance to clinical progression. Future work should examine the performance of these standards in cohorts with a larger proportion of individuals progressing to AD. ◇

Other: Clinical Trial Data Security

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Improving the Efficiency and Data Integrity of REDCap Data Entry with Automated Software Validation Testing

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A large quality improvement project with REDCap, an open-source database used for the entry of human subject clinical trial data, improves the data integrity and efficiency of data entry through automated software validation. Confidence with data entry is essential for statistical analysis and presentation of clinical trial results, and engaging real-time data entry improves accuracy and timeliness of data reporting. Validation of the open-source software functions has historically been a very manually intensive process. With new focus on new automated software validation testing, the process now provides more combinations and allows for re-testing with a higher degree of efficiency than traditional methods. The software validation process ensures that the audit trails track data manipulation by user. The Division of Geriatrics within the University of Wisconsin-Madison Department of Medicine has implemented automated software validation for ensuring the reliability of secure data, proper software user rights, and field ranges to validate entries. The method of validating the REDCap software involved a series of four steps across different browsers and platforms. Both automated and manual validation testing were performed, with Cypress.io used as the underlying platform for the automated validation test scripts. This quality improvement project to validate REDCap software is anticipated to be significant on five key levels. The amount of paper use would be decreased significantly, the mass consumption of storage for documents would be eliminated, the potential loss of data would be greatly reduced, data security would be improved, and real-time data entry into the database would be possible. ◇

Other: Genetic Epidemiology

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38 CSF metabolites are highly predictive of CSF total tau and phosphorylated tau

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Background: Darst, B. F. et al., 2018 identified 38 metabolites in Cerebrospinal fluid (CSF) that were highly correlated with total tau (T-tau) and phosphorylated tau (P-tau) in the Wisconsin Registry for Alzheimer's Prevention (WRAP). Replication of these findings, along with a detailed investigation, may reveal additional mechanistic information behind the development of tau tangles.

Methods: The discovery sample included 137 cognitively unimpaired individuals with 224 longitudinal CSF samples from WRAP. The replication sample included 282 individuals with 289 samples from the Wisconsin Alzheimer's Disease Research Center (W-ADRC). Metabolite relative abundance in CSF was measured via Metabolon's UHPLC/MS metabolomics platform. We assessed the amount of T-tau and P-tau variance explained by the 38 CSF in W-ADRC using linear mixed effect models, adjusting for age, gender, batch and sample storage time. Additionally, 34 of these metabolites presented in plasma samples from WRAP were tested too.

Results: In W-ADRC, the 38 CSF metabolites together explained 59.5% of the variance in T-tau and 59.3% of the variance in P-tau. These results were very similar to those reported in WRAP, where the 38 CSF metabolites explained 62.9% and 63.2% of the variance in T-tau and P-tau, respectively. Additionally, the 34 plasma metabolites explained 27.5% and 29.1% of the T-tau and P-tau variance.

Conclusion: This study provides evidence of CSF metabolites that are strongly correlated with T-tau and P-tau and, thus, may provide insight into the mechanisms involved in tau tangles. Next steps include Mendelian randomization using genomic instrumental variables to assess directionality of these correlations. ◇

Other: Imaging Science

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Intracranial Pulse Wave Velocity in Alzheimer's Disease using Flow Encode Split and Low Rank Reconstructed 4D Flow MRI

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Background: Evidence shows vascular factors play a role in Alzheimer's Disease (AD); however, whether AD has a basis in vascular diseases is controversial. This feasibility study investigates the non-invasive measurement of intracranial pulse wave velocity (PWV) as a potential parameter that can probe arterial stiffness changes in AD using 4D flow MRI.

Methods: Subjects: 10 AD, 4 mild cognitively impaired (MCI), 6 controls and 6 impact subjects were studied. The impact group was defined as a cognitively healthy late middle-aged group enriched for risk factors that predispose to AD. MRI: Volumetric, time-resolved phase contrast (PC) MRI data were acquired on a 3.0T system with an 8-channel head coil. PWV analysis: Cardiac waveforms in the cervical and petrous internal carotid artery (ICA) were recorded in MATLAB (Mathworks, Natick, MA). PWV was defined as vessel length between measured waveform location over the temporal shift. Group differences were assessed using ANOVA followed by post-hoc analysis.

Results: Overall PWV was larger in AD and MCI groups than in control and impact groups. The impact group showed higher PWV than controls. The AD group had a statistically larger PWV when compared to control ($P<0.001$) and impact groups ($P=0.032$). Finally, regression models of PWV vs age showed the AD group is moderately described by a linear model with $R2 = 0.63$.

Conclusions: Statistically higher apparent PWV in the AD group suggests arterial stiffening of the ICAs and macrovascular damage. Which support the hypothesis that functional changes to the arterial system are involved in the pathogenesis of AD. ◇

Other: Measures/Screening or Assessment Tools

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Does the Format of Performance-Based Tests Influence Performance Outcomes Among Older Adults?

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Background: Research comparing outcome differences between structured versus unstructured performance-based tests (PBTs) of functional cognition is limited. Structured PBTs instruct individuals to complete tasks following a step-by-step format, whereas unstructured PBTs instruct individuals to complete tasks following an open-ended format. This study evaluates differences in performance between PBT formats.

Method: 200 community-dwelling older adults completed the following pairs of PBTs: (1) screening tools such as the structured revised-Medication Transfer Screen (revised-MTS) and the unstructured Menu Task (MT), and (2) assessment tools such as the structured Performance Assessment of Self-Care Skills (PASS) and the unstructured Weekly Calendar Planning Activity (WCPA). Participants were categorized into pass/fail groups for each measure using scale-specific criterion cutoff scores. Performance across the two pairs of PBT formats were compared using chi-square analyses.

Results: Participant demographics included an average age of 70.42 years, 15.09 years of education, 76.1% female, and 79.6% white. Among the screening tools, 23% of participants failed the structured revised-MTS and 37% failed the unstructured MT. Among assessment tools, 49.5% of participants failed the structured PASS and 17.9% failed the unstructured WCPA. Chi-square tests for independence indicated the difference in percentages between screening tool formats was significant, ($X2 = 31.23$, $p < .001$). The difference in percentages between assessment tool formats was also significant, ($X2 = 14.42$, $p < .001$).

Conclusion: On the assessment tools, older adults were more likely to fail the structured PBT of functional cognition. However, on the screening tools, older adults were more likely to fail the unstructured PBT. ◇

Other: Psychophysiology

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Psychophysiological Measures of Negative Emotional Responses Predict Mortality ~10 Years Later

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Abnormal emotional responses can impair functioning, increasing vulnerability to psychopathology and stress-related disorders. Disorders characterized by dysregulated negative affect, such as depression, are associated with an increased risk of mortality. To test the importance of negative emotional response styles for health outcomes, we tested whether psychophysiological measures of emotional responses recorded from 2005-2009 would predict mortality status roughly ten years later. Psychophysiological responses to negative, neutral, and positive pictures were measured in 331 participants with corrugator electromyography and eyeblink startle magnitude. Data from those participants who provided good quality data and whose decedent status was able to be determined roughly 10 years later were analyzed with logistic regressions: Deceased = 17 (aged 42-84 at MIDUS 2), Living = 144 (aged 36-79 at MIDUS 2). The change in magnitude measures between emotional reactivity (during the picture) and recovery (after picture offset) of both corrugator electromyography and eyeblink startle responses on negative pictures trials were significant predictors of decedent status. (Responses on neutral and positive picture trials were not.) Change in eyeblink startle measures on negative picture trials was a significant predictor of mortality status, even when controlling for age, Nagelkerke $R2 = .25$, WALD for eyeblink startle response magnitude negative reactivity-recovery difference = 4.93, $p = .03$. Even with the small sample, this finding provides critical support for the importance of individual differences in the temporal dynamics of emotional responses for long-term health and wellbeing. ◇