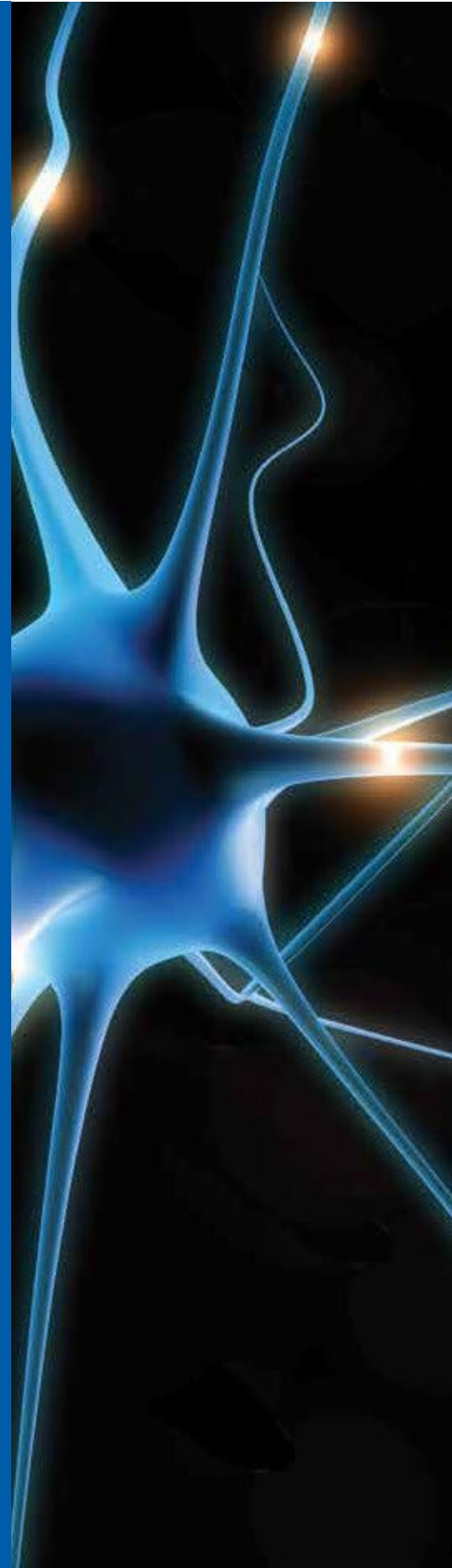


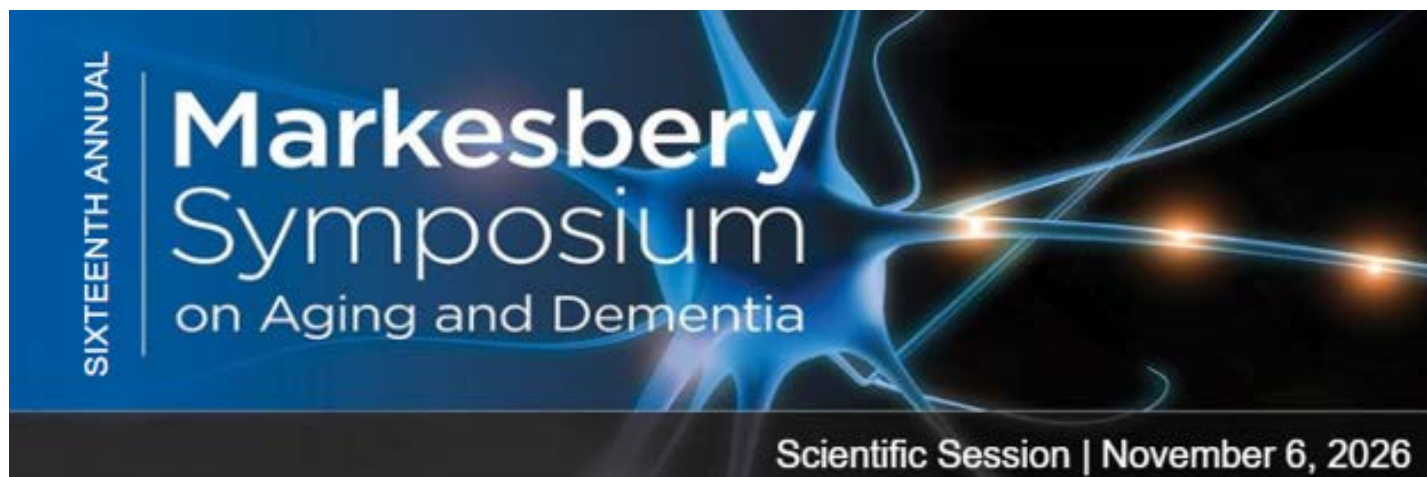
SIXTEENTH ANNUAL

Markesbery Symposium

on Aging and Dementia

Scientific Session
November 6, 2026
09:30a.m.- 3:00p.m.





On behalf of the Sanders-Brown Center on Aging, our philanthropy council, and the symposium planning committee, I am pleased to welcome you to the 16th annual “Markesbery Symposium on Aging and Dementia.”

The symposium is named in honor and memory of the late William R. Markesbery, M.D., founding director of the Sanders-Brown Center on Aging and Alzheimer’s Disease Research Center at the University of Kentucky. Dr. Markesbery’s legacy of groundbreaking research at the Center on Aging has formed the bedrock for our quest to understand and treat Alzheimer’s disease and to improve the quality of life of the elderly. We have no doubt that Dr. Bill Markesbery’s work will live on for generations to come as we continue the work he started here four decades ago.

In the scientific session today you will have the opportunity to hear clinicians and researchers from the University of Kentucky and other institutions share current findings, trends, and latest updates on dementia and aging disorders particularly as related to Alzheimer’s disease.

We are honored that so many of you have chosen to join us in seeking to expand our knowledge and friendships. I hope the symposium will be both scientifically rewarding and enjoyable.

Sincerely,

Linda J. Van Eldik, Ph.D.
Director, Sanders-Brown Center on Aging & Alzheimer’s Disease Research Center

Symposium Planning Committee:

Linda Van Eldik, Ph.D.	Josh M. Morganti, Ph.D.	Beverly Baesler	April Stauffer
Anika Hartz, Ph.D.	Elizabeth Rhodus, Ph.D.	Laura Clewett	Charlotte Wood
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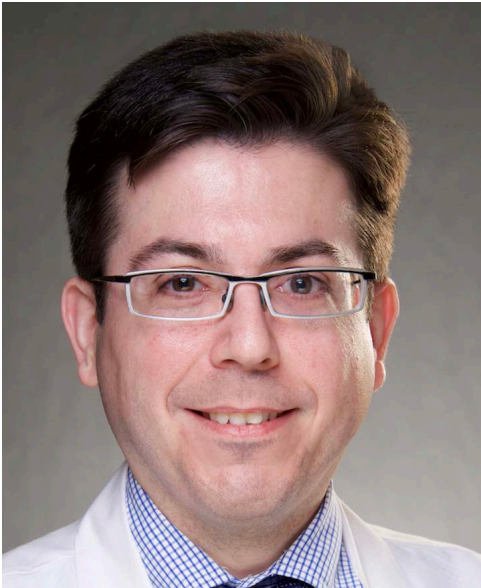
Contact Allen Chapa, M.Ed., Executive Director of Philanthropy
allen.chapa@uky.edu | (859) 254-5417

2026 Markesbery Scientific Symposium Agenda

Friday, November 6, 2026

9:30a.m.	Coffee and Registration	<i>Executive Board Room - GSC 375</i>
9:45a.m.	Symposium Welcome Linda Van Eldik, Ph.D. Director, Sanders-Brown Center on Aging and University of Kentucky ADRC	<i>Harris Ballroom</i>
10:00a.m.	<i>Deciphering Reactive Astrogliosis in Alzheimer's Disease: From Human Neuropathology to Mechanistic Insights</i> Alberto Serrano-Pozo, M.D., Ph.D., Associate Professor of Neurology at Harvard Medical School, Director, Massachusetts ADRC Clinical Core	
10:45a.m.	Coffee Break	
11:00a.m.	<i>From Preclinical to Clinical Studies: Lessons Learned in Alzheimer's Drug Discovery</i> Linda Van Eldik, Ph.D. Director, Sanders-Brown Center on Aging and University of Kentucky ADRC	
11:30a.m.	Lunch Boxed lunches	
12:00p.m.	<i>Poster Session #1</i>	
12:50p.m.	<i>Poster Session #2</i>	
1:45p.m.	<i>Understanding Plasma Biomarker Heterogeneity Across the Spectrum of Cognitive Aging and Population Characteristics</i> Cellas Hayes, Ph.D., Assistant Professor of Neuroscience, SBCoA	
2:00p.m.	Trainee Data Blitz	
2:45p.m.	Poster Award Presentations	
3:00p.m.	Closing Remarks	

KEYNOTE SPEAKER



"Deciphering Reactive Astrogliosis in Alzheimer's Disease: From Human Neuropathology to Mechanistic Insights"

**Alberto Serrano-Pozo, M.D., Ph.D.
Associate Professor of Neurology at
Harvard Medical School, Director,
Massachusetts ADRC Clinical Core**

Alberto Serrano-Pozo, M.D., Ph.D. is a neurologist at the Memory Division of the Mass General Brigham Neurology Department and an Associate Professor of Neurology at Harvard Medical School. He is the Director of the Massachusetts Alzheimer's Disease Research Center Clinical Core. His research focuses on the role of reactive astrocytes and APOE in Alzheimer's disease and related dementias and on the validation of fluid and imaging biomarkers via quantitative neuropathology. His research has been funded by the National Institute on Aging and the Alzheimer's Association among other funding agencies. He is the recipient of the 2021 Grass Foundation - American Neurological Association Award in Neuroscience.





"Understanding Plasma Biomarker Heterogeneity Across the Spectrum of Cognitive Aging and Population Characteristics"

Cellas Hayes, Ph.D., Assistant Professor of Neuroscience
Sanders-Brown Center on Aging

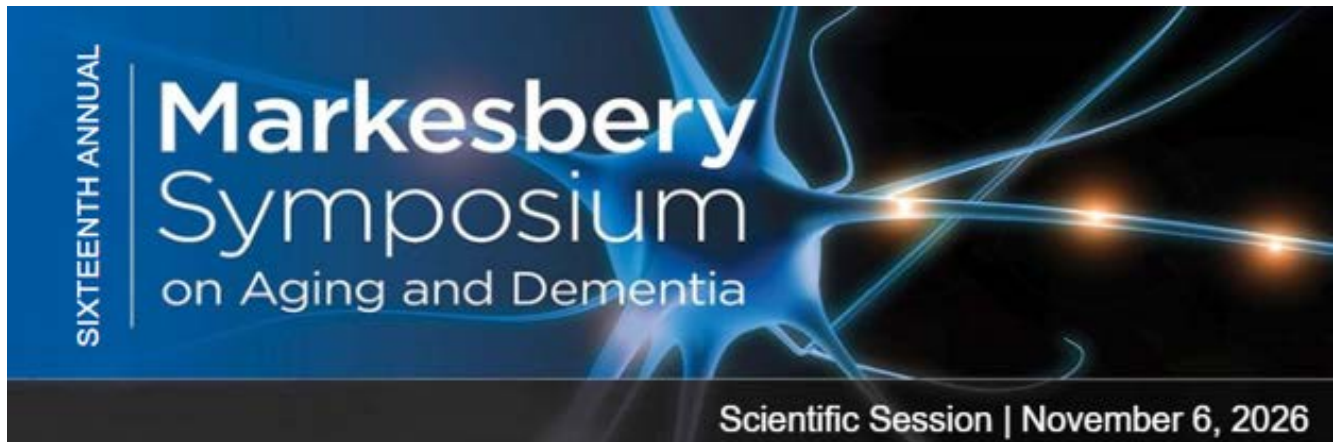
Cellas Hayes, Ph.D., is an Assistant Professor of Neuroscience at the University of Kentucky and fully appointed Sanders-Brown Center on Aging faculty member. He has a Ph.D. in Pharmaceutical Sciences with an emphasis in pharmacology (2022). He also received a certificate in observational epidemiology and biostatistics from the University of Mississippi Medical Center Graduate Training Education Center in 2022 and completed four years of postdoctoral training in neuroepidemiology at Stanford University prior to joining the University of Kentucky as faculty. Dr. Hayes combines advanced epidemiological and biostatistical tools with multimodal biological, clinical, and social data including plasma proteomic biomarkers, neuroimaging, and demographics to better understand cognitive and vascular aging. The laboratory has three focuses: 1) evaluating longitudinal changes in blood-based biomarkers and their relationships with neurodegenerative and cerebrovascular outcomes; 2) applying multi-omics approaches, including proteomics and genomics, to identify novel biomarkers and mechanistic pathways relevant to ADRD heterogeneity; 3) understanding population differences in brain aging and health by investigating the biological and social determinants of ADRD.



"From Preclinical to Clinical Studies: Lessons Learned in Alzheimer's Drug Discovery"

**Linda Van Eldik, Ph.D.
Director, Sanders-Brown Center on Aging and
University of Kentucky ADRC**

Linda Jo Van Eldik, Ph.D., is Director of the Sanders-Brown Center on Aging and the NIA-funded Alzheimer's Disease Research Center, Co-Director of the Kentucky Neuroscience Institute, and Professor of Neuroscience at the University of Kentucky. Her background includes a Ph.D. in Microbiology and Immunology from Duke University, postdoc in Virology and Cell Biology at Rockefeller University in NY, and faculty positions at Vanderbilt University and at Northwestern University in Chicago. Dr. Van Eldik has received a number of honors during her career, including a Zenith Award from the Alzheimer's Association and an NIA MERIT award. She is a fellow of the American Academy for the Advancement of Science (AAAS), a former member of the National Advisory Council on Aging, and an Alzheimer's Association Lifetime Achievement Awardee. Her research focuses on dysregulated neuroinflammation, identifying potential points of intervention, and developing new small molecule drug candidates to slow the progression of cognitive impairment and neurodegeneration. In collaborative translational efforts, she has shepherded a set of novel small molecule compounds from design and synthesis; to preclinical animal model testing for pharmacodynamics, efficacy and selectivity; through IND-enabling preclinical development; and into phase Ib/2a human clinical trials for CNS disorders.



Please take an opportunity to review the posters from our emerging scientists that are located in the Harris Ballroom.

Poster Abstracts



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13	3	Amon	Kelsey	Graduate Student
14	4	Ashley	Clair	Graduate Student
15	5	Caldwell	Mackenzie	Graduate Student
16	6	Brock	Kaitlyn	Graduate Student
17	7	Cox	MaKayla	Graduate Student
18	8	Eskandari	Sania	Graduate Student
19	9	Coskun	Pinar	Faculty
20	10	Fariduddin	Osswaah	Graduate Student
21	11	Foster	Elodie	Graduate Student
22	12	Fox	Grant	Graduate Student
23	13	Gaugler	Abbigail	Graduate Student
24	14	Hernandez Gonzalez	Andrea	Staff
25	15	Irmen	Riley	Graduate Student
26	16	Jacobs	Amunet	Graduate Student
27	17	Johnson	Halley	Graduate Student
28	18	Karki	Bikram	Graduate Student
29	19	Lanning	Matthew	Graduate Student
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31	21	Qiao	Qi	Staff
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45	35	Xu	Xizhi	Graduate Student
46	36	Sales	Johnathan	Staff
47	37	Aung	Khine Zin	Postdoctoral Scholar
48	38	Bailey	Caleb	Postdoctoral Scholar
49	39	Humburg	Bree	Postdoctoral Fellow
50	40	Islam	Jahid	Postdoctoral Scholar

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53	43	Lu	Ting-Hsuan	Postdoctoral Scholar
54	44	Lundt	Samuel	Postdoctoral Scholar
55	45	Lysaker	Colton	Postdoctoral Fellow
56	46	Shahidehpour	Ryan	Postdoctoral Scholar
57	47	Turner	Meghan	Postdoctoral Fellow
58	48	Wu	Xian	Postdoctoral Scholar
59	49	Eslamian	Ali	Graduate Student
60	50	Barber	Justin	Staff
61	51	Chebby	Rohini	Staff
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63	53	Kimseng	Rungreudee	Staff
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65	56	Poe	Lauren	Staff
66	57	Munoz-Gil	Susana	Graduate Student
67	58	Speaks	Hannah	Graduate Student
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77	68	Roberts	Taylor	Undergraduate Student
78	69	Shearer	Ella	Undergraduate Student

Microglial HIF1 α is necessary to restrict demyelination and maladaptive neuroinflammatory responses in a mouse model of white matter degeneration

Sophia H. Dimas^{1,2}, Kai Saito¹, Danielle S. Goulding¹, Lauren Moore², Josh M. Morganti^{1,2}

¹Sanders-Brown Center on Aging, College of Medicine, University of Kentucky;

²Department of Neuroscience, College of Medicine, University of Kentucky

Graduate Student

Background: White matter (WM) degeneration, though commonly affiliated with Multiple Sclerosis (MS), is also a feature of several neurodegenerative conditions, suggesting convergent mechanisms. Previous studies across different WM degenerative conditions demonstrate a commonality- reactive microglial subsets responsive to WM pathology, differentially enriched for expression of HIF1 α , a master regulator of cellular glycolytic metabolism. HIF1 α has been demonstrated to be instrumental in myeloid responses to inflammatory challenges *in vitro* and *in vivo* and plays a significant role in driving a disease responsive phenotype within mouse models of amyloidosis. The degree to which HIF1 α drives microglial disease responses to WM pathology, however, remains a critical gap in knowledge.

Methods: We generated microglial-specific conditional knockouts of HIF1 α via Tmem119CreERT2⁺ Hif1 α ^{fl/fl} ('cKO') and their wildtype littermates: Tmem119CreERT2⁻ Hif1 α ^{fl/fl} ('WT'). Following recombination, mice were subjected to cuprizone-mediated demyelination for 5 weeks or cuprizone-mediated demyelination with endpoints of histopathology and spatial transcriptomics. A parallel approach was taken using immortalized murine microglia (BV2 cells), in which cells were pre-treated pharmacological inhibitor of HIF1 α transcriptional activity (PX-478) prior to a type I interferon challenge. Endpoints included bulk RNA sequencing, Seahorse functional analysis, and metabolomic analysis.

Results: Our findings demonstrate that compared to WT, cKO mice exhibited enhanced demyelinating pathology demonstrated by MBP and increased microglial reactivity (CD68, Iba1, Clec7a, Stat1). Using a novel 433 gene panel in our Xenium spatial transcriptomic workflow, we demonstrated the spatial accumulation of several subsets of microglia demonstrating varying heterogeneity across anatomical locales. Specifically, we observed significant accumulation of disease-reactive microglial subsets in response to cuprizone, while cKO mice demonstrated a dramatic expansion of an interferon-responsive population, concurrent with histological findings. *In vitro*, we observed significant increases in interferon-responsive transcripts in PX-478 pre-treated wells, as well as potentially maladaptive bioenergetic and metabolic disturbances.

Conclusions: Our findings are the first to demonstrate that HIF1 α is a necessary restraint of microglial over activation in response to cuprizone-mediated demyelination, and loss of this transcription factor drives exacerbated outcomes during both demyelination as well as remyelination. These findings may point toward targeting glycolytic intermediates in microglia as a potential therapeutic to combat against WM degeneration.

Acknowledgements: R01AG070830

More than meets the eye: Distance vision and cognitive decline across two decades

Rawon Alfatlawi,¹ Folorunsho, Sunkanmi,² Ibrahim Abdullahi,³ Farouq B.U Muhammad,³ Dahwa S. Daniel.,³ Maji D. Attalawo,³ Esiaka Darlingtona K. ^{4,5}

¹University of Kentucky College of Medicine, Lexington, KY; ²Department of Sociology, University of Nebraska, Lincoln, NE; ³Federal University of Health Sciences, Azare. Bauchi, Nigeria; ⁴Department of Behavioral Science, University of Kentucky College of Medicine, Lexington, KY; ⁵Center for Health, Engagement and Transformation, University of Kentucky College of Medicine, Lexington, KY.

Graduate Student

Background: Vision impairment was added to the Lancet Commission's list of modifiable dementia risk factors in 2024, but it remains unclear which aspect of vision is most strongly associated with cognitive decline and whether this association is independent of depressive symptoms. Depressive symptoms are particularly relevant because they may represent a pathway linking poorer vision to cognitive decline, potentially accounting for part of the observed vision-cognition association.

Methods: We analyzed 34,905 adults aged 50 years and older from 1996 to 2016 waves of the Health and Retirement Study. Multilevel growth curve models estimated associations of self-rated overall, distance, and near vision with trajectories of a 35-point cognitive composite, adjusting for hearing, entry cohort, and sociodemographic and health covariates.

Results: Better distance vision was associated with slower cognitive decline (age $\times$ vision, $b = 0.098$, $p < .001$), with a larger coefficient than near vision ($b = 0.064$) and overall eyesight ($b = 0.053$). The age-by-distance-vision coefficient remained similar after adjustment for depressive symptoms ($b = 0.094$ before adjustment; $b = 0.098$ after adjustment), suggesting that depressive symptoms did not account for the observed association.

Conclusion: These findings position distance vision as a potentially overlooked marker of cognitive aging and raise an important question: could preserving vision also help preserve cognition? If so, distance vision may offer not only a window into cognitive aging, but also a potentially modifiable target for preserving cognitive health.

Relationship between depressive symptoms, physical activity, and Alzheimer's disease biomarkers

Kelsey K. Amon¹, Marta Stojanovic¹, Denise Head²

¹Dept. of Psychology, College of Arts and Sciences, University of Kentucky, Lexington, KY; ²Dept. of Psychology, Washington University in St. Louis, St. Louis, MO

Graduate Student

Background: Physical activity is a modifiable risk factor for Alzheimer's disease (AD), yet individuals at risk of developing AD show lower levels of physical activity. Understanding determinants of physical activity behavior, including affective factors, can help develop interventions to prevent dementia. Prior work suggests that depressive symptoms predict lower levels of physical activity across disease severity. Hence, our goals were to examine whether more depressive symptoms were associated with lower concurrent physical activity, and whether tau pathology moderated this relationship.

Methods: 149 cognitively normal middle-aged and older adults at the Washington University Knight Alzheimer Disease Research Center completed measures of depressive symptoms and physical activity. Participants wore an actigraphy watch that provided an objective measure of physical activity. Depressive symptoms were measured with the Geriatric Depression Scale (GDS), with participants divided into a group with depressive symptoms (n=75) and a group without depressive symptoms (n=74). A linear regression model examined whether depressive symptoms predicted concurrent physical activity levels. We also conducted preliminary analyses in a subsample (n=61) to examine whether tau PET moderated the association between depressive symptoms and concurrent physical activity.

Results: Results did not indicate that depressive symptoms predicted physical activity levels ($p=.195$). We also did not find a significant moderating effect of tau PET ($p=.802$) on the association between depressive symptoms and physical activity.

Conclusion: These results suggest that depressive symptoms might not be a significant predictor of physical activity levels cross-sectionally. However, depressive symptoms might be predictive of future physical activity levels and play a mediating role. Future research should examine longitudinal relationships in a larger sample.

Acknowledgments: Funding includes AG026276 and AARFD-23-1149509.

Microglial lactate metabolism links amyloid pathology and neuroinflammation in Alzheimer's disease

Clair C. Ashley^{1,2}, Nicholas J. Constantino³, J. Andy Snipes¹, Evan M. Neary¹, Rui Zhang⁴, Celeste M. Karch⁴, Lance A. Johnson^{2,3}, Shannon L. Macauley^{1,2}

¹Department of Physiology, ³Neuroscience, College of Medicine, University of Kentucky; ²Sanders-Brown Center on Aging, University of Kentucky; ⁴Department of Psychiatry, Washington University, St. Louis, MO

Graduate Student

Background: Alzheimer's disease (AD) is increasingly recognized as a disorder of early immunometabolic dysfunction. Late-stage AD is characterized by brain hypometabolism, but emerging evidence suggests that early amyloid- β (A β) pathology is associated with hypermetabolism. Microglia undergo metabolic reprogramming in response to A β ; however, the drivers and consequences of this adaptation remain poorly understood. We hypothesized that A β -associated microglial glycolytic reprogramming contributes to elevated brain lactate and may promote amyloid pathology and neuroinflammation.

Methods: Brain metabolism was characterized in APP^{swe}/PSEN1dE9 (APP/PS1) and WT mice using *in vivo* microdialysis and GC-MS metabolomics. Mouse and human AD transcriptomic datasets and immunohistochemistry identified the sources of lactate relative to amyloid plaques. Lactate metabolism was pharmacologically inhibited in APP/PS1 mice using stiripentol, an FDA-approved lactate dehydrogenase inhibitor. Ongoing studies utilize *Ldha*^{fl/fl}::*Tmem119-2a-CreERT2*; APP/PS1 mice to directly test the contribution of microglial lactate production to amyloid pathology.

Results: A β pathology increased interstitial fluid (ISF) lactate by ~50% and decreased ISF glucose by 25%. Metabolomics revealed increased glycolysis alongside reductions in TCA cycle intermediates. *Ldha* was enriched in the peri-plaque microenvironment and preferentially associated with diffuse A β . IHC and transcriptomic analyses identified reactive microglia as a major source of lactate, with *Ldha* enriched in microglia in APP/PS1 mice and human AD brains. Pharmacological inhibition of LDH with stiripentol reduced ISF lactate by ~60% and ISF A β by ~50%, accompanied by reductions in plaque-associated CD68⁺ and Clec7a⁺ microglia. Preliminary studies of microglia-specific *Ldha* depletion similarly suggest reduced microglial burden and altered plaque morphology.

Conclusion: These data support a model in which microglial lactate links altered brain metabolism to neuroinflammation and amyloid pathology and position lactate as a possible therapeutic target in early AD.

Acknowledgements: NIA R01 AG068330, NIA R01AG093847 AG068330, NIA K01 AG050719, BrightFocus Grant, CNS Metabolism COBRE P20 GM14832, CART grant (PI: Macauley); NIH T32 AG078110 "Training in Translational Research in Alzheimer's and Related Dementias (TRIAD)"

Occupational therapy utilization by Hispanic individuals with memory loss in the United States: A narrative review

Mackenzie Caldwell¹, Andrea Hernandez^{2,3}, Abby Gaugler¹, Riya Patel¹, Nancy Wolff², Kennedy Walcott-George², Elizabeth Rhodus²

¹ College of Medicine, University of Kentucky; ² Sanders-Brown Center on Aging, University of Kentucky; ³

Graduate Student

Background: Hispanic older adult populations are 1.5 times more likely to experience Alzheimer's or other dementias, compounded with decreased utilization and access to dementia care services. Limited research explores the usage of occupational therapy amongst Hispanic individuals with cognitive decline. This narrative review explores how Hispanic individuals with memory loss utilize occupational therapy with their care in the United States.

Methods: A review of literature was conducted of PubMed, Scopus, Embase, and Cochrane Library for articles published after 2020 that detailed Hispanic individuals with memory loss interacting with occupational therapy services or principles.

Results: Ten articles were identified to address occupational therapy utilization of Hispanic individuals with memory loss, three of which coached Hispanic caregivers to provide occupational therapy to their loved one with cognitive decline. Caregiver-focused trainings to manage behavioral and psychological symptoms of dementia and mobility reported benefits in care efficacy and problem solving. Calander systems, stimulative nature tasks, exercise, and social activities were completed by Hispanic individuals with memory loss through goal setting and alleviating participation barriers. Hispanic individuals with cognitive decline who participated in found studies improved in overall daily functioning, organizational skills, and neurocognitive function. Community partnerships and cultural consideration were highlighted as intervention facilitators. Disparities in activities in daily living and occupational therapy referrals amongst Hispanics with memory challenges were identified despite strong acceptability of cognitive stimulation therapy within this population.

Conclusion: Occupational therapy services can improve symptoms of memory loss, cognitive function, and care delivery within Hispanic populations. Future interventions should be tailored to the cultural needs of Hispanic individuals and imbed community partnerships to solidify trust amongst this population and target disparities in utilization.

Acknowledgments: This research was supported by the University of Kentucky Medical Center Library.

INDICATE: Novel approach to post-stroke cognitive outcome prediction in an Appalachian population

Kaitlyn E. Brock¹, Xiaotong Song¹, Jacqueline A. Frank^{2,5}, Elise L. Dahlke², Christopher J. McLouth^{3,4,5}, Justin F. Fraser^{2,3,5}, Keith R. Pennypacker^{2,3,5}, Jordan P. Harp^{3,5}

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²Department of Neurosurgery, College of Medicine, University of Kentucky; ³Department of Neurology, College of Medicine, University of Kentucky; ⁴Department of Biostatistics, College of Public Health, University of Kentucky; ⁵Center for Advanced Translational Stroke Science, College of Medicine, University of Kentucky

Graduate Student

Background: Stroke survivors often face lingering cognitive deficits such as dementia. Those from rural Appalachia are at even greater risk for poor clinical outcomes. Predictive models are needed to identify patients who may require extensive post-stroke care. The prospective observational cohort study INDICATE identifies novel proteomic biomarkers associated with post-stroke dementia in Appalachian and non-Appalachian patients treated with mechanical thrombectomy with the aim of identifying patients who require post-stroke care.

Methods: Blood samples are collected for proteomic analyses, and a full neuropsychological battery is completed to track cognition at various longitudinal timepoints. A manual chart review is used to collect patient characteristics, demographics, and comorbid health conditions.

Results: Out of 400 eligible patients, 103 have been enrolled in INDICATE. Initial recruitment analyses revealed a significant association between age and enrollment status. Patients who canceled their 90-day follow-ups were located significantly farther away from the study site, and patients from Appalachian counties were less likely to attend their 90-day follow-ups. No significant differences in clinical stroke characteristics across enrollment groups were found.

Conclusion: INDICATE is in a unique position to identify biomarkers predictive of long-term cognitive outcomes and examine disparities in such outcomes in rural Appalachian populations. Given challenges recruiting older patients and patients living farther away, we propose strategies to further improve recruitment and retention.

Acknowledgements: INDICATE is funded by National Institutes of Health (NIH) grant #R01NS127974.

Investigating the effects of chronic viral antigen exposure on neuroinflammation and Alzheimer's disease pathology

MaKayla F. Cox^{1,2,4}, Jill Pflugheber³, Marissa Donofrio³, Taylor K. Roberts^{1,2,4}, Kelly Roberts^{1,2,4}, Leke Bytyqi^{1,2,4}, Teresa Macheda^{1,2,4}, Amelia Pinto³, and Adam Bachstetter^{1,2,4}.

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Graduate Student

Background: Alzheimer's disease (AD) is characterized by amyloid- β and tau pathology accompanied by progressive neuroinflammation. Growing evidence suggests that infection and immune history may influence dementia risk, but the mechanisms linking viral exposure to AD-related neuroinflammation remain unclear. Lymphocytic choriomeningitis virus (LCMV) provides a well-characterized experimental system for comparing resolving infection (Armstrong) with persistent infection and chronic viral antigen exposure (Clone 13). This study investigates whether these distinct viral immune states differentially affect neuroinflammation and AD-related pathology in App^{SAA} KI mice.

Methods: 56 AppSAA KI mice were infected with LCMV at 4–6 months of age and aged for 6 months following infection. At the terminal endpoint, brain, meninges, brainstem, and spleen were collected. Splenocytes were processed for flow cytometry to characterize peripheral immune responses. Brain tissue was regionally dissected and collected for biochemical and molecular analyses. Cortical tissue was fractionated for MSD-based assessment of inflammatory mediators, and an additional cortical sample was collected for qPCR analysis of immune- and inflammation-related genes, including Cxcl10, Clec7a, Tnf, Il1, Il6, Tim1, Tim3, Cst7, Lcn2, Cd4, and Cd8.

Results: Tissue collection has been completed, and molecular and biochemical analyses are ongoing.

Conclusion: These studies will determine whether persistent viral antigen exposure produces a distinct neuroinflammatory response compared with resolving infection in the context of AD-related pathology. By comparing persistent and resolving LCMV infection, this work will help define how the duration and persistence of antiviral immune activation influence neuroinflammatory pathways relevant to AD.

Acknowledgments: This publication was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1TR001998. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Brain age gap estimation from MRI biomarkers: Benchmarking machine learning regressors for an interpretable aging marker

Sania Eskandari¹, Luis Gonzalo Sanchez Giraldo¹ for the Alzheimer's Disease Neuroimaging Initiative*

¹Department of Electrical and Computer Engineering, University of Kentucky

Graduate Student

Background: Brain-age prediction from MRI-derived biomarkers provides a compact measure of biological brain aging and may support early characterization of neurodegenerative risk. The brain age gap (BAG), defined as predicted brain age minus chronological age, offers an interpretable deviation from normal aging. Here, we benchmark multiple machine learning regressors for brain-age estimation from ADNI MRI summary measures and provide an interpretable baseline for downstream BAG-based neurodegenerative risk modeling.

Method: We analyzed data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), totaling 1,556 participants (49.7% women). Data were partitioned into training (n=664; 57.4% women) and test (n=892; 44.1% women) sets. Imaging-derived predictors included hippocampal volume, white matter hyperintensity (WMH) burden, cerebrum total cerebellar volume as a global volumetric reference, and demographic covariates (sex and education). We trained and compared five regression models to predict chronological age: linear regression, support vector regression (SVR), k-nearest neighbors (KNN) regression, gradient-boosted trees (XGBoost), and TabPFNRegressor. Regional volumetric measures were normalized by the global volume reference where applicable, and continuous variables were standardized for scale-sensitive models (SVR, KNN). Performance was summarized primarily by MAE (years), with RMSE and R^2 as secondary metrics (Table 1).

Result: Across evaluated baselines (Table 1), TabPFNRegressor achieved the best performance (MAE=5.3666 years; RMSE=6.6840 years; $R^2=0.2502$), substantially outperforming linear regression, XGBoost Regressor, KNN, and SVR. Model interpretability (SHAP for TabPFNRegressor) highlighted hippocampal volume and WMH burden among the most influential predictors, providing both cohort-level feature importance and subject-level explanations for predicted brain age.

Conclusion: This comparative benchmark identifies TabPFNRegressor as a strong regressor for brain-age prediction from MRI summary measures and supports interpretable brain-aging biomarkers (e.g., BAG). Future work will develop supervised classifiers for neurodegenerative disease detection that incorporate BAG as a key feature for diagnostic discrimination in MRI datasets.

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Efficacy of a local registry for clinical trial recruitment and engagement: The Behavioral & Biomedical Research In General Health & Thinking study (BeBRIGHT)

Coskun EP, Siddiqi A, Barber J, Holloman H, Jicha GA

Alzheimer's Disease Research Center, Sanders-Brown Center on Aging; Department of Neurology, College of Medicine, University of Kentucky, Lexington, KY

Faculty

Background: Engaging and recruiting potential research participants is a challenge at the site level. Many national on-line platforms have been developed to address these issues, and yet, referrals from these platforms have been limited leaving large numbers of participants unengaged in further research. Feedback that we have received from our local community indicate that a lack of personal contact, useful feedback, and regular engagement are major issues .

Methods: The Behavioral & Biomedical Research In General Health & Thinking (BeBRIGHT) study was developed as a semiautomated, locally implemented, hybrid (E & human contact) registry to enhance clinical trial engagement, tracking cognition/lifestyle longitudinally. Immediate and sustained disclosure/education/research invitations are provided. Participants (age ≥ 50 years, or their caregivers) were enrolled through an on-line REDCap system, completing preliminary data collection, followed by a telephone contact (30-45 minutes) for collection of an abbreviated medical history, medication use, subjective memory concerns, cognitive battery (validated components of the MoCA), depression screen (derived from the GDS and SF-36), and a brief lifestyle activity survey.

Results: In the first month of activation, we enrolled 116 participants with mean age 71.65 ± 8.81 years, education 16.84 ± 2.95 years, 29% male sex, with 7.5% racial/ethnic minorities. Few participants reported a known diagnosis ($n=8$; 6.9%), although BeBRIGHT data demonstrated that 27.6% potentially met criteria for MCI or ADRD. A significant percentage of participants, ($n=37$; 31.9%) were potentially eligible for currently enrolling clinical trials at our site. Twelve were ineligible on further review and 4 declined engagement beyond BeBRIGHT, leaving 21 (18.1%) participants that are in active recruitment in just 2 months. This stands in stark contrast with referrals from the 5 active on-line National registries we engage with that produced no potentially eligible participants over the same time period, despite much larger numbers registered.

Conclusions: The concept and application of research engagement registries need to be re-imagined. The present data suggest that local, on-line, research registries, with human touchpoints, and rapid disclosure/educational materials may be more effective than sterile National programs as a method for enhancing clinical research engagement at the local site level.

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Differential associations of MMP-9 and GFAP with cortical structure in older adults

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Background: Blood-based glial fibrillary acidic protein (GFAP) and matrix metalloproteinase-9 (MMP-9) reflect astrocyte reactivity, neurovascular injury, inflammation, and extracellular matrix remodeling in brain aging. We examined whether plasma MMP-9 and GFAP were associated with regional cortical volume and thickness in older adults.

Methods: Plasma MMP-9 (N=23) and GFAP (N=16) concentrations were examined in older adults with structural MRI data from the University of Kentucky Alzheimer's Disease Research Center (UK-ADRC). Pearson correlations tested associations between biomarker concentrations and regional cortical volume and thickness measures. Sensitivity analyses with and without outliers were conducted.

Results: Higher plasma MMP-9 levels were associated with smaller right precuneus volume ($r = -.475$, $p = .022$) and reduced cortical thickness across several frontal and temporal regions, including bilateral rostral middle frontal, right superior frontal, and left middle temporal cortices ($r = -.418$ to -0.471 , $p < .05$). GFAP showed no significant associations with cortical thickness, although higher GFAP levels were associated with a trend toward smaller left superior temporal volume ($r = -0.45$, $p = 0.080$).

Conclusion: Plasma MMP-9 showed stronger and more consistent associations with cortical structure than GFAP, with inverse associations spanning frontal, temporal, and parietal regions. These findings support MMP-9 as a correlate of regional brain structural variation in brain aging. Larger longitudinal samples with greater overlap in biomarker availability are needed to clarify the role in Alzheimer's Disease pathology.

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Age and Alzheimer's disease pathology as predictors of affective response to exercise

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Graduate Student

Background: Identifying determinants of affective response to exercise in later adulthood may predict long-term physical activity engagement, with positive affective response being linked to greater physical activity levels. Older adults might experience increased physiological symptoms during acute exercise and, thus, less positive affect. Further, amyloid and tau pathology have been linked to symptoms of depression, anxiety, and affective dysregulation, which might lead to reduced positive affective response to exercise. The goals of the study were to examine whether age and AD pathology impact the affective response to exercise.

Methods: 127 cognitively normal middle-aged and older adults were recruited from the Knight ADRC Adult Children Study. Participants completed a bout of moderate-intensity exercise, with affect measured before, during, and after. A subset of participants also underwent PET-Amyloid (n=82) and PET-Tau (n=45). Generalized additive mixed effects models examined whether age and AD pathology predicted affective trajectories during and after exercise.

Results: Age was significantly associated with affective response across exercise periods ($p < .001$). Older individuals experienced a delayed increase in positive affective valence during and post-exercise ($p < .001$). Amyloid levels predicted affective response ($p = .032$): individuals with lower amyloid levels demonstrated an increase in positive affect at the beginning of acute exercise, while those with higher amyloid levels showed an increase mainly post-exercise. Tau pathology did not predict affective response across exercise periods ($p = .435$).

Conclusion: These results suggest that age and amyloid pathology can impact the trajectory of affective response to exercise in middle-aged and older adults. These findings provide insight into potential targets for optimizing affective response to exercise and increasing physical activity engagement in later adulthood, including those at risk of developing AD.

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Mapping multiple mRNA modifications across Alzheimer's Disease genes with deep direct RNA sequencing

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Background: The transcriptome extends well beyond gene expression, with ~170 RNA modifications are known (~50 in humans), including N6-methyladenosine (m⁶A), 5-methylcytidine (m⁵C), pseudouridine, and adenosine-to-inosine (A-to-I) editing, which regulate RNA biology. These modifications are linked to cancer, infectious disease, cardiovascular disease, and neurological disorders, and mutations in modification writers (e.g., NSUN2, PUS7, WDR4) are directly the cause of neurodevelopmental disorders. In Alzheimer's disease (AD), m⁶A, its writer METTL3, and A-to-I editing are reduced, and A-to-I editing of circular *MAPT* RNAs promotes tau tangle formation. Because RNA modifications are dynamic, they are compelling therapeutic targets, yet how multiple mRNA modifications are distributed across AD genes remains unknown. Direct RNA sequencing (dRNA-seq) is a high-throughput approach that can sequence RNA directly, simultaneously identifying high-confidence RNA modifications within their full sequence context with nucleotide-level, single-molecule resolution. We therefore mapped RNA modifications in case and control brains across medically relevant genes.

Methods: Postmortem dorsolateral prefrontal cortex (Brodmann area 9/46) from 6 AD cases and 6 age- and sex-matched controls was obtained from the Banner Sun Health Research Institute Brain and Body Donation Program. Total RNA (RIN >8.0) was prepared with the Oxford Nanopore SQK-RNA004 kit, and dRNAseq was performed. Reads were basecalled with Dorado v1.4.0, which also called m⁶A, m⁵C, inosine, and pseudouridine, and aligned to GRCh38. Modkit quantified modification rates, and differential modification between cases and controls was tested at sites with ≥30 reads, with ≥10% of those reads being modified in ≥3 cases and controls (Benjamini-Hochberg FDR).

Results: We identified >9,000 genes with at least one mRNA modification, including 104 brain disease genes and 30 AD genes. Across m⁶A, m⁵C, inosine, and pseudouridine, genes carried 1 to 10+ unique sites per modification type individually, with distinct distributions. For example, inosines are the rarest while m⁶A are substantially more common. Similarly, we identified the most modified AD genes, which included *TSPAN14*, *MAPT*, *PSEN1*, *SORL1*, and *TMEM106B*. Most AD genes were enriched for m⁶A, whereas *SORL1*, *TMEM106B*, and *SNX1* were enriched for pseudouridine and several genes, including *MAPT*, had inosine sites. Pseudouridine and inosine can directly alter translation. Three modifications (two m⁶A, one inosine) were differentially modified between cases and controls, based on the percentage of RNA molecules carrying each modification.

Conclusion: AD genes, including *MAPT*, *PSEN1*, and *SORL1*, are heavily modified with gene-specific m⁶A, pseudouridine, and inosine profiles, providing a basis for new therapeutic targets. Ongoing work will identify RNA modification quantitative trait loci, which are genetic variants associated with RNA modification sites, and modifications associated with splicing events.

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Support helps and strife hurts: Family, friends, and caregiver burden

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Background: Alzheimer's disease and related dementias (ADRD) alter areas of daily life, impacting the person with ADRD and their caregivers. Social support and assistance from family and friends may help mitigate caregiver burden, while family conflict regarding caregiving strategies and illness beliefs has been associated with greater burden. This study examines how the amount of assistance and caregiving-related strife or disagreement from family and friends are associated with caregiver burden among caregivers of individuals with ADRD living at home.

Methods: This study conducted secondary analyses of data from adults with ADRD enrolled in a behavior-based clinical trial and their caregivers. Caregiver burden was measured using the Zarit Burden Inventory (ZBI), with higher scores indicating greater burden. Spearman correlation assessed relationships between caregiver burden and social support, measured by caregiver-reported help or strife/disagreement related to caregiving from family and friends. A one-sided t-test compared ZBI scores between caregivers who did and did not receive help.

Results: Data were analyzed from 37 caregivers of individuals with ADRD. Most caregivers were female (n=29), $\bar{x}$ age=62.97 ($SD=11.23$), spouses (n=19), and in rural areas (n=24). Caregivers who received help from family and friends had lower mean Zarit Burden scores than those who did not (33.06 ± 12.36 vs. 39.39 ± 14.15 ; $t(34)=1.430$, $p=.081$). Among caregivers receiving help, greater amounts were associated with lower caregiver burden ($r_s=.284$, $p=.088$, $n=18$). Strife or caregiving-related disagreement was positively correlated with caregiver burden, although not statistically significant ($r_s=.129$, $p=.447$).

Conclusion: Larger studies should examine specific types of support caregivers receive, as different forms of social support may affect caregiver burden differently. Our findings suggest that support related to caregiving approaches may contribute to disagreement and stress, highlighting the need for interventions and policies that promote collaborative assistance rather than simply increasing support.

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Cultural and linguistic adaptation of 'Harmony' behavioral intervention for Latino dementia caregivers

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Background: Current literature states that 14% of Latino adults over 65 years of age in the US have Alzheimer's disease and related dementias (ADRD). Latino caregivers provide home care for long periods of time, face transportation barriers and lack adequate dementia care education and support due to linguistic and cultural barriers. These factors exacerbate the burden experienced by caregivers. Our previous research developed a behavioral intervention, Harmony, that trains and educates caregivers on managing behavioral symptoms associated with ADRD through sensory-based assessment and intervention. The purpose of this project is to present a protocol planned to adapt Harmony to be culturally/linguistically acceptable for Latino caregivers.

Methods: This adaptation will follow a heuristic model for cultural adaptations of evidence-based interventions. The model also includes the Participatory and Iterative Process Framework for Language Adaptation (PIPFLA) model for Spanish translation. Adaptation entails, 1) conducting qualitative interviews with 10-12 caregivers to identify cultural needs, 2) creating a pilot study using data from step 1 and all 11 steps from the PIPFLA translation framework, 3) integrating data from steps 1-2 to adapt intervention protocols/materials, and 4) piloting the newly modified protocol with 20-25 dyads to evaluate feasibility/acceptability within the Latino population.

Results: The current study protocol has been developed based on prior research indicating efficacy of the intervention to improve the functional performance in daily activities ($p=0.039$) in addition to caregiver satisfaction ($p=0.02$) among individuals with ADRD. Thus far, Latino caregivers have reported a lack of resources for understanding and managing behaviors associated with dementia. A newly adapted Harmony protocol will provide personalized education and training to address this barrier.

Conclusion: Limited resources on the understanding and management of ADRD behavioral symptoms exacerbates caregiver burden within the Hispanic community. Adaptation of the Harmony intervention is a novel approach to dementia caregiving that provides personalized education and environment-based modification to support caregivers and their loved ones at home.

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Tau pathology disrupts inhibitory regulation of sleep, excitation, and neurovascular coupling

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Graduate Student

Background: Tauopathies, like Alzheimer's disease (AD), are characterized by progressive impairments in neuronal activity, network synchrony, and excitatory/inhibitory (E/I) imbalance. Despite extensive investigation of tau-mediated neuronal dysfunction, considerably less is known about how these changes impact the neurovascular unit and coupling. Our previous studies demonstrate that tau pathology disrupts sleep, reduces EEG beta power, and promotes cortical hyperexcitability, suggesting widespread network dysfunction. Importantly, inhibitory signaling remains a plausible therapeutic target. Because coordinated neuronal activity is a primary regulator of cerebral blood flow, we hypothesize that tau-dependent E/I imbalance contributes to neurovascular uncoupling.

Methods: EEG/EMG recordings were performed on 9 month P301S and wildtype (WT) mice to assess sleep quantity, relative frequency, and oscillatory activity. Stable isotope-resolved metabolomics quantified glucose-derived and total metabolite abundance. Wide-field optical imaging (WFOI) measured glutamatergic calcium dynamics and hemodynamics during rest and stimulation. Zolpidem, a GABAergic positive allosteric modulator (GABA PAM), and stiripentol a weak GABA PAM and potent LDH inhibitor were used to therapeutically restore inhibition.

Results: Tau pathology reduced time spent in NREM and REM sleep while reducing EEG beta power, coherence, and altering oscillatory activity. Metabolomics revealed an overall reduction in metabolite abundance; however, P301S mice exhibited an increase in ¹³C labeled glutamate at the expense of GABA production. WFOI revealed increased glutamatergic calcium dynamics during stimulation in P301S mice. P301S mice exhibited abnormal hemodynamic responses and altered vascular structure. Both zolpidem and stiripentol restored time spent in NREM and REM and reduced cortical hyperexcitability.

Conclusions: Tau pathology is associated with progressive network dysfunction characterized by E/I imbalance, metabolic reprogramming, impaired synchrony, and neurovascular uncoupling. Our findings support a model in which tau pathology disrupts network regulation and provides potential therapeutic targets to restore sleep, E/I balance and neurovascular coupling in tauopathies.

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Microglial metabolic reprogramming alters lactate homeostasis and metabolic flexibility in Alzheimer's disease

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Graduate Student

Background: Alzheimer's disease (AD) is associated with profound alterations in glucose metabolism. Previous studies have shown that, in the presence of amyloid pathology, microglia exhibit greater increases in glucose uptake than astrocytes and neurons, suggesting distinct metabolic reprogramming early in AD progression. Increased total abundance and interstitial fluid (ISF) lactate in APP/PS1 mice further suggest a shift toward glycolysis and lactate production. However, the contribution of microglia to altered lactate metabolism and broader metabolic homeostasis during AD progression remains unclear.

Methods: APP/PS1 mice were used to examine metabolic alterations across disease progression. Total cortical metabolite abundance was assessed using gas chromatography mass spectrometry (GC-MS) at 12 months of age and hydrophilic interaction liquid chromatography (HILIC) based metabolomics at 6 months of age. To determine the contribution of microglia to altered lactate metabolism, APP/PS1 mice were treated with the CSF1R inhibitor PLX3397 to deplete microglia. ISF lactate and cortical lactate dehydrogenase (LDH) isoenzyme profiles were subsequently assessed.

Results: GC-MS analysis demonstrated increased total lactate abundance in 12 month old APP/PS1 mice, consistent with a shift toward increased glycolytic metabolism. Microglial depletion significantly reduced brain ISF lactate and altered LDH isoenzyme composition, with decreased LDH5 and increased LDH3 abundance. This shift from LDH5 toward LDH3 suggests reduced commitment to lactate production and increased metabolic flexibility following microglial depletion. Additionally, HILIC based metabolomic analysis of cortical tissue from 6 month old APP/PS1 mice revealed broadly decreased metabolite abundance, suggesting that the metabolic landscape varies with the extent of amyloid accumulation and may reflect distinct metabolic alterations across different stages of disease progression.

Conclusions: These findings support a role for microglial metabolic reprogramming in altered cerebral lactate metabolism in AD. Increased microglial glucose uptake and lactate abundance, together with reduced ISF lactate and LDH5 following microglial depletion, suggest that microglia increasingly direct glucose toward glycolysis and lactate production during disease progression. Ongoing studies will examine how this shift affects astrocyte metabolism and redox homeostasis to better define glial metabolic interactions in AD.

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The effects of Zileuton on rat fentanyl self-administration

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Background: A major barrier to successful cessation of an addictive substance is the highly characteristic withdrawal aversive symptoms, including anxiety, irritability, and depression. Preclinical studies have demonstrated that nicotine withdrawal produces anxiety-like behavior and microglial dysfunction, suggesting that neuroimmune signaling may contribute to withdrawal-associated behavioral changes. Microglial dysfunction has also been observed following chronic exposure to and withdrawal from multiple drugs of abuse, suggesting a shared neuroimmune mechanism. Cysteinyl leukotrienes (CysLTs) are a G-protein-coupled receptor protein that is apart of allergy and inflammation responses. Microglia from mice were exposed to nicotine, opioids, or cocaine and identified similar alterations in genes associated with CysLT synthesis and release. CysLTs are pro-inflammatory lipid mediators that primarily signal through CysLT receptor 1 and CysLT receptor 2. Zileuton is an FDA-approved drug used to treat asthma and is a 5-lipoxygenase inhibitor that decreases the synthesis of leukotrienes, including CysLTs, by inhibiting an upstream enzymatic step in the arachidonic acid inflammatory pathway. Therefore, targeting CysLT synthesis with Zileuton may provide a means of determining whether this pathway contributes to neuroimmune effects associated with fentanyl exposure.

Methods: A cohort of 12 Sprague Dawley rats, 6 males and 6 females, were used for this study. Rats were first trained to respond for sucrose pellets within an operant conditioning chamber. With food restriction to increase motivation, rats progressed through fixed-ratio (FR)1, FR3, and FR5 schedules, requiring 1, 3, or 5 lever presses for each reinforcement pellet, respectively. Each FR schedule occurred for two 1-hour sessions before jugular catheter insertion surgery. Following surgical recovery, rats underwent daily 1-hour self-administration sessions in which animals received either fentanyl or saline. Zileuton or vehicle was administered via I.P. injection 10 minutes prior to each self-administration session. Following behavioral testing, animals will be euthanized and brain tissue collected for biochemical analyses, such as qPCR, to evaluate molecular markers associated with CysLT signaling and neuroinflammation.

Results: We hypothesize that inhibition of CysLT synthesis via Zileuton will decrease neuroinflammatory signaling and alter behavioral responses associated with chronic fentanyl exposure in rats, including drug-seeking behavior and withdrawal-related symptoms.

Conclusion: These studies will aim to evaluate the contribution of CysLT signaling to neuroimmune responses associated with chronic fentanyl exposure. This work will help determine whether pharmacological inhibition of CysLT synthesis alters fentanyl-related behavioral responses and aversive withdrawal symptoms. Therefore, this would identify CysLT signaling as a potential target for future therapeutic investigations.

Genome-wide short tandem repeat expansion analysis Identifies novel loci associated with Alzheimer's Disease

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Background: Alzheimer's Disease (AD), the leading cause of dementia in older adults, has established genetic risk factors including mutations in *APP*, *PSEN1*, *PSEN2*, and *APOE*. While short tandem repeats (STRs) are highly mutable sequences that are implicated in various neurodegenerative disorders (NDD), their contribution to AD pathogenesis remains largely understudied.

Methods: We analyzed whole-genome sequencing data from 10,721 Alzheimer's Disease Sequencing Project participants (5,132 AD cases, 5,589 without AD) of multiple ancestries. ExpansionHunter genotyped 172,415 STR loci. Primary analyses (PLINK and associaTR) adjusted for age, sex and ancestry principal components. Continuous deviation and bin-based expansion models were run as additional analyses, and ExpansionHunter Denovo searched for expansions outside the reference catalog. We also tested loci from a published UK Biobank STR GWAS.

Results: PLINK yielded 20 loci as Bonferroni-significant associations, 13 with lower and 8 with higher odds of AD, strongest at *LINC00595*, *GSE1* and *TLE4* (odds ratios 0.57–0.61), and *PAN3* (OR 1.39). associaTR identified 74 loci (46 risk-increasing, 28 protective), led by *PAQR5* ($P = 3.6 \times 10^{-30}$). Six loci (*PAQR5*, *LINC00595*, *TLE4*, *SNTG2*, *ZNF404* and *MIR8054*) were significant in the PLINK, associaTR, both continuous deviation, and bin-based analyses. In targeted testing of loci from the UK Biobank study, three (*APOE*, *ACE* and *CR1*) replicated in our ADSP study as well. In additional analyses, the inverse-normal continuous deviation model found 41 loci, all intronic or intergenic and enriched for SVA retrotransposons (3 of 41 versus 0.11% of tested loci), and bin-based tests found 27 significant comparisons at 20 loci, with higher odds in larger bins at *SNTG2*, *ZNF404* and *LG11*. ExpansionHunter Denovo found 34 non-catalog expansions (six high confidence), including an AGAT expansion near *TPH2* in 75 cases and no controls at $z \geq 5$.

Conclusion: STR length variation is associated with AD across several complementary models, with six loci supported by both primary, the continuous deviation and the bin-based analyses. Replication of three loci (*APOE*, *ACE*, and *CR1*) from UK Biobank study supports our approach as well. To further validate these results, replication in independent cohorts and confirmation with long-read sequencing are needed.

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Microglial contributions to neurovascular adaptations in tauopathy

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Graduate Student

Background: Tauopathy increases cortical excitability despite neuronal loss, with accompanying changes in brain metabolism, but how these alterations relate to neurovascular remodeling remains unclear.

Methods: Metabolomics, EEG/EMG recordings, and wide-field GCaMP imaging assessed metabolic and neuronal alterations in P301S mice relative to wild-type controls. Immunohistochemistry, confocal microscopy, and three-dimensional reconstruction quantified vascular architecture and microglial distribution.

Results: P301S mice exhibited increased glutamate abundance and fractional enrichment, decreased GABA abundance and enrichment, reduced EEG beta power, and increased cortical activity. These changes were accompanied by hypervascularization, increased vascular tortuosity, and increased microglial abundance at cortical vascular branch points. Microglia also closely associated with neuronal processes and blood vessels.

Conclusion: These findings support a model in which tau-associated neuronal hyperexcitability and altered metabolism drive vascular remodeling, with microglia potentially mediating this response. Ongoing microglial depletion studies will test whether microglia support vascular adaptation or contribute to neurovascular dysfunction.

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***APOE4* drives changes in microglial reactivity after low-dose Aducanumab immunotherapy**

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Graduate Student

Background: Anti-amyloid β (A β) monoclonal antibodies, such as Aducanumab, are the first disease modifying therapies for AD. Despite this, amyloid related imaging abnormalities (ARIA), findings of edema or microbleeds on MRI, are adverse effects sometimes associated with severe symptoms. *APOE4* (E4) and pre-existing vascular amyloid deposition are thought to be the greatest risk factors for ARIA. E4 carriers, however, are predisposed to increased cerebral amyloid angiopathy (CAA) development, presenting an important confound for understanding the mechanism of ARIA. Using single cell (SC) and spatial transcriptomics (ST), we sought to dissect the transcriptional changes induced by anti-A β treatment in E4 mice.

Methods: Nine-month-old humanized E4 mice crossed to 5XFAD ("EFAD") received 12 weeks of a low dose (1.56 mg/kg) of chimeric Aducanumab (chAdu) or IgG isotype control. Six female E4FADs (n=3 per group) underwent Xenium ST and SC. Hemibrains were mounted on Xenium slide cassettes which were run on the Xenium Analyzer using a custom 480-gene panel. Post-Xenium, slides were stained with Thioflavin-S for downstream image co-registration and plaque-proximity analyses. Analysis of SC and ST data was performed in R using Seuratv5 and DESeq2. Packages including SPLIT, Squidpy, and CellChat were used for cell purification, image analyses, and cell-cell inferred interactions. Clusters were manually annotated, and microglia were subclustered to explore differences in cellular heterogeneity.

Results: After data processing, over 346k cells were analyzed, 35k of which were microglia. Vascular populations including endothelial cells, pericytes, and vascular smooth muscle cells were also present. Microglial subclustering revealed 10 unique clusters, including disease-associated (DAM), interferon responsive (IRM) and homeostatic microglia. Treatment with chAdu increased DAM microglia and decreased primed homeostatic microglia relative to IgG controls. Plaque-proximity analyses revealed distinct microglial states near parenchymal plaques and CAA. In addition, the immune and vascular spatial neighborhoods differed with chAdu treatment.

Conclusions: Even at low doses of chAdu, microglia were reprogrammed to respond to inflammation, especially when located near vasculature. These findings provide a window into the potential mechanisms between E4 and CAA driven ARIA.

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Distinct single-nucleus RNA-Seq changes among non-neuronal cells in ADNC, LATE-NC, and mixed pathologies

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Staff

Background: Limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) frequently co-occurs with Alzheimer's disease neuropathologic change (ADNC), complicating classification. Cell-type-specific molecular features distinguishing LATE-NC-dominant, ADNC-dominant, and mixed LATE-NC and ADNC pathology remain incompletely characterized.

Methods: We analyzed single-nucleus RNA sequencing data from the SEA-AD consortium, focusing on non-neuronal cells in the middle temporal gyrus (MTG). Donors were stratified into LATE-NC-dominant, ADNC-dominant, and mixed LATE-NC and ADNC. Differential expression and gene set enrichment analyses were performed across glial and vascular cell supertypes.

Results: Distinct transcriptional patterns differentiated pathologies. Astrocytes, microglia, and oligodendrocytes exhibited differential expression between LATE-NC- and ADNC-dominant cases. Representative genes and pathways highlighted these distinctions, with LATE-NC-dominant showing enrichment in signaling and RNA regulation, ADNC-dominant in mitochondrial dysfunction, and mixed pathology in translational dysregulation and lipid remodeling, suggesting a distinct biological state.

Conclusion: Findings highlight biological heterogeneity and non-neuronal molecular features relevant to disease classification and future research.

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NOX at the blood-brain barrier: A new therapeutic target for Alzheimer's disease?

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Background: Blood-brain barrier dysfunction is a key contributor to cognitive decline in Alzheimer's disease (AD). One factor that drives barrier dysfunction is oxidative stress. We recently identified NOX2, an isoform of NADPH oxidase, as a key source of A β -induced oxidative stress at the blood-brain barrier. The goal of this project is to identify signaling steps underlying NOX2-mediated barrier dysfunction and explore the role of other NOX isoforms present at the blood-brain barrier. We hypothesize that A β activates NOX2, leading to oxidative stress that upregulates matrix metalloproteinases, which in turn degrade tight junction proteins and ultimately cause barrier dysfunction.

Methods: Mouse capillaries were isolated according to our established protocol (Hartz et al., 2004). Isolated capillaries were divided into three groups: 1) Ctrl, 2) 100nM A β 40, 3) 100nM A β 40 plus 1 μ M Phoxl2 for 24 hours at room temperature. The same experiment was conducted for A β 42. Following incubation, samples were lysed and used for ELISA to quantify protein expression levels of NOX2, NOX4, MMP2, MMP9, and Claudin-5. Bradford protein assay was used to determine protein concentrations in each sample and normalize the data obtained with ELISA. Isolated brain capillaries were immunostained for NOX1,2,3, and 4.

Results: We detected NOX1, 2, 3, and 4 protein expression in isolated mouse brain capillaries by immunostaining, confirming that all four NOX isoforms are expressed at the blood-brain barrier. We found that capillaries exposed to A β 40 and A β 42 had significantly higher NOX2 protein levels than control capillaries. We also found that capillaries incubated with A β 40 and A β 42 expressed higher mean fluorescent pixel intensity for NOX2 and NOX4 compared to control capillaries. Phoxl2 abolished both the A β 40- and A β 42-mediated increase in MMP2 and MMP9 protein levels and restored Claudin-5 to control levels. Importantly, Phoxl2 prevented A β -mediated capillary leakage. We also found that capillaries incubated with A β 40 and A β 42 expressed higher mean fluorescent pixel intensity than the control capillaries for NOX2 and NOX4.

Conclusion: Our data indicate that A β activates NOX2, inducing oxidative stress that increases MMP2 and MMP9, degrades tight junctions, and leads to capillary leakage. These findings highlight NOX2 as a critical mediator of A β -induced barrier dysfunction and suggest that NOX2 could be a potential therapeutic target to prevent blood-brain barrier dysfunction in Alzheimer's disease.

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APOE4 reduces vascular plasticity and increases perivascular glial reactivity after aducanumab immunotherapy

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Background: Anti-amyloid monoclonal antibodies, such as Aducanumab and Lecanemab, are the first disease modifying therapies for AD. Despite this benefit, amyloid related imaging abnormalities (ARIA), findings of fluid effusion or microbleeds on MRI, are key adverse effects sometimes associated with severe symptoms and death. While the cause of ARIA is unknown, there is a strong link with APOE4 (E4). E4 is the strongest genetic risk factor for late onset AD, making it critical to understand the mechanisms of E4 driven ARIA.

Methods: Nine month old human APOE-expressing mice (E2, E3, or E4) crossed to the 5XFAD model of amyloidosis ("EFAD") received 12 weeks of a low dose (1.56 mg/kg) treatment with chimeric Aducanumab (chAdu) or IgG isotype control. Mice underwent MRI and images were mapped to the Allen reference atlas for regional assessments of ARIA pathology, with microbleeds quantified on SWI imaging. Histological assessment of microbleeds (Prussian Blue), plaque (AmyloGlo) and associated gliosis (IBA1, GFAP, CD68, Clec7a, CD206) were performed in parallel with vascular labeling (isolectin). A group of six female E4FADs underwent single cell and xenium spatial transcriptomics analysis, with data analysis in R and python.

Results: Low dose treatment with chAdu was sufficient to reduce histological plaque burden, though we found no differences when measured through ELISA. E4FADs also demonstrated increased microbleed pathology, particularly in the hippocampus, detected both by SWI MRI and Prussian Blue histology. Decreased plaque load and increased microbleeds were also correlated to increased vascular-associated microgliosis and astrogliosis in E4FADs only. We also found increases in DAM and activated microglia in E4FADs. Vascular branching analysis revealed increased vascular reorganization in E2 and E3FADs but not in E4FADs after chAdu treatment. Single cell and spatial transcriptomics analysis revealed spatial reorganization and increased peripheral immune and inflammatory signaling in the vascular niche.

Conclusion: Even at low doses of chAdu, we can reproduce plaque clearance and ARIA like events in EFAD mice. Furthermore, APOE4 modulates perivascular glial reactivity after anti-A β therapy, and drives spatial and transcriptional reprogramming of microglia and vascular cells in the perivascular niche. These findings provide a window into the potential vascular mechanisms of E4 driven ARIA and associated pathologies.

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Cell-type specific transposable element expression across Alzheimer's disease neuropathological stages in the medial entorhinal cortex

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Graduate Student

Background: Alzheimer's disease (AD) is the most common neurodegenerative disorder, however many of the underlying mechanisms remain poorly understood. Transposable elements (TEs) are mobile genetic elements which compose approximately 45% of the human genome, are increasingly being recognized as potential contributors to neurodegeneration, but their cell-type specific dysregulation through disease progression remains unclear.

Methods: We analyzed single-nucleus RNA sequencing data from the medial entorhinal cortex of 81 individuals across four AD neuropathological stages (ADNC) from SEA-AD: Not AD, Low, Intermediate, and High. After quality control and cell-type annotation using scVI and scANVI, 615,262 cells were assigned to 7 cell types. TE expression was quantified using soloTE at the family (43) and subfamily (1,182) levels, summed per sample and cell type (pseudobulk), and compared between each ADNC stage and the Not AD group using DESeq2, adjusting for sex.

Results: At the family level, significant changes were found when comparing High ADNC with Not AD, in excitatory neurons (25 of 43 families), inhibitory neurons (25), astrocytes (17), and oligodendrocytes (4). SVA and HERV-K showed increased expression across all four cell types, while older TE families such as L2, MIR, and CR1 showed decreased expression. L1 showed no significant change and Alu increased in Excitatory and Inhibitory neurons. Subfamily-level analysis revealed distinct patterns for *Alu* and L1. The youngest *AluY* subfamilies generally increased, older groups were largely unchanged, and the oldest monomer FAM decreased. Several older L1 subfamilies showed decreased expression, particularly in astrocytes, while the youngest subfamily of L1, L1HS, showed no significant change.

Conclusion: Overall, these findings suggest that TE expression changes are cell-type specific, are detected primarily at later stages of AD pathology, and vary across TE families.

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Assessing ADRD care and caregiver burden in Kentucky through Harmony telehealth program outcomes

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Graduate Student

Background: Alzheimer's disease and related dementias (ADRD) are progressive neurodegenerative conditions that impose substantial cognitive, behavioral, and functional impairments, effecting both patients and their caregivers. These challenges are exacerbated in rural regions, where factors like limited access to specialists, and long travel distances to healthcare, impede comprehensive care. Telehealth-based interventions offer a promising solution to reduce these disparities. For example, the Harmony program provides an occupational therapy telehealth intervention designed to educate caregivers with ADRD behavioral management strategies. However, the reach to rural communities via the Harmony telehealth program is unknown.

Methods: This study assessed demographics of caregivers enrolled in the Harmony program to evaluate whether rural residence influences program engagement. Participants were categorized based on rurality using the standardized Rural Health Information Hub, and engagement was measured using program contact sessions.

Results: Thirty-eight caregivers were included in this analysis. Of those enrolled, 55.9% resided in rural communities and 44% resided in urban areas. Of the 17 contact sessions, rural residents attended $\bar{x}=13.5$ contact sessions, and urban residents attended $\bar{x}=13.7$ contact sessions. Findings demonstrate no significant difference (p -value=0.875) in levels of participation between rural and non-rural caregivers across engagement metrics of session attendance and participation.

Conclusion: These results show that rural community-residing residents accessed and utilized telehealth services at the same rate as urban residents. This finding indicates opportunities for expanded telehealth programming for this population.

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Intravital imaging methods to visualize cerebrovascular structure and function

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Graduate Student

Background: Cerebrovascular pathology is highly comorbid with Alzheimer's disease (AD), exacerbating brain injury, accelerating cognitive decline, and reducing treatment efficacy. However, investigation of these vascular abnormalities in the living brain remains limited. Conventional postmortem thin-section histology is not well suited for assessing the dynamic structural and functional alterations of the cerebral vasculature.

Hypothesis: To overcome the limitations of histology, we propose using longitudinal intravital imaging to directly visualize and quantify cerebrovascular architecture and function in AD mouse models.

Methods: A chronic cranial window was implanted over the barrel cortex of wild-type and 5xFAD mice to enable longitudinal visualization of cerebrovascular architecture using light and two-photon microscopy. To visualize the cerebral vasculature, rhodamine-dextran was administered via retro-orbital injection. Neurovascular function was assessed in awake mice by delivering air-puff stimulation to the contralateral whiskers, which evoked arteriolar dilation. In parallel, laser speckle contrast imaging was used to quantify stimulus-evoked cerebral blood flow (hyperemic) responses following contralateral whisker stimulation.

Results: Our results found vascular curvature was significantly increased in aged 5xFAD mice compared with age-matched wild-type controls. Neurovascular function was also impaired in 5xFAD mice, as evidenced by reduced stimulus-evoked vascular responses. Furthermore, we identified cerebral vessels exhibiting both amyloid- β (A β) deposition and cerebral amyloid angiopathy (CAA) pathology in 5xFAD mice.

Conclusion: Collectively, these in vivo imaging approaches provide direct access to cerebrovascular structural and functional alterations in awake mice, establishing a robust and translational platform for investigating cerebrovascular pathology and therapeutic interventions.

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Effects of anti-amyloid- β therapeutics on the blood-brain barrier

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Graduate Student

Background: Understanding how anti-amyloid therapeutics (AAT) interact with the blood-brain barrier is essential for developing safer treatments. Lecanemab and donanemab, two FDA-approved AATs, reduce brain amyloid burden and slow cognitive decline in early symptomatic Alzheimer's disease. However, their use is associated with amyloid-related imaging abnormalities (ARIA) detected on MRI, which reflect damage and increased permeability of large leptomeningeal and cerebral arteries. AATs' effects on small capillaries comprising the blood-brain barrier remain unclear. Our study addresses this gap by investigating the effects of AATs on barrier integrity and function.

Methods: Brain capillaries were isolated from 8-week-old male CD1 mice using an established protocol (Hartz et al., JOVE, 2018), resuspended in DPBS supplemented with pyruvate and glucose, and incubated for 24 hours at room temperature with lecanemab, donanemab, or the corresponding isotype IgG control. Treatment concentrations were based on CSF lecanemab (BAN2401) levels measured in an early-phase clinical trial (Logovinsky et al., Alzheimer's Research & Therapy, 2016). Claudin-5, ICAM-1, and integrin β 1 levels were quantified by ELISA. Tight junction proteins claudin-5 and ZO-1 and endothelial inflammatory markers ICAM-1 and VCAM-1 were assessed by immunohistochemistry.

Results: We found that both murine lecanemab and murine donanemab significantly reduced claudin-5 protein levels compared with their respective isotype IgG controls. We also observed a disrupted claudin-5 immunostaining pattern in isolated capillaries, with significantly decreased fluorescence intensity compared with controls. Similar staining changes and reductions in fluorescence intensity were observed for ZO-1. In contrast, neither murine lecanemab nor murine donanemab altered ICAM-1 protein levels measured by ELISA. ICAM-1 and VCAM-1 fluorescence intensity were comparable to their respective isotype IgG controls. Integrin β 1 protein levels were significantly decreased following murine donanemab exposure but were not altered following murine lecanemab exposure.

Conclusion: These findings suggest that AATs alter proteins involved in blood-brain barrier integrity, while endothelial inflammatory markers remained unchanged. Our findings support further investigation into how AAT-associated changes in proteins affect blood-brain barrier function and integrity in Alzheimer's disease.

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Wearable optical monitoring of attenuated cerebral blood flow responses to hypercapnia and treadmill exercise in conscious aged and Alzheimer's Disease mice

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Background: Cerebrovascular dysfunction associated with aging and Alzheimer's disease (AD) impairs cerebral blood flow (CBF) regulation and vascular responsiveness. Conscious, freely moving mouse models provide a controlled platform for investigating these cerebrovascular changes during aging and AD progression. However, continuous CBF monitoring in conscious, freely moving mice remains technically challenging. We developed, optimized, and evaluated an innovative, wearable, fiber-free diffuse speckle contrast flowmetry (DSCF) system for continuous and longitudinal CBF monitoring during hypercapnia (8% CO₂) and treadmill exercise in conscious mice.

Methods: A skull-conforming head-stage with three-point fixation and a detachable fiber-free DSCF probe was developed to improve measurement stability and reproducible positioning. Data processing incorporated intensity-based pixel selection, noise correction, synchronized behavioral video, and structural similarity index-based quality control to identify and exclude motion-contaminated measurements. DSCF was evaluated in young and aged wild-type (WT) mice and aged AD (APOE4+/5XFAD) mice under anesthetized and conscious states.

Results: Young WT mice exhibited the greatest relative CBF increases during hypercapnia and exercise, whereas responses were attenuated in aged WT mice and further impaired in aged AD mice. Hypercapnic responses also differed between anesthetized and conscious states, particularly in young WT mice.

Conclusion: Wearable DSCF enables continuous and longitudinal assessment of age-, disease-, and state-dependent cerebrovascular function in conscious mice under physiologically relevant conditions, providing a practical platform for investigating cerebrovascular dysfunction and supporting future translation to large-animal and human studies.

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Stroke severity and thrombus location predict post-stroke cognitive performance

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Graduate Student

Background: Patients from rural Appalachia are at a greater risk for post-stroke dementia. Predictive models are needed to identify patients who may require extensive post-stroke care. We examine whether stroke thrombus locations and patient rurality can predict cognitive performance post-mechanical thrombectomy (MT).

Methods: 49 stroke patients received MT and completed neuropsychological testing 6 months post-MT. Multiple linear regression models were used to examine associations between cognitive performance and thrombus locations and rurality while controlling for age, sex, education, stroke severity (NIHSS) at admission, and reperfusion (TICI).

Results: Compared to patients with right Middle Cerebral Artery thrombus, patients with left Internal Carotid Artery thrombus performed more poorly on Craft Story Memory immediate paraphrase recall ($\beta = -1.34$, $p = .021$) and Trail-Making-Test A ($\beta = 1.41$, $p = .03$) at 6-months post-MT. NIHSS at admission significantly predicts performance on HVLT-R total immediate recall ($\beta = -0.41$, $p = .002$), Craft Story Memory immediate paraphrase recall ($\beta = -0.31$, $p = .033$), and Benson Complex Figure immediate copy ($\beta = -0.32$, $p = .049$) at 6 months post-MT. Full reperfusion post-MT is associated with better Craft Story Memory immediate paraphrase recall ($\beta = 0.33$, $p = .039$) at 6 months after controlling for NIHSS at admission. No significant associations were found between patient rurality and cognitive performance.

Conclusion: Thrombus location differentially impacts cognitive abilities and is broadly in line with the hemispheric localization of these abilities. NIHSS score at admission has the potential to serve as a predictor of post-stroke memory functioning and visuospatial construction abilities regardless of stroke thrombus location. These results provide a basis for future studies to create and refine predictive models of post-stroke cognitive functioning.

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Neuropathologic burden and clinical heterogeneity in autopsy-confirmed limbic-predominant age-related TDP-43 encephalopathy

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Staff

Background: Limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy neuropathologic change (LATE-NC) is common in older adults, yet its clinical expression is heterogeneous and may be influenced by co-pathology. We investigated whether neuropathologic burden and composition distinguish minimal, moderate, and maximal clinical progression in autopsy-confirmed LATE-NC.

Methods: We identified participants with autopsy-confirmed LATE-NC from the National Alzheimer's Coordinating Center who entered observation with a global Clinical Dementia Rating (CDR) ≤ 0.5 . We classified progression by final CDR as minimal (MinP; 0–0.5), moderate (ModP; 1–2), or maximal (MaxP; 3). Neuropathologies included LATE-NC severity, Alzheimer's disease neuropathologic change (ADNC), Lewy body disease (LBD), hippocampal sclerosis (HSCL), and cerebrovascular disease. We compared overall neuropathologic burden, individual neuropathology prevalence, and patterns of co-occurrence across progression phenotypes and used regression models to identify neuropathologic features associated with progression phenotype.

Results: Among 357 participants with LATE-NC, 98 (27.5%) were classified as MinP, 169 (47.3%) as ModP, and 90 (25.2%) as MaxP. Mean neuropathologic burden was 3.89 (SD, 1.63) in MinP, 5.00 (SD, 1.52) in ModP, and 4.74 (SD, 1.60) in MaxP. HSCL frequency increased from 31.6% in MinP to 41.4% in ModP and 48.9% in MaxP, while ADNC frequency increased from 67.3% to 90.5% and 97.8%, respectively. In adjusted models using ModP as the reference, ADNC was associated with lower odds of MinP (OR = 0.32; $p=0.003$). Greater vascular burden was associated with lower odds of both MinP (OR = 0.71; $p = 0.002$) and MaxP (OR = 0.78; $p = 0.025$).

Conclusion: Clinical cognitive progression in LATE-NC was associated with differences in both overall neuropathologic burden and co-pathology frequency. Despite minimal clinical progression, MinP participants had an average of 3.89 neuropathologies, with multiple individual pathologies present in >30% of participants. ADNC showed the clearest association with greater clinical progression; however, the MinP participants exhibited a remarkable resistance to cognitive decline in the presence of co-pathologies including ADNC. These findings suggest that clinical heterogeneity in LATE-NC may reflect specific patterns of co-occurring neuropathology.

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Perilipin-2 loss reprograms microglial lipid droplet biology and immunometabolic responses to Alzheimer's stimuli

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Graduate Student

Background: Lipid droplet accumulation is increasingly recognized as a feature of dysfunctional microglial states in neurodegeneration. In Alzheimer's disease (AD), lipid droplet-rich glia have been linked to impaired phagocytosis, inflammatory activation, and altered cellular metabolism. Perilipin-2 (Plin2), a lipid droplet-associated protein elevated in AD, may promote maladaptive lipid storage and impair microglial homeostasis. Thus, we sought to determine the role of Plin2 in microglial responses to AD stimuli, and if reduction of Plin2 would protect microglia from adopting a lipid-laden state.

Methods: We generated a Plin2 knockout (KO) BV2 microglial cell line to define how Plin2 regulates lipid droplet accumulation, lipid composition, phagocytic function, and transcriptional responses to AD-relevant stimuli. WT and Plin2 KO BV2 microglia were treated with oleic acid (250 μ M), amyloid-beta (1.5 μ M), myelin debris (15 μ g/cm²), or dead neurons to model lipid loading and neurodegeneration-relevant stress. Lipid droplets were quantified by Lipi-Green staining and HALO analysis. Phagocytosis was assessed using pHrodo-zymosan particles under lipid-loading conditions. Lipidomics was performed by LC-MS after 24-hour treatment, and bulk RNA-seq was performed on identically treated samples. We also examined amyloid plaque pathology in Cx3cr1/+ mice carrying floxed Plin2 alleles on the 5xFAD background.

Results: Across treatment conditions, Plin2 KO microglia showed a consistent reduction in lipid droplet burden together with enhanced phagocytic capacity. Lipidomic profiling revealed depletion of triacylglycerols and diacylglycerols with increased cholesterol esters, indicating substantial remodeling of intracellular lipid storage. Transcriptomic analyses demonstrated increased oxidative phosphorylation and reduced inflammatory signaling, particularly following amyloid-beta exposure, consistent with a shift away from a lipid droplet-accumulating, dysfunctional state. Preliminary in vivo observations indicated reduced amyloid plaque burden in Cx3cr1/+ mice carrying floxed Plin2 alleles on the 5xFAD background.

Conclusion: Together, these findings identify Plin2 as a regulator of microglial lipid droplet biology, immunometabolic state, and functional responsiveness to AD-relevant stressors. In vitro, Plin2 loss limits lipid droplet accumulation while promoting phagocytic and metabolic adaptation. Preliminary in vivo observations suggest a potential link to amyloid pathology and support further investigation of PLIN2 as a candidate therapeutic target in AD.

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Astrocytic Ca²⁺ signaling differentially regulates cocaine-related behaviors across dorsal striatal subregions

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Graduate Student

Background: Emerging evidence has recognized astrocytes as active regulators of neural circuit function and addiction-related behaviors. Astrocytes modulate neuronal excitability, neurotransmitter homeostasis, and synaptic transmission within brain regions implicated in substance use disorders. These functions are thought to be mediated through Ca²⁺-dependent signaling. Although growing evidence suggests that astrocytic signaling contributes to cocaine-seeking behavior, the specific role of astrocytic Ca²⁺ dynamics within dorsal striatal circuits remains poorly understood.

Methods: To address this gap in knowledge, we suppressed astrocytic Ca²⁺ signaling through selective overexpression of the plasma membrane Ca²⁺ ATPase pump (hPMCA) or activated astrocyte Ca via GqDREADD. We bilaterally targeted astrocytes throughout the dorsal striatum (DS), dorsomedial striatum (DMS), or dorsolateral striatum (DLS) of rats trained to self-administer cocaine or saline. To determine the effects of astrocyte Ca signaling on neuronal Ca transients, ex vivo calcium imaging and in vivo fiber photometry was utilized.

Results: DS-wide suppression of astrocytic Ca²⁺ significantly increased cocaine self-administration and enhanced cue-induced reinstatement of cocaine-seeking compared to control animals. Ex vivo neuronal Ca²⁺ imaging using GCaMP6f revealed increased amplitudes of neuronal Ca²⁺ transients following astrocytic suppression in cocaine-seeking animals, suggesting increased neuronal activity after disruption of astrocytic Ca²⁺ signaling. Interestingly, DMS astrocyte suppression significantly reduced cocaine self-administration while DLS suppression increased cocaine self-administration. DMS astrocyte Ca²⁺ alterations did not affect neuronal transients during cue-induced reinstatement of cocaine, while DLS astrocyte suppression increases neuronal transients.

Conclusion: Astrocyte Ca²⁺ signaling differentially regulates cocaine-related behavior and press-associated neuronal activity across dorsal striatal subregions, revealing distinct DMS and DLS contributions that vary across behavioral phases.

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Gait impairment as a predictor of cognitive transition in Alzheimer's Disease: A random forest analysis

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Graduate Student

Background: Gait impairment is a potential early indicator of neurodegeneration. However, its relevance to different stages of cognitive decline remains unclear in Alzheimer's disease (AD).

Methods: We analyzed longitudinal data from the National Alzheimer's Coordinating Center. Participants aged ≥ 65 years with normal cognition (NC) or mild cognitive impairment (MCI) were followed for up to five years. Baseline gait performance was derived from clinician-rated gait variables and Unified Parkinsons Disease Rating System (UPDRS)-based gait items. Three binary random forest models classified transitions from NC to amnesic MCI, NC to dementia, and MCI to dementia and Shapley additive explanations (SHAP) assessed predictor importance.

Results: Among baseline NC (N=3606), 76.6% remained stable, 18.0% developed aMCI, and 7.7% progressed to dementia; among baseline MCI (N=1094), 78.4% progressed to dementia. Gait impairment ranked among the top predictors (5th) for transitions from NC but was less influential for MCI to dementia (8th). Greater gait impairment at baseline was associated with higher predicted probability of cognitive transitions from NC.

Conclusion: Gait impairment showed greater predictive importance in transitions from normal cognition than in later-stage progression, suggesting its prognostic value may be greatest during earlier disease stages.

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Heterogeneity of neuropathological profiles across cognitive trajectories

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Graduate Student

Background: Mixed neuropathological profiles can be present in markedly different cognitive trajectories from older adults. The individual contributions of these neuropathologies to cognitive progression subtypes remain unclear.

Methods: We analyzed harmonized longitudinal cognitive and neuropathological data from National Alzheimer's Coordinating Center (NACC) participants with available autopsy data and baseline Clinical Dementia Rating (CDR) ≤ 0.5 . Participants were classified by Alzheimer's Disease neuropathologic change (ADNC), limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC), Lewy body disease, hippocampal sclerosis, and neurovascular pathologies. Participants were stratified into progression groups MinP (CDR 0-0.5), ModP (CDR 1-2), and MaxP (CDR 3), and decline groups moderate, slow, and rapid. Multivariable logistic regression models evaluated associations of neuropathological profiles and individual pathologies with progression and decline group membership.

Results: Among 997 participants, 44.9% (n = 448) were classified as MinP, 35.8% (n = 357) as ModP, and 19.3% (n = 192) as MaxP. For cognitive decline, 72.8% (n = 726) were classified as moderate decliners, 14.7% (n = 147) as rapid, and 12.4% (n = 124) as slow. Substantial intra-profile heterogeneity was observed in both progression and decline groups. For example, among participants with pure ADNC, 43.0% were MinP, 37.7% ModP, and 19.3% MaxP, while 72.3% were moderate, 15.6% rapid, and 12.1% slow decliners. ADNC and hippocampal sclerosis showed the strongest associations across both progression and decline groups.

Conclusion: Specific neuropathologic factors, including ADNC, hippocampal sclerosis, and arteriolosclerosis, were associated with differences in the rate and extent of cognitive decline, while substantial heterogeneity remained among individuals with similar neuropathological profiles.

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Genetic fine-mapping of Braak neurofibrillary tangle staging identifies YBEY and PIK3R5 as high-confidence risk genes

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Background: Neuropathological endophenotypes (NPEs) provide biologically proximal measures of brain disorders that can be useful for studies of genetic etiology of diseases. Braak staging of neurofibrillary tangle (NFT) pathology is a well-validated indicator of tau-related disease progression and was used here to illustrate our fine-mapping approach.

Methods: We applied a novel causal transcriptome-wide association study (cTWAS) framework to investigate the genetic architecture of Braak NFT staging. Shade et al. (2025) recently conducted a large NPE genome wide association study (GWAS) analyzing data from 7,804 autopsied participants from the following three sources: the National Alzheimer's Coordinating Center, the Religious Orders Study and Rush Memory and Aging Project, and the Adult Changes in Thought study. Resulting GWAS summary statistics for Braak NFT stage were integrated with gene expression and splicing prediction models derived from GTEx v8 eQTL and sQTL data in the PredictDB format for all 13 available brain regions. SNP and linkage disequilibrium (LD) reference data were also used to support Bayesian fine-mapping, enabling cTWAS to jointly model multiple molecular traits within each genomic region and estimate posterior inclusion probabilities (PIPs) for putatively causal genes.

Results: cTWAS fine-mapping prioritized two genes, YBEY and PIK3R5, as putatively causal for Braak NFT stage variability, each supported by high combined PIPs across brain regions (YBEY: 1.00; PIK3R5: 0.96). These findings were consistent with a sparse genetic architecture, characterized by a small number of high-confidence risk genes underlying tau-related neuropathology.

Conclusion: Using Braak NFT staging as a neuropathological endophenotype, this study identified YBEY and PIK3R5 as high-confidence risk genes for influencing tau pathology progression and demonstrated that cTWAS, through integration of expression and splicing regulation across brain tissues, provides a powerful approach for elucidating the molecular mechanisms underlying Alzheimer's disease neuropathology.

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Spatial TDP-43 dysregulation contributes to mitochondrial respiratory dysfunction after severe CCI: implications for the eIF5A pathway

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Background: Traumatic brain injury (TBI) and neurodegenerative diseases share overlapping pathological features, yet the mechanisms driving cognitive decline remain unclear. Transactive response DNA-binding protein 43 (TDP-43) is a nuclear RNA/DNA binding protein that regulates RNA processing. Cytoplasmic mislocalization and aggregation of TDP-43 represent a toxic gain of function mechanism in both TBI and other NDs. Additional hallmarks of sustained injury include oxidative stress, excitotoxicity, synaptic loss, and mitochondrial dysfunction. We have identified eukaryotic initiation factor 5A (eIF5A) as a regulator of TDP-43 aggregation and mislocalization. eIF5A is post-translationally modified at lysine 50 by hypusination, a modification linked to TDP-43 pathology.

Methods: Aged (17–22 mo) male and female heterozygous TAR6 mice (hTDP-43 expressing line) underwent controlled cortical impact (CCI) to model severe TBI or sham surgery. Brains were collected 24 h post-injury. Whole-brain homogenates were analyzed by Western blot using antibodies against TDP-43, pTDP-43 (S409/410), citrullinated TDP-43 (R83, R191, R268/272), GFAP, citrullinated GFAP (R416), and UCHL1. Immunohistochemistry was performed to assess total TDP-43 and eIF5A^{hypK50}. Mitochondrial function was evaluated using the Seahorse XF OXPHOS assay on freshly isolated mitochondria.

Results: Immunohistochemistry revealed increased eIF5A^{hypK50} and spatial TDP-43 expression in non-Tg mice following severe CCI. TDP-43 overexpression promoted mitochondrial dysfunction after injury, with Complex III impairment in the anterior cortex of both non-Tg and TAR6 mice and Complex I impairment in TAR6 mice. Hippocampal Complex I deficits were also observed in TAR6 mice following CCI. CCI reduced TDP-43 citrullination at R191 and R268/272 in the anterior cortex, with a selective reduction of R268/272 in the hippocampus. GFAP cit^{R416} increased in both regions, accompanied by decreased total GFAP in the hippocampus. The reduction in hippocampal TDP-43 seen in sham TAR6 mice was absent after CCI. UCHL1 levels were reduced in the hippocampus of TAR6 mice compared to WT but were unaffected by CCI.

Conclusion: These findings highlight region- and complex-specific vulnerabilities driven by TDP-43 pathology in the context of traumatic injury and suggest that eIF5A hypusination may contribute to mitochondrial dysfunction in TBI.

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Data-driven subtypes of brain arteriolosclerosis progression and their links to hypertension and other neuropathologies

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Background: Brain arteriolosclerosis (B-ASC), a form of cerebral small blood vessel pathology, affects more than 50% of individuals aged 80 years or older and is associated with cognitive, motor, and sleep disturbances. We aimed to identify spatiotemporal anatomic progression patterns of B-ASC and their associations with vascular risk factors and other neuropathologies.

Methods: The presence or absence of moderate-to-severe B-ASC pathology was evaluated across 21 brain regions in the University of Kentucky Alzheimer's Disease Research Center (UK-ADRC) autopsy cohort, and correlated with clinical and neuropathological data. After excluding individuals with extremely low or high burden of B-ASC (0,1,20, or 21 regions), we applied the Subtype and Stage Inference (SuStain) algorithm, selecting the number of subtypes by 10-fold cross-validation. Subtypes and 101 participants without B-ASC (controls) were compared using logistic regression adjusted for age at death and sex, with likelihood-ratio tests with Holm-adjusted pairwise comparisons. Blood pressure was categorized using the 2024 European Society of Cardiology threshold for hypertension (SBP ≥ 140 or DBP ≥ 90 mmHg).

Results: Four B-ASC pattern subtypes were identified: cortical-first (Subtype 1, n = 57); early occipital, cingulate, and insular involvement (Subtype 2, n = 61); concurrent early cortical and basal ganglia involvement (Subtype 3, n = 42); and basal ganglia-first (Subtype 4, n = 121). Subtype 3 showed the highest prevalence of SBP ≥ 140 mmHg and of higher BP despite antihypertensive treatment, and higher odds of vascular dementia than in controls and Subtype 2. Subtype 2 had higher odds of cerebral amyloid angiopathy than Subtype 1. Compared with controls, Subtype 4 has a higher odds of Braak stage III–VI. HS-Aging was only associated with increased B-ASC (more regions affected).

Conclusion: B-ASC follows characteristic spatiotemporal trajectories which can be correlated with different neuropathologic profiles. Subtype 2 may reflect a CAA-related pattern, and Subtype 4 is a pattern associated with more AD-type tau pathology. Early basal ganglia involvement together with cortical spread (Subtype 3), rather than basal ganglia onset alone, was linked to uncontrolled hypertension and vascular dementia.

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Think inside the (operant) box: Translational behavioral assessments reveal divergent decision-making processes in 5xFAD mice relative to wildtype littermates

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Background: Translation of animal to human behavior requires more sensitive approaches to data acquisition and analysis. We therefore utilized highly translational and data-rich operant behavioral cognitive assessments combined with trial-by-trial computational modeling to reveal subtle differences between wildtype (WT) and amyloid overexpressing 5xFAD mice.

Methods: 5xFAD (n=6; 1F) and WT (n=6; 2F) mice performed an executive function 2-arm bandit (bandit) task and a working memory delayed non-match to sample (DNMS) task. Aggregate ANOVAs were performed for both tasks. Bayesian Reinforcement Learning and Drift-Diffusion computational models were performed for the bandit and DNMS, respectively.

Results: Aggregate ANOVAs showed no effect of genotype on high-payout lever presses following contingency changes in the bandit task nor accuracy or reaction time across retention intervals in the DNMS task. However, computational modeling indicates that 5xFAD mice are slower to update but commit more strongly following high-payout contingency changes in the bandit task. Further, 5xFAD mice likely maintain accuracy in the DNMS task by responding more slowly across retention intervals.

Conclusion: Such tasks and computational modeling herein could be transformative for early detection of cognitive impairment in AD and related dementias that may otherwise be hidden by aggregate analyses.

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Assessing the role of astrocyte p38 α MAPK in a delayed non-match to sample test of working memory

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Background: We previously reported that early loss of astrocyte p38 α leads to wide-ranging effects on brain metabolism, inflammation, and synaptic function in aged mice. This follow-up study aimed to determine the effects of p38 α loss in a test of working memory and global metabolism.

Methods: Knockout (KO) of astrocyte p38 α was driven by Tamoxifen-inducible Cre under control of the Aldh1l1 promoter at 7 months of age. At 10 months old, a delayed non-match to sample (DNMS) operant task required mice to select a lever opposite to that shown in the previous sampling period over variable retention intervals of up to 16 seconds. After behavior was complete, mice were housed for 5 days in indirect calorimetry chambers to assess alterations in global metabolism. Standard aggregate analysis and full drift-diffusion modeling were used to assess WT vs KO performance in the DNMS cognitive task.

Results: Astrocyte p38 α KO mice achieved a higher accuracy rate compared to WT mice, with an overall reduced reaction time. Computational modeling revealed differences in latent decision processes needed for the DNMS task. Specifically, KO mice had lower boundary separation across retention intervals suggesting less evidence was needed before committing to a choice. This was associated with dynamic alterations in global metabolism as detectable by indirect calorimetry.

Conclusion: In agreement with our previous findings of widespread brain changes produced by astrocyte-specific p38 α KO, we detected differences in working memory and in global metabolism. Additional operant-based assays are in progress to better understand the neural processes affected by p38 α KO. Given the role of astrocytic changes across neurodegenerative and other injury contexts, it is important to better define how astrocyte function relates to overall brain and body physiology.

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Modeling human donor-specific microglial function in iPSC-derived brain spheroids

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Background: Current human models of Alzheimer's disease and related dementias (AD/ADRD) have presented problems in two distinct ways. Postmortem tissue captures donor-specific genotype, aging, and pathology but lacks experimental controls and cannot provide functional readouts. Conversely, iPSC-derived models are often reproducible and can be controlled but do not reflect decades of aging and disease exposures. Human microglia in AD has primarily been studied by single-nucleus RNA sequencing, which provides cellular static states but not function information. Moreover, donor-derived microglia with well-annotated AD/ADRD remain scarce. Therefore, we sought to establish a modular model that combines standard iPSC-derived neural environment as a static component and annotated postmortem donor microglia as the experimental variable, leveraging the UK ADRC brain donation and rapid autopsy program.

Methods: Cryopreserved superior middle temporal gyrus (SMTG) collected at autopsy was dissociated with either TrypLE or papain, both with DNase I, using matched tissues from the same donor. Myelin was removed by Percoll density gradient centrifugation followed by magnetic enrichment of CD11b⁺ cells. Cells were cultured for 3-weeks in either ScienCell astrocyte medium containing 2% FBS or microglia medium containing 5% FBS. The cells were then stained for IBA1, P2RY12 and GFAP. Separately, neural, astrocyte and microglial progenitors were differentiated from iPSCs, validated in 2D by immunocytochemistry, and combined in Corning Elplasia microwells to form tri-lineage spheroids.

Results: The donor cells were IBA1 and P2RY12 double positive with no GFAP expression, and the P2RY12 held despite the serum, which was the part we did not expect. TripLE gave the higher viable CD11b⁺ yield. The iPSC panel confirmed NeuN, MAP2 and β -tubulin III in neurons, GFAP and ALDH1L1 in astrocytes and IBA1 with P2RY12 in microglia. The spheroid staining showed all three types of cells co-resident with microglia integrated among neurons rather than sitting at the surface. Planned work will incorporate donor-derived microglia into spheroids, enabling microglia from each annotated donor to be evaluated within a constant neural background, with iPSC-derived microglia serving as the naïve reference. Donors will be grouped by ADNC, sex, and APOE, with morphology, phagocytosis, cytokine release, synaptic markers and Fluo-4 calcium imaging as readouts.

Conclusion: Functional microglia can be recovered from cryopreserved postmortem brain tissue and retains their identity in culture at a working standard. Together this system provides a platform to determine whether donor disease status and genotype produce measurable difference in microglial behavior within a defined human neural environment.

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The effects of FeTMPyP on neurovascular and hippocampal synaptic function in 30-month-old mice

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Background: Oxidative stress contributes to age-related synaptic and neurovascular dysfunction and represents a potential therapeutic target for preserving brain function during advanced aging. FeTMPyP (FeT), a peroxynitrite scavenger with antioxidant properties, may attenuate these impairments. This study examined the effects of FeT on hippocampal synaptic function, dendritic spine density, neurovascular responses, and lipofuscin-associated autofluorescence in super-aged mice.

Methods: Adult and old mice received vehicle or FeT (10 mg/kg) by subcutaneous injection twice weekly for four weeks. Neurovascular responses to whisker stimulation were assessed using laser speckle contrast imaging through a cranial window. In vivo fluorescence imaging was performed before treatment and at two and four weeks, with lipofuscin-associated mean fluorescence intensity compared between baseline and four weeks. Following treatment, brains were harvested to determine hippocampal synaptic function and dendritic spine analysis.

Results: The old vehicle-treated mice exhibited impaired LTP and reduced synaptic strength, measured by the excitatory postsynaptic potential-to-fiber volley ratio (EPSP/FV; 0.23 ± 0.11 vs. 1.95 ± 0.68 , $p = 0.0364$). FeT partially restored LTP and increased synaptic strength relative to vehicle treatment (0.72 ± 0.15 vs. 0.23 ± 0.11 , $p = 0.0362$). FeT also increased dendritic spine density in CA1 (11.87 ± 0.96 vs. 5.52 ± 0.97 spines/10 μm , $p = 0.0003$) and DG (7.82 ± 1.96 vs. 3.68 ± 0.70 spines/10 μm , $p = 0.0256$). All examined spine types increased significantly in CA1, whereas only mushroom spine density increased significantly in DG. Whisker-evoked neurovascular responses were numerically lower in aged than young mice (107.18 ± 2.16 vs. 119.75 ± 4.53 , $p = 0.1414$) and showed modest improvement following FeT treatment. In addition, lipofuscin-associated mean fluorescence intensity was significantly reduced after four weeks of FeT treatment compared with pretreatment levels.

Conclusion: FeT improved hippocampal synaptic strength and dendritic spine density, partially restored synaptic plasticity, and reduced lipofuscin-associated autofluorescence in super-aged mice. These findings support further investigation of FeT as a potential intervention for age-related brain dysfunction. Its effects on neurovascular function warrant additional study.

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Brain asymmetry in emotional and cognitive control networks in older adults: Implication for ADRD risk

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Background: Neuropsychiatric symptoms can be early symptoms of dementia or a co-occurring independent symptom. Neuroimaging studies suggest that anxiety is associated with altered neural circuits involved in emotional processing and decision-making, while structural and functional brain asymmetries are altered in Alzheimer's disease (AD) and may contribute to clinical symptoms. Furthermore, AD biomarkers have been associated with altered brain connectivity in cognitively normal older adults, suggesting that network-level changes may emerge before substantial cognitive decline. This study aimed to examine hemispheric differences in bilateral brain measures and their potential relevance to neuropsychiatric symptoms and long-term cognitive outcomes. We hypothesized that asymmetrical hemispheric differences will be displayed and will positively correlate with psychiatric symptoms and cognitive decline.

Methods: MRI-derived bilateral brain measures and neuropsychiatric assessments, including the Geriatric Depression Scale (GDS) and Neuropsychiatric Inventory Questionnaire (NPI-Q), were obtained from 41 cognitively normal or mildly impaired older adults enrolled in the UK-ADRC. Repeated measures ANOVA analyzed hemispheric differences across different brain regions. Generalized linear regression will examine associations between hemispheric measures, neuropsychiatric symptoms, and cognitive status approximately 13 years after imaging.

Results: Significant differences were observed in basal ganglia regions implicated in affect and cognitive processing: the caudate ($p=0.0008$), the pallidum ($p=0.0007$), and the putamen ($p<0.0001$). The accumbens area ($p<0.0001$) and ventral diencephalon ($p<0.0001$) also display asymmetries. Significant hemispheric differences were observed across multiple brain regions including cerebellum ($p<0.0001$), and cerebellum white matter ($p=0.0023$). Structures involved in cerebrospinal fluid (CSF) production and regulation demonstrated asymmetry, including the choroid plexus ($p<0.0001$) and lateral ventricle ($p=0.0120$). Results for associations with neuropsychiatric symptoms and cognitive change are in preparation.

Conclusion: Older adults demonstrated significant hemispheric asymmetries in brain regions involved in emotional regulation, reward processing, and cognitive control. Given that psychiatric symptoms like depression can be seen as an independent risk factor or co-occurring disorder, being able to differentiate when depression is an early symptom of Alzheimer's would be beneficial.

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Astrocytic insulin signaling regulates neurovascular function and cerebral blood flow

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Background: Brain insulin resistance contributes to neurovascular dysfunction in metabolic and neurodegenerative disorders, including diabetes and Alzheimer's disease. Intranasal insulin (INI) enhances central insulin signaling without causing systemic hypoglycemia, yet the cellular mechanisms linking brain insulin signaling to cerebrovascular regulation remain unclear. Astrocytes are strategically positioned within the neurovascular unit to coordinate signaling between neurons and blood vessels, suggesting that astrocytic insulin signaling may contribute to neurovascular coupling. Our prior work further shows that INI alters cerebral blood flow (CBF) and enhances neuronal network synchrony. Here, we tested whether enhancing astrocytic insulin receptor signaling alters astrocyte network activity and cerebrovascular responses by overexpressing a constitutively active, truncated human insulin receptor β subunit (IR β) in cortical astrocytes.

Methods: Two-photon calcium imaging in awake, freely ambulating mice was used to quantify astrocyte activity and vascular dynamics during rest and ambulation. The effects of INI on the relationship between norepinephrine (NE) signaling and vascular responses were assessed by correlating nLightG signals with vessel diameter changes measured using retro-orbital rhodamine dextran. MRI-based CBF measurements were used to further assess the impact of astrocytic IR β enhancement on cerebral perfusion in 5xFAD mice.

Results: Astrocytic IR β overexpression reduced the fraction of astrocytes responsive during ambulation and increased the spatial separation between responsive astrocytes, indicating altered astrocyte network organization. Despite reduced astrocyte recruitment, IR β enhancement was associated with larger baseline vessel diameters, a greater proportion of vessels undergoing dilation, and greater dilation amplitudes during ambulation. INI also strengthened the temporal correlation between nLightG signals and vessel diameter changes, consistent with enhanced coupling between NE-related signaling and vascular dynamics. Complementing these local vascular measurements, MRI revealed an exaggerated CBF change in 5xFAD mice that was attenuated at the IR β -overexpressing site of hemisphere compared with the contralateral non-injected site, further supporting a role for astrocytic insulin signaling in regulating cerebral hemodynamics.

Conclusion: Together, these findings demonstrate that enhanced brain insulin signaling modulates astrocyte network organization and cerebrovascular responsiveness. Astrocytic IR β enhancement promotes vascular responsiveness despite reduced astrocyte recruitment and attenuates abnormal CBF responses in 5xFAD mice, while INI strengthens the relationship between NE signaling and vascular dynamics. These findings identify astrocytic insulin signaling as a potential regulator of neurovascular function and support central insulin pathways as a therapeutic target for neurovascular dysfunction associated with metabolic and neurodegenerative disease.

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Induced PAD4 activity worsens hippocampal function and TDP-43 pathology in FTD mice

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Background: Alzheimer's disease and related dementias (ADRD) are a group of neurological conditions that result in the loss of many cognitive abilities, including memory loss. Importantly, TDP-43 is a driving factor or co-pathology in many neurodegenerative diseases. TDP-43 undergoes many post-translational modifications (PTMs), notably phosphorylation. PTMs have long been associated with neurodegenerative diseases, including AD, FTD, and ALS. Citrullination is a PTM where arginine is irreversibly converted to citrulline by peptidyl arginine deiminases (PADs). Recently, we found TDP-43 citrullination is a marker of TDP-43 proteinopathy progression, with the citrullination site potentially affecting different aspects of TDP-43 pathology.

Methods: Non-transgenic (nTg) and hemizygous human TDP-43 over-expression mice (TAR6) were used. At 16 months, mice were surgically injected with rAAV9-empty capsid or rAAV9-CAG-PADi4 bilaterally in anterior cortex and hippocampus. After 6 months, ex vivo hippocampal slice recording and biochemical assays (Revvity/WB) were performed.

Results: We found that PAD4 over-expression reduced hippocampal activity (synaptic strength and LTP), increased hippocampal phosphorylation and aggregation of TDP-43.

Conclusion: Neuronal PAD4 can worsen hippocampal TDP-43 pathology and significantly impair hippocampal function.

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A MACS-based pipeline for lipidomic analysis of oligodendrocyte lineage cells

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Background: Oligodendrocyte lineage cells are becoming increasingly recognized as active contributors to Alzheimer's disease (AD). This is evidenced by studies showing oligodendrocyte and myelin dysfunction preceding and driving AD pathology. Transcriptomic analyses further reveal alterations in genes associated with metabolic function, lipid metabolism, and myelination in oligodendrocyte progenitor cells (OPCs) and mature oligodendrocytes (OLs). However, most of these findings rely on whole-brain or bulk tissue analyses, which cannot resolve cell-type-specific changes in lipidomic and metabolomic profiles. To address this gap, we validated a magnetic-activated cell sorting (MACS) method to isolate oligodendrocyte lineage cells from whole mouse brain for downstream lipidomic analysis.

Methods: Using MACS MicroBeads, we isolated OPCs (anti-CD140a/PDGFR α), pre-myelinating/early myelinating OLs (anti-O4), and purified myelin (anti-myelin) from single *APOE2*-TR mouse hemibrains. Positive, negative, and myelin/cell-debris fractions were evaluated for cell yield and viability. Purity of each fraction was quantified by RT-qPCR for markers of OPCs, OLs, neurons, astrocytes, and microglia. Lipid composition of positive fractions was measured using targeted LC-MS analysis.

Results: We found that all three isolations showed relatively high viability and strong enrichment of expected lineage markers relative to the negative fraction with depletion of non-target markers. Lipidomic profiling of each isolated fraction by LC-MS is ongoing, with preliminary data expected to reveal fraction-specific lipid compositions.

Conclusion: This pilot study establishes a feasible, reproducible MACS-based pipeline for isolating OPCs, OLs, and myelin from a single mouse hemibrain for downstream lipidomics analysis. Future efforts include applying this workflow to *APOE*-TR and *APOE4s2* 'switch' 5xFAD mice enabling cell-type-resolved investigation of how *E4*-to-*E2* conversion affects oligodendrocyte lineage lipid and metabolic profiles relevant to AD.

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Digital phenotyping of aging-related tau astrogliopathy (ARTAG) reveals distinct astrocytic tau pathologic associations in the human amygdala

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Background: Aging-related tau astrogliopathy (ARTAG) is a common 4R tauopathy characterized by hyperphosphorylated tau (pTau) in astrocytes. Tau-immunoreactive thorn-shaped astrocytes (TSAs) and granular-fuzzy astrocytes (GFAs) are the pathognomonic features of ARTAG. We investigated whether digitally quantified astrocytic tau morphologies in the amygdala (and their anatomic distributions), including ARTAG subtypes, were associated with comorbid neuropathologies and genetic variation.

Methods: PHF-1-immunostained amygdala sections from 296 autopsy cases in the University of Kentucky Alzheimer's Disease Research Center were analyzed using a HALO AI-assisted pipeline that classified neuronal and astrocytic pTau phenotypes, including neurofibrillary tangles, TSAs, GFAs, tufted astrocytes, ramified astrocytes, and astrocytic-plaque-like structures. Genotyping data including *MAPT*, *TMEM106B*, *ABCC9*, and *GRN* variants, were available for 221 cases. Associations with presence and anatomic ARTAG extent, Alzheimer disease neuropathologic change (ADNC), and limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) were evaluated using nonparametric tests and multivariable regression.

Results: Digital phenotyping demonstrated distinct astrocytic pTau patterns within the amygdala. As expected, GFAs, expressed as a percentage of the total detected pTau-positive structures, were strongly enriched in ARTAG-positive cases ($P=3.4 \times 10^{-6}$). TSAs increased with white-matter ARTAG extent (Spearman $\rho=0.42$; $P=0.003$), comprising a median 50.7% of total pTau-positive structures in cases with widespread white-matter ARTAG. Within ARTAG-positive cases, the proportion of GFAs also increased with LATE-NC stage ($\rho=0.27$; $P=0.048$). *MAPT* H2-carrier status (for which the single nucleotide variant rs8070723 is a proxy) was associated with greater adjusted odds of ARTAG (OR=3.65, 95% CI 1.33–10.00; $P=0.012$). Finally, ARTAG-positive carriers of *ABCC9* rs704180 had a greater proportion of GFAs than noncarriers (median 8.59% vs 4.74% of total pTau-positive structures; $P=0.022$).

Conclusion: Digital pathologic phenotyping identified distinct biological patterns of ARTAG and/or astrocyte pTau. TSAs tracked white-matter ARTAG distribution, whereas GFAs (comprising much of the ARTAG pathology) were enriched in cases with comorbid LATE-NC. *MAPT* H2 status predicts genetic susceptibility to ARTAG, while genetic variation in *ABCC9* also appeared to influence the ARTAG phenotype(s).

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Asprosin as a potential mediator of oxytocin-dependent cognition and Alzheimer's pathology

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Background: Alzheimer's Disease (AD) is heavily associated with metabolic dysregulation, hypertension and sympathoactivation. Decreased oxytocin (OT) signaling has been directly linked to both AD and learning/cognition. OT neurons originate from the paraventricular nucleus of the hypothalamus (PVN) and the Suprachiasmatic Nucleus (SCN) and project throughout the brain. Asprosin is a newly-discovered adipokine that is elevated in obesity and metabolic conditions. Asprosin's neural receptor, protein tyrosine phosphatase receptor type delta (Ptpd) was recently identified.

Methods: Immunohistochemistry of PVN brain sections for anti-OT and -Ptpd and co-labeling quantified. Ex vivo ephys of tdTomato-labeled oxytocin neurons was performed in slice culture of PVN sections. Mice with genetic ablation of Ptpd in OT neurons were implanted with telemeters, blood pressure recorded and spectral analysis of heart rate variability performed. Urine was analyzed by HPLC for epinephrine and norepinephrine. Asprosin was assessed by ELISA from plasma of AD and healthy patients, and from 5XFAD mice.

Results: 83% of oxytocin neurons in the PVN were found to express Ptpd. In addition, it was found that 43% of oxytocin neurons are asprosin-responsive. Ptpd in oxytocin neurons increases blood pressure and sympathetic activity. In plasma samples from patients with AD, asprosin is significantly increased. In 5XFAD mice, plasma asprosin is also elevated.

Conclusion: Asprosin-Ptpd signaling in oxytocin neurons should be explored as a metabolic contributor to AD.

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Comprehensive gene-environment interactions in dementia-related neuropathologies

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Background: We evaluated cumulative genetic and environmental risk and whether gene-environment interaction effects on dementia-related neuropathologies (NPs) differ between midlife and later life.

Methods: Data were from NACC and ADGC. We constructed AD-related polygenic risk score (PRS) using LDpred2, while generated midlife (ages 40-64) and later-life (≥ 65) environmental risk scores (ERSs) using multidimensional item response theory (IRT)-based generalized partial credit models. Logistic models were used to test PRS $\times$ ERS interactions on binary NPs, incorporating genetic relationship matrices and adjusting for age at death, sex, three principal components, and *APOE* $\epsilon 4$ dosage.

Results: Four environmental risk profiles reflecting behavioral function, physical conditions, marriage/living status, and language/education. These midlife and later-life ERSs modified PRS' effects on different NPs.

Conclusion: Multidimensional ERSs modified PRS effects on NPs, with distinct patterns across life stages.

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Comparing different machine learning approaches in the longitudinal prediction of Clinical Dementia Rating from multimodal MRI

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Background: Early identification of individuals at risk for dementia may be enhanced by modeling longitudinal trajectories of brain structure (regional brain volume/cortical thickness/white matter hyperintensities) and neuropsychological data. The availability of large repositories of neuroimaging and neuropsychological data, from consortia studies such as SCAN and ADNI, provide an opportunity to explore the accuracy of multimodal data in predicting progression of cognitive impairment.

Method: Longitudinal MRI and neuropsychological data (Clinical Dementia Rating global scores; CDRGLOB) from SCAN and ADNI participants with at least three visits were analyzed. The cohort (N = 604) included individuals with baseline MRI and two follow-up visits, with a mean baseline age of 71.6 years (260M/344F). Imaging predictors included entorhinal cortical thickness, hippocampal volume, and white matter hyperintensities, among others, with models adjusted for age, sex, and education. Time-by-predictor interaction terms were included, and subject-specific random intercepts and slopes were used to capture within-person change.

Three mixed-effects modeling approaches were evaluated: Mixed-Effects Random Forest (MERF), GPBoost with grouped random effects, and a one-vs-rest logistic linear mixed-effects (LME) model implemented using BinomialBayesMixedGLM. Data were split into training (80%) and testing (20%) sets at the subject level. For the test set, predictions were generated using fixed-effects only, and model performance was assessed using classification accuracy.

Result: MERF and GPBoost more closely tracked observed longitudinal trends compared to the LME model. In subject-wise testing, GPBoost achieved the highest multiclass accuracy (0.740), followed by LME (0.727) and MERF (0.715). This indicates a modest performance advantage using grouped random effects. At the population level, MERF and GPBoost captured temporal variation in CDRGLOB more effectively than the flatter trajectory produced by the LME.

Conclusion: These findings show that mixed-effects models effectively integrate longitudinal multimodal MRI and demographic measures to predict CDRGLOB. On the other hand, GPBoost captures nonlinear associations and achieves higher accuracy than the linear mixed-effects model and MERF. Future validation using longer follow up time and other participant cohorts are needed.

Examining a training protocol for neurocognitive test raters

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Staff

Background: Raters who administer neurocognitive tests (NTs) for research studies may not have formal training with NTs, so on-the-job training is often needed. For a fixed battery (i.e., UDS3/4), we developed a training protocol for progressing through direct NT instruction, shadowing, self-practice, and practice testing to live administration sessions. The training assessment distills requirements of NT administration into 10 observable domains and yields actionable, analyzable data that are examined in the present study.

Methods: Trainers observed trainees administering NTs and, for each test, recorded each observable domain for fidelity to standard procedures to determine if the administration was adequate.

Results: Of 17 trainees without formal NT training, those with prior exposure to NTs tended to have fewer pacing ($p = 0.07$) and stimulus presentation ($p = 0.08$) inadequacies at the first live NTing session. There were 102 inadequacies across all first live sessions; only 4 threatened test validity. For 8 trainees with data, inadequacies of instructional speech ($p = 0.007$) and gestures ($p = 0.06$) were notably lower on the second than the first live session, but there were no differences in pacing, stimulus presentation, or timing inadequacies ($ps > 0.29$).

Conclusion: The training protocol appears to promote NT administration adequacy among naïve raters. Limitations include a small, convenience sample and inconsistent data availability. Future directions include measuring battery-specific knowledge and evaluating capture of test behaviors and process data.

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Longitudinal profiling of blood clones from University of Kentucky Alzheimer's Disease Research Center cohort

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Background: Clonal hematopoiesis (CH) is the presence of a population of hematopoietic stem cells (HSCs) that share an acquired somatic mutation—a form of genetic mosaicism. The most studied form of CH is clonal hematopoiesis of indeterminate potential (CHIP), where mutations in leukemia-associated genes drive the expansion of HSCs. Mosaic chromosomal alterations (mCAs), mutations that span large genomic segments, are also known to drive HSC expansion. An HSC expansion (a clone without detectable CHIP or mCAs) is called CH-without a known driver. CHIP is associated with increased risk of illnesses like blood cancer. Studies of CH have reported both positive and negative associations for CH mutations with Alzheimer's Disease and Related Dementias (ADRD), a disease that affects over 5 million Americans. We conducted whole genome sequencing (WGS) and targeted error-corrected (barcode) sequencing of serially collected blood samples from the UK Alzheimer's Disease Research Center (ADRC). Through this pilot study, we aim to characterize how CH clones evolve in advanced-age individuals and further our understanding of how clonal dynamics impact ADRD.

Methods: The UK-ADRC clinical cohort comprises a continuously replenished group of approximately 800 participants followed longitudinally. We selected 12 donors using the following criteria: each donor had 3 blood draws and at least 2 years between draws. The median age at first blood draw was 80.5 and median age at last blood draw was 87. Somatic variant calling of WGS data was performed using Illumina's DRAGEN Somatic pipeline (average = 54X). Post pipeline filtering steps included removing variants in low complexity/blacklisted regions, and removal of germline variants. Barcode sequencing of CHIP genes was performed for ultra-sensitive detection of the most common CH driver mutations.

Results: 11/12 donors had one or more detectable CH-driver mutations. CH-drivers were defined as CHIP using the standard 2% mutant allele fraction (maf) cut-off or having a detectable mCA including loss of X or Y chromosomes. Detectable mCAs had maf 5% or lower. We observed co-occurring CH-driver mutations in 3 of the 12 donors, all of whom remained cognitively intact throughout life. Although observational, we observe that donors who remain cognitively intact throughout life have larger clones that emerge earlier in life.

Conclusion: Our preliminary results suggest that CHIP clones are present over several years, and co-existing clones with or without CH driver mutations are both associated with a reduced risk of dementia and lower AD pathology. The presence of co-occurring CH drivers and large CHIP clones has previously been associated with reduced ADRD risk. Further work is needed to better understand the evolution of CH in advanced age to further understand the potential role of CH clones in modulating ADRD risk.

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Electrostatic anchoring and helical rearrangement drive APOE lipidation: A comparative MD study of APOE2, APOE3, and APOE4

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Background: Apolipoprotein E (APOE) isoforms differ in their association with Alzheimer's disease (AD) risk. APOE4 confers the highest genetic risk, whereas APOE2 is partly protective relative to APOE3. Impaired lipidation has been proposed as a contributor to APOE4 dysfunction. We examined how membrane interactions couple initial anchoring to isoform-specific structural remodeling.

Methods: We used four independent all-atom molecular dynamics simulations of APOE2, APOE3, and APOE4 interacting with an asymmetric neuronal plasma membrane model containing cholesterol, POPC, POPI, and POPS. Each simulation was run for 1,000 ns. We analyzed membrane association, lipid hydrogen bonding, per-residue interaction energies, protein flexibility, and secondary-structure changes across functional APOE regions.

Results: APOE2 remained stably membrane-associated throughout the simulations, APOE3 showed weaker association, and APOE4 showed markedly reduced membrane attachment. Mean lipidation-region membrane hydrogen bonding was 4.05 for APOE2, 2.50 for APOE3, and 0.30 for APOE4, with POPI providing the largest lipid contribution in APOE2 and APOE3. Per-residue interaction energies identified a shared electrostatic core involving Arg191, Arg206, Arg213, and Arg217, while Trp210 provided a strong nonpolar contribution in APOE2. Membrane association preferentially increased flexibility within the lipidation-only region (residues 192-247). This region also underwent helix/coil remodeling, whereas the receptor-binding region (residues 136-150) remained predominantly helical across the three isoforms.

Conclusion: These results support a two-step model of APOE lipidation in which electrostatic and hydrogen-bond interactions first promote membrane anchoring, followed by region-selective structural reorganization. Reduced anchoring and altered lipidation-region remodeling distinguish APOE4 from APOE2 and APOE3 and provide a molecular basis for isoform-specific lipidation differences relevant to AD.

Recovery of astrocyte calcium signaling, intracellular redox state and cerebrovascular dynamic from general anesthesia

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Staff

Background: The mechanisms underlying astrocyte activity and cerebrovascular function during recovery from general anesthesia remain poorly understood. In this study, we investigated how isoflurane anesthesia modulates astrocyte Ca^{2+} signaling, intracellular NAD⁺/NADH redox state, and neurovascular responses across distinct stages of consciousness.

Methods: Wild-type mice received intracortical injections of AAV expressing the astrocyte-specific Ca^{2+} biosensor GCaMP or the metabolic biosensor Peredox-mCherry under the Gfa promoter. Following cranial window implantation and a 3–4-week recovery period, mice underwent in vivo MP imaging. Astrocyte Ca^{2+} activity and penetrating arteriole diameter were simultaneously recorded during 10s contralateral whisker stimulation at three consciousness states: fully anesthesia (FA), partial unconscious (PA), and fully awake (FW) on 1.5%, 0.3% and 0% isoflurane respectively. Intracellular NAD⁺/NADH dynamics were assessed using FLIM and fluorescence intensity ratios under the same experimental conditions. Similarly, superficial blood flow change could be observed under LSCI.

Results: Astrocyte Ca^{2+} responses to whisker stimulation were markedly suppressed during anesthesia and progressively recovered during partial unconscious, reaching the greatest responses in the awake state. Functional hyperemic responses were also state-dependent: vessel diameter remained unchanged during whisker stimulation under FA, transient vasoconstriction was observed during PA, and robust vasodilation occurred in FW animals. Metabolic imaging further revealed that astrocytes in the PA state exhibited significantly prolonged Peredox lifetime and increased green-to-red intensity ratio, indicating a transient shift in intracellular NADH/NAD⁺ redox state compared with both FA and FW. Superficial blood flow change was diminished during whisker stimulation under deep anesthesia condition and significantly increased under PA and FW conditions.

Conclusions: These findings demonstrate that recovery from isoflurane anesthesia is accompanied by progressive restoration of astrocyte Ca^{2+} signaling, dynamic regulation of intracellular redox metabolism, and re-establishment of neurovascular coupling. The distinct metabolic and vascular characteristics observed during the transitional recovery phase suggest that astrocyte-dependent metabolic regulation may contribute to the restoration of cerebrovascular function and cognitive processes as consciousness returns following general anesthesia.

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Transcutaneous spinal cord stimulation to improve glucose regulation in SCI and diabetes: Protocol for a pilot randomized trial

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Background: Individuals with spinal cord injury (SCI) are at increased risk of metabolic dysfunction, with the prevalence of type 2 diabetes (T2D) approximately threefold higher than in the general population. Additionally, insulin resistance associated with autonomic dysfunction, sarcopenia, and physical inactivity further contribute to metabolic dysfunction. This impaired metabolic state contributes to chronic hyperglycemia and elevated cardiometabolic risk. Importantly, current strategies for managing dysglycemia in SCI remain suboptimal, with limited therapeutic options targeting the neural and autonomic mechanisms that may contribute to impaired glucose regulation in this population. Emerging evidence suggests that noninvasive transcutaneous spinal cord stimulation (tSCS) may modulate autonomic and metabolic pathways and improve glucose homeostasis. This pilot clinical trial aims to evaluate the preliminary efficacy of tSCS for improving metabolic function in individuals with SCI and T2D.

Methods: A total of 40 participants with SCI and T2D will be enrolled and randomized in a single-blind, sham-controlled design to receive either active tSCS (n=20) or sham stimulation (n=20) for 6 weeks, followed by a 6-week open-label stimulation phase and a 6-week washout period. Comprehensive metabolic assessments, including oral glucose tolerance testing, continuous glucose monitoring (CGM), and biomarker analyses, will be conducted longitudinally.

Results: Primary outcomes include changes in glucose regulation and insulin sensitivity, while secondary outcomes include glycemic variability (CGM-derived time-in-range), metabolic profiling, and HbA1c levels.

Conclusion: Findings will inform larger trials and support the development of neuromodulation-based therapies for metabolic dysfunction in SCI.

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Rapid evaluation of cognition via animal naming and list learning (RECALL)

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Background: Cognitive screening in primary care can be time-consuming, limiting early identification of cognitive impairment. In a retrospective analysis of a community-based longitudinal cohort, a 3-minute abbreviated cognitive assessment combining animal naming and 5-word delayed recall demonstrated an AUC of 0.87 (95% CI 0.84-0.90). These findings support the possible utility of a brief cognitive assessment and provide the basis for active prospective validation of these findings in a primary care setting.

Methods: RECALL is a prospective validation study of an abbreviated cognitive assessment in adults aged ≥ 65 presenting for their routine primary care visits. Participants will be enrolled across low-, intermediate-, and high-risk groups (10:20:10 ratio) for cognitive impairment. The abbreviated assessment consists of animal naming and 5-word list learning with delayed recall and will be administered during the annual primary care visit. Participants will subsequently undergo a complete gold-standard cognitive assessment during a single research visit. Diagnostic accuracy will be evaluated using AUC as the primary outcome, with sensitivity and specificity as secondary outcomes. The feasibility of incorporating this cognitive assessment into routine primary care visits will also be evaluated.

Results: In the retrospective cohort, the full cognitive battery demonstrated an AUC of 0.90 (95% CI 0.87-0.93), compared with 0.87 (95% CI 0.84-0.90) for the abbreviated assessment. Using Youden's J cut points, the Boolean "and" rule demonstrated 93.06% specificity, while the Boolean "or" rule demonstrated 86.43% sensitivity. These findings provide preliminary diagnostic performance against which the abbreviated assessment will be prospectively evaluated in RECALL.

Conclusion: A brief assessment combining animal naming and 5-word delayed recall may provide a practical approach to cognitive screening in primary care. RECALL will prospectively evaluate whether the diagnostic performance demonstrated in the prior cohort is maintained in a real-world primary care setting and whether the assessment can be feasibly incorporated into routine primary care visits.

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Atypical deoxysphingolipids: Molecular drivers of peripheral neuropathy. Can L-serine stop them?

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Background: Taxane-induced peripheral neuropathy (TIPN) is a major dose-limiting side effect of taxane (paclitaxel and docetaxel) chemotherapy, affecting up to 60% of patients. Despite its clinical burden, there are currently no effective treatments to prevent or reverse TIPN. Previous work from our laboratory has shown that increased levels of atypical sphingolipids, the 1-deoxysphingolipids (deoxySLs), are associated with the incidence and severity of neuropathy in patients treated with paclitaxel. DeoxySLs are generated when the first enzyme of the sphingolipid biosynthetic pathway, serine-palmitoyltransferase (SPT), utilizes a less preferred substrate, L-alanine, instead of its higher affinity substrate, L-serine, which is the precursor of canonical sphingolipids. DeoxySLs generation is increased in TIPN because taxanes increase SPT activity in the periphery. In addition, deoxySLs have a slower degradation rate and accumulate when produced in excess leading to neurotoxicity. Therefore, we investigated whether addition of the preferred SPT substrate, L-serine, will decrease deoxySL production and alleviate neuropathic pain-related behaviors in TIPN preclinical models.

Methods: In a proof of principle experiment, we tested if the deoxySL neurotoxicity due to taxane treatment can be prevented, by the addition of L-serine in RSC96 schwannoma cells treated with paclitaxel. Next, in mice treated with paclitaxel we tested a diet enriched with L-serine for its effects on the levels of deoxySLs and on mice neuropathic pain related behaviors.

Results: Our data showed that L-serine addition resulted in decreased cellular levels of deoxySLs in RSC96 cells. In mice, L-serine in the diet resulted in decreased levels of deoxySLs in plasma and in the dorsal root ganglia of mice under paclitaxel. Importantly, the enrichment of L-serine in the diet rescued neuropathic pain related behaviors (mechanical allodynia, thermal hyperalgesia and motor deficits) due to paclitaxel administration.

Conclusions: Future studies will evaluate if L-serine administration interferes with paclitaxel antitumor efficacy in a breast cancer syngeneic mouse model treated with paclitaxel. Ultimately, these findings provide basis for a clinical investigation to test whether reducing deoxySL levels with L-serine can alleviate symptoms of TIPN in patients.

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Hearing, vision, and cognitive functioning in later life: An exploratory structural equation modeling analysis

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Background: Cognitive decline and sensory impairment frequently co-occur in later life, with both vision and hearing recognized as modifiable risk factors of dementia and cognitive decline. An exploratory structural equation modeling (ESEM) analysis may help distinguish the contribution of sensory disorders among other contributing risk factors on general cognitive ability. This study examines a theoretical structural path diagram using ESEM to model the associations between cognition and sensory risk factors.

Methods: We will use National Health and Aging Trends Study (NHATS) data from community-dwelling adults aged 65 years and older. Hearing and vision indicators will be modeled as a specific sensory latent factors with multiple indicators, while allowing theoretically plausible cross-loadings. Other risk factors for cognitive decline will be included as a single, general factor associated with both sensory factors and cognitive decline, modeled as a bi-factor ESEM. The model will estimate the association between cognition and sensory-specific factors while accounting for other relevant risk factors. Model analysis will be completed using Mplus.

Results: Analyses are currently in progress and will be completed in time for conference presentation. Preliminary results show contributions of variance for both hearing and vision constructs on global cognition.

Conclusion: A bifactor ESEM approach may provide a more nuanced understanding of the relationship between sensory health and cognition compared to traditional regression methods.

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Immunohistochemistry profiling of citrullinated TDP-43 in LATE-NC

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Background: TDP-43 (TAR DNA-Binding Protein 43) is implicated in the clinical and pathological course of various neurodegenerative diseases, including Limbic predominant age-related TDP-43 encephalopathy (LATE). Phosphorylation is one of the most studied post-translational modifications (PTM) of pathological TDP-43. While using specific phospho-Serine TDP-43 epitopes (ie. pS409/410 or pS403/404) is effective in identifying TDP-43 pathological hallmarks, utilization of irreversible PTMs could potentially provide a better biomarker for early differentiation of TDP-43 proteinopathies or disease severity. Our laboratory has identified citrullination (citR) of eleven (11) arginine epitopes in TDP-43 protein, followed by generation of six (6) citR-specific TDP-43 antibodies, characterized in various systems models. We hypothesize that activity of this irreversible PTM increases with pathology; thus, understanding citrullinated TDP-43 patterns can provide information on disease-staging and severity.

Methods: *Human Tissue:* (Control and LATE positive) Amygdala and hippocampus tissue was provided by the UK-ADRC Brain Bank at SBCoA. Sections were used to investigate citR TDP-43 profiles across a spectrum of LATE-NC severity. *Immunohistochemistry (IHC):* We investigated the morphological patterns of citR TDP-43 inclusions using custom, site-specific citR-TDP-43 antibodies (citR83, citR191, and citR268/272 TDP-43) on paraffin-embedded formalin-fixed (PFFE) tissue sections. Tissue was also stained with pS409/410 TDP-43 (Clone 1D3, Biolegend, Cat #829901) per conventional protocols.

Results: Our IHC analysis demonstrated that epitope-specific profiles of citR TDP-43 expressed at different levels across HPC neuronal CA1-CA3 and DG layers. We further revealed that citR TDP-43 conformers manifested novel morphologies based on disease severity, and displayed different spatio-temporal hippocampal profiles. We confirmed pS409/410 TDP-43 increases according to disease stage and also demonstrated spatial differences following moderate and severe LATE-NC presentation.

Conclusion: The small cohort used for this investigation provides promising data towards utilization of citR TDP-43 as a biomarker for early detection of pathology across LATE-NC severity. Future studies will include a larger patient cohort across 1-3 stages of LATE-NC, AD with LATE-NC, and FTDs to establish the citR TDP-43 patho-clinical profile disease progression and clinical utilization.

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The guanine deaminase cypin regulates autophagy and promotes clearance of pathological tau in primary cortical neurons

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Background: Alzheimer's disease (AD) and related tauopathies are characterized by the accumulation of hyperphosphorylated and misfolded tau, which contributes to neuronal dysfunction and degeneration. Autophagy-lysosomal dysfunction has been implicated in pathological tau accumulation. Identification of endogenous regulators of autophagy and tau clearance may provide insight into mechanisms underlying tau pathology. Our laboratory has reported that, cypin, the main guanine deaminase in the brain, plays an important role in learning and memory after injury, shaping neuronal morphology, regulating synaptic content, and modulating neural circuit function; however, its role in autophagy and pathological tau clearance remains incompletely understood.

Objective: We investigated whether cypin regulates autophagy and pathological tau accumulation in primary rodent cortical neurons and examined the effect of pharmacological activation of cypin using the small molecule G5.

Methods: Primary cortical neurons were transduced with lentivirus for cypin overexpression and loss-of-function. Cypin was pharmacologically activated with G5 treatment. Levels of autophagy markers, such as LC3-I/II, p62, and LAMP1, and total and phosphorylated tau were assessed by Western blot analysis. Autophagic flux was evaluated in the presence of bafilomycin A1, an inhibitor of autophagosome-lysosome fusion.

Results: Cypin overexpression increased LC3-II and LAMP1 levels and reduced phosphorylated tau levels, suggesting enhanced autophagy-associated tau clearance. In contrast, cypin loss-of-function reduced autophagy-associated proteins, supporting a role for cypin in maintaining neuronal autophagy. Pharmacological activation of cypin with G5 increased LC3-II levels and altered p62 abundance. Co-treatment of the cultures with G5 and bafilomycin A1 further supported that cypin activity increases autophagic flux. Importantly, G5 treatment reduced phosphorylated tau levels, consistent with enhanced clearance of pathological tau.

Conclusions: These findings identify cypin as a potential regulator of neuronal autophagy and pathological tau homeostasis. Both cypin overexpression and pharmacological activation with G5 enhanced autophagy-related responses and reduced phosphorylated tau in primary cortical neurons. Ongoing studies will determine whether cypin modulation can rescue autophagy dysfunction and tau accumulation in PS19 tauopathy mice and will further define the role of cypin in tau-associated neurodegeneration.

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KATP channel inhibition with glyburide modules tau pathology

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Background: Neuroinflammation, metabolic dysfunction, and neurodegeneration are key features of Alzheimer's disease (AD) and tauopathies. ATP-sensitive potassium (KATP) channels regulate metabolism, neurovascular function, inflammation, and disease processes. We investigated whether chronic KATP channel inhibition with glyburide affects tau pathology, neuroimmune responses, neuronal health, and neurodegeneration in P301S PS19 and GCaMP-P301S mice.

Methods: Five- to six-month-old P301S PS19 and wild-type mice received slow-release glyburide or placebo for three months. Interstitial fluid (ISF) tau and lactate were measured by microdialysis. Tau pathology, neuronal abundance, lysosomal-autophagic markers, neuroinflammation, and transcriptomic changes were assessed in the hippocampus and cortex. Wide-field optical imaging was performed monthly in GCaMP-P301S and wild-type mice.

Results: Glyburide reduced ISF tau and showed a trend toward lower ISF lactate. Transcriptomic analyses demonstrated normalization of neuroimmune and inflammatory pathways, including reduced reactive microglial and astrocytic signatures, alongside increased pathways related to mitochondrial ATP production, protein synthesis, autophagy, and lysosomal function. These changes were associated with increased neuronal abundance, reduced glial reactivity, altered lysosomal-autophagic markers, and preservation of cortical structure. Glyburide also reduced somatic AT8-positive tau accumulation and altered its neuronal localization, consistent with tau redistribution.

Conclusion: KATP channel inhibition with glyburide attenuates tau pathology and modulates neuroimmune, metabolic, and neurodegenerative processes in mouse models of tauopathy, supporting KATP channels as a potential therapeutic target.

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A mixed-methods study of functional communication in people with dementia

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Background: Declining communication ability is a well-known symptom of Alzheimer's disease and related disorders (ADRD), making care tasks increasingly difficult for people living with ADRD (pwADRD) and their caregivers (CGs). Despite being an established symptom of ADRD and a significant concern among CGs, few studies investigate language abilities of pwADRD as a functional skill within a social context. This study aims to clarify links between functional communication and caregiving.

Methods: This study used a mixed-methods design to assess relationships between language and communication abilities of pwADRD and potential impacts on their primary CG. The Montreal Cognitive Assessment assessed overall cognition (MoCA) and Language ability (MoCA-L) of pwADRD. Functional communication was evaluated using the Socialization score from the Situational Assessment of Activity and Function (SAAF-S) and the Clinical Dementia Rating Scale Language score (CDR-L). The Zarit Burden Interview (ZBI) and Neuropsychiatric Inventory (NPI) assessed CG burden and distress. Semi-structured interviews were conducted with CGs to explore the impact of communication on caregiving. Interviews were qualitatively coded in Atlas.ti 26.0. Quantitative analyses were performed in SPSS 32.0.

Results: Data from 21 pwADRD-CG dyads were analyzed ($N=42$). PwADRD were majority male ($n=12$), $\bar{x}$ age=77.29 ($SD=7.65$), and $\bar{x}$ MoCA score=12.63 ($SD=9.9$). CGs were majority female ($n=19$), $\bar{x}$ age=63.48 ($SD=12.14$), and were most often a spouse ($n=10$) or child ($n=10$) of the pwADRD. Correlational analyses revealed significant negative correlations between CDR-L and SAAF-S ($r^s=-.5$; $p<.05$) and qualitative code "Communication:Normalcy" ($r^s=-.5$; $p=.05$), a code reflecting maintained normal communication as reported by the CG. "Communication:Normalcy" was positively correlated with SAAF-S ($r=.56$; $p<.05$) and negatively correlated with ZBI ($r=-.48$; $p<.05$). SAAF-S was also negatively correlated with NPI ($r=-.58$; $p<.05$). MoCA-L was not significantly associated with CDR-L, "Communication:Normalcy," or ZBI.

Conclusion: These findings highlight the relevance of functional communication by pwADRD as a significant factor in CG distress and burden. Specifically, the negative relationship between "Communication:Normalcy" and CG burden--and its lack of a significant relationship with MoCA-L scores--indicates that functional communication may not be fully captured by standard tests of raw language ability. This should be considered in future research targeting CG burden and ADRD intervention goals.

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Targeting mitochondrial homeostasis with EGCG to mitigate neuroinflammation in Alzheimer's disease

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Background: Neuroinflammation contributes to Alzheimer's disease (AD) progression and is closely linked to mitochondrial dysfunction. Amyloid- β (A β)-associated activation of microglia can increase mitochondrial reactive oxygen species (ROS) and stimulate inflammatory pathways, including NLRP3, JAK/STAT3, and C/EBP β signaling. These responses may further impair mitochondrial function and exacerbate A β -associated pathology, creating a feed-forward cycle of cellular stress and inflammation. Epigallocatechin gallate (EGCG), a green tea polyphenol, has antioxidant and anti-inflammatory properties. We hypothesize that EGCG attenuates inflammatory activation in microglia by improving mitochondrial function. This study evaluates whether EGCG suppresses inflammatory pathway activation in human microglia.

Methods: Human microglial HMC3 cells were subjected to inflammatory stress with lipopolysaccharide (LPS) and treated with EGCG. Whole-cell lysates were collected, and equal amounts of protein were resolved using 4–20% gradient SDS-PAGE and transferred to membranes for Western blot analysis. Changes in inflammatory signaling were evaluated using antibodies against IL-1 β , STAT3, TLR4, and other inflammation-associated proteins. Protein expression was compared between LPS-stimulated cells with and without EGCG treatment.

Results: Western blot analyses showed that EGCG treatment reduced protein levels of IL-1 β , STAT3, and TLR4 in LPS-stimulated HMC3 microglial cells compared with LPS treatment alone. These findings suggest that EGCG suppresses multiple components of microglial inflammatory signaling, including pathways associated with TLR4-mediated inflammatory activation and STAT3 signaling. Additional experiments are ongoing to determine the effects of EGCG on mitochondrial homeostasis and related inflammatory pathways.

Conclusion: Our preliminary findings demonstrate that EGCG attenuates LPS-induced inflammatory activation in human HMC3 microglial cells, as evidenced by reduced IL-1 β , STAT3, and TLR4 protein levels. Together with previous reports that EGCG regulates inflammasome signaling and autophagy-related pathways, these findings warrant further investigation of EGCG as a strategy to interrupt the link between mitochondrial dysfunction and chronic neuroinflammation in AD.

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Association of neighborhood deprivation and brain health in later life: Results from the UK Alzheimer's Disease Center Cohort

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Background: Neighborhood socioeconomic disadvantage, measured by the Area Deprivation Index (ADI), has been linked to mental health disorders, which may contribute to cognitive decline. However, these associations remain understudied in older adults. We investigated associations between ADI, mental health, and cognitive outcomes in older Kentuckians.

Methods: Data were drawn from the UK Alzheimer's Disease Research Center. Included participants were ≥ 55 years with ≥ 1 Uniform Data Set v4.0 assessment. Characteristics were compared across national ADI tertiles.

Results: Across ADI tertiles, participants (N=524) had similar age and smoking status, and similarly felt safe in their homes. Participants in the most deprived tertile were more likely to be female ($p=0.01$), had less education ($p=0.007$), worse global cognition ($p=0.044$), were more likely to feel unsafe in their community ($p=0.008$), and reported less alcohol consumption ($p<0.0001$). Major depression, anxiety, and PTSD were similar across tertiles, but depressive symptoms were higher ($p=0.013$) in the most deprived tertile.

Conclusion: ADI was associated with demographic, psychosocial, cognitive, and mental health measures in this cohort. Because of the cross-sectional design, temporal ordering cannot be determined. Future research will examine longitudinal associations between neighborhood deprivation and brain health.

Acknowledgments: Thank you to the UK College of Public Health and Dr. Erin Abner.

Exploring genetic moderators of glutamatergic/GABAergic signaling and cognitive performance in older adults

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Background: Previously, we demonstrated that genetic variation in the glutamatergic receptor gene GRIN2B is associated with individual differences in processing speed during working-memory retrieval in older adults, suggesting that genetic variation in neurotransmission pathways likely contributes to cognitive aging (Jiang et al., 2017). Building on this work, this exploratory pilot study examined whether combined glutamatergic and GABAergic genetic variation is associated with cognitive performance in older adults and whether these associations are moderated by COMT, BDNF, or APOE $\epsilon 4$ status.

Methods: Legacy genetic, behavioral, and neuropsychological data were obtained from 30 older adults (28 cognitively normal, 2 mild cognitive impairment) from the University of Kentucky ADRC cohort. A composite glutamatergic / GABAergic genetic score was calculated from effect-allele counts across four glutamatergic genes (GRIN1, GRIN2A, GRIN2B, GRIN2C) and two GABAergic genes (GAD1, GAD2). Regression analyses examined association between working memory accuracy, reaction time, and neuropsychological outcomes, controlling for age and education using R package. Follow-up analysis tested COMT (GABAergic signaling/prefrontal cognition), BDNF (GABAergic circuit development), and APOE $\epsilon 4$ (inhibitory interneuron loss) as moderators.

Results: Glutamatergic/GABAergic genetic balance score showed nominal associations with cognitive outcomes. However, COMT significantly moderated the association between glutamatergic/GABAergic score and working memory accuracy (interaction $p = .008$); the link weakened as COMT dosage rose, suggesting COMT may buffer against this imbalance. The effect remained after excluding persons with mild cognitive impairment ($p = .009$). APOE $\epsilon 4$ status also moderated this relationship ($p = .016$), although the effect was attenuated in the cognitively normal-only subsample ($p = .056$). No significant moderation effects were observed for BDNF ($ps > .20$).

Conclusion: These preliminary findings suggest that glutamatergic/GABAergic associations with cognition depend on broader genetic contexts such as COMT and APOE $\epsilon 4$, highlighting the value of considering multi-pathway interactions in future and larger cohorts.

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Hippocampal sclerosis of aging: A common and under-appreciated dementia-associated pathology

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Background: Hippocampal sclerosis of aging (HS-A) is a brain pathology, characterized by cell loss and astrogliosis in the medial temporal lobe. Current consensus-based methods for diagnosing HS-A rely on a dichotomous (absent/present) operationalization. HS-A is known to be associated with TDP-43 pathology but its association with Alzheimer's disease pathology is not well characterized.

Methods: Autopsied participants from the University of Kentucky Alzheimer's Disease Research Center community-based cohort (n=303) were assessed for HS-A pathology. For each participant, hematoxylin and eosin stains of bilateral hippocampus, entorhinal cortex, and amygdala were graded on a scale of 0-2 based on HS-A severity (0: none; 1: mild/incipient; 2: moderate/severe). HS-A pathology was correlated with selected other brain pathologies and with antemortem global cognitive status as measured by Mini-Mental State Examination (MMSE) scores.

Results: Overall, 50.2% (n=152) were HS-A grade 0, 18.5% (n=56) were HS-A grade 1, and 31.4% (n=95) were HS-A grade 2. Using all six regions increased the number of HS-A grade 1 and 2 cases by 11.0% (n=25/228) when compared to using only left hippocampus and entorhinal cortex. Braak neurofibrillary tangle (NFT) stage and Limbic Predominant Age-Related TDP-43 Encephalopathy Neuropathologic Change (LATE-NC) stage were correlated with HS-A grade. Older participants were more likely to have HS-A, and MMSE scores decreased as HS-A grade increased. More specifically, factoring in comorbid pathologies, HS-A grade 1 had MMSE scores that were significantly lower than HS-A grade 0, and higher than HS-A grade 2.

Conclusion: We here propose an updated grading system that separates mild HS-A from more severe HS-A. Factoring in these grade 1 cases, almost ½ of cases had HS-A pathology. HS-A was associated with NFT stages in addition to LATE-NC. Diagnosis of HS-A with a 0-2 grading system, as compared to the current dichotomous system, may assist in future research by better operationalizing HS-A as it relates to pathological and clinical factors.

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Resilience predicts short term memory performance in Black adults

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Undergraduate Student

Background: Black adults experience a disproportionate burden of cognitive decline and may encounter cumulative social and environmental stressors across the life course that require adaptation and resilience. Psychological resilience, defined as the capacity to adapt to and recover from adversity, may therefore be particularly relevant to cognitive health in this population. Emerging memory difficulties may also provide important early indications of vulnerability to later cognitive decline. However, the relationship between psychological resilience and short-term memory among Black adults remains understudied. This study therefore examined the association between psychological resilience and short-term memory among Black adults.

Method: Participants (N = 94; Mean age 53.53) provided demographic information and completed a 10-item resilience measure assessing adaptability, persistence, coping with stress, and recovery from challenging situations. Participants also completed the number span forward test, which assessed their ability to accurately repeat increasingly longer sequences of numbers in the order presented. A Pearson correlation analysis was conducted to examine the association between psychological resilience scores and number span forward performance.

Results: Results indicated a significant association between resilience scores and performance on the number span forward test ($r = 0.264$ $p = .016$), demonstrating a relationship between psychological resilience and short-term memory in this sample.

Conclusion: Psychological resilience was significantly associated with short-term memory among Black adults. Given the disproportionate burden of cognitive decline among Black adults and the potential importance of memory changes for identifying cognitive vulnerability, these findings underscore the value of further examining resilience as a psychosocial factor associated with cognitive health. Longitudinal research is needed to determine whether resilience is associated with subsequent trajectories of cognitive functioning.

Behavioral and biochemical analysis of BNC-1 treatment strategies to reduce tau hyperphosphorylation after traumatic brain injury

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Background: Preclinical models demonstrate that amyloid and tau pathology increase neurodegeneration after traumatic brain injury (TBI). Overexpression of TAK1 induces tau hyperphosphorylation in vitro, suggesting TAK1 is a driver of tau pathology. Previous research shows BNC-1 selectively inhibits injury-induced TAK1 phosphorylation of tau.

Methods: We used MAPT P301S mice, which exhibit tauopathy exacerbated by activated TAK1. Mice were split into multiple cohorts of drug, vehicle, SHAM, and CHI. Mice received BNC-1 via oral gavage post-surgery then received a BNC-1 enriched diet. We analyzed physiological factors such as righting reflex time and analyzed body weight. We performed biochemical analysis with immunohistochemistry and MSD assays.

Results: Righting reflex time was significantly higher for CHI than SHAM. Female mice with CHI lost significantly more body weight than SHAM mice and this effect was rescued with BNC-1 administration. MSD tau immunoassay and IHC analysis are ongoing.

Conclusion: Body weight loss in females was rescued with BNC-1 treatment showing its physiological impact. Although biochemical analysis is ongoing, previous research showed BNC-1 prevented tau hyperphosphorylation inhibiting a key cascade involved in neurodegeneration post TBI. Future research aims to further investigate biochemical changes post TBI in mice treated with BNC-1.

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Temporal dynamics of amyloid clearance and microglial plaque engagement following donanemab treatment in 5xFAD mice

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Undergraduate Student

Background: Anti-amyloid antibodies such as donanemab lower plaque burden in Alzheimer's disease, but amyloid-related imaging abnormalities (ARIA) remain the principal dose-limiting toxicity. Because ARIA likely reflects the glial response to rapid plaque removal rather than amyloid lowering itself, we asked which amyloid pools donanemab depletes and how microglia respond between 4 and 8 weeks of dosing.

Methods: Male 5xFAD mice were aged to 11 months and dosed weekly with chimeric donanemab (mouse IgG2a) or IgG2a isotype at 10 mg/kg for 4 or 8 weeks (n = 5 to 6 per group). Cortex, hippocampus, and thalamus were extracted sequentially into PBS-soluble and formic acid-insoluble fractions and assayed for A β 38, A β 40, and A β 42 by electrochemiluminescence immunoassay (MesoScale). The contralateral hemisphere was immunolabeled for A β 42, AmyloGlo, and multiple markers associated with microglial reactivity and quantified in HALO.

Results: Donanemab depleted soluble A β 42 well before the fibrillar pool. Soluble A β 42 fell in hippocampus at 4 weeks (-44.9%, p = 0.007) and 8 weeks (-46.3%, p = 0.025), and in cortex (-52.4%, p = 0.005) and thalamus (-45.8%, p = 0.014) by 8 weeks, whereas insoluble A β 42 was unchanged in every region. Histological A β 42 area was 23 to 39% lower. Microglial density within 15 μ m of plaques rose at both intervals in all regions, and A β 42 area inside IBA1+ microglia roughly doubled in hippocampus by 8 weeks (+100%, p < 0.001), with similar gains in cortex (+71%) and thalamus (+43%).

Conclusion: Donanemab clears soluble A β 42 while the fibrillar core resists removal, and microglia bridge that gap by accumulating at plaques and internalizing progressively more amyloid. This engagement intensifies between 4 and 8 weeks rather than resolving. If ARIA reflects that phagocytic load, the risk window should widen with continued dosing.

Acknowledgments: Alzheimer's Association (JMM and LAJ)

Sanders-Brown Center on Aging



The Sanders-Brown Center on Aging (SBCoA) was established in 1979, and received funding as one of the original ten National Institutes of Health Alzheimer's Disease Centers in 1985. Internationally acclaimed, the SBCoS is recognized for its contributions to the fight against brain diseases that are associated with aging.

Our vision: The University of Kentucky Sanders-Brown Center on Aging will be recognized locally and nationally as a premier, vitally productive and innovative aging center that effectively translates research findings into interventions and information that will benefit older adults.

ALZHEIMER'S DISEASE FACTS

Normal Age-Related Memory Changes

- Missing a monthly payment
- Forgetting which day it is and remembering later
- Sometimes forgetting which word to use
- Losing things from time

Warning Signs of Dementia

- Poor judgment and decision making
- Inability to manage a budget
- Losing track of the date or the season
- Misplacing things and being unable to retrace steps



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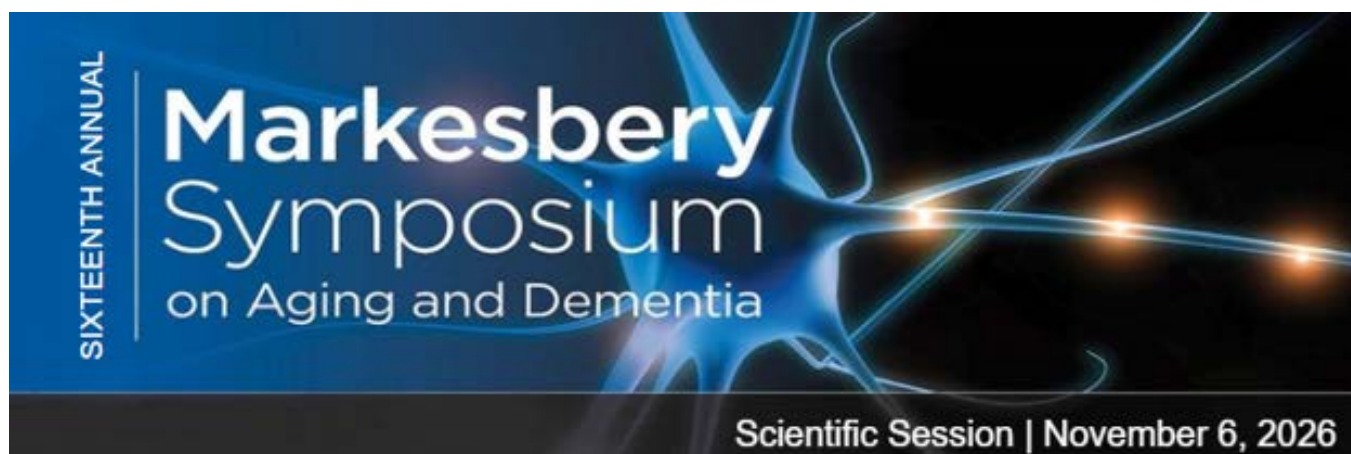
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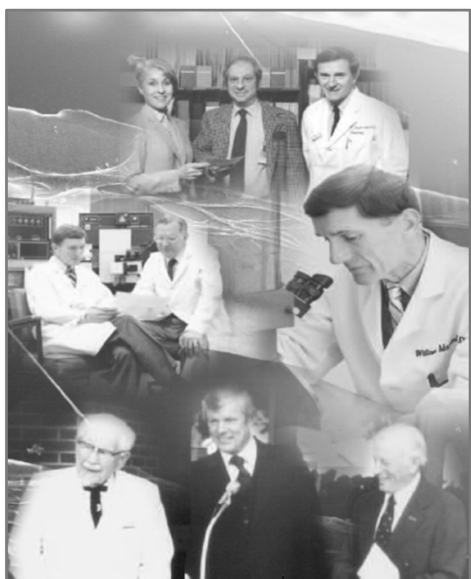
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WILLIAM R. MARKESBERY, M.D. (1932-2010)



The Markesbery Symposium on Aging and Dementia is named in honor of William R. Markesbery, M.D., a gifted scientist and internationally recognized neurologist and neuropathologist. Dr. Markesbery's creativity and commitment to aging research provided the impetus for the University of Kentucky to establish the Sanders-Brown Center on Aging in 1979 and name him as the first director. He held that position until his death in January 2010.



In 1985, Bill Markesbery became the director of the Alzheimer's Disease Research Center, one of the original 10 National Institute on Aging (NIA) funded centers in the United States, with a primary focus on neuropathology. After more than 40 years, the Alzheimer's Disease Research Center continues to be funded by NIA, a remarkable achievement that demonstrates the strength and caliber of this program. During his academic career, Dr. Markesbery published more than 400 scientific papers and was one of the world's leading experts on Alzheimer's disease and oxidative stress. He will always be remembered as a compassionate and caring physician, a brilliant researcher, and an inspirational leader.

Notes

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