32nd Annual

Alzheimer Day

May 19, 2026 | 10:30 AM - 4 PM
Feinberg Pavilion Conference Center

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Conference Planning Team

Thank you to all Mesulam Institute staff and faculty who have made this day a success! The Mesulam Institute appreciates your dedication and commitment to making this day possible.

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32nd Annual

Alzheimer Day

May 19, 2026 | 10:30 AM - 4 PM
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Schedule of Events

Time	Event
10:30 - 11:30 AM	Registration and Sponsor Fair
11:30 - 11:55 AM	Welcome and Institute Update **Robert Vassar, PhD** Director, Mesulam Institute for Cognitive Neurology and Alzheimer's Disease; Davee Professor of Alzheimer Research Northwestern University Feinberg School of Medicine
11:55 - 12 PM	Presentation of Marie and Carl Duncan Prize in Memory Research **Tamar Gefen, PhD** Associate Professor, Department of Psychiatry and Behavioral Sciences Director, Laboratory for Translational Neuropsychology Co-Director, Northwestern University SuperAging Program (NUSAP) Co-Director, Clinical Core, Alzheimer's Disease Research Center Mesulam Institute for Cognitive Neurology and Alzheimer's Disease Northwestern University Feinberg School of Medicine
12 - 1 PM	Mendelson Lecture: Alzheimer's Disease 2026: Challenges and Hope **Ronald C. Petersen, MD, PhD** Professor of Neurology Distinguished Mayo Clinic Investigator Cora Kanow Professor of Alzheimer's Disease Research Emeritus Cadieux Director, Mayo Alzheimer's Disease Research Center Director, Mayo Clinic Study of Aging
1 - 2:30 PM	Lunch, Research Poster Session, and Sponsor Fair
2:30 - 4 PM	Quality of Life Symposium: Understanding Symptom Evolution in Dementia: A Framework for Families and Professionals Sponsored by the Glen and Wendy Miller Family Foundation **Sandra Weintraub, PhD** Professor, Psychiatry and Behavioral Sciences, Neurology, and Psychology at Northwestern University Feinberg School of Medicine Co-director, Clinical Core and Admininstrative Core Northwestern Alzheimer's Disease Center (CNADC)

Welcome to the 32nd Annual Alzheimer Day

Dear Friends and Colleagues:

Hello everyone! It is my great pleasure to welcome you to the 32nd annual Alzheimer Day. It is an honor that you have decided to spend your valuable time with us today. We welcome you and thank you for your continued support.

You will be pleased to know that the past year has witnessed exceptional growth and progress. The Mesulam Center, having enjoyed international leadership in frontotemporal dementia (FTD) research for over three decades, was designated as an interdepartmental Institute to also include the newly named Kathryn Aring Piper Center for Frontotemporal Cognitive Disorders (Piper Center) — funded through a generous $10-million endowment — last summer.

The Piper Center's mission is to conduct ground-breaking clinical, basic, and translational research on frontotemporal dementia syndromes caused by FTLD-tau and FTLD-TDP and contrast them with those caused by Alzheimer's disease (AD) and other diseases. A search is being conducted for the Director of the Piper Center, an FTD researcher of international stature. The Mesulam Institute and the Northwestern Alzheimer's Disease Research Center (ADRC) are exceptionally well positioned to propel progress in this area into the future, in concert with the new Piper Center and the broader Chicago and Evanston Northwestern research community in Alzheimer's disease and related disorders.

The Mesulam Institute, including the ADRC, the Northwestern SuperAging Program, the Primary Progressive Aphasia Program, the Glen and Wendy Miller Family Buddy Program, the Ken and Ruth Davee Laboratories, the Clinical Trials Program and the Neurobehavior Clinic are all thriving.

The Northwestern SuperAging Program (NUSAP), is now 27 years old and is advancing our knowledge of superior cognitive aging in "SuperAgers," who are individuals over the age of 80 with memory performance equivalent to those at least 20 to 30 years younger. Northwestern continues to lead research on SuperAgers and is making discoveries on how SuperAgers may have achieved their exceptional cognitive status.

NUSAP research is pushing back the boundaries of the unknown and is helping us understand SuperAging with studies spanning from diet to sleep to social life to molecular genetics and proteomics. For example, Drs. Mesulam, Weintraub, Geula, and Gefen contributed to a publication in the journal Nature that identified a distinct profile of neurogenesis in SuperAgers that may reflect a "resilience signature" that protects against the ravishes of Alzheimer's disease.

Additionally, they published a perspective in Alzheimer's and Dementia recounting the quarter-century history of NUSAP, which created a deluge of media attention and fanfare. NUSAP promises to unlock secrets that may lead to new treatments for Alzheimer's disease and other neurodegenerative disorders. We are so grateful to our SuperAgers for their dedication to our program!

Primary progressive aphasia (PPA) is a clinical dementia syndrome, which initially affects speech and language, has been a major focus of the Mesulam Institute since its inception in 1994. The Mesulam Institute continues to work on the leading edge of PPA research. Together, Dr. Mesulam and Dr. Elena Barbieri lead the PPA program.

This past year, the team made a major accomplishment in the multi-level characterization of PPA due to TDP-43 Type C proteinopathy. Their investigation of linguistic, neuroimaging, neuropathological, and genetic aspects of PPA with TDP-C has contributed to 1) understanding the progression of language, atrophy and pathology of TDP-C over time, 2) reinforcing the link between left temporal pole degeneration and word comprehension impairment, and 3) elucidating the linkage between TDP-C and Annexin A11, a protein that co-aggregates in TDP-C. Findings from these studies have been published in journals including Brain, Annals of Neurology, Neurology Genetics and Imaging Neuroscience. Additionally, the Mesulam Institute's programs for sustaining language and communication between individuals with PPA and their study partners have been going strong and have been well received by participants.

We continue our participation in the first ever clinical trial for PPA testing the drug verdiperstat. These research efforts of the Mesulam Institute may someday lead to new therapies for this devastating neurodegenerative disorder.

The Glen and Wendy Miller Family Buddy Program, which

matches persons living with dementia with students and fellows, continues to flourish and expand under Dr. Morhardt and her team's leadership. This program was initiated at the Mesulam Institute 29 years ago and has been replicated by other institutions around the country. Buddies enjoy mutual benefits. Some aspects include patients mentoring and socially engaging with a first-year medical student, and students obtain valuable first-hand experience around patients' lived experience with dementia. We look forward to supporting the Buddy Program for another successful year.

The research education component of our Alzheimer's Disease Research Center, led by Dr. Geula, has continued its mission of training and education. Dr. Geula's Brain Scholars Program maintains their goal to train the future research workforce. This program provides exposure to research and clinical aspects of aging and dementia to high school and middle school students primarily in the African American community. Last summer, the Brain Scholar's Program continued its internship program hosting students at the Mesulam Institute to participate in various research activities. The program culminated in an event where students gave presentations about their projects to proud parents and Institute staff. This year, the internship program will expand to hosting college students from Chicago State University. Given its resounding success, we are excited to continue the Brain Scholars Program and look forward to inspiring the next generation of dementia researchers.

The Mesulam Institute Neurobehavior and Memory Clinic on Arkes 13 continues its mandate to serve those living with dementia and their families. At the Neurobehavior and Memory Clinic, behavioral neurologists, neuropsychologists, psychiatrists, and clinical social workers all work in the same space — a unique situation where care providers consult one another in a collaborative setting providing thoughtful and efficient treatment, care, and support.

Our Memory Clinic has been treating Alzheimer's patients with the recently approved disease-modifying therapies lecanemab (Leqembi) and donanemab (Kisunla). These amyloid immunotherapies bring new hope for the treatment and, perhaps someday, the prevention of Alzheimer's disease. Under the direction of Dr. Ian Grant, the Mesulam Institute continues its participation in the Alzheimer's prevention clinical trial called AHEAD 3-45, which treats cognitively normal individuals with Leqembi, those of whom have evidence of elevated amyloid in the brain. Our Clinical Trials Team reports that we have retained all enrolled participants and most have passed their two-year halfway point in the double-blind arm of the four-year study. The goal of the study is to see if Leqembi can delay the onset of cognitive impairment. We eagerly await the results of this study. Additionally, Institute researchers are increasly interested in how these immunotherapies clear amyloid from the brain mechanistically. Drs. Castellani, Cahan, and Vassar contributed to a publication in Nature Medicine reporting on the role that microglia play in the process of amyloid clearance, led by Dr. David Gate, director of the Abrams Research Center on Neurogenomics. These studies promise to someday lead to safer and more efficacious treatments for Alzheimer's disease.

Our faculty's accolades and achievements are always important to cite and to celebrate, and this year is no exception. We are proud to announce that Dr. Sandra Weintraub received a Lifetime Achievement Award from the Society for Behavioral and Cognitive Neurology of the American Academy of Neurology, the first time this award has been given to a neuropsychologist. Dr. Weintraub was recognized for her pioneering contributions to neuropsychology and behavioral neurology, her leadership in shaping the field, and her enduring commitment to mentorship and education.

Dr. Joshua Cahan, Assistant Professor in the Mesulam Institute, received the New Investigator Award from the National Alzheimer's Coordinating Center and the Alzheimer's Association. Dr. Cahan will use this prestigious award to partly fund his Study of Anti-amyloid Monoclonal Antibodies and Biospecimens in ARIA (SAMBA). We applaud Dr.Weintraub, Dr. Cahan, and all our esteemed faculty's accomplishments!

Historically, we have organized an action-packed Alzheimer Disease Day event for you, and we plan on following suit this year. Festivities begin with my Welcome and State of the Center Address, followed by the award of the annual Duncan Prize for best Alzheimer Day poster. We will then be honored by Dr. Ronald Petersen — professor of neurology and director Mayo Clinic Study of Aging— who will be giving the Mendelson Lecture Alzheimer's Disease 2026: Challenges and Hope. We are very fortunate to have him with us today to provide his deep insights into landscape of Alzheimer's disease today and in the future.

Following Dr. Petersen's lecture, we invite you to enjoy lunch

while you peruse our researchers' posters describing the exciting research that is being conducted at the Mesulam Institute. Our researchers, many of whom are our trainees, will be present in front of their posters and would very much appreciate hearing your questions and comments about their work. Be sure also to investigate the sponsor fair and our many sponsors who are represented there. We thank them for their generous support.

To conclude this year's Alzheimer Day, we will have our Quality-of-Life Symposium, with a keynote address by Sandra Weintraub, PhD, professor of psychiatry and behavioral sciences, neurology, and psychology at Northwestern University Feinberg School of Medicine and co-director of the Clinical Core and of the Admininstrative Core of the Northwestern Alzheimer's Disease Center (CNADC). I look forward to seeing you in person at the 32nd Alzheimer Day festivities! Enjoy!

Robert J. Vassar

Robert Vassar, PhD
Director, Mesulam Institute for Cognitive Neurology and Alzheimer's Disease
Davee Professor of Alzheimer Research

Thank You

(Left to Right): Marsel Mesulam, MD, Linda Mendelson, Allan Levey, MD, PhD (2025 Mendelson Lecture Presenter), Robert Mendelson

The Mendelson Family

The Mesulam Institute for Cognitive Neurology and Alzheimer's Disease would like to thank the Mendelson Family for their generous support of this event.

In honor of Robert and Linda Mendelson's 50th wedding anniversary, David and Blythe Mendelson, Sharon and Scott Markman, and Debbie Mendelson Ponn established the Mendelson Lectureship, which brings a keynote speaker to the Mesulam Institute's annual Alzheimer Day.

(Left to Right): Glen Miller, Wendy Miller, Marsel Mesulam, MD

The Miller Family

The Mesulam Institute for Cognitive Neurology and Alzheimer's Disease would also like to thank the Miller Family for their generous support of this event.

Since 2008, Glen and Wendy Miller and their daughter Lauren Izaks, have supported the Glen and Wendy Miller Family Buddy Program, which was named in their honor in 2021. In addition, they helped establish the Glen and Wendy Miller Family Post Graduate Social Work Fellowship in Neurocognitive Disorders.

Event Sponsors

We would like to thank our sponsors for the 32nd annual Alzheimer Day.
This event would not be possible without their generous support

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Sponsor Fair & Venue Map

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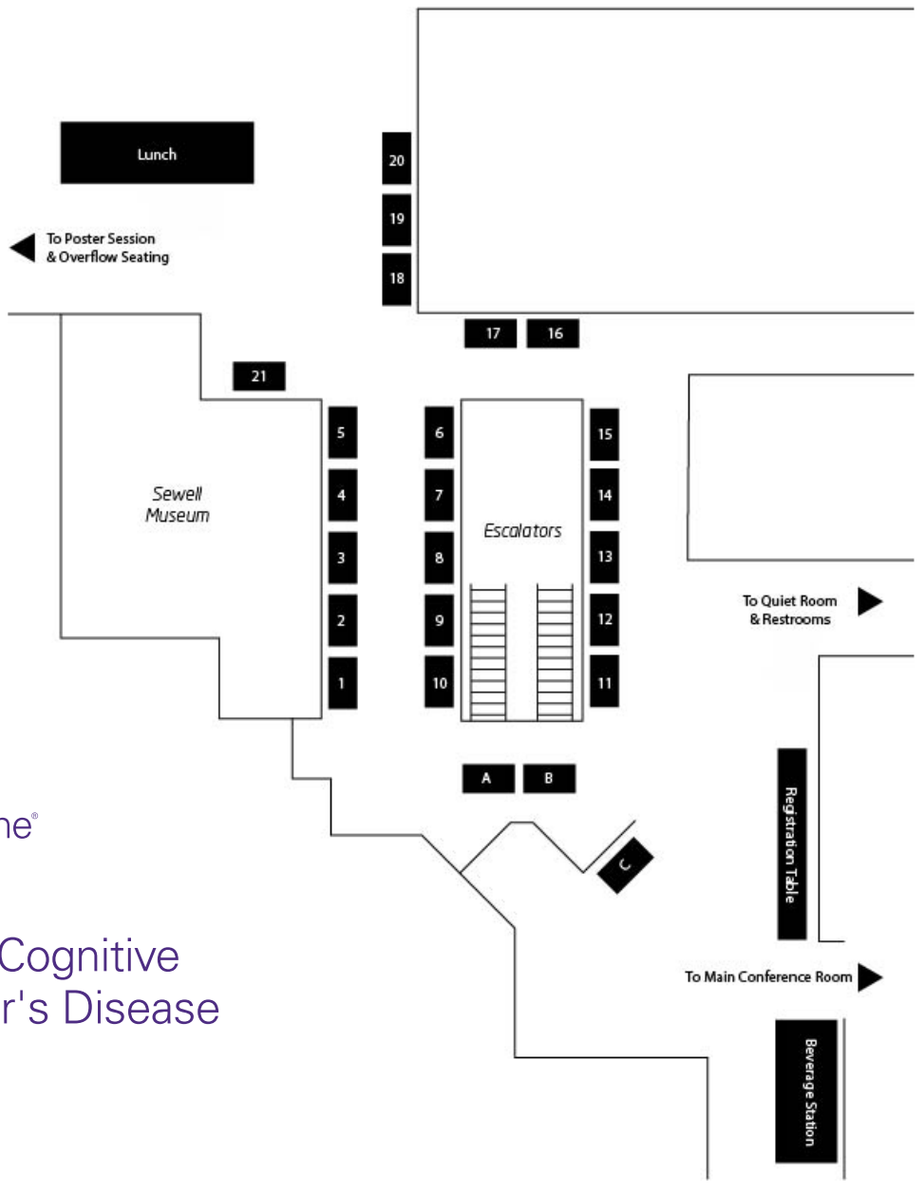

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Presentation of the Duncan Prize

Tamar Gefen, PhD

Associate Professor, Department of Psychiatry and Behavioral Sciences
Director, Laboratory for Translational Neuropsychology
Co-Director, Northwestern University SuperAging Program (NUSAP)
Co-Director, Clinical Core, Alzheimer's Disease Research Center
Mesulam Institute for Cognitive Neurology and Alzheimer's Disease
Northwestern University Feinberg School of Medicine

Tamar Gefen, PhD is an academic clinical neuropsychologist researching neurodegenerative disorders and successful trajectories of aging including "normal" aging and SuperAging.

She and her laboratory are studying the relationship between features of dementia or cognitive "resilience" during life with postmortem microscopic neuropathology found at autopsy.

Dr. Gefen is the Co-Director of the Northwestern SuperAging Program and the Co-Director of the Clinical Core of the Northwestern Alzheimer's Disease Research Center funded by the National Institute of Aging. Her clinical work at Northwestern Medicine is focused on the deep neuropsychological characterization of dementia syndromes (mainly due to frontotemporal lobar degeneration or Alzheimer's disease) and other age-related disorders.

Dr. Gefen and her colleagues have produced numerous high-impact publications and drawn global media attention for their findings detailing how some individuals maintain remarkable cognitive health into advanced age.

She is most proud of her students, those of whom are training to become the next generation of clinician-scientists. She hopes to continue cultivating their skill, dedication, and passion, so that they can translate their laboratory discoveries to patients in the clinic.

Mendelson Lecture:
Alzheimer's Disease 2026: Challenges and Hope

Ronald C. Petersen, MD, PhD

Professor of Neurology
Distinguished Mayo Clinic Investigator
Cora Kanow Professor of Alzheimer's Disease Research
Emeritus Cadieux Director, Mayo Alzheimer's Disease Research Center
Director, Mayo Clinic Study of Aging

Dr. Ronald C. Petersen received a PhD from the University of Minnesota and graduated from Mayo Medical School in 1980. He completed an internship in Medicine at Stanford University Medical Center and returned to the Mayo Clinic to complete a residency in Neurology that was followed by a fellowship in Behavioral Neurology at Harvard University Medical School/Beth Israel Hospital in Boston, Massachusetts.

Dr. Petersen was named the Cora Kanow Professor of Alzheimer's Disease Research in 2000 and Mayo Clinic Distinguished Investigator in 2011. He was the Director of the Mayo Alzheimer's Disease Research Center for 33 years and is the Director of the Mayo Clinic Study of Aging.

He has authored over 1000 peer-reviewed articles on memory disorders, aging, and Alzheimer's disease. Dr. Petersen has received the 2004 MetLife Award for Medical Research in Alzheimer's Disease and the 2005 Potamkin Prize for Research in Picks, Alzheimer's and Related Disorders of the American Academy of Neurology.

In 2011 he was appointed by the Secretary of Health and Human Services to serve as the Chair of the Advisory Committee on Research, Care and Services for the National Alzheimer's Disease Plan. In 2012 he received the Khachaturian Award and the Henry Wisniewski Lifetime Achievement Award in 2013 from the Alzheimer's Association. He has been a member of the World Dementia Council.

Quality of Life Symposium:

Understanding Symptom Evolution in Dementia: A Framework for Families and Professionals

Welcome and Introduction

Darby Morhardt, PhD, LCSW

Presentation: Understanding Symptom Evolution in Dementia: A Framework for Families and Professionals

Sandra Weintraub, PhD

Panel Discussion

Moderator: **Darby Morhardt, PhD, LCSW**

Panelists: **Ian Grant, MD, Karrie Stanley, MS, OTL, Lauren Dowden, MSW, LCSW, Treasyri Williams Wood, SLPD, CCC-SLP/L, CDP**

Community Conversation

Quality of Life Symposium Presenters

Sandra Weintraub, PhD

Presenter \ professor of psychiatry and behavioral sciences, neurology, and psychology \ Northwestern University

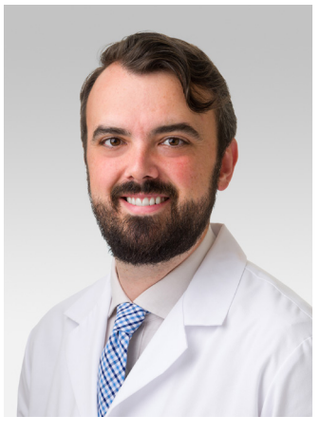
Sandra Weintraub, PhD, is a professor of psychiatry and behavioral sciences, neurology, and psychology at Northwestern University Feinberg School of Medicine. She is the Co-director of the Clinical Core and of the Admininstrative Core of the Northwestern Alzheimer's Disease Center (CNADC), funded since 1996 by the National Institute on Aging (NIA). She was one of two Scientific Honorees recognized at the Rita Hayworth Gala of the Alzheimer's Association in 1997. She served on the Alzheimer's Disease Clinical Task Force, a special advisory committee to the NIA, to create a method f or standardizing data collection at all 30 centers funded by the NIA across the US to capture all forms of dementia and the spectrum of cognitive aging. She was a member of three special work groups to redefine the 2011 criteria for the clinical diagnosis of dementia of the Alzheimer type, behavioral variant frontotemporal dementia, and primary progressive aphasia. Dr. Weintraub received her bachelor's degree from McGill University and PhD from Boston University. She is board certified in Clinical Neuropsychology by the American Board of Professional Psychology. She directs the outpatient clinical neuropsychology service at the Neurobehavior and Memory Clinic of Northwestern Medicine, a multidisciplinary clinic dedicated to state-of-the-art diagnostic, treatment and research resources for patients with dementia and their caregivers. Dr. Weintraub has authored over 300 articles and book chapters on the neuropsychology of dementia and aging and on aphasia. She was recently awarded the recipient of the Lifetime Achievement Award from the Society of Behavioral and Cognitive Neurology of the American Academy of Neurology.

Darby Morhardt, PhD, LCSW

Moderator \ research professor and clinical social worker \ Northwestern University

Darby Morhardt, PhD, LCSW is a research professor at the Mesulam Institute for Cognitive Neurology and Alzheimer's Disease and Department of Preventive Medicine (Public Health Practice), Northwestern University Feinberg School of Medicine. Dr. Morhardt directs the Mesulam Institute's Outreach, Recruitment and Engagement Core, Clinical Social Work Services, Quality of Life Initiatives, and the Miller Post-Graduate Social Work Fellowship in Neurocognitive Disorders. Areas of research include the experience of individuals and families living with dementia; the process of tailoring care to specific needs and symptoms; and the development and evaluation of quality-of-life enrichment interventions. Dr. Morhardt has a long history of community engaged research partnerships to address inequities in dementia education, awareness, research participation and quality of life enhancing programs throughout Chicago especially with underrepresented groups. Appointed to the State of Illinois Alzheimer's Disease Advisory Committee since 2000, she has contributed to the writing of the Illinois Alzheimer's Disease State Plan and was a founding leader of the Illinois Cognitive Resources Network (Ilbrainhealth.org). Dr. Morhardt also serves on the Illinois Supreme Court Commission on Elder Law, tasked to more effectively address the needs and legal issues of older adults.

Quality of Life Symposium Presenters



Ian Grant, MD

Panelist \ behavioral neurologist \ Northwestern Medicine

Dr. Ian Grant is a behavioral neurologist in the Neurobehavior and Memory Clinic at Northwestern Medicine where he diagnoses and cares for patients with neurodegenerative dementias. He is also the Director of Clinical Trials Operations for the Mesulam Institute for Cognitive Neurology and Alzheimer's Disease. In this role, he oversees interventional clinical trials examining new potential treatments for Alzheimer disease and other dementias, including the first medication trial for primary progressive aphasia.

In addition to interventional trials, he also oversees several long-running observational studies including the most recent iteration of the Alzheimer's Disease Neuroimaging Initiative (ADNI4) and the ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) study. Dr. Grant graduated from Indiana University School of Medicine where he received a master's degree in bioethics in addition to his MD. He completed neurology residency and behavioral neurology fellowship at Northwestern University Feinberg School of Medicine.

Karrie Stanley, MS, OTL

Panelist \ occupational therapist and founder \ Vitalize Home Therapy

Karrie Stanley MS, OTL is an occupational therapist and founder of Vitalize Home Therapy, PLLC based in Chicago. Vitalize Home Therapy provides home-based and telehealth outpatient OT & PT services for older adults throughout Chicagoland. Karrie is passionate about this work and sees her role as a problem-solver and partner to navigate the challenges of aging in order for older adults to remain in their home of choice with a lifestyle they find meaningful. Her areas of expertise include dementia, Parkinson's disease and other neurological conditions. She is certified in LSVT BIG treatment for Parkinson's disease and the Skills2Care program supporting persons with dementia and their care partners. Karrie has been an OT for over 25 years and holds a Bachelor's degree in OT from Xavier University and Master's degree in Disability Studies and Social Policy from the University of Illinois at Chicago. She lives in Chicago with her husband and two children and enjoys traveling on a quest to visit all the National Parks.

Quality of Life Symposium Panelists

Lauren Dowden, MSW, LCSW

Panelist \ clinical social worker \ Northwestern Medicine

Lauren Dowden, MSW, LCSW is a clinical social worker and the Assistant Director of the Outreach, Recruitment and Community Engagement Core at the Northwestern University Feinberg School of Medicine Mesulam Center for Cognitive Neurology and Alzheimer's Disease. Lauren is committed to addressing the unique care needs of those living with dementia and their care partners by working collaboratively and creatively with them focusing on the person's strengths and ongoing potential for contribution. Lauren provides clinical care and supports the research, coordination, and facilitation of quality of life programs – The Miller Family Buddy Program, PPA Tele-Savvy and care partner support groups. Lauren co-developed the storytelling workshop, Don't Look Away: Using Storytelling to Give Voice, Find Connections, and Change Perceptions, which invited individuals living with dementia and their care partner to co-create a story about their lived experience and recently created a storytelling program with Lorenzo's House for members of their NextGen movement who are children of a parent living with young-onset dementia. Lauren is a Medical Improv instructor teaching medical students at NUFSM and healthcare professionals around the country, notably at Northwestern Medicine, Indiana University-Purdue University Indianapolis, Rush-Esperanza Health Center, UCLA and Sloan-Kettering Cancer Center. Lauren has also developed therapeutic improv workshops for populations navigating substance use disorders, trauma, anxiety, Parkinson's disease, and major neurocognitive disorders and is developing a program for care partners of those living with dementia.

Treasyri Williams Wood, SLPD, CCC-SLP/L, CDP

Panelist \ speech-language pathologist \ Willwood Consulting Services

Dr. Treasyri (pronounced "treasure") **Williams Wood, SLPD, CCC-SLP/L, CDP** resides and practices on the south side of Chicago, Illinois. She graduated from Western Michigan University in Kalamazoo with a Bachelor of Science degree in audiology and speech-language pathology and later earned a Master of Arts degree in communicative sciences and disorders from Hampton University in Virginia. Dr. Williams Wood then obtained a clinical doctorate in speech-language pathology (SLPD) from Northwestern University in Evanston, Illinois. Clinically, Dr. Williams Wood is passionate about developing person-centered interventions for individuals with aphasia, voice, and cognitive-communication challenges as a result of neurogenic conditions and neurodegenerative disease. She specializes in teaching topics related to advocacy, neural basis of communication, and cultural competency. Her research focuses on social determinants of health as they relate to individuals with neurogenic disorders of communication and their care partners. Dr. Williams Wood enjoys fostering partnerships to increase access among underserved populations through holistic, culturally responsive care. She was elected to the American Speech-Language-Hearing Association's Board of Directors as member at large in 2021 and served a two-year term.

Mesulam Institute Faculty Members

Robert Vassar, PhD
Director, Mesulam Institute for Cognitive Neurology and Alzheimer's Disease

Davee Professor of Alzheimer Research

M. Marsel Mesulam, MD
Founding Director Emeritus, Mesulam Institute for Cognitive Neurology and Alzheimer's Disease

Ruth Dunbar Davee Professor in Neuroscience and Neurology

Elena Barbieri, PhD
Research Assistant Professor of Physical Medical and Rehabilitation

Borna Bonakdarpour, MD, FAAN
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Joshua Cahan, MD
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Professor of Psychiatry and Behavioral Sciences, Psychology, and Neurology

Debby Zemlock, MS
Assistant Director of DMS Core, Mesulam Institute for Cognitive Neurology and Alzheimer's Disease

Hui Zhang, PhD
Professor of Preventive Medicine

Mesulam Institute Advisory Board

We would like to graciously thank our Advisory Board, founded and led from 1998 to 2008 by the late Jerome Rosenstone.

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The Mesulam Institute Advisory Board was formed to increase public awareness and knowledge of the Institute, and to help garner ongoing philanthropic support for the Mesulam Institute's programs and facilities. The Board helps promote the Institute both locally and nationally, and assists in securing the funding necessary to position the Institute among the premier Alzheimer's research and patient care facilities in the United States.

If you are interested in learning more about the Mesulam Institute Advisory Board, please contact Eskedar Alem at 312.503.2832 or visit our website: **brain.northwestern.edu/about/advisory-board.html**.

Marie and Carl Duncan Prize in Memory Disorders Research

Professor Carl Duncan is widely regarded as the first to demonstrate the existence of memory consolidation, showing the vulnerability of recently stored memories. His landmark work is cited more than half a century later. Upon his passing in 1999, his wife, Dr. Marie Duncan, who received her medical degree from Northwestern, set up the Duncan Fund to encourage research and discussion on issues related to memory.

In addition to an annual lecture on fundamental research on memory in the name of Professor Duncan, the Duncan Fund inaugurated in 2006 the Marie and Carl Duncan Prize in Memory Disorders Research to award accomplishments in clinically relevant arenas of inquiry. Previous winners are listed below.

2025: Grace Minogue, Raisa Monteiro

2024: Allegra Kawles, Rachel Keszycki, Alyssa Macomber, Molly Mather, Lynn van Olst, Nalini Rao, & Zacharia Cross

2023: Ivan Ayala

2022: Allegra Kawles & Rachel Keszycki

2021: Erfan Taefi

2020: Chloe Parker & Adam Martersteck

2019: Kyla Guillaume & Timothy J Hark

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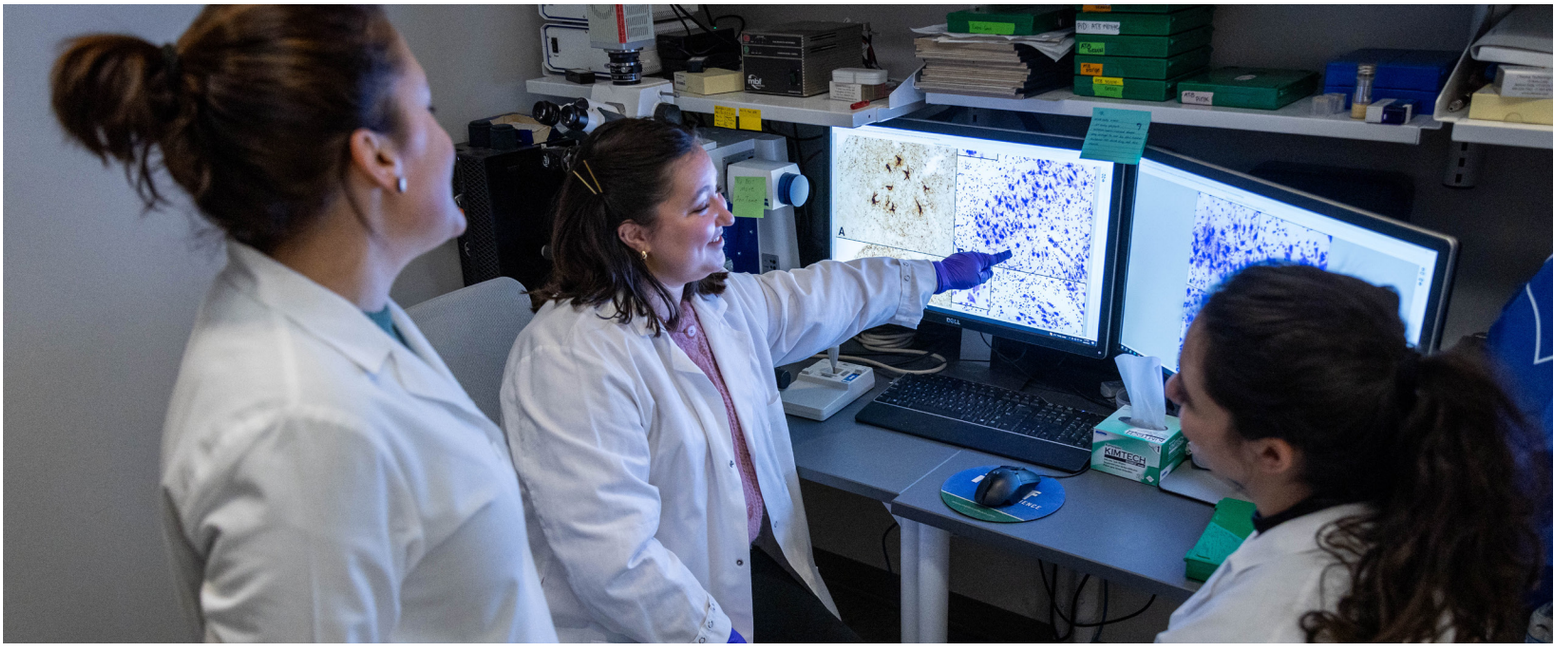
2009: Katherine Sadleir

2008: Carmen Westerberg



About the Mesulam Institute

The Mesulam Institute has a number of research studies for which we are seeking volunteer participants. If you are interested in participating in memory research and/or would like to be placed on our mailing list, please contact us at 312.926.1851 or join a study at **brain.northwestern.edu/join.**

Mission

The Mesulam Institute for Cognitive Neurology and Alzheimer's Disease (Mesulam Institute) is a multidisciplinary organization dedicated to the following pursuits:

- Conducting research to discover how the brain coordinates cognitive functions such as memory, language, attention, and emotion.
- Discovering causes and treatments for diseases that disrupt these functions, such as Alzheimer's disease and related dementias.
- Transferring the benefits of this research to patients and their families.
- Training researchers and clinicians who want to work in this field.

Research Areas

- Treatment and Prevention of Alzheimer's Disease
- Causes and Treatments of Primary Progressive Aphasia, Frontotemporal Degeneration, and other Younger Onset Dementias
- Nature of Cognitive and Behavioral Changes in Alzheimer's Disease
- Human Cognitive Brain Mapping
- Experimental Treatments
- Chemistry of Memory
- Maintenance of Cognitive Functions in Aging
- Genetics
- Impact of Non-Pharmacological Interventions on Quality of Life

Contact Us

300 E. Superior Street, Tarry 8th Floor, Chicago, IL 60611
brain.northwestern.edu \ Phone: 312.908.9339 \ Fax: 312.908.8789 \ mesulam-center@northwestern.edu

Northwestern Medicine Neurobehavior and Memory Clinic

Our dedicated clinical team includes behavioral neurologists, neuropsychiatrists, neuropsychologists, and social workers. **Call for an appointment: 312.695.9627**.

Care for Patients and Families

The Neurobehavior and Memory Clinic is designed to meet the needs of persons experiencing memory loss or other symptoms of dementia, and their families

Services Include:

- Evaluation and follow-up care by behavioral neurologists who specialize in the diagnosis and treatment of dementia syndromes
- Evaluation of memory and other thinking abilities with the use of specialized tests given by a clinical neuropsychologist
- Management of medication for memory disorders
- The opportunity to participate in clinical research and clinical drug trials
- Psychiatric evaluation and treatment for mood and behavior disorders associated with neurological disease
- Education and counseling for patients and families
- Symptom specific interventions and strategies
- Information and referral to other supportive services

Contact Us

676 North Saint Clair Street, Suite 1310. Chicago, IL,60611
brain.northwestern.edu/care-and-support \ Phone: 312.695.9627 \ Fax: 312.695.6072

Neurobehavior and Memory Clinic Team

Behavioral Neurologists
Marsel Mesulam, MD, Director
Borna Bonakdarpour, MD
Joshua Cahan, MD
Ian Grant, MD
Allison Lapins, MD
Malik Nassan, MD
Sarah Doran, MD

Neuropsychiatrists
Fred Ovsiew, MD
Razvan Daniel Popescu, MD

Neuropsychologists
Sandra Weintraub, PhD
Maureen Daly, PhD
Tamar Gefen, PhD
Molly Mather, PhD
Jane Stocks, PhD

Clinical Social Workers
Darby Morhardt, PhD, LCSW
Lauren Dowden, MSW, LCSW
Jordyn Cohen, MSW, LCSW

Nurse
Carly Liebst, RN
Collin Bartsch, RN

Psychometrist
Eli Nuzzo-Dozzier

Physician Assistant
Brianna Lee, MPAS
Kaitlyn Allen, PA-C

Clinic Manager
Kevin Reyes, BA

Resource Coordinator
Nicole Wright, BA, CSP

Admin Team
Anthony Nowaske
Sandra Zuniga, AA
Sarah Barnes

Neuropsychology Technicians
Gregory Tesnar
Connor Morfoot

Strength in Numbers Join ADNI4

There is no way to prevent or cure Alzheimer's

Research is key to better understanding this incurable disease.

We need your help.

ADNI4 needs volunteers who:

- **Are 55 to 90 years of age**
- **Have either:**
  - Normal memory,
  - Mild Cognitive Impairment*, or
  - Dementia*
- **Have a study partner**
- **Are willing to commit to the study for 5 years**
- **Are available for in-person visits with some virtual options**

**Diagnosis is not required (testing is part of study screening).*

For nearly 20 years, the Alzheimer's Disease Neuroimaging Initiative (ADNI) has made amazing discoveries in how the brain functions.

ADNI4 is the next frontier.

Connect with your local research location to join ADNI4.

ADNI4 is funded by a grant from the National Institute on Aging to the Northern California Institute for Research and Education, and being conducted by a network of leading academic Alzheimer's research partners.

ADNI Alzheimer's Disease Neuroimaging Initiative

Frequently Asked Questions

What is the AHEAD Study?

The AHEAD Study tests whether intervening **AHEAD** of symptoms may help prevent future memory loss and dementia caused by Alzheimer's disease.

The study looks at an investigational treatment aimed at delaying memory decline in people up to 20 years before the symptoms of Alzheimer's disease appear. Discovering a treatment that targets brain changes early means doctors may be able to one day prevent memory loss.

The AHEAD Study needs participants of every race and ethnicity to help find a treatment for Alzheimer's disease that works for everyone.

Who is eligible?

Individuals eligible for the AHEAD Study:

- Are healthy, non-smoking adults, ages 55–80.
- Have not been diagnosed with Alzheimer's disease.
- Have elevated or intermediate levels of amyloid in their brains (a protein shown by brain imaging, as part of the study screening process).
- Have a close friend or relative who the participant sees or talks to every week who can serve as their study partner.

What makes this study unique?

It is made up of two different clinical trials testing the same investigational medication BAN2401 (lecanemab), which can remove amyloid, a protein that builds up in the brains of people who can go on to have memory problems because of Alzheimer's disease.

Study participants will receive tailored dosing of the investigational treatment, depending on which study they qualify for, instead of a one-size-fits-all approach.

- **AHEAD A-3 Trial:** participants with intermediate amyloid levels will receive BAN2401 (lecanemab) once every four weeks for four years. The AHEAD A-3 trial aims to intervene at the very earliest signs of Alzheimer's disease.
- **AHEAD A-45 Trial:** participants with elevated amyloid levels will receive BAN2401 (lecanemab) once every two weeks for about two years, in an effort to clear amyloid from the brain, then once every four weeks for the remainder of the study.

What do participants need to do?

The AHEAD Study is a four-year commitment that includes in-person and telephone visits with study researchers every two to four weeks. At these visits, participants receive intravenous (IV) infusions of BAN2401 (lecanemab) or a placebo—an inactive substance designed to mimic the appearance of the drug. The infusion process takes approximately 60 minutes.

At different points in the study, participants will have a PET scan (or Positron Emission Tomography brain scan) to look at amyloid and tau, another protein in the brain.

Study participants receive $50 per visit for their time.

Why is a study partner needed?

Like many other Alzheimer's trials, the AHEAD Study requires two individuals—a study volunteer (or participant) as well as his or her study partner. The study partner plays an important role in helping researchers track changes in the participant's memory or behavior that he or she may not notice themselves. For this reason, a study partner should be someone who has contact with the participant weekly, like a family member or trusted friend. Often the study partner is the participant's spouse, adult son or daughter, friend, or neighbor.

Study partners must participate in one study visit per year, in-person or by phone, over the four-year trial and will receive $50 per each required visit they attend.

Will information from the study be shared with a participant's doctor?

Participant study information is not released to personal physicians without the participant's permission, and participant study information is coded to protect confidentiality. With permission, some information can be shared with a participant's physician.

How will personal information be used, and how is privacy protected?

By law, the study is required to maintain the privacy and security of participants' protected health information. Data privacy of AHEAD Study participants is a top priority. The study will not use or share participant information, other than as described on AHEADStudy.org, unless otherwise told in writing.

Who funds the AHEAD Study?

The AHEAD Study is funded by the National Institutes of Health (NIH) and several philanthropic organizations, as well as Eisai, the company that makes the investigational treatment used in the study. It is led by Alzheimer's disease research experts and academic leadership at the University of Southern California's Alzheimer's Therapeutic Research Institute, Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, and the Alzheimer's Clinical Trials Consortium.

Help us get AHEAD of Alzheimer's disease

For more information about the AHEAD Study, please visit **AHEADStudy.org/LearnMore** or call **1-800-AHEAD-70** (1-800-243-2370), or **scan the QR code** with your smartphone.

BenfoTeam

The BenfoTeam clinical research trial aims to increase the amount of thiamine (Vitamin B1) in the brain to slow cognitive decline in people with Mild Cognitive Impairment and mild Alzheimer's Disease

The trial is designed for people who are age 50-89, and experiencing significant memory concerns, or who have already been diagnosed with Mild Cognitive Impairment (MCI) or mild Alzheimer's disease (AD). This stage of the disease, MCI through mild AD, is also known as early AD.

Basic Eligibility Criteria

- Aged 50-89
- Diagnosed with early AD, including Mild Cognitive Impairment (MCI) or mild dementia (with blood test confirmation at screening)
- Stable on current FDA-approved acetylcholinesterase inhibitors (with or without memantine) for at least three months prior to screening
- Living in the community (not in a long-term care nursing facility)
- Willing to participate in the BenfoTeam study for up to 18 months

What happens during the BenfoTeam Study?

Trial participation will take up to 18 months. Potential participants will first go through the screening process to see if they are eligible to take part in the clinical trial. Half of the participants are given the study drug, benfotiamine, and half are given an inactive pill (called a placebo) to take twice daily.

Screening includes: Memory and thinking tests, blood tests, EKGs (a look at your heart rhythms), and MRI scans (a picture of your brain that shows changes related to AD).

For more information or to volunteer, please contact:

Northwestern University

NAME Aaliyah Korkoyah
Title Sr. Research Study Coordinator
Phone: 312-503-5673
Email: clinicaltrials.mesulam@northwestern.edu
www.BenfoTeam.org

ALLFTD
ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration

ALLFTD Longitudinal Research Study

ALLFTD is a multisite research study aimed at understanding the changes in brain function that occur as a result of frontotemporal lobar degeneration (FTLD) syndromes. FTLD syndromes can include bvFTD, bvFTD with ALS, PPA, PSP, or CBD. Some forms of FTLD are genetic, while others are not. ALLFTD is interested in all forms of FTLD.

We can learn about changes in your brain in a variety of ways, including a clinical examination, memory and thinking tests, and MR imaging of your brain. We also measure different proteins in your blood or cerebrospinal fluid (CSF) that we think change in response to disease progression.

If you are interested in helping us learn more about FTLD, and you've been diagnosed with an FTLD syndrome or are at risk due to your family history, please consider participating in our ALLFTD Longitudinal Research Study.

Why am I being asked to participate in the ALLFTD Longitudinal Study?

You're being asked to participate in the ALLFTD Longitudinal Study because you've either:

1. Been diagnosed with an FTLD syndrome like bvFTD, bvFTD with ALS, PPA, PSP, or CBD
2. Are from a family with a mutation in a gene known to cause FTLD (such as *C9orf72*, *MAPT*, and *GRN*)
3. Have a significant family history of FTLD suggesting a familial genetic mutation.

If you are from groups 2 or 3, you don't have to have symptoms to participate and you don't need to know your mutation status to participate.

What happens in the ALLFTD Longitudinal Study?

The ALLFTD Longitudinal Study is an annual visit to the clinic, each lasting 2–3 days. You will complete some questionnaires and memory and thinking questions, meet with a clinician for a neurological exam, and have your blood drawn and an MRI.

Where can I find more information about the study?

You can find more information about the study on our website at www.allftd.org.

I am interested in participating. What do I do next?

Please tell your neurologist that you would like to participate in the ALLFTD Longitudinal Study. You can also find contact information for ALLFTD site study coordinators at www.allftd.org and can also email a coordinator to say that you would like to join. We suggest you choose the site most convenient for you.

Study Sites

Brown University
Case Western Reserve University/University Hospitals Cleveland Medical Center, Cleveland
Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas
Columbia University in the City of New York
Emory University, Atlanta
Houston Methodist Hospital, Nantz National Alzheimer Center
Indiana University
Johns Hopkins University, Baltimore
Massachusetts General Hospital, Boston
Mayo Clinic, Jacksonville
Mayo Clinic, Rochester
Mt Sinai, New York City, New York
National Institutes of Health (NIH), Bethesda
Northwestern University, Chicago
University of Alabama at Birmingham
University of British Columbia, Vancouver
University of California, Los Angeles
University of California, San Diego
University of California, San Francisco
University of Colorado Denver
University of Michigan
University of North Carolina at Chapel Hill
University of Pennsylvania, Philadelphia
University of Texas Health Science Center at San Antonio
University of Toronto
University of Washington, Seattle
Vanderbilt University
Washington University in St. Louis

Contact your site:

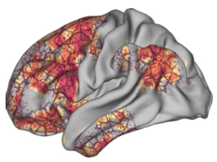
More information at www.allftd.org/sites.
Contact us at info@allftd.org.
IRB00227492 Drs. Boeve, Boxer, and Rosen.

FTLD Genetics

Familial FTLD (f-FTLD) occurs in about 30% of FTLD cases where multiple members of a family are affected. This occurs due to changes in the genetic code called mutations, which are associated with a high risk of developing FTLD during a person's lifetime. These mutations follow an autosomal dominant inheritance pattern, meaning each child of someone with a mutation has a 50% risk of inheriting the mutation. Mutations that cause f-FTLD can present with any FTLD syndrome, and in a given family each affected individual can potentially present with a different syndrome. There are three gene mutations commonly associated with f-FTLD (*MAPT:* microtubule associate protein tau; *GRN:* progranulin; and *C9orf72:* chromosome 9 open reading frame 72), however through research studies like this one we are learning about other mutations that cause f-FTLD.

FTLD Syndromes

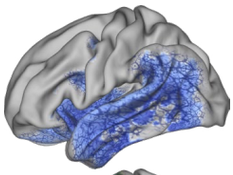
Behavioral Variant of Frontotemporal Dementia (bvFTD)



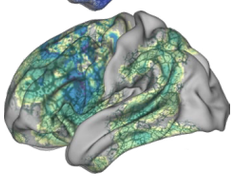
Behavioral Variant of Frontotemporal Dementia (bvFTD)

Early symptoms in bvFTD usually include loss of interest in previously enjoyed activities (apathy), loss of empathy, loss of knowledge about how to behave in social situations, impulsiveness, and fixations or obsession about certain topics or ideas.

Semantic Variant of Primary Progressive Aphasia (svPPA)



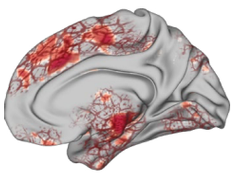
Non-Fluent Variant of Primary Progressive Aphasia (nfvPPA)



Primary Progressive Aphasia (PPA)

The main symptoms are early and progressive language difficulties. Spoken and written words are affected. Words lose their meaning and there can be issues recognizing objects and people, or there is difficulty in getting words out so speech seems hesitant and effortful.

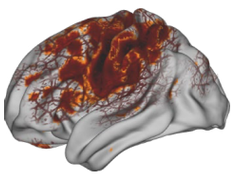
Progressive Supranuclear Palsy (PSP)



Progressive Supranuclear Palsy (PSP)

Those with PSP have stiffness and slowness of the body, poor balance with falling, trouble moving the eyes, and also problems with social skills, judgment, language, and thinking abilities.

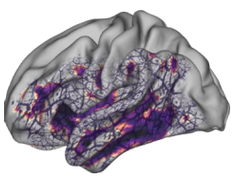
Corticobasal Syndrome (CBS)



Corticobasal Syndrome (CBS)

CBS is identified by worsening stiffness that affects one side of the body (arm or leg) and similar language and behavioral problems as those seen in bvFTD and PPA.

bvFTD with Amyotrophic Lateral Sclerosis



bvFTD with Amyotrophic Lateral Sclerosis

Often referred to as *motor neuron disease* or *Lou Gehrig's disease*, ALS is caused by degeneration of nerves in the brain and spinal cord that control muscles. The main symptoms are twitching, atrophy (shrinking), and weakness of the muscles in the limbs, torso, neck and face, usually starting in one part of the body and spreading to others.

Northwestern University

SuperAging Program

Over 80 and Still Going Strong?

Are you 80+ and still actively engaged in life?
Does this sound like you or someone you know?

Who are we?

We are the Northwestern University SuperAging Program (NUSAP) and we would love to hear from you!

Why are YOU important?

You can help us better understand and identify factors that contribute to exceptional cognitive aging.

What is involved?

- Visiting our Institute every year
- Pen and paper cognitive tests
- Surveys and questionnaires
- MRI/PET brain scans (optional)
- Blood draws for research studies of genetic and other biological factors

Compensation will be offered for your time and travel to the Mesulam Institute will be covered.

Interested? Please contact us for more information:

312.908.9339 | clinicalcore@northwestern.edu | brain.northwestern.edu/SuperAging

Mesulam Institute
for Cognitive Neurology & Alzheimer's Disease

Northwestern Medicine
Feinberg School of Medicine

Study Funded By: National Institute on Aging
Principal Investigator: Sandra Weintraub PhD
Grant#: 1P30AG072977-01, IRB# STU00023196, Core B
Study Title: Alzheimer's Disease Research Center, Northwestern University SuperAging Program Sub-Study

ADVANCING BRAIN SCIENCE, EMPOWERING LIVES

Brain diseases, like Alzheimer's disease and other dementias, can affect everyone.

Join CLARiTI and help us discover ways to prevent and treat diseases that affect brain health.

Make an impact and be a part of groundbreaking discoveries in brain health.

We cannot do this without you!

PARTNERS IN DISCOVERY

CLARiTI

ADRC Consortium for Clarity in ADRD Research Through Imaging

Thank you for your interest in participating in CLARiTI. To learn more, please contact us:

Northwestern ADRC: (312) 908-9339

300 E. Superior St, Chicago, IL 60611

www.brain.northwestern.edu

CLARiTI is funded by the National Institute on Aging.

CLARiTI

ADRC Consortium for Clarity in ADRD Research Through Imaging

Clarity in Alzheimer's Disease and Related Dementias Research Through Imaging (CLARiTI)

JOIN THIS NATIONWIDE STUDY TO ADVANCE BRAIN HEALTH AND EMPOWER LIVES

Many different changes in the brain can lead to memory and thinking problems.

CLARiTI is an exciting new study that uses brain imaging to understand these different changes.

You may be a great candidate to participate!

Everyone is unique and so is their brain.

We welcome:

1. Adults aged 50 or older.
2. Both people with AND without memory concerns.
3. Those currently enrolled in an Alzheimer's Disease Research Center or interested in enrolling.

PARTNERS IN DISCOVERY

Your participation in CLARiTI may benefit people in the future by helping us learn more about how to detect Alzheimer's disease and related dementias.

As a participant, you will receive brain health education and may also be able to learn the results of your brain imaging tests.

We value your time and effort.

Benefits of participating include:

- Personalized support through each step of the study
- Compensation for your time and participation
- Health education resources
- Access to some of your personal results from the study *
- Transportation assistance for study visits *

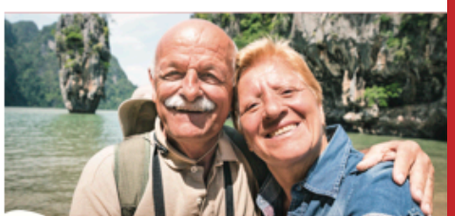
What will I be asked to do?

You will be asked to complete brain imaging and blood tests. These tests may be scheduled across multiple visits at your local research center.

You will complete these activities when you first enroll and again about two years later. We will work with your schedule to plan these visits. By comparing the results from these two times, we can look for changes in brain health.

Our Commitment

We are committed to including all individuals affected by Alzheimer's disease and related dementias in our research to ensure study results help everyone.



Scan Me

TOGETHER WE CAN SHAPE THE FUTURE OF BRAIN HEALTH

clariti.naccdata.org

Northwestern Medicine®

Mesulam Institute
for Cognitive Neurology & Alzheimer's Disease

LANGUAGE IN PRIMARY PROGRESSIVE APHASIA

Observational Research Study

Funded in part by the National Institute on Aging
Principal Investigators: Marsel Mesulam, MD & Emily Rogalski, PhD; STU00026372

Currently Recruiting!

PURPOSE

The Language in Primary Progressive Aphasia (PPA) research program seeks to enroll and follow individuals living with PPA over time using neuropsychological testing and advanced imaging techniques to:

1. better understand progression in PPA and its link to brain changes,
2. increase awareness of PPA and educate those living with PPA, their families, clinicians, and the community,
3. identify biomarkers that will lead to earlier and effective diagnosis and intervention.

STUDY ACTIVITIES

At study visits, participants will be asked to:

- Have an examination by a neurologist
- Answer questions about their health and family history
- Have brain scans
- Take paper and pencil tests that evaluate memory and thinking

DETAILS

Study visits last four days total, for about seven hours each day, including breaks.

Participants are asked to return every two years to compare changes between visits.

The study takes place at Northwestern University in downtown Chicago, IL.

Travel arrangements are provided for both the person with PPA and study partner at no cost.

Participants will be compensated for their time and effort.

Eligibility Requirements:

- Diagnosed with PPA
- Right-handed
- Native English speaker
- Have a study partner who can accompany them to visits
- Not claustrophobic
- Safe for an MRI Scan

Individuals not seen at the Mesulam Center Neurobehavior and Memory Clinic will need to send medical records and have a phone interview before being approved to participate.

FOR MORE INFORMATION
please contact:

Michelle Los , Operations Manager
PPA.Research@northwestern.edu
312-908-9681
www.brain.northwestern.edu

The Importance of Brain Donation for Research and Diagnosis

Brain donation helps researchers understand cognitive aging.

- Brain donation from an individual who participated yearly in cognitive research during their lifetime is the ultimate gift.
- The Northwestern Mesulam Institute has been dedicated for over 30 years to studying brain aging in individuals with annual cognitive tests, brain imaging, and blood tests.
- Some individuals we follow have neurodegenerative brain diseases, such as Alzheimer's disease, Lewy body disease, or frontotemporal lobar degeneration, that cause progressive dementia syndromes.
- Some individuals we follow are cognitively healthy—that is, they have normal cognitive scores for their age. We also follow "SuperAgers," who have better-than-average memory for their age.
- By studying the brains of individuals with and without neurodegenerative diseases, we gain priceless information that may one day help us to promote healthy brain aging and combat age-related dementia.

Brain donation provides valuable information to families.

A postmortem brain autopsy not only provides valuable tissue for scientific discovery, but—for individuals who suffered with dementia during their lifetime—the brain autopsy determines what disease caused the dementia. Such information is useful if other family members develop dementia in the future or if there is a known strong family history. Brain donation also gives the family a way to potentially help others, which can create a sense of hope and power over the illness that affected their loved one.

Northwestern Medicine®
Feinberg School of Medicine

Mesulam Institute
for Cognitive Neurology & Alzheimer's Disease

Members of the professional staff at the Northwestern University Mesulam Institute are available to discuss brain donation and answer your questions.

312-908-9339 | clinicalcore@northwestern.edu | brain.northwestern.edu

The Glen and Wendy Miller Buddy Program

The Buddy Program is a unique opportunity for persons living with dementia to mentor first-year medical students.

As a Buddy Program Mentor, you will:

- Be paired with a first- year medical student to visit with on a regular basis throughout the academic year (October – May).
- Engage in activities hosted by the program throughout the year including a Match Day, Valentine's Day Lunch, and End of the Year Celebration.
- Help to inform a future physician's understanding of how dementia affects a person and their family..

"I found the experience to be fantastic: I felt I had a 'friend' in my disease. I felt privileged and grateful to learn from him. I felt the mutual empathy was inspiring."

Former Buddy Program Mentor

Interested in learning more? Visit brain.northwestern.edu/buddy or email Darby Morhardt, PhD, LCSW at d-morhardt@northwestern.edu.

Care Partner Support Groups

The Mesulam Institute offers three monthly support groups for family members and care partners of persons living with dementia. Currently, we are offering these groups through Zoom.

New care partners are always welcome to join the group. There is no fee to participate. If you have not been to the group before and would like to join, please reach out to the contact listed on the group to set up a brief telephone screening.

Care Partners of Individuals Living with PPA

- **Time:** first Monday of each month from 4:30 to 6 p.m. CT.

This monthly support group is for family members and care partners of people living with primary progressive aphasia (PPA).

Contact:
Darby Morhardt, PhD, LCSW
d-morhardt@northwestern.edu
312.908.9432

Care Partners of Individuals Living with Younger-Onset Dementia

- **Time:** second Monday of each month from 4:30 to 6 p.m. CT.

This monthly support group is for family members and care partners of people living with younger-onset (under age 65) dementia

Contact:
Jordyn Cohen, MSW, LCSW
jordyn.cohen@northwestern.edu
312.503.5764

Care Partners of Individuals Living with FTD

- **Time:** third Monday of each month from 4:30 to 6 p.m. CT.

This monthly support group is for family members and care partners of people living with frontotemporal dementia (FTD).

Contact:
Lauren Dowden, MSW, LCSW
lauren.dowden@northwestern.edu
312.503.5761

Interested in learning more? Visit brain.northwestern.edu/SupportGroups.

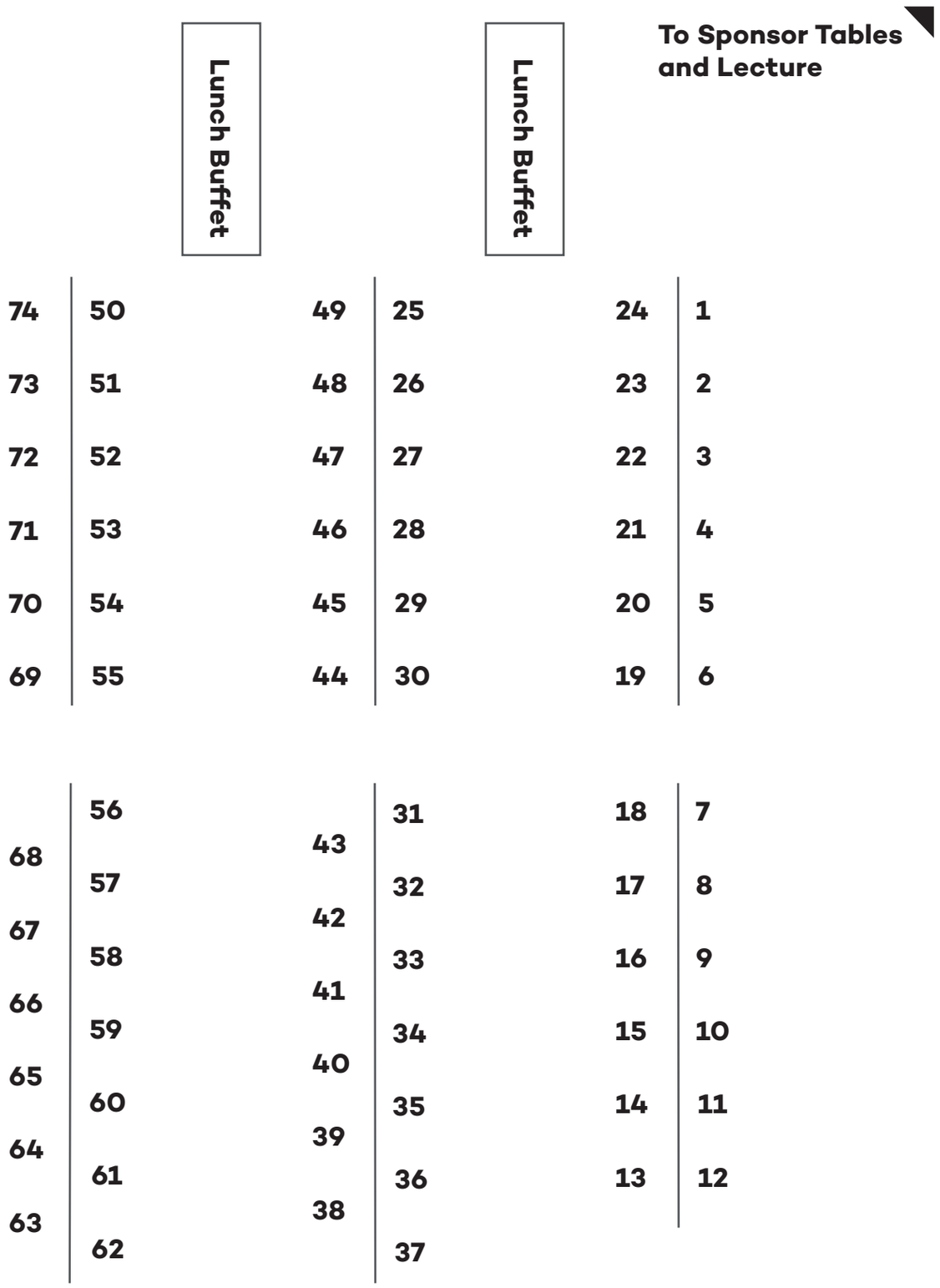
Northwestern Music and Medicine Program

The Northwestern Music and Medicine Program (NMMP) was founded by Borna Bonakdarpour and Clara Takarabe in May of 2021. The goal of the program is to bring clinically oriented music to patients, investigate the efficacy of interventions and their mechanisms of action, and to educate the public and trainees.

Music Interventions for Neurocognitive Disorders (MIND) include NMMP's current programs and research trials for persons with neurocognitive disorders and encompasses the following:

- **Musical Museum:** Music sessions with discussions for mild to moderate neurocognitive disorders.
- **Clinical Improvisation for Alzheimer's disease and Caregivers (CIMAC):** This research trial targets individuals with mild to moderate Alzheimer's disease anxiety and Alzheimer's caregivers who experience significant burden.
- **NMH Music Intervention:** Individualized bedside music interventions for individuals with dementia admitted to the Northwestern Memorial Hospital.
- **Musical Bridges to Memory:** A collaboration with Institute for Therapy through the Arts, this study investigates the role of music interventions on social engagement in moderate to severe dementia.
- **Group singing:** A collaboration with Sounds Good and Good Memory choirs in which individuals with mild to moderate dementia are eligible for participation in Good Memory Choir.
- **Music Empathy Treatment for Frontotemporal Dementia (MET-FTD)**: This study is performed in collaboration with University of Chicago, investigating the role of music therapy in alleviating symptoms of decreased empathy in FTD.

Poster Session Map



Poster Session Order

Cell & Molecular Biology

1. Long-Lived Nucleolar Proteins in the Mammalian Brain: A Potential Driver of Protein Homeostasis Decline in Aging
   Poster Presenter: SangEun Yeom
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    Poster Presenter: Joshua Pasaye

Poster 1

Long-Lived Nucleolar Proteins in the Mammalian Brain: A Potential Driver of Protein Homeostasis Decline in Aging

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Advanced age has emerged as a major risk factor for neurodegenerative disease, cancer, and cardiovascular dysfunction. Despite its pervasive impact, the molecular mechanisms that drive cellular and organismal aging remain incompletely understood. Defining these mechanisms is essential for increasing healthspan and preventing age-associated diseases. Previous research has established 12 hallmarks of aging, including loss of protein homeostasis, which can arise from dysregulated protein synthesis or degradation. Most mammalian proteins turn over within hours to days, enabling efficient removal of old and damaged proteins. However, in mammals, a rare subset of proteins is extremely long-lived, persisting for months and even years. These extremely long-lived proteins (ELLPs) comprise <1% of the total proteome in the brain, suggesting unique vulnerability to age-associated chemical or physical damage.

To better characterize the long-lived nuclear proteome in vivo, I employed a two-generation ‘heavy-to-light’ pulse-chase labeling paradigm in mice. Through this approach, I distinguished old proteins by tracking heavy nitrogen atoms containing an extra neutron from newly synthesized proteins with light nitrogen atoms. High-resolution isotope imaging of the mouse hippocampus showed a pool of long-lived nitrogen molecules that co-registered with immunofluorescence of the nucleolus, a membraneless sub-nuclear organelle. Consistently, deep proteomic profiling of biochemically enriched nucleolar fractions of pulse-chase labelled mouse identified a population of nucleolar ELLPs in which more than 5% of the labeled pool persists for over 300 days in the brain. Upon characterization of these ELLPs, I found that this pool is made up primarily of small nucleolar RNA binding proteins that are essential for proper protein synthesis. Notably, homologs of these proteins have been directly implicated in lifespan regulation across several organisms including human.

To assess changes in the abundance of these nucleolar ELLPs during human aging, I performed quantitative proteomics of postmortem young and aged human brain extracts. These analyses revealed a trend towards decreased abundance of the identified nucleolar ELLPs in aged (>80 years) compared to young (<45 years) humans. This reduction suggests that there may be altered expression of ELLPs during aging, potentially leading to an increase in the proportion of old and damaged proteins. Such changes could disrupt the machinery responsible for new protein synthesis and contribute to protein homeostasis decline during aging.

Lay Language: All living things age, but we still do not fully understand why. My project aims to study one aspect that contributes to aging at the molecular level. Normally, cells stay healthy by constantly removing old or damaged proteins and replacing them with new ones. While proteins are typically replaced within hours to days, my lab’s work shows that a small group of proteins in the brain can last for months to years. Because these proteins stay in cells for so long, they are known to accumulate damage, misfold, and not function properly. I found that several of these long-living proteins are known to influence lifespan in organisms such as worms and humans. This suggests that damage to these proteins may contribute to aging in the brain. By studying these relatively overlooked proteins, I aim to uncover new biological factors that influence aging and could eventually help promote healthier aging.

Poster 2

Loss of Annexin A6 Exacerbates Neuronal Vulnerability, Dystrophic Neurite Formation, and Cognitive Impairment in Alzheimer's Disease

Achint Kaur[1], Mychal Grames[1], Shreya Mahesh[1], Abigail Edwards[1], Makenna Ley[1], Jelena Popovic[1], Shatakshi Chatterjee[1], Arwa Abukchm[1], Andy Tsai[2], Devi Krishna[1], Alexis Demonbreun[1], Hongxin Dong[1], Katherine Sadleir[1], Robert Vassar[1]

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Alzheimer's disease is the leading cause of dementia worldwide and is defined by two hallmark pathologies: extracellular amyloid-beta plaques and intracellular neurofibrillary tau tangles. Although amyloid-targeting therapies modestly slow cognitive decline, they fail to halt progression, likely because the cellular and molecular events linking amyloid accumulation to downstream pathology remain incompletely understood. A critical but underappreciated feature of Alzheimer's disease is the formation of dystrophic neurites, swollen neuronal structures clustered around amyloid plaques. We propose that dystrophic neurites are focal sites where amyloid-induced membrane injury, calcium dysregulation, and tau pathology converge. Mechanistically, extracellular amyloid disrupts neuronal membrane integrity, facilitating calcium influx that activates calpain and remodels the cytoskeleton, culminating in dystrophic neurite formation. The resulting proteolytic and calcium-dependent kinase activity within these structures promotes tau cleavage and phosphorylation, establishing dystrophic neurites as focal points of tau pathology. Thus, membrane injury represents a critical initiating event linking amyloid deposition to tau-related neurodegeneration.

Given the centrality of membrane integrity to neuronal survival, effective repair mechanisms are essential to counteract amyloid-induced damage. Annexin A6, a calcium-dependent phospholipid-binding protein, rapidly repairs injured membranes. Bulk RNA sequencing of human AD cortex reveals that Annexin A6 expression is reduced in Alzheimer's disease and inversely correlates with plaque burden, suggesting that impaired repair increases neuronal vulnerability to amyloid toxicity. To test this, we utilized primary cortical neurons from wild-type and Annexin A6 knockout mice. In vitro, A6 knockout neurons exhibited increased membrane permeability following laser ablation and greater amyloid-induced caspase cleavage compared to wild-type controls, with no difference observed under vehicle treatment. This demonstrates that loss of Annexin A6 specifically sensitizes neurons to amyloid-mediated injury. In vivo, 5xFAD;A6 knockout mice performed significantly worse on Barnes maze compared to 5xFAD controls at 12 months of age. Preliminary histological analyses suggest increased dystrophic neurite burden and pTau-181 accumulation in 5xFAD;A6 knockout mice.

Together, these findings demonstrate that defective neuronal membrane repair exacerbates amyloid-driven neuronal vulnerability, cognitive impairment, and tau pathology. This work defines a previously underappreciated mechanism of Alzheimer's progression and positions Annexin A6-mediated membrane repair as a novel therapeutic avenue for Alzheimer's Disease.

Lay Language: Alzheimer's disease is the leading cause of dementia and affects millions of people worldwide. It is characterized by two major changes in the brain: amyloid plaques outside neurons and tau tangles inside neurons. Scientists believe these processes are connected, but the mechanisms linking them remain unclear. Without understanding this link, discovering new treatments will remain a challenge.

One clue to this missing link comes from structures called dystrophic neurites, which are swollen, damaged parts of neurons that cluster around amyloid plaques. These structures form when plaques damage the outer membrane of nearby neurons. I study a protein called Annexin A6 that repairs this membrane damage. In Alzheimer's brains, this protein is reduced. Using mice lacking Annexin A6, I show that its loss worsens dystrophic neurite formation, tau pathology, and cognitive impairment. Identifying this mechanism reveals a new therapeutic target that current treatments have overlooked.

Poster 3

Single-cell Long-Read Sequencing Reveals Immune Changes with Aging and Alzheimer's

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Background: Single-cell long-read sequencing was performed on immune cells from cerebrospinal fluid (CSF) and blood to assess isoform diversity in healthy aging individuals and those diagnosed with mild cognitive impairment (MCI) or Alzheimer's disease (AD).

Methods: cDNA from single-cell experiments was subjected to long-read sequencing using Oxford Nanopore Technologies. The dataset included immune cells from CSF (45 controls, 13 MCI/AD) and blood (22 controls, 28 AD). Computational analysis incorporated scNanoGPS for extracting cell barcodes and mapping reads to the genome, IsoQuant for isoform modeling, SQANTI3 for filtering artifacts, and ScIsoX for assessing isoform diversity, and Hypatia for diversity and differential transcript usage analyses.

Results: Single-cell long-read sequencing of immune cells identified 97,920 unique transcripts in CSF and 139,351 in blood. Approximately half of expressed genes in both compartments were expressed through multiple isoforms, and 20% of detected isoforms were previously unannotated in the human genome. In the CSF, several AD risk genes - including APOC1 and MS4A6A - expressed multiple isoforms within single cells, suggesting complex isoform-level regulation in immune populations. Novel isoforms were also identified in AD risk genes such as BIN1 and PTK2B, with BIN1 displaying lymphoid cell-specific isoform expression.

Conclusion: Human immune cells demonstrate extensive isoform diversity, including previously unannotated isoforms, particularly in genes implicated in AD.

Lay Language: The immune system plays an important role in Alzheimer's disease. Using a new genetic sequencing method, we explore how immune cells change as people age, and how they differ in people with Alzheimer's. Our goal is to identify more specific treatment targets that can help correct harmful immune responses without affecting healthy ones.

Poster 4

Single-Nucleus RNA Sequencing Reveals Hippocampal Neuron Network Dysfunction and Inflammatory Responses in Alzheimer's-Linked Mutant ACE1 Mice.

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Background: Angiotensin-converting enzyme (ACE) is a validated risk locus for developing late-onset Alzheimer's disease (LOAD). ACE1 controls blood pressure through the renin-angiotensin system (RAS), but it is also present and acts locally in the brain. Hypertension is associated with increased risk for developing AD, and people taking select RAS-targeting therapeutics have reduced incidence of AD. ACE variant rs4980 (R1284Q mutation) is associated with increased risk for developing LOAD. Our group has shown that ACE1 R1284Q caused age-associated hippocampal neurodegeneration and gliosis in mutant knock-in (KI) mice. Importantly, these phenotypes were rescued by treatment with anti-hypertensive therapeutics. The mechanism by which this mutation caused neuron death is still unknown. This work aims to identify vulnerable hippocampal cell populations and pathways to uncover the mechanism of ACE1 R1284Q-mediated neurodegeneration.

Methods: Single nuclei were extracted from flash-frozen hippocampi from 6- and 12-month-old R1284Q ACE1 KI and wild-type mice and processed using 10X Genomics. Libraries were sequenced and the reads were processed for quality control before integration. We analyzed the reads using hierarchical clustering, differential expression, and pathway analysis.

Results: 143,395 nuclei clustered into hippocampal cell types including neuronal and glial populations. We identified the expression of RAS components and found decreased expression of Mas1, a protective RAS receptor, in KI excitatory neurons (ExNs). Furthermore, granule neurons of the dentate gyrus (DG) displayed oxidative stress and neuron death transcripts together with expression of Agtr1a, the primary RAS receptor. This was associated with dysregulated synaptic transmission-related transcripts in other ExN clusters, suggesting broad hippocampal network breakdown. Finally, in KI hippocampi, we found upregulation of inferred inflammatory communication from endothelial cells to other glial cells.

Conclusions: We propose that increased RAS signaling in KI hippocampi causes DG neuron death due to oxidative stress beginning at 6-months causing a cascade of neuronal dysfunction throughout the hippocampus at 12-months. In addition, inflammatory signaling from endothelial cells, astrocytes, and microglia exacerbate neuronal stress and death. We plan to validate our findings in vivo through immunofluorescence, qPCR, and fluorescence in situ hybridization (FISH).

Lay Language: My project focuses on studying how genetics can affect the risk for developing Alzheimer's disease (AD). The protein I study is angiotensin-1-converting enzyme (ACE1), which has the role of controlling blood pressure and hypertension in your blood stream. ACE1 has been linked to AD because specific mutations, or changes, in the protein can result in an increased risk for developing AD. In my study, I am working to understand how a type of mutation in ACE1 caused brain cells to die in an AD model system. Importantly, my work can be related back to humans because we can repurpose common therapies for hypertension to potentially help those who are at risk of developing AD.

Poster 5

Endoplasmic Reticulum Structure Links Amyloid-β Modulation of Cholesterol Turnover with Tau Dynamics via ER-Microtubule Contact Sites in Alzheimer's Disease

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Background: Alzheimer's disease (AD) is characterized by the pathological accumulation of both amyloid-beta (Aβ) plaques and cytoplasmic tau tangles. However, the mechanistic crosstalk between the two proteins remains to be further investigated. Moreover, while cholesterol dyshomeostasis has been implicated in AD, its role in pathogenesis is still not completely understood. Cholesterol homeostasis is tightly regulated at the endoplasmic reticulum (ER), a highly dynamic and structurally complex organelle, where the ACAT1 enzyme turns over cholesterol into cholesteryl esters. Importantly, the ER also dynamically tethers to microtubules at ER-microtubule contact sites which have been implicated in dendritic spine stability and memory. However, whether Aβ functionally interacts with ACAT1 to regulate ER cholesterol and ER structure and whether this affects downstream ER-microtubule contact sites and tau dynamics have never been studied.

Method: We utilized super-resolution live Lattice SIM2 microscopy to uncover a novel mechanistic pathway connecting cholesterol turnover, Aβ function, and tau aggregation in AD. We examined the role of ER cholesterol in modulating ER ultrastructure and dynamics over time, and a converging role for Aβ production and Aβ42 versus Aβ40 in regulating this pathway. We further conducted in silico structural multimer modeling of Aβ42 and Aβ40's structural interactions with ACAT1's catalytic pocket. Finally, we investigated cholesterol's role in modulating ER-microtubule contact site tethering via STIM1-EB binding, and its impact on downstream tau microtubule dynamics and aggregation.

Results: We found that accumulation of ER cholesterol results in the formation of novel structures within the network including ER spheres. Remarkably, inhibition of Aβ generation also induced ER sphere formation, supporting a role for Aβ regulation of ER cholesterol's turnover. Mechanistically, Aβ42 but not Aβ40 structurally interacted with key catalytic residues of ACAT1 to promote ACAT1's turnover of cholesterol, which was supported by reduced ER sphere formation in AD-associated mutant APP with increased Aβ42 production. Functionally, ER cholesterol resulted in the downstream untethering of ER-microtubule contact sites mediated by STIM1 and EB, ultimately leading to tau dissociation from microtubules and oligomerization.

Conclusion: Our work provides evidence for a unifying mechanism linking Aβ function with tau dynamics through cholesterol-mediated regulation of ER-microtubule contact sites, and identifies a novel cellular pathway underlying AD pathogenesis.

Lay Language: Alzheimer's disease is the leading cause of dementia in older adults. After decades of research, the underlying mechanisms responsible are still unclear. Examinations of patient brains revealed two hallmark proteins: amyloid-beta (Aβ), which forms large clumps outside of cells, and tau, which clumps inside the cell. However, how these two proteins are linked in disease onset is still unclear. In this study, we utilized powerful microscopes to study how cholesterol interacts with Aβ and tau. We found that Aβ helps regulate cholesterol at the endoplasmic reticulum (ER), a complex network of tubes responsible for many important cellular functions. Changes to the ER structure affects their contact sites with microtubules, long strands of protein that act as cellular scaffolding, which causes tau, a microtubule stabilizer, to fall off and clump up. Thus, we identified a new cellular pathway that may explain early aspects of Alzheimer's disease onset.

Poster 6

ER-Microtubule Contact Misregulation by STIM1 as A Converging Mechanism for Tau and TDP-43 Mutations in Frontotemporal Dementia

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Abstract: Frontotemporal dementia (FTD) is a major early-onset neurological disease and the second most common dementia1. FTD is characterized by distinct clinical syndromes and pathological hallmarks including Tau or TDP-43 protein dysregulation and can also be caused by genetic mutations in either Tau or TDP-43. However, how Tau and TDP-43 mutations converge mechanistically in FTD still remains elusive. In this study, we identified a novel mechanistic convergence of FTD disease-associated mutations in both Tau and TDP-43 on STIM1, a critical endoplasmic reticulum (ER) calcium sensor that regulates store-operated calcium entry. Using live Super-Resolution Lattice SIM2 microscopy of STIM1 dynamics, we demonstrated that TDP-43 disease-associated mutations result in STIM1 translocation from ER-microtubule contacts to ER-plasma membrane contacts. Similarly, Tau disease-associated mutations also result in STIM1 translocation from ER-microtubule contacts. We further found that this may be mediated by the phosphatase PP1, which plays a crucial role in its dynamic localization on the ER. These findings identify STIM1 contact site defects as a potential converging pathway in FTD, offering insights into the overlapping molecular mechanisms of Tau and TDP-43 pathology in neurodegeneration.

Lay Language: Frontotemporal dementia (FTD) is an early-onset brain disease affecting language, movement, and behavior, and currently has no cure. Understanding its underlying mechanisms is critical for developing new treatments. Inside brain cells, the endoplasmic reticulum (ER) acts like a factory and storage center, producing proteins and fats and storing calcium signals while microtubules (MTs) are like highways that transport materials within the cell. At specific contact points, the ER and MTs meet to exchange signals and regulate calcium, which is essential for learning and memory. STIM1 is a calcium sensor in the ER “factory” that helps control these contact sites. Our research shows that two FTD-linked proteins, Tau and TDP-43, disrupt STIM1: disease-related mutations cause it to move abnormally, misregulating calcium, breaking down ER-MT contacts, and impairing brain cell function. Identifying STIM1 misregulation as a shared mechanism offers new insight into FTD and a potential target for therapies to protect brain cells and slow disease progression.

Poster 7

Investigating Annexin A6-Mediated Membrane Repair as A Mechanism to Limit Dystrophic Neurite Formation and Tau Seeding and Spreading in AD

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One of the major challenges for advancing the discovery for cures or disease-modifying therapies for Alzheimer's disease (AD) has been pinning down the neuropathological timing and mechanistic interplay of the two hallmark AD proteins, amyloid-beta (Aβ) and tau. Recent work suggests Aβ peptides have a propensity to disrupt the cell membrane and induce neuronal membrane damage, which could be involved in the etiology of AD via increased intracellular Ca2+ influx), resulting in a downstream cascade implicating alterations in kinase/phosphatase activities, hyperphosphorylation of tau, and depolymerization of microtubules. These events subsequently precipitate the disruption in vesicular trafficking, axonal swelling, and the formation of dystrophic neurites (DNs). Evidence suggests DNs surrounding Aβ plaques have been implicated in the seeding and spreading of pathological tau, however, the formation of dystrophic neurites and the progression of AD-related neurodegeneration is not well understood. We demonstrated that annexin A6 (A6), which plays a key role in membrane resealing in skeletal muscle, also participates in neuronal membrane repair. We previously observed that A6 overexpression in an amyloid model of AD (5XFAD mice) led to a decline in DN formation and a decrease in the accumulation of phospho-tau. Thus, the main goal of this project is to elucidate the mechanisms of neuronal membrane repair via A6 in AD-related neurodegeneration. Our central hypothesis is that overexpression of A6 to increase membrane repair capacity will decrease the formation of dystrophic neurites, thus limiting propagation and progression of tau pathology. To determine a causal link and to explore the potential for disease-modifying mechanism(s) for A6 in neuronal membrane repair and AD progression, we will assess the role of A6-mediated membrane repair and functional outcomes in primary neurons after membrane damage and Aβ-related injury. Additionally, using AD-patient derived tau injections in 5XFAD mice, we will determine the role for A6 overexpression in slowing the seeding and spreading of pathological tau and mitigation of AD-related behavioral deficits. Our work for identifying the critical link between Aβ and tau neuropathologies can provide us with new insights into a therapeutic intervention to alleviate the pathogenic progression of AD.

Lay Language: Currently, we observe that enhancing membrane repair in neurons curbs the progression of Alzheimer's disease-related pathology in the brain. We are actively researching to determine whether these findings relate to reducing the spread of Alzheimer's disease and alleviating the subsequent cognitive decline. We are optimistic that these novel mechanisms can provide new insights for a potential window for disease-modifying intervention in the future.

Poster 8

Uncovering the Genetic Architecture of Middle-Onset Alzheimer's Disease: A Whole Genome Sequencing Study of Pathologically Confirmed Cases

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Background: Alzheimer's disease (AD) is characterized by accumulation of β-amyloid plaques and phosphorylated tau. Age at onset varies widely and is associated with distinct genetic architectures. Early-onset AD (EOAD; typically defined <65 years with onset usually much earlier) is rare and often linked to high-penetrance variants in APP, PSEN1, and PSEN2, though these explain only a small proportion of cases. Late-onset AD (LOAD; typically defined >65 years) is largely polygenic and strongly associated with APOE ε4. Less is known about AD patients with symptom onset between 45-60 years and don't carry the genetic associations of MOAD and LOAD, defined here as middle-onset Alzheimer's disease (MOAD). We hypothesized that MOAD has a distinct genetic architecture.

Method: Autopsy-confirmed cases from the Mesulam Institute at Northwestern University included MOAD (onset ≤60 years, n=109), LOAD (rigorously defined with onset ≥70 years, n=109), and controls without dementia (death >70, n=17). After quality control, whole-genome sequencing was performed on MOAD (n=84), LOAD (n=79), and controls (n=14). APOE ε4 carrier frequencies were 42% in MOAD, 56% in LOAD, and 21% in controls. Candidate gene analyses focused on 309 AD-associated genes identified through familial studies and genome-wide association studies. Variants were prioritized based on ACMG pathogenicity classification, predicted deleteriousness (REVEL ≥0.75), and ClinVar annotations. P-values calculated using Fisher's exact test. Pathway analyses were conducted using the Reactome database.

Results: Rare pathogenic variants in APP, PSEN1, or PSEN2 were identified in 11 MOAD cases (13.1%) compared with one LOAD case (1.3%) [p= 0.005]. Three MOAD cases carried rare likely pathogenic variants in APOE. Two likely pathogenic variants in MME (encodes neprilysin, a β-amyloid degrading enzyme) were identified in two MOAD cases. A likely pathogenic rare variant ABCA7 (implicated in lipid metabolism) was identified in one LOAD case. Five LOAD cases carried a single rare variant in WDR81 (involved in endolysosomal trafficking and adult hippocampal neurogenesis) vs none in MOAD [p= 0.025]. Immune pathway-level analyses further suggest that MOAD is triggered by dysregulated immune inhibition while LOAD is associated with dysregulated microglial clearance of misfolded proteins

Conclusion: MOAD appears to represent a genetically distinct subgroup of AD with some features overlapping EOAD and LOAD. These findings support genetic testing in MOAD patients and suggest that AD may represent a genetic continuum across age at onset, with different biological mechanisms contributing to disease development.

Lay Language: Alzheimer's disease can begin at many different ages, but most research focuses on cases that start either before age 65 (familial case) or after age 65. Much less is known about people whose symptoms begin in midlife, between about 45 and 60 years old. In this study, we analyzed the complete DNA sequence of individuals with pathologically confirmed Alzheimer's disease to better understand the genetics of this middle-onset group. We found that these patients often carry rare genetic variants related to amyloid processing, while older patients show more changes in genes involved cellular waste removal. These findings suggest that Alzheimer's disease may develop through different biological mechanisms depending on when symptoms begin. Our results provide novel insights into different therapeutic targets based on the specific mechanism involved in the disease process.

Poster 9

A Spatial Proteomic Atlas of the Human Anterior Cingulate Cortex in Physiological Cognitive Aging and SuperAging

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Background: SuperAgers are defined as unique individuals ≥80 years of age who show exceptional memory equivalent to individuals at least 20 years their junior. Our prior work has identified the selective sparing of the anterior cingulate cortex (ACC) to age-related neurodegeneration as a strong and early biological correlate of SuperAging. In this preliminary study, we aimed to further characterize the cellular, molecular, and proteopathic changes to the ACC by performing highly multiplexed spatial proteomics on this region in SuperAgers and their cognitively average peers.

Method: We obtained brain specimens from SuperAgers (n = 10) and cognitive-average peers (n = 11) who were enrolled in the Northwestern University SuperAging Research Program. We performed multiplexed immunofluorescence (Quanterix/Akoya Phenocycler) using a custom 50-parameter panel on paraffin-embedded human ACC tissue to identify neuronal, glial, and endothelial cell subtypes and states, as well as proteopathic hallmarks at subcellular resolution. We then performed machine learning-based cell segmentation and quantification of protein expression followed by dimensional reduction and unbiased clustering for cell type and state identification.

Results: Using this imaging and analysis pipeline, we identified major neuronal and non-neuronal cell classes, proteopathic markers, and their spatial relationships within intact ACC tissue across phenotypes.

Conclusion: We establish a scalable spatial proteomics framework for quantitative analysis of the cellular and molecular organization in the aging human cortex and provide an unbiased approach to characterize alterations in cell type abundance and protein expression across physiological and "supraphysiological" cognitive aging. Future work will investigate the multiscale cellular and molecular landscape of the aging ACC, with particular interest in defining the molecular signatures of Von Economo neurons, which have been shown to be more abundant in SuperAgers.

Lay Language: SuperAgers are individuals aged 80 or older who have memory abilities as strong as people 20-30 years younger. Previous research has shown that a brain region called the anterior cingulate cortex (ACC), involved in attention, motivation, and memory, appears to stay more intact in SuperAgers compared to cognitively average peers. In this study, we examined brain tissue from SuperAgers and cognitively average older adults to better understand which cells are selectively spared in this region of the brain, as well as the mechanisms driving this sparing. Using advanced imaging techniques, we simultaneously measured the levels of 50 molecules in the ACC to identify neurons, support cells, and disease-related proteins, while mapping precise locations within tissue. This work provides a novel way to study the detailed organization of cells and proteins in the aging brain. Understanding the cellular features that distinguish SuperAgers may reveal biological factors supporting preserved cognition in aging.

Poster 10

Interrogating a Novel APP Processing Pathway via η-Secretase

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Background: Although the two canonical pathways of Amyloid Precursor Protein (APP) processing have been studied extensively, there exists a relatively new (η-secretase) pathway. In this pathway, η-secretase cleaves APP in its mid-domain region. The resulting membrane-bound N-truncated APP may subsequently be cleaved either by β- or α-secretase, releasing soluble Aη-β and Aη-α, respectively. Collectively these fragments are known as AETAs and have been reported to hold important physiological functions. Notably, their levels increase following β-secretase inhibition. There continues to be interest in revitalizing low-dose β-secretase inhibitors as an AD prevention strategy. Thus, it is vitally important to understand what the physiological processing of APP down the η-secretase pathway entails and how this processing might change during AD. The metabolism of AETA in living humans has never been measured. We hypothesize that the kinetics of these fragments are measurable in human cerebrospinal fluid (CSF).

Method: To develop a method to quantify AETA kinetics in CSF as surrogates of η-secretase, β-secretase, and α-secretase cleavage of APP in humans who have undergone stable isotope labeling kinetics (SILK), our initial tests utilized conditioned media from H4APPwt cells that had been treated with a β-secretase inhibitor, to enrich for AETA. An assortment of commercially available and custom-made N-terminal, mid-domain, and C-terminal AETA antibodies will be utilized for immunoprecipitation of various APP fragments from the media. The APP fragments will be digested using proteases (trypsin, LysN, LysC, ArgC, rAspN, or a combination of these) and resultant peptides will be assessed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The superior method will then be tested on CSF and further optimized ahead of kinetic analyses.

Results: We will present the ongoing developments from cell culture media and modification of the method to optimize it for AETA measurement in human CSF by SILK-IP-LC-MS/MS.

Conclusion: This method development is the crucial first phase in our study aiming to determine the physiological and pathological turnover of AETA in humans. When paired with known turnover rates of sAPPβ, sAPPα, and Aβ, it will allow for the development of a comprehensive model of physiological APP processing in healthy aged humans and in AD.

Lay Language: Alzheimer's disease (AD) is linked to how a brain protein called amyloid precursor protein (APP) is broken down. Research has focused on two well-known processing pathways, but scientists have recently identified another pathway involving an enzyme called η-secretase. This pathway produces fragments (AETAs), which may have important roles in normal brain function. Interestingly, these fragments increase when β-secretase—an enzyme targeted by some AD drugs—is inhibited. Because low-dose β-secretase inhibitors are being reconsidered as a prevention strategy, it is crucial to understand how this lesser-known pathway works in healthy aging and AD. So far, AETAs have never been measured in living humans. In this study, we are developing sensitive laboratory methods to detect and track how quickly these fragments are made and cleared in human cerebrospinal fluid. This will provide essential groundwork for building a more complete picture of APP processing in the human brain and changes in AD.

Poster 11

Overexpression of Noggin Rescues The Behavioral Phenotype and Related Pathology in Multiple Tauopathy Models

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Background: Tauopathies, including Alzheimer's disease (AD), frontotemporal dementia (FTD), and progressive supranuclear palsy (PSP), are characterized by abnormal aggregation of tau protein and present with diverse clinical symptoms such as cognitive, language, and motor impairments. Aging is the strongest risk factor and may drive disease-related biological changes. Our prior work shows that bone morphogenetic protein (BMP) signaling increases with age and exacerbates tau phosphorylation and secretion in human induced neurons, while inhibition of BMP signaling via Noggin delays disease progression in animal models, suggesting BMP signaling as a key contributor to tau pathology.

Method: To test whether increased BMP signaling drives disease progression, we overexpressed Noggin using dentate gyrus-targeted lentiviral delivery in P301S tauopathy and 5XFAD AD mouse models, and generated transgenic APOE4 × NSE-Noggin mice. Behavioral performance was assessed using the Barnes maze, and molecular pathology was evaluated through Western blot analysis of phospho-tau and Fluoro-Jade staining for neuronal degeneration.

Results: Noggin overexpression improved hippocampus-dependent behavioral performance across all models. Additionally, phospho-tau levels and neuronal death were significantly reduced, indicating attenuation of disease-related pathology.

Conclusion: These findings demonstrate that downregulation of BMP signaling mitigates tau pathology and preserves cognitive function across multiple tauopathy models. Targeting BMP signaling may represent a promising therapeutic strategy, and future studies will focus on translating these findings toward clinical applications.

Lay Language: Many brain diseases, such as Alzheimer's and certain forms of dementia, are linked to the buildup of a protein called tau, which damages brain cells and leads to memory, language, or movement problems. Aging is the biggest risk factor for these conditions, but the biological changes that connect aging to disease are not fully understood. Our research suggests that a signaling pathway in the brain becomes more active with age and may contribute to this buildup of harmful proteins. By blocking this pathway in several mouse models of dementia, we were able to reduce brain damage and improve memory-related behaviors. These findings highlight a promising new direction for developing treatments that could slow or prevent the progression of dementia-related diseases.

Poster 12

Multi-omic Mapping of the Human Cortical Synaptome in Neurodegeneration

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Synapses are specialized neuronal sub-compartments that mediate cell-to-cell communication throughout the nervous system. Individual neurons form thousands of synapses, resulting in hundreds of trillions of connections across the human brain and creating immense molecular and functional complexity. Synaptic dysfunction is a hallmark of many neurological disorders, including neurodegenerative diseases, yet the molecular mechanisms governing synaptic regulation in the human brain remain incompletely understood. While synaptic biology has traditionally focused on neuronal subtypes, neurotransmitter signaling, and protein composition, emerging evidence suggests that RNA regulation and local translation are critical contributors to synaptic function and plasticity. Here we aim to characterize the “synaptomic” landscape of the human cortex and its relationship to neurodegeneration. Using biochemical fractionation of healthy and disease human post-mortem tissue, we isolate synaptosome-enriched and total homogenate fractions across multiple cortical regions and integrate sample-matched transcriptomic and proteomic profiling. This multi-omic framework enables the identification of thousands of gene-protein pairs and their relative enrichment across synaptic compartments and cortical regions. By analyzing concordant and discordant RNA-protein enrichment patterns, we investigate regulatory processes including local translation, RNA trafficking, and post-transcriptional control at the synapse. Together, these analyses provide a systems-level view of synaptic molecular organization in the human cortex. This work establishes a framework for understanding how synaptic regulatory programs vary across brain regions and may reveal mechanisms underlying synaptic vulnerability and resilience in neurodegenerative diseases, which may ultimately inform the development of new therapeutic strategies.

Lay Language: The brain relies on trillions of specialized connections between nerve cells called synapses. These tiny structures allow neurons to communicate and form the complex networks that support memory, movement, and behavior. Damage to synapses is one of the earliest and most important features of many neurodegenerative diseases, including Alzheimer’s disease. However, we still know relatively little about the molecular processes that regulate synapses in the human brain. In this project, we study synapses using multiple regions across the healthy and diseased human brain. By combining measurements of both RNA and proteins at synapses we can determine how these patterns differ across brain regions and disease states. This approach allows us to better understand how synapses are regulated and why some may be more vulnerable during neurodegeneration. Ultimately, this research may help identify new biological pathways and potential therapeutic targets for neurodegenerative diseases.

Poster 13

Novel nNOS Inhibitors Targets Aβ Oligomer-Driven pathology in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder that affects nearly 57 million individuals worldwide. An effect of the disease is characterized by a disruption in the signal from the production of Nitric Oxide (NO), which highly contributes to negative symptoms that AD patients experience. In neurons, nitric oxide is mainly produced by a compound called neuronal nitric oxide synthase (nNOS). Therefore, there has been production to find therapeutic strategies to target nNOS production. nNOS is one of three isozymes that is present in neurons and responsible for NO production. We will assess the cellular efficacy of newly synthesized derivatives of an inhibitor that is selective only to nNOS by using live-cell fluorescence detection with DAF-FM dye. DAF-FM dye is a cell-permeable fluorescent probe that detects NO in the brain cells; when it interacts with NO, a chemical reaction resulting in a highly fluorescent derivative occurs. We also add Amyloid-beta oligomers (AβO) to the cells to induce neurotoxic effects, and with the selective inhibitor we tested the viability through fluorescence. This study focused on testing newly synthesized nNOS inhibitors to potentially decrease excessive nNOS activity that could lead to neuronal damage in Alzheimer's disease.

Lay Language: Alzheimer's disease can cause cells in the brain to slowly stop working and eventually die. This leads to memory loss and difficulty with thinking. Scientists believe that stress signals inside the brain cells contribute to this damage. One of these signals comes from a molecule called nitric oxide which is normally important for the brain to communicate, but it becomes harmful when it is produced in excessive amounts. In this study, we test new compounds designed to block the production of nitric oxide. By measuring the levels with a fluorescent dye, we can see whether these compounds can reduce harmful signaling, which can help with strategies for further development in Alzheimer's disease.

Poster 14

Sleep disturbances leading to cortical hyperarousal caused by BACE1 inhibition can be modulated with low doses of inhibitor

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Background: β-Site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) initiates the formation of β-amyloid (Aβ) in Alzheimer's disease (AD). BACE1 is a prime AD therapeutic target and small molecule BACE1 inhibitors are in clinical trials. However clinical trials with BACE1-targeting drugs were halted due to mild, non-progressive, reversible cognitive worsening, and volumetric brain loss. Some BACE1 inhibitor trials have been terminated due to toxicity or lack of efficacy. High-dose BACE1 inhibitors may cause side effects, as BACE1 has substrates with functions in neurons. The recent trial failures suggest AD patients with dementia may be too late for clinical benefit from BACE1 inhibitors. These drugs may achieve greater efficacy in early presymptomatic AD patients, so BACE1 inhibitor prevention trials are being planned. High-dose BACE1 inhibitors may cause side effects, as BACE1 has substrates with functions in neurons. The recent trial failures suggest AD patients with dementia may be too late for clinical benefit from BACE1 inhibitors. These drugs may achieve greater efficacy in early presymptomatic AD patients, so BACE1 inhibitor prevention trials are being planned.

Methods: Here we administered mice with chow with low and high doses of Merck BACEi-10 (MBi-10) (11 and 109 mg/kg, respectively) and performed sleep and behavioral studies to assess the effects of BACEi on sleep-wake cycle. We also performed unbiased proteomics to understand the substrates affected by BACE1 inhibition.

Results: The doses that have shown cognitive worsening have been those that strongly inhibit BACE. We observed that 109mg/kg of MBi-10 leads to 90% reduction in amyloid plaques but causes REM sleep disturbances and cortical hyperarousal, which are reversible when the inhibitor is washed out. Also, 11mg/kg of MBi-10 lead to partial reversal of sleep disturbances.

Cnclusion: The A673T Icelandic mutation, which protects from AD, only reduces production of Ab42 by 30-40%, there is interest in determining if there is a dose at which amyloid buildup is reduced, while mechanism-based toxicity is avoided. However, the key questions regarding safe level of BACE1 inhibitors for AD prevention remain unanswered. Therefore, it is crucial to determine the therapeutic window of BACE1 inhibition that is both safe and efficacious to administer in AD patients.

Lay Language: Alzheimer's disease (AD) is characterized by amyloid plaques, fibrillary tangles and neuronal death. Amyloid plaques are made up of aggregates of β-amyloid (Aβ) protein, which are generated by the cleavage of the amyloid precursor protein by the enzyme, β-secretase (BACE1). Therefore, inhibiting BACE1 has been a prime AD therapeutic strategy to prevent Aβ production thereby reducing the plaque production. BACE1 inhibitors (BACEi) have been in clinical trials for patients with mild cognitive impairment or mild AD but were halted due to mild, non-progressive, reversible cognitive worsening. Since BACEi are easy to administer via oral route of delivery, and are already developed, there is great interest in resuming their clinical trials. To this end, we are investigating the underlying mechanism of sleep disturbances related to BACE1 inhibition so that BACEi could be used in the clinic to treat and prevent AD by limiting the buildup of plaques without these side effects.

Poster 15

Production of Reactive Oxygen Species by Human Microglia in Response to Soluble Oligomeric and Fibrillar Amyloid-β Peptide

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Human microglia are responsible for the first line of immune defense in the central nervous system and have been found to have a central role in the pathobiology of cognitive decline. Among various factors associated with cognitive decline is the deleterious effect of the amyloid-β (Aβ) peptide that is a hallmark of Alzheimer's disease (AD). When Aβ accumulates in the brain, an inflammatory immune response is triggered in activated microglia. Activated microglia produce reactive oxygen species (ROS) to foreign or abnormal substances. Prolonged activation of microglia in chronic conditions such as AD can have adverse effects on neurons. Most studies of microglia response to Aβ have utilized rodent models. The purpose of this study was to investigate this response in microglia isolated and cultured from postmortem human brains. Microglia from the gray matter of fresh autopsied prefrontal cortical tissue of two elderly participants with above average memory abilities were extracted and cultured. Cells from passage 3 - 5 were seeded in 8 chamber slides (3x10 cell/well). Microglial cells were cultured in the presence of microglia medium (SienCell, Inc), supplemented with 5% fetal bovine serum, 100 U/ml penicillin, 100 µg/ml streptomycin, 1 ml/500ml primocin, 1% microglia growth supplement (ScienCell), and 10 ng/ml GM-CSF (Sigma-Aldrich). After the cells reached 70% confluence, the media was removed and replaced by 100µl of 1mg BSA/RPMI. Various concentrations of fibrillar or soluble oligomeric Aβ (2.5ug, 5ug, and 10ug), prepared using specific aging protocols, or vehicle were added to the wells. After a 30-minute incubation at 37°C, 20 µl of 6 mg/ml Nitroblue Tetrazolium (NBT) was added to each well and incubated for an additional 90 minutes. The media was then removed, and 100µl/well methanol was added (5 minutes) to fix the cells. The slide was rinsed 3 times in xylene and coversliped with SubX mounting media. Optical density of the blue ROS reaction product (formazan salt) in individual microglia was measured using the Image J software. Dose-dependent increases in ROS production by microglia were observed in response to stimulation by both oligomeric and fibrillar Aβ. Oligomeric Aβ had a greater effect on ROS production by human microglia when compared with fibrillar Aβ in the 5ug (1.54x difference) and 10µg (2.2x difference) doses. These preliminary findings demonstrate that human microglia are activated in the presence of both oligomeric and fibrillar Aβ, but more so after stimulation by oligomeric Aβ. Cultured primary human microglia will be useful in studies of microglia function and inflammation.

Lay Language: Microglia are specialized immune cells of the brain and play an important role in responding to foreign substances and misfolded proteins, such as the amyloid beta (AB) peptide, that can lead to Alzheimer's disease. When these misfolded proteins accumulate, an immune response is initiated, and activated microglia release reactive oxygen species (ROS), which are damaging to cells, in an attempt to combat invaders. In this experiment, we measured the levels of ROS production by microglia in SuperAgers and normal controls in the presence of increasing concentrations of AB and found that there is an increased response in SuperAgers. This may indicate a superior protective response to foreign materials by SuperAgers compared to normal individuals.

Poster 16

Cortical White Matter Integrity in Cognitive SuperAgers

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Introduction: SuperAgers are individuals over age 80 who demonstrate superior episodic memory equal to that of individuals 20-30 years younger. Previously we observed significantly lower density of activated microglia as well as increased immunohistochemically visualized myelin in SuperAger cortical white matter compared to cognitively normal controls. In this study we utilized western blot analysis to further investigate the integrity of white matter, measured through markers of myelin and axonal integrity. We hypothesized that SuperAgers would display enhanced white matter integrity compared to age-matched cognitively average peers.

Methods: Western blot analysis was performed to detect levels of myelin basic protein (MBP, Abcam EPR21188, rabbit monoclonal, 1:1,000 concentration) and phosphorylated neurofilament H (SMI-31, Millipore Sigma NE1022, mouse monoclonal, 1:1,000 concentration), a marker of axons, in 10 Caucasian participants; 5 SuperAgers and 5 controls. The SuperAging group consisted of 2 females and 3 males, and the control group consisted of 4 females and 1 male. Frozen postmortem human white matter harvested from matching frontal cortex centrum semiovale in coronal slabs was homogenized for western blot, and protein concentrations were measured through BCA protein assay. Optical density of the protein bands was analyzed in ImageJ and expressed as a percentage of the housekeeping protein GAPDH. Students' t-tests were used to compare protein levels across groups.

Results: The SuperAging and control groups did not differ significantly in postmortem interval (PMI) or mean age at death (SuperAgers: M = 90.6 years; controls: M = 88.8 years). Quantitative analysis of the MBP western blots revealed an expected band at 18 kDa, and an additional prominent band at 45 kDa. Both bands appeared darker in the SuperAgers than controls. Levels of the 18 kDa MBP band were significantly higher in the frontal cortex white matter of SuperAgers compared to controls ($p<0.05$). Analysis of the axonal marker SMI-31 revealed a prominent band at the expected molecular weight of ~180 kDa, which was significantly higher in SuperAgers compared to controls ($p<0.05$).

Conclusion: These preliminary results suggest enhanced myelin and axon integrity in the white matter of SuperAgers compared to controls in the frontal cortex, which plays a crucial role in working memory. Further quantitative analysis will include additional specimens and white matter regions, including white matter tracts such as the fornix and corpus callosum.

Lay Language: SuperAgers are individuals aged 80+ with memory abilities equal to or better than people 20-30 years younger. We have previously identified differences in the brains of SuperAgers compared to normal agers, such as decreased neuroinflammatory markers and higher levels of protein that forms myelin. Myelin is the insulating coating that surrounds nerve fiber (or axon), that helps electrical signals travel efficiently throughout the brain. During normal aging and neurodegeneration, damage to axons and myelin weakens these signals, which may contribute to symptoms of cognitive decline such as memory loss. In this study, we examined the brains of SuperAgers and controls to compare proteins that indicate the integrity of myelin and axons. We found higher levels of both proteins in SuperAgers, suggesting increased structural integrity of their fiber pathways. This work may help us better understand the mechanism through which memory abilities are preserved in successful aging.

Poster 17

Subfield-Specific Glial Architecture of Memory Preservation in SuperAgers with Primary Age-Related Tauopathy

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Background: Cognitive SuperAgers are individuals age 80+ with episodic memory equal to or better than individuals 20-30 years their junior. Prior investigations of SuperAgers reveal significantly lower microglial activation in neocortical white matter and neurofibrillary tangle burden compared to their age-matched, cognitively-average peers. Primary age-related tauopathy (PART), defined by neurofibrillary tangles confined to the medial temporal lobe and relatively sparse amyloid-β plaques, is observed at relatively high frequency in successful agers. In this study, we examined glial immunoreactivity in grey and white matter hippocampal subregions to identify putative factors contributing to the superior memory phenotype that defines SuperAging.

Methods: Nineteen successful agers (n=9 SuperAgers, n=10 age-matched cognitively-average controls) with postmortem PART were identified from the Northwestern ADRC brain bank. Paraffin-embedded hippocampal sections were immunohistochemically stained with AT-8 (pTau), GFAP (astrocytes and astrocytic reactivity), HLA-DR (MHC-II+ microglia), and Olig2 (oligodendrocytes and OPCs). Percent area of immunoreactivity was quantified in 20x digital images using HALO software (v4.0.1, Indica Labs) across hippocampal subregions (CA1-3 and dentate gyrus) and layers (molecular layer of the dentate gyrus, lacunosum-moleculare, radiatum, oriens, alveus, and fimbria). Mixed-effects models examined regional and group differences. Associations between pTau and glial immunoreactivity were determined using generalized estimating equations.

Results: SuperAgers and controls with PART showed similar hippocampal pTau burden. Relative to controls, SuperAgers displayed unique subregional and layer-specific patterns of glial immunoreactivity, namely heightened Olig2 density in the fimbria ($p<0.01$), heightened astrocytic GFAP reactivity in grey and white matter subregions ($p<0.05$), and lower MHC-II+ microglia expression in white matter ($p<0.05$). Across the entire cohort, there was a surprisingly inverse relationship between pTau and astrocytic immunoreactivity ($\beta=-0.35$, $r2=0.21$; $p<0.001$).

Conclusions: In aged individuals with postmortem PART, higher pTau accumulation was associated with lower astrocytic reactivity. SuperAgers with PART pathology exhibited a unique, neuroanatomically-specific glial profile in hippocampus involving elevated astrocytic reactivity and lower MHC-II+ microglia expression in white matter. Future studies will integrate multiplexed spatial proteomics with proteoform-resolved technology to define tau-glia interactions and mechanisms of memory preservation involving proteins in SuperAging.

Lay Language: SuperAgers are individuals aged 80+ with memory abilities equal to or better than individuals 20-30 years younger. SuperAgers may hold clues about how the brain stays healthy and resilient during aging.

In this study, we examined support cells in the brain, called glial cells, which help maintain brain health and respond to damage. Three types of glial cells we focused on were 1) microglia, 2) astrocytes, and 3) oligodendrocytes. We compared how glial cells respond to age-related protein changes in SuperAgers versus normal controls.

Results showed that SuperAgers had distinct glial patterns in the hippocampus, which is the memory center of the brain. Compared to normal controls, SuperAgers had more astrocyte activity but less microglia activation. Surprisingly, higher levels of pTau, a protein linked to age-related brain changes, were associated with lower astrocyte activity.

Better understanding of this support cells in the brain may help identify resiliency factors during aging.

Poster 18

Molecular Signatures of Hippocampal Vulnerability in LATE-AD Across the Cognitive Aging Continuum: Insights into TDP-43-ANXA11 Interactions

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Background. Late-life cognitive phenotypes span a continuum from abnormal vulnerability (i.e., dementia) to supranormal resilience (i.e., “SuperAgers,” individuals age 80+ who demonstrate memory performance at levels 20-30-years their junior). Particularly in oldest-old individuals, Alzheimer’s disease (AD) is frequently accompanied by comorbid TDP-43 (“LATE-AD”) in the hippocampus; however, the molecular interactions that govern this are unknown. We examined postmortem hippocampus with LATE-AD or AD-only changes from individuals with antemortem amnestic dementia and SuperAgers. To probe the molecular basis of hippocampal vulnerability in LATE-AD, we quantified colocalization of TDP-43 with Annexin-A11 (ANXA11), a phospholipid-binding protein that was recently found to co-assemble with TDP-43.

Methods. Twenty-eight SuperAgers (AD, n=15; LATE-AD, n=13) and 25 individuals with amnestic dementia (AD, n=10; LATE-AD, n=15) were identified from the Northwestern ADRC brain bank. Hippocampi sections were stained with AT8 (tau) or phosphorylated TDP-43 (pTDP) antibodies. In a subset of LATE-AD cases (n=16; 8 SuperAgers+8 amnestic dementia), sections were double stained with pTDP and ANXA11. HALO software (Indica Labs) was used to generate %area occupied by immunopositivity of tau and pTDP in the dentate gyrus (DG), CA1, CA2, and CA3 hippocampal subfields. A semi-manual approach identified colocalized TDP-43+ANXA11. T-tests and one-way ANOVAs were used to determine group differences.

Results. As expected, SuperAgers exhibited lower pathologic burden across hippocampal subfields compared to the amnestic group. Consistent with our prior work on amnestic dementia (Minogue et al., 2023), tau immunoreactivity was significantly greater in the DG ($p<0.05$) and the CA3 (trend, $p=0.07$) in SuperAgers with LATE-AD vs SuperAgers with AD alone. Within a subset of LATE-AD cases, TDP-43+ANXA11 colocalized inclusions were found within 11 of 16 cases at 120 unique sites and were predominantly isolated to the DG and to a lesser extent the CA1.

Conclusions. Findings suggest that LATE-AD imposes a specific molecular and regional signature on the hippocampus, even in individuals who remain cognitively resilient into advanced age. The preferential colocalization of ANXA11 with TDP-43 in the DG and CA1, independent of cognitive phenotype, raises questions about these subfields as critical nodes of anatomic vulnerability and further positions ANXA11 as a mechanistically important contributor in TDP-related neurodegenerative diseases.

Lay Language: Late-life cognitive phenotypes span a continuum from abnormal vulnerability (i.e., dementia) to supranormal resilience (i.e., "SuperAgers," individuals age 80+ who demonstrate memory performance at levels 20-30-years their junior). This study aimed to investigate two proteins that frequently appear together: 1) Alzheimer's disease characterized by amyloid plaques and tau-tangles and 2) abnormal inclusions in brain cells known as TAR DNA-binding protein 43 (TDP-43). The goal was to distinguish the role each disease plays across the aging continuum. We focused our analysis on 4 regions of the memory-center of the brain, the hippocampus. We found significant differences between the amount and location of tau vs TDP-43 in regions of the hippocampus. We also examined how TDP-43 interacts with another protein, Annexin-A11. These proteins frequently co-assembled in specific hippocampal regions. Understanding these molecular interactions may help clarify how these distinct diseases contribute to memory loss or resilience in aging.

Poster 19

Striatal Tau Burden in Autopsy-Confirmed FTLD-tau and Relationship to Neuropsychiatric Symptoms

Jillian Brunner, BS, Rachel Keszycki, PhD, Caroline Nelson, BS, Sandra Weintraub, PhD, M.-Marsel Mesulam, PhD, Rudolph Castellani, MD, Pouya Jamshidi, MD, Changiz Geula, PhD, and Tamar Gefen, PhD

Background: Neuropsychiatric symptoms are common in behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA) due to frontotemporal lobar degeneration with tau pathology (FTLD-tau). In addition to cortical regions, dysfunction in the striatum, a subcortical region, has been implicated in neuropsychiatric symptoms. The objective of this study was to examine the relationship between striatal tau pathology and neuropsychiatric symptoms, representing a target for intervention.

Design/Methods: We identified 16 right-handed participants with autopsy-confirmed FTLD-tau from the Northwestern Alzheimer's Disease Research Center (NU-ADRC) brain bank (bvFTD: n = 8; PPA: n = 8; 3R tau: n = 8; 4R tau: n = 8). Participants completed annual research visits through the NU-ADRC PPA Research Program or clinical core. Level of neuropsychiatric symptoms at the final visit was quantified via the Neuropsychiatric Inventory Questionnaire (NPI-Q). For each participant, unilateral caudate was sectioned and immunostained with AT8 to detect phosphorylated tau, and percent AT8-positive area was quantified in QuPath. We compared regional phosphorylated tau burden in the striatum between tau species 3R and 4R, dementia diagnosis, and relationship to neuropsychiatric symptoms endorsed at the final visit before death via mixed-effects linear regression.

Results: 3R tau cases showed significantly greater percent area of phosphorylated tau immunopositivity vs. 4R tau cases in the nucleus accumbens ($p<0.05$), putamen ($p<0.05$) and caudate ($p<0.001$). Clinical diagnosis (bvFTD, PPA) or presence of neuropsychiatric symptoms were not significantly associated with striatal tau burden. However, the ratio of putamen AT-8 to caudate AT-8 was significantly related to final visit NPI-Q score ($p<0.05$), such that a greater relative burden of caudate tau was associated with more neuropsychiatric symptoms.

Conclusions: Results suggest a potential contribution of striatal tau burden, particularly the relative burden between the caudate and putamen, to neuropsychiatric symptoms in bvFTD and PPA due to FTLD-tau. Future analyses focused on how tau influences neuronal integrity and inflammation in this region may yield additional insights into the biological substrates underlying these symptoms.

Lay Language: Some types of dementia mainly cause changes in behavior or language when a protein called tau becomes abnormal and builds up in the brain. Tau affects not just the cortex, or the brain's outer layer, but also deeper brain regions such as the striatum, which helps control movement, behavior, and emotions. We found that different types of abnormal tau protein damage the striatum in different ways, and the amount of tau in specific parts of the striatum is linked to psychiatric symptoms that many dementia patients experience. This suggests that some patients may develop more behavioral and psychiatric problems than others due to the balance of tau between deep brain structures. Future studies aimed at understanding this relationship could lead to better management of psychiatric symptoms and disease in these brain regions.

Poster 20

Modeling the Selective Predilection of TDP-C Through Normal Annexin A11 Distribution

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Background: Annexin A11 (ANXA11) is a calcium-dependent phospholipid-binding protein recently implicated in frontotemporal lobar degeneration with TDP-43 pathology, type C (FTLD-TDP Type C, or TDP-C). Prior studies indicate that TDP-C pathologic inclusions consist of heterodimers of hyperphosphorylated TDP-43 and truncated ANXA11. To better understand ANXA11's potential role in TDP-C pathophysiology, we examined its expression in individuals with no neurologic impairment (NNI).

Method: Six individuals with NNI were identified from the Northwestern University Alzheimer's Disease Research Center (ADRC) Brain Bank. Four underwent longitudinal annual cognitive testing and were confirmed within normal limits antemortem. Two were younger (ages 28-29), with no family history of dementia or evidence of cognitive deficits upon clinical record review. Paraffin-embedded sections of the following regions of interest (ROIs) were fluorescently immunohistochemically stained for ANXA11: anterior temporal lobe (ATL), inferior frontal gyrus (IFG), inferior parietal lobule (IPL), amygdala, posterior hippocampus, globus pallidus, nucleus accumbens, and dorsal striatum. ROIs were selected based on prior comprehensive neuropathologic studies identifying regions uniquely vulnerable or invulnerable in TDP-C. QuPath software was used to quantify the density of ANXA11-rich neurons (counts/μm²). In neocortical regions, ANXA11-positive neurons were quantified separately in upper (layers I-IIIa), middle (layers IIIb-Va), and lower (layers Vb-VI) neuronal layers.

Results: ANXA11 immunoreactivity was most prominent in layer II of the neocortex, the fascia dentata of the hippocampus, and the amygdala. Quantitative analyses revealed a bilaminar pattern of cortical ANXA11 expression, with the highest density in superficial cortical layers (layers II-IIIa) compared with middle (layers IIIb-Va) and deep cortical layers (layers Vb-VI) ($p < 0.001$). Across all cases, the anterior temporal lobe exhibited the greatest density of layer II ANXA11-positive neurons relative to other neocortical regions. Subcortically, regions considered relatively invulnerable to TDP-C, including the thalamus and globus pallidus, contained significantly fewer ANXA11-rich neurons than highly vulnerable regions such as the amygdala and nucleus accumbens (mean density = 6,838.66 vs. 195,951.40 counts/μm², respectively).

Conclusion: ANXA11 expression in neurologically normal individuals largely mirrors the regional vulnerability pattern observed in TDP-C. Cortical expression follows a bilaminar pattern, concentrated in superficial layers, while relatively resistant subcortical regions exhibit minimal ANXA11 immunoreactivity. These findings suggest that ANXA11 localization may contribute to the selective neuronal vulnerability characteristic of TDP-C.

Lay Language: Include a couple sentences (word limit for this section is 150 words or less) that describes the impact of your research in a way that is accessible to individuals without a scientific background. Avoid using scientific jargon. Annexin A11 (ANXA11) is a protein recently linked to a type of frontotemporal dementia called TDP-C. In this disease, ANXA11 forms abnormal complexes with another protein, TDP-43, in vulnerable brain regions. To better understand ANXA11's role, we examined its distribution in brains from six people without neurological disease. We stained multiple brain regions and measured the number of ANXA11-rich neurons. We found the highest levels in layer II of the cortex, the hippocampus, and the amygdala, regions known to be affected early in TDP-C. In contrast, regions usually resistant to this disease, such as the thalamus and globus pallidus, had very few ANXA11-positive neurons. These results suggest that ANXA11 may be naturally concentrated in brain areas that later show pathology in TDP-C, providing clues about why some neurons are more vulnerable than others and highlighting ANXA11 as a promising target for understanding and eventually treating this devastating disease.

Poster 21

Regional Cortical Thinning Patterns Distinguish TDP-C and Pick's Disease in Primary Progressive Aphasia

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Background: Anterior temporal lobe (ATL) degeneration is a hallmark of several primary progressive aphasia (PPA) syndromes, particularly TDP-43 type C pathology (TDP-C). However, Pick's disease (PiD), a subtype of FTLD-tau, can also affect the ATL early, along with the inferior frontal gyrus (IFG). We examined differences in ATL atrophy between TDP-C and PiD and tested whether combined ATL and IFG thinning could distinguish TDP-C from PiD pathology.

Method: 28 right-handed PPA cases (PiD, N = 11; TDP-C, N = 17) and 35 age-matched controls underwent structural MRI at their initial visit to the Northwestern PPA Program. T1-weighted images were acquired on a Siemens 3T scanner and processed with FreeSurfer to extract cortical thickness. Two global regions of interest (ROIs) were defined using the HCP atlas: the left anterior temporal lobe (ATL; 9 parcels) and inferior frontal gyrus (IFG; 6 parcels). Cortical thickness values were converted to z-scores relative to the control mean for each ROI. Logistic regression models evaluated whether mean ATL and IFG thickness predicted pathology, first at the global ROI level and then at the sub-ROI (parcel) level. We then tested whether a composite measure of ATL and IFG thinning better predicted postmortem pathology than models including each ROI separately, with models compared using AIC.

Results: ROI-wise analyses revealed a dissociation in regional vulnerability. Logistic regressions showed ATL thinning predicted TDP-C ($\beta = -1.95$, $p = 0.006$), and IFG thinning predicted PiD ($\beta = 1.59$, $p = 0.018$). When examining individual ROIs, thinning in several ATL parcels specifically predicted TDP-C (TGd, STSda, STGa, TGv, PeEC, TE2a, STSva, and TE1a), whereas thinning in IFG parcels FOP4, FOP5, and area 44 significantly predicted PiD (FDR-corrected $p < 0.05$). As expected, no group differences were observed in V1. A model including ATL and IFG as independent predictors provided the best fit and resulted in near-complete separation of the pathology groups.

Conclusion: TDP-C and PiD exhibit distinct regional atrophy patterns, with TDP-C showing predominant ATL thinning and PiD greater IFG involvement. Despite early ATL degeneration, IFG atrophy alone remained the best predictor of underlying PiD. Future studies will assess other imaging modalities (e.g., white matter tracts) to further characterize ATL vulnerability across these pathologies.

Lay Language: We studied people with primary progressive aphasia (PPA) caused by either TDP-C or Pick's disease, along with healthy controls. Using MRI, we measured the thickness of specific brain regions, focusing on the anterior temporal lobe (ATL) and inferior frontal gyrus (IFG), which are often affected in these diseases. Statistical models showed that thinner ATL strongly predicted TDP-C, and thinner IFG predicted PiD. No differences were seen in a control region. Using both regions together best distinguished the two diseases, highlighting that the distinct pattern of temporal versus frontal atrophy is key to distinguishing TDP-C from PiD. These findings may help improve early identification and diagnosis of PPA subtypes and their underlying pathology, providing greater specificity in clinical trials and clearer guidance for families of affected individuals.

Poster 22

Discriminate Pathologic Correlates of Apathy and Disinhibition in Behavioral vs. Aphasic Dementia due to Pick Disease

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Background: Patients with behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA) due to frontotemporal lobar degeneration (FTLD) commonly present with apathy and/or disinhibition. Changes in frontal and limbic regions, including the frontal cortex and amygdala, underlie these symptoms; however, the specific relationships to regional pathology remain unclear. This study investigated tau pathology and microglial activation in the frontal cortex and amygdala in bvFTD and PPA in Pick's disease (PiD), a form of FTLD, and their differential associations with apathy and disinhibition.

Participants and Methods: Seventeen participants with autopsy-confirmed PiD (9 bvFTD, 8 PPA) were identified from the Northwestern ADRC brain bank. Apathy and disinhibition were assessed at annual visits using the Neuropsychiatric Inventory Questionnaire (NPI-Q) and clinician evaluation. Unilateral amygdala and bilateral middle frontal gyrus (MFG) sections were immunostained for phosphorylated tau (AT-8) and activated microglia (HLA-DR). Pick body density was quantified using unbiased stereology, and HLA-DR percent area was measured via digital image analysis (HALO, Indica Labs). Mixed regression models examined regional pathology differences between groups (bvFTD, PPA) and associations with apathy and disinhibition symptoms at participants' final research visit before death.

Results: At final visit, 71% of participants showed apathy, and 53% showed disinhibition. Microglial activation (HLA-DR) was significantly higher in the MFG white matter vs. gray matter ($p<0.01$) and in the amygdala vs. MFG gray matter ($p<0.05$). Across both regions, bvFTD showed greater overall HLA-DR immunopositivity than PPA ($p<0.05$). Pick body densities did not significantly differ between regions or clinical groups. There was a significant, positive association between tau inclusions and neuroinflammation across both the MFG and amygdala ($p<0.05$). Apathy at final visit was associated with increased Pick body density in both amygdala and MFG ($p<0.05$), while disinhibition was associated with elevated microglial activation in the amygdala, particularly when this exceeded MFG levels ($p<0.05$).

Conclusions: This study demonstrates distinct pathogenic processes underlying behavioral symptoms in Pick's disease, with apathy linked to tau pathology and disinhibition associated with microglial activation in frontolimbic regions. Findings also suggest varying susceptibility to neuroinflammatory processes across clinical phenotypes, despite similar tau burdens. Results provide insight into the neurobiological basis of behavioral symptoms in FTLD and highlight the potential for symptom-specific therapeutic approaches. Future investigations examining white matter connectivity and neuronal integrity may further elucidate these relationships.

Lay Language: Patients with dementia commonly experience loss of motivation and interest and/or difficulty regulating impulsive or inappropriate behavior. These symptoms may occur when key brain areas such as the amygdala, which sends emotional signals, and the frontal cortex, which decides how to act, are affected. We studied brain tissue from patients with dementia who showed mainly behavioral or language symptoms due to abnormal tau protein. More tau protein in the amygdala and frontal cortex was related to loss of motivation and interest, whereas difficulty regulating impulsive or inappropriate behavior was related to inflammation in the amygdala. Patients with primarily behavioral symptoms also showed more brain inflammation than those with mainly language problems. This research suggests that certain behavioral symptoms may help us predict where and how brain areas are being targeted by disease so that we can better treat patients.

Poster 23

ALLFTD

Nikitha Damera; Nathaniel Houghtaling; Aaliyah Korkoyah; Kailey Zajicek; Caila Ryan, MS; Joshua Cahan, MD; Allison Lapins, MD; Malik Nassan, MD; Sarah Doran, MD, PhD; Sandra Weintraub, PhD; Ian Grant, MD

Mesulam Institute for Cognitive Neurology and Alzheimer's Disease,

Abstract: The ARTFL LEFFTDS Longitudinal Frontotemporal Dementia (ALLFTD) study seeks to evaluate and characterize cohorts of familial and sporadic frontotemporal lobar degeneration (FTLD) longitudinally through clinical, functional, imaging, and fluid biomarker data analyses. Genetic mutations associated with familial FTLD include microtubule associated protein tau (MAPT), progranulin (PGRN), and chromosome 9 open reading frame 72 (C9orf72), whereas sporadic cases are those with no known cause. Clarifying the mechanisms of these mutations, in addition to advancing the development of FTLD biomarkers for diagnosis, prediction, and disease monitoring, is imperative to inform novel clinical trial methodologies aimed at prevention and treatment. Primary endpoints within this multi-site, longitudinal, observational natural history study include the investigation of annualized changes in: 1) NIH EXAMINER executive function battery; 2) frontotemporal brain volumes measured on MRI; 3) Clinical Dementia Rating (CDR) plus NACC FTLD dementia severity score; and 4) time of conversion from asymptomatic to symptomatic familial-FTLD mutation carrier.

Lay Language: The ARTFL LEFFTDS Longitudinal Frontotemporal Dementia (ALLFTD) project aims to better understand cases of sporadic and familial frontotemporal lobar degeneration (FTLD) by studying persons with diagnoses and their asymptomatic family members. The study seeks to inform methods for future clinical trials, develop tools sensitive to changes in FTLD, and identify markers that may predict onset or progression of disease. Participants complete a neurological examination, blood draw, MRI scan, questionnaires, memory testing, and an optional lumbar puncture as part of this observational study to help achieve these objectives.

Poster 24

Assessing the Reading Ability of Those Living with Dementia

Mary Beth Riedner

American Library Association, Library Services for Dementia/Alzheimer's (LSDA) Interest Group

Purpose: To examine how the reading ability of those living with dementia is currently assessed and to determine if there are better alternatives or if a new instrument needs to be developed.

Methods: The author has collected articles on the topic of reading and dementia for over a decade. Search strategies included searching databases such as ERIC and Pub Med, conducting Internet searches, extracting citations from reference lists of identified articles, and seeking recommendations from colleagues/experts in the field.

Results: Several reading tests use lists of irregularly spelled words to assess premorbid intelligence of patients living with dementia, including the National Adult Reading Test, the Hopkins Adult Reading Test and the Wechsler Test of Adult Reading. Several standardized tests assess the reading ability of adults, including the National Adult Reading Test (2003, Department of Education), the Reading Evaluation Adult Diagnosis, and the Comprehensive Adult Student Assessment Systems tests. Readability tests such as Flesch-Kincaid Readability Test and the Dale-Chall Readability Formula can be used to determine the reading level/difficulty of various texts. It can then be determined which reading level is most comfortable for each person. The font size of reading materials must be considered. The Center for Dementia Research provides a free Reading Observation resource using different size fonts to evaluate which is best for each person, as does Michele S. Bourgeois in her 2014 book Memory & Communication Aids for People with Dementia.

Conclusion: While several neuropsychological tests using reading have been developed in the last 40 years, it appears that they do not adequately test the everyday reading ability of those living with dementia. Rather most of them use lists of irregularly spelled words to estimate pre-morbid intelligence. During the same time period, other studies have demonstrated that reading and other literacy activities can be of benefit to many people living with dementia, but none of them use a testing instrument to obtain actual data. It is becoming clear that a more precise instrument to measure preserved reading abilities needs to be developed in order to obtain the most accurate results.

Lay Language: Do you think that your loved one with dementia can no longer read? Tests like the National Adult Reading Test (NART) have been utilized for several decades. However, they are used to estimate intelligence levels prior to the onset of dementia, not current reading ability. Other tests of adult reading are designed for anyone from age 16-85+ and usually measure functional literacy, such as medical and financial literacy. People living with dementia have different purposes for reading than in the past. They are reading more for pleasure and to engage in a meaningful activity. No test has yet been developed to assess their everyday reading ability. Perhaps it is time for the medical community to develop a new test, which also addresses font size, to assess their current reading ability.

Poster 25

Mesulam Institute Brain Scholars Program: Empowering a Next Generation of Neurologists and Neuroscientists

Paige Barenthin, Ivan Ayala, Dani Chitwood, Elizabeth Haynes, Carolina Hernandez, Grace Minogue, Caroline Nelson, Elizabeth Haynes, Sarah Simon, Antonia Zouridakis, Debby Zemlock, Melvin Thompson, Eskedar Alem, Darby Morhardt, Tamar Gefen and Changiz Geula

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The Brain Scholars Program is an initiative of the Mesulam Institute for Cognitive Neurology and Alzheimer's Disease committed to providing meaningful scientific and professional experiences in brain sciences for students at all levels. To date, the Brain Scholars Program has forged partnerships with St. John de la Salle Catholic Academy (a K-8 school), Butler College Prep (a high school) and Chicago State University. We are working on expanding our program to partner with more schools across Chicago. Our program has hosted 14 visits at the Mesulam Institute with students ranging from elementary to university. At these visits students are exposed to various aspects of brain function and health. Students explore careers in neuroscience; study brain function, and dementia; examine human brains and brain tissue in our laboratories; discuss the lived experiences of a dementia diagnosis on individuals, families, and communities; observe groundbreaking neuroimaging technology; and partner with Mesulam Institute scientists and researchers. In addition to hosting students at our Institute, the Brain Scholars Program has conducted 9 satellite visits at our partner schools. During these visits students learn about brain function and health; dementia and Alzheimer's Disease; and neuropsychological testing. Overall, over 600 students have participated in activities offered by the Brain Scholars Program.

Another facet of the Brain Scholars Program is our 6-week summer internship program. We implemented this aspect of our program in 2023 and have hosted 20 summer interns (8 high schoolers and 12 middle schoolers). We are currently in the process of recruiting our 2026 summer interns which will also include students from Chicago State University. Over the course of the summer program, students dive further into brain function and health by engaging with the work carried out in various sections of our Institute. This includes laboratory work, neuropsychological testing, neuroimaging, social work, data science, and more.

Continuing and expanding its efforts, the Brain Scholars Program hopes to empower increasing numbers of students to pursue education and professional careers in the health sciences, including clinical and research efforts related to brain aging and dementia.

Lay Language: The Brain Scholars Program is an initiative of the Mesulam Institute for Cognitive Neurology and Alzheimer's Disease committed to providing meaningful, positive scientific and professional experiences in the health sciences for students at all levels. So far over 600 students have participated in activities offered by the Brain Scholars Program through visits hosted and/or conducted by the Mesulam Institute. In addition, 20 students have participated in our 6-week summer internship program. Continuing and expanding its efforts, the Brain Scholars Program hopes to empower increasing numbers of students from underserved groups at all levels, from elementary school to university, to pursue education and professional careers in the health sciences, including clinical and research efforts related to brain aging and dementia.

Poster 26

The Power of Faith: Community Engagement meets Apostolic Faith Church

Dani Chitwood ABD/MSW[1], Jonathan Banks MBA[2], Alicia Kelly MJ, M Ed [2], Eugenia Sanders MD [2], Gerrie Peacock MD [2] Lauren Dowden, MSW, LCSW[1], Sandra Weintraub, PhD [1] , Darby Morhardt PhD LCSW[1]

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[2] Apostolic Faith Church

Background: The Black community has been disproportionately impacted by several chronic health conditions, including dementia. In the United States, Black Americans are diagnosed with dementia at approximately 1.5 to 2 times the rate of White Americans. Efforts to understand and address this disparity are complicated by longstanding barriers to access and historical mistrust of medical and research institutions. To bridge these gaps, the Mesulam Institute's Outreach, Recruitment, and Engagement (ORE) Core efforts rely on community-centered strategies that build authentic relationships with local stakeholders and organizations to support sustained, long-term engagement. Faith-based institutions—particularly the Black Church—have proven to be trusted spaces that provide meaningful access to community members. This work highlights the Mesulam Institute's partnership with Apostolic Faith Church and examines strategies for effectively recruiting and retaining Black participants for proactive brain health practices and educational initiatives.

Methods: Through initial conversations, the Mesulam Institute ORE-Core team learned from Apostolic Faith Church about the current experiences within their community related to dementia and the importance of building trust so that we could become a reliable resource. Our work together began with a dementia conference that included a keynote speaker, a panel discussion, and a community resource fair. Using a mixed-methods survey, we assessed the impact of the conference titled "When Memory Changes: Myths and Truths." The event featured a keynote presentation focused on understanding and dispelling myths about dementia, a panel discussion with professionals working in the dementia field, and a resource fair designed to connect attendees with supports and services for individuals and families navigating dementia.

Results: 144 individuals attended and participated in the conference. Post-event surveys were completed. A total of 25% of attendees completed the evaluation. Likert-scale responses produced a mean score of 4.57 out of 5 (91%), suggesting that respondents agreed or strongly agreed that the content presented was both meaningful and necessary. Attendees also frequently noted the importance of receiving continued brain health education and resource fairs related to dementia in the near future.

Conclusion: Our initial efforts were successful and helped strengthen the partnership between the Mesulam Institute and Apostolic Faith Church. The collaboration will continue through ongoing conversations and the development of supports for members of the AFC community affected by dementia. AFC continues to serve as a trusted space where community members can receive medical information and connect to supportive resources.

Lay Language: Black communities have been affected by many long-term health issues, including dementia. In the United States, Black Americans are diagnosed with dementia about 1.5 to 2 times more often than White Americans. Understanding why this happens – and how to help – can be difficult, especially because of past experiences that have led to mistrust of the healthcare system. To bridge this gap, the Mesulam Institute's community team works closely with trusted community partners. Churches, especially Black churches, are important because they are places people turn to for support, guidance, and reliable information. This work highlights the partnership between the Mesulam Institute and Apostolic Faith Church and shares ways to better reach and support Black families with education, resources, and tools to care for brain health.

Poster 27

“People Don’t Know Where to Start:” Outcomes from A Community Academic Partnership Listening Session

[1]Pastor Michael Neal, [1]Deloris Neal, [2]Ingrid Fowler-Wrather, [2]Robert Vassar, [2]Aaliyah Korkoyah, [2]Nicole Patel, [2]Molly A Mather, [2]Dani Chitwood, [2]Lauren Dowden, [2]Darby Morhardt

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Background: With an aging population, there is growing concern regarding Alzheimer’s disease and related dementias. Black Americans are twice as likely as older White Americans to have Alzheimer’s or another dementia, for reasons that continue to remain unclear. Although culturally tailored dementia education and information can promote healthful behavior change and action, many Black Americans face challenges in accessing such information, further contributing to disparities in service and care. In order to capture community insights, participation, and connect feedback to action, the Mesulam Institute offers listening sessions in collaboration with our community partners.

Methods: To better understand perceptions of dementia, caregiving and brain health among the Black American community in Chicago’s South Side Bronzeville neighborhood, the Northwestern University Mesulam Institute (NUMI) engaged in a bidirectional community academic partnership with the health-oriented community-based organization, Timothy Community Corporation (TCC). In a collaborative two-way process, preliminary meetings representing both TCC and NUMI staff co-identified the need to better understand community needs and perspectives on dementia, brain health, and caregiving to facilitate alignment between expressed community needs and NUMI’s mission, goals and resources and to inform culturally responsive programming As a result, a listening session was co-designed by both TCC and NUMI and led by NUMI staff and faculty at TCC. A flyer advertising the listening session was distributed to the community. A 90-minute listening session was held on a Saturday in November 2025 using a pre-determined question guide. Two NUMI staff took notes during the meeting (in lieu of audio recording) and provided their summaries. Summaries were reviewed by TCC and NUMI staff for emergent themes.

Results: Six individuals, all Black, 5 female and 1 male attended the listening session co-facilitated by NUMI staff. TCC and NUMI reviewed notes and coded resulting themes and identified needs: 1) Dealing with caregiver and family emotional burden; 2) Finding community connection and social engagement; 3) Identifying culturally tailored education on dementia, brain health, and research; and 4) Addressing practical barriers to accessing care.

Conclusion: This community academic partnership listening session allowed members of the Black community in Bronzeville to express their lived experiences, perspectives and needs regarding dementia, caregiving and brain health. Next steps include incorporating these listening session findings into practice.

Lay Language: A community academic collaboration between Timothy Community Corporation and the Northwestern Mesulam Institute led to the development of listening sessions where members of the older adult and caregiving community in Bronzeville expressed their experiences regarding dementia, caregiving, and brain health. Results will help the collaboration move forward with next steps to address caregiver burden, need for social engagement, culturally tailored education and access to care.

Poster 28

Mesulam Institute Community Engagement as Infrastructure: Continuing to Build Community Partnerships for Brain Health and Dementia Outreach

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Background: Disparities in dementia risk, access to care, and research participation persist across historically underrepresented communities. The Mesulam Institute has developed a partnership-centered community engagement approach focused on sustained community relationships, education, and collaboration with trusted local organizations to expand brain health awareness and dementia education, and community readiness for research participation. For more than two decades, the Mesulam Institute has prioritized community engagement and trust building as essential components of dementia education, research awareness, and equitable access to brain health resources.

Methods: A partnership-centered engagement model was implemented through collaborations with community organizations, senior residential communities, libraries, and faith-based institutions. Activities included brain health education sessions, dementia awareness trainings, caregiver resource sharing, and co-hosted community programs. Engagement data were extracted from the ORE Core community engagement tracking system documenting event type, partner organization, attendance estimates, and engagement outcomes. Descriptive statistics summarized engagement activity and partnership continuity.

Results: During the past year, there were 105 community engagement 94 activities (educational sessions, health fairs, listening sessions, and resource tables) with 38unique community partners across Chicago reaching 8048 community members across 14 neighborhoods. Partnership milestones included co-hosted programming with faith institutions, community-based organizations, senior residential communities, and public libraries; repeat programming with established partners; and expansion of dementia education into new community settings. Qualitative analysis of community engagement fieldnotes indicate that these engagements strengthened trust, increased visibility of the Mesulam Institute within community networks, and supported ongoing dialogue around dementia awareness and research participation.

Conclusion: Sustained community engagement through trusted partnerships provides an important foundation for expanding dementia education, strengthening community trust, and increasing awareness of research opportunities. The Mesulam Institute's partnership-centered model demonstrates how long-term collaboration with community organizations can extend the reach of brain health education and support inclusive pathways to dementia research participation.

Lay Language: The Mesulam Institute works with community organizations across Chicago to share information about brain health, dementia, and research opportunities. Through partnerships with local organizations, faith communities, libraries, and senior residential sites, the Institute brings education and resources directly into community spaces. These collaborations help build trust, increase awareness of dementia, and support more inclusive participation in research.

Poster 29

Neuroanatomy

Altered Resting-State Connectivity of the Auditory Cortex in Alzheimer's Disease

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Background: Alzheimer's disease (AD) is marked by reduced resting-state functional connectivity (RSFC), reflecting synaptic loss and disrupted neural communication (Sheline & Raichle, 2013). Structural MRI studies have reported decreased cortical volumes in auditory cortical (AC) regions including the Planum Polare (PP), Planum Temporale (PT), and Heschl's Gyrus (HG) in AD (Sousa Menezes et al., 2025). However, the relationship between connectivity of specific AC subregions and cognitive performance remains poorly understood. This study examined AC subregion connectivity differences between AD patients and healthy controls and evaluated how these connectivity patterns relate to cognitive measures available in the ADNI cohort.

Method: Structural and RSFC data were obtained from 51 healthy controls and 33 AD patients (84.8% mild, 15.2% moderate). Seed-based connectivity analyses were performed for bilateral PP, PT, and HG. Group differences were assessed using two-sample t-tests (AD<controls, $p<0.001$, cluster-size FDR $p<0.05$). Within the AD group, regression analyses evaluated associations between AC connectivity, Montreal Cognitive Assessment (MoCA) letter fluency, and Rey Auditory Verbal Learning Test (RAVLT) scores. All analyses included sex, age, handedness, and gray-matter volume as covariates.

Results: The AD patients had reduced RSFC of the right PP with the lateral and medial cortical regions, with clusters located in frontal and parietal lobes. Reduced clusters in the medial cortices involved are the bilateral anterior cingulate and right paracingulate gyri, while lateral reductions included bilateral insula, left inferior frontal gyrus, and left inferior temporal gyrus. Within the AD group, stronger right PP connectivity was positively associated with letter fluency, with clusters in left prefrontal, parietal, putamen, and thalamic regions. Greater right PP connectivity was also linked to better RAVLT performance, with clusters in the posterior cingulate cortex, precuneus, and medial frontal areas.

Conclusion: AD is associated with reduced connectivity between AC subregions and lateral/medial fronto-parietal and cingulate networks. Reduced AC connectivity with left lateral cortical and subcortical regions contributes to impaired letter fluency, while decreased connectivity with medial limbic structures underlies episodic memory deficits (Buckner et al., 2008). These findings highlight the involvement of central auditory cortical processing in cognitive decline in AD.

Lay Language: Although Alzheimer's Disease (AD) is widely known for causing memory problems, it can also affect how different parts of the brain communicate with each other. In this study, we examined brain regions that process sounds and investigated how strongly they are connected to other areas involved in memory, language, and attention. Using brain scans from people with AD and healthy adults, we found that these sound-processing regions were less connected to other important brain areas in individuals with AD. We found that people with stronger brain connections perform better on tasks that measured memory and language abilities. These results suggest that changes in the brain's sound-processing networks may play a role in the cognitive difficulties experienced in AD. Understanding these changes may help researchers better track disease progression and identify new ways to support communication and cognitive function in affected individuals.

Poster 30

Contribution of Inflammatory Markers to Symptomatic Alzheimer's Disease

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Background: Our current understanding of the proteomic changes driving aging-related cognitive decline and symptomatic Alzheimer's Disease (sAD) remains elusive. However, several maladaptive and neuroprotective pathways associated with aging and sAD have been recently uncovered. In particular, neuroinflammation via astrogliosis and microgliosis is proposed to exacerbate sAD pathology and aging phenotypes by keeping the brain in a prolonged, chronic proinflammatory state. Yet, the specific utility of neuroinflammatory pathways in predicting sAD progression remains under-characterized– a critical gap for identifying the proteomic drivers of cognitive decline and developing targeted therapeutics. Given that traditional amyloid beta (Aβ) and tau pathologies do not fully account for variations in cognitive decline, we hypothesized that the dysregulation of neuroinflammatory pathways was a more significant driver of sAD.

Methods: The present study utilizes the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to evaluate the predictive impact of cerebrospinal fluid (CSF) protein markers across healthy, mild cognitive impairment (MCI), and sAD cohorts. Age-related protein trajectories were assessed via linear regression, from which p-values and R2 correlations were derived. A LASSO binary classifier was trained to predict symptomatic status, i.e. healthy vs sAD & MCI. This allowed for the quantification of predictive improvement when incorporating neuroinflammatory markers into a standard baseline model of Aβ and tau.

Results: Proteomic analysis from ADNI revealed significant dysregulations of key pro- and anti-inflammatory proteins including vascular cell adhesion protein 1 (VCAM1), triggering receptor expressed on myeloid cells 2 (TREM2) and neurofilament light (NfL) in symptomatic individuals compared to healthy controls. Furthermore, these markers tracked with advancing age, suggesting a complex interplay between disease-driven pathology and age-related neuroprotective responses. Notably, other markers including interleukin (IL)-6, IL-7, IL-10 and tumor necrosis factor-α (TNF-α) were uncorrelated with age, likely due to earlier aggregation and plateauing following symptom onset. When integrated into a LASSO classifier to predict sAD, the addition of neuroinflammatory proteins significantly enhanced model performance over a baseline model limited to only Aβ and tau proteins as predictors.

Discussion: These findings elucidate the role of CSF inflammatory markers–notably TREM2, VCAM1, and NfL–as strong predictors of AD- and aging-related cognitive symptoms. This thus advances our understanding of the proteomic architecture of cognitive impairment and paves the way for more precise therapeutics, specifically prodromal interventions that target these proteins with antibodies.

Lay Language: An estimated 7.2 million Americans are currently living with Alzheimer's. While we know brain inflammation plays an important role in Alzheimer's, we still don't fully understand how specific protein changes drive memory loss. This study analyzed cerebrospinal fluid–the fluid surrounding the brain–from healthy adults and those with Alzheimer's to identify better ways to predict the disease. We found that specific proteins causing inflammation in the brain are significantly altered in Alzheimer's patients. Some markers increased with age, suggesting inflammation rises as the disorder progresses. Interestingly, others did not, suggesting they serve as early warning signs. By using computer models, we found that adding these inflammatory markers to standard predictive tests–which usually only look at "plaques and tangles"–significantly improved our ability to predict Alzheimer's. These results pinpoint brain inflammation as a powerful tool for understanding Alzheimer's and cognitive decline, paving the way for better therapeutics and diagnostic tools.

Poster 31

Defining the Impact of Amyloid Pathology on Synaptic Homeostasis Across the Sleep-Wake Cycle

Ivan Santiago Marrero

Alzheimer's disease (AD) is a progressive brain disorder causing dementia, diagnosed post-mortem by amyloid plaques and neurofibrillary tangles. In the early stages of AD, amyloid-beta (Aβ) peptides are produced through the amyloidogenic processing of the amyloid precursor protein (APP) in a synaptic activity dependent manner. During wakefulness, learning promotes synaptic strengthening and enhances transmission, that returns to baseline levels during sleep.

This homeostatic downscaling of synapses involves an array of cellular and molecular changes including receptor and ion channel endocytosis and the posttranslational modification of synaptic proteins. However, how amyloid pathology affects this process during sleep remain unexplored. Here I propose to determine whether amyloid pathology alters the synaptic proteome and phosphoproteome across the sleep-wake cycle. To determine whether amyloid pathology alter synaptic proteins dynamics across the sleep-wake cycle, I harvested brains and purified synaptosomes during the dark (active) and light (inactive) phases from WT and a knock-in mouse model of aggressive amyloid pathology AppNL-F;PS1/ NL-F;PS1 (PS1).Crude synaptosomal preparations were digested and labeled with tandem mass tags for the identification and quantification of synaptic proteins across sleep and wake.

I hypothesize that amyloid pathology disrupts synaptic protein expression across the sleep-wake cycle, that sleep restriction exacerbates this disruption, and that enhancing sleep can restore normal turnover. To this end, I performed electroencephalography (EEG) recordings AppNL-F/NL-F(NL-F), PS1 and WT mice to characterize how amyloid pathology alters sleep in these animals. After recovery from electrode implantation, animals underwent 48 hours of continuous recording with manual and automated scoring of wake, non-REM (NREM), and REM sleep.

Across the dark phase, NL-F mice exhibited reduced percent wake accompanied by increased NREM and REM sleep relative to WT controls. NL-F animals also showed increased bout number for wake and NREM across both light and dark phases, and increased REM bout number selectively during the dark phase. Together, these findings indicate a fragmented sleep phenotype associated with amyloidogenic APP processing.

To examine whether amyloid pathology disrupts synaptic protein dynamics across the sleep-wake cycle, we isolated crude synaptosomes from WT PS1 mice during dark (active) and light (inactive) phases and quantified proteins using TMT-based proteomics. Volcano plot revealed robust phase-dependent remodeling of the synaptic proteome within genotypes, supporting dynamic regulation of protein abundance across the sleep-wake cycle. Comparison of protein abundance between dark and light cycles of PS1 and WT mice, showed that differentially abundant proteins differ between genotypes. This supports the notion that circadian regulation of the proteome is altered by amyloid pathology.

Lay Language: Alzheimer's disease (AD) is a progressive brain disorder that causes memory loss and dementia. One of the earliest changes in AD is the buildup of amyloid-beta proteins in the brain. These proteins are produced at synaptic terminals, which are the connections between neurons, especially during wakefulness. During sleep, the brain normally restores balance by weakening or "downscaling" synapses. However, it is unclear how amyloid buildup affects this process. In this study, we examined whether amyloid pathology disrupts normal changes in synaptic proteins across the sleep-wake cycle. Using mouse models of amyloid pathology, we recorded brain activity to measure sleep patterns and analyzed synaptic proteins using quantitative proteomics. Mice with amyloid pathology showed more fragmented sleep and altered patterns of wake and sleep. We also found that normal daily changes in synaptic proteins differed between diseased and healthy mice, suggesting that amyloid pathology disrupts how the brain regulates synapses across sleep and wakefulness.

Poster 32

Lecanemab Treatment Alters Proteomic Profiles in Alzheimer's Disease Mouse Models

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Background: Lecanemab, an FDA-approved monoclonal antibody, targeting amyloid-beta (Aβ) protofibrils, has demonstrated therapeutic potential in Alzheimer's disease (AD). This study elucidates its molecular and cellular effects using two AD mouse models: AppNL-F/NL-F(NL-F) and AppNL-F/NL-F Psen1P117L/WT NL-F mice carrying the PS1 mutation (NL-F-PS1).

Methods: Eight-month-old mice (n=6 per group) received weekly intraperitoneal injections of mAb158 (40 mg/kg) for 8 weeks, while control animals were administered an equivalent dose of IgG. To characterize the proteomic landscape associated with mAb158 treatment, cortical and hippocampal homogenates from NL-F, NL-F-PS1, and control groups were subjected to 12-plex tandem mass tag (TMT)-based bottom-up proteomics. These findings were further validated and complemented through Aβ42 ELISA, western blotting for various Aβ species and APP metabolites, thioflavin staining, and immunohistochemistry (IHC).

Results: TMT proteomics of NL-F cortical homogenates identified 95 significantly upregulated proteins. Gene Ontology (GO) enrichment analysis indicated that these proteins are predominantly associated with presynaptic membrane components, including synaptic vesicle glycoprotein 2A (SV2A), syntaxin-1B (STX1B), and syntaxin-4 (STX4), as well as membrane transport and protein complexes. In the NL-F-PS1 cortical homogenates, 53 proteins were significantly upregulated, with GO terms enriched for classical complement cascade components – namely C1QA, C1QB, and C1QC – suggesting microglial activation and recruitment. These complement proteins are integral to innate immune signaling and synaptic pruning mechanisms. Aβ42 ELISA revealed a significant reduction in both cortical and hippocampal Aβ42 levels across NL-F and NL-F-PS1 mice following mAb158 treatment. Concordantly, western blot, thioflavin staining, and IHC collectively confirmed a robust decrease in amyloid burden in both models, consistent with the ELISA findings.

Conclusion: Lecanemab treatment effectively reduced amyloid burden in both NL-F and NL-F-PS1 models. Proteomic analysis revealed model-specific responses – upregulation of presynaptic proteins in NL-F mice suggesting enhanced synaptic integrity, and enrichment of complement cascade components in NL-F-PS1 mice indicative of heightened microglial activation.

Lay Language: Alzheimer's disease is partly driven by the buildup of sticky protein clumps called plaques in the brain, which gradually damage connections between nerve cells and impair memory and thinking. Lecanemab is a recently FDA-approved treatment designed to target and clear these plaques. Using two mouse models with different severities of Alzheimer's, we found that Lecanemab successfully reduced plaques in both. Beyond clearance, the treatment triggered other distinct responses. In the milder model, synaptic proteins which support nerve cell communication were increased, suggesting a protective effect on brain connectivity. In the more aggressive model, the brain's immune cells appeared more activated, potentially enhancing the clearance of harmful material. These findings suggest Lecanemab influences the brain beyond simply reducing the amyloid plaques with effects that may vary by disease stage.

Poster 33

Neuroscience

Interferon Signaling and Microglial Senescence in Alzheimer's Disease

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Background: Aging is the strongest risk factor for Alzheimer's disease (AD), yet the mechanisms by which aging promotes disease onset and progression remain poorly understood. Cellular senescence, a hallmark of aging characterized by irreversible cell-cycle arrest in response to cellular stress, has recently emerged as a potential contributor to neurodegenerative diseases. Senescent cells exhibit altered metabolism and secrete pro-inflammatory factors collectively known as the senescence-associated secretory phenotype (SASP), which can disrupt tissue homeostasis and promote chronic inflammation. Increasing evidence suggests that senescent brain cells may contribute to AD pathology; however, the identity of the vulnerable brain cell types and the mechanisms driving senescence under AD conditions remain unclear. Microglia, the brain-resident macrophages, play essential roles in maintaining brain homeostasis by clearing cellular debris, apoptotic neurons, and aggregated proteins. Notably, microglia are highly prone to cellular senescence with aging. Despite these observations, how AD-related pathological conditions promote microglial senescence and how senescent microglia influence disease progression remain largely unknown.

Methods: To investigate the mechanisms of microglial senescence in AD, we analyzed human AD postmortem brain tissues and the 5xFAD mouse model, a widely used amyloidosis model that rapidly develops amyloid plaque pathology. We also utilized cultured microglia for a mechanistic study. Microglial senescence and molecular signaling changes were assessed using immunostaining, RNA sequencing, and western blot analysis.

Results: We observed a pronounced accumulation of senescent microglia surrounding amyloid plaques in both the 5xFAD mouse brain and human AD brain tissues. We found a strong activation of the interferon (IFN) signaling pathway in these senescent microglia. Interferon (IFN) signaling is a classical antiviral immune pathway that also contributes to age-associated chronic inflammation (inflammaging). In cultured microglia, direct activation of the IFN pathway was sufficient to induce senescence phenotypes. Similarly, exposure to amyloid-beta 1-42, a major component of amyloid plaques, activated IFN signaling and induced microglial senescence.

Conclusion: Our findings demonstrate that activation of IFN signaling within the amyloid plaque microenvironment promotes microglial senescence. Targeting interferon signaling or eliminating senescent microglia may therefore represent promising therapeutic strategies for slowing disease progression in AD.

Lay Language: Alzheimer's disease (AD) becomes more common with aging, but the biological changes that link aging to this disease are still not fully understood. Our research focuses on microglia, the brain's immune cells that normally help protect the brain by removing harmful substances and damaged cells. We found that near amyloid plaques, one of the key features of AD, many microglia develop features associated with cellular aging and become less able to maintain brain health. These cells also activate inflammatory signals that are commonly associated with aging-related chronic inflammation. Our findings suggest that aging-related immune changes may drive harmful changes in microglia and contribute to disease progression. Understanding this process may help identify new treatment strategies aimed at reducing harmful inflammation or restoring healthy immune function in the brain.

Poster 34

Neuroscience

Auditory Cortex Connectivity Disruption in Behavioral Variant Frontotemporal Dementia

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Background: Behavioral variant frontotemporal dementia (bvFTD) is the most common FTLD syndrome and is characterized by progressive behavioral and cognitive decline with prominent frontal and anterior temporal atrophy (Seeley, 2019; Boeve, 2022). bvFTD is associated with impaired sound processing, auditory emotion recognition, and sound localization, suggesting selective vulnerability of the auditory cortex (Johnson et al., 2025). Prior studies report reduced gray matter density in this region (Aylward et al., 2020), but changes in auditory network connectivity and its relationship to auditory-based cognitive functions including verbal working memory remain unclear. In this study, we examined auditory-network connectivity changes in bvFTD and associations with auditory working memory measures.

Methods: Resting-state fMRI data from 15 bvFTD patients and 35 controls from the ALLFTD database were preprocessed using the CONN toolbox. Seed-based whole-brain connectivity was examined for secondary auditory cortices: planum polare (PP) and planum temporale (PT), regions involved in acoustic processing (Upadhyay et al., 2008). Age, sex, handedness, and gray matter volume were included as covariates. Group differences between bvFTD and controls were assessed using a voxel-wise threshold of $p < 0.001$ and cluster-FDR $p < 0.05$. Regression analyses using auditory working memory tasks-Digit Span and California Verbal Learning Test (CVLT) immediate free recall-were assessed using a voxel-wise threshold of $p < 0.01$ and cluster-FDR $p < 0.05$. Benson Complex Figure test scores were evaluated as a nonverbal control task.

Results: In bvFTD, we found decreased connectivity in the insular, perisylvian, and parieto-temporal regions for both the PP and PT seeds (PT > PP). Digit Span and CVLT immediate free recall were positively associated with resting-state connectivity in auditory seeds, particularly the PT seed (PT > PP). PP/PT connectivity correlations with the Benson test revealed regions outside the perisylvian zone.

Discussion: These findings support selective vulnerability of the associative auditory cortex in bvFTD, aligning with prior research. The pronounced decreases in PP and PT connectivity and their association with Digit Span and CVLT measures suggest that spectrotemporal pattern analysis required for phonological encoding is disrupted at later stages of auditory processing in bvFTD (Aylward et al., 2020; Griffiths et al., 2002). Lack of perisylvian connectivity for the visual task supported specificity of our findings. These findings support a role for decreased network connectivity in auditory verbal impairment in bvFTD.

Lay Language: Behavioral variant frontotemporal dementia (bvFTD) is a neurodegenerative disease that progressively affects behavior, cognition, and personality. People with bvFTD often have difficulty processing sounds and recognizing emotions in voices, but it is not fully understood how communication breaks down between the brain's sound-processing regions. In this study, we compared brain scans from individuals with bvFTD and healthy adults to examine how strongly key auditory regions remain connected to the rest of the brain. We found that these connections were weaker in bvFTD, and that individuals with stronger connections performed better on auditory short-term memory tasks. These results suggest that disruptions in auditory brain networks may contribute to the language and memory difficulties seen in bvFTD, and that auditory processing changes may help track disease progression.

Poster 35

Synaptic loss and stability of synaptic proteins in a conditional transgenic mouse model of human TDP-43 proteinopathy

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Abstract: Frontotemporal lobar degeneration (FTLD) is a common early-onset dementia marked by tauopathy or TAR DNA-binding protein 43 (TDP-43, FTLD-TDP) proteinopathy. We utilized a biallelic mouse model of FTLD on a mixed FVB/129SVE background overexpressing wild-type human TDP-43 (hTDP-43) under a tetracycline transactivator (tTA) system (TET off).

Cortical intraneuronal punctate phosphorylated TDP-43 positive inclusions appeared at 14 days expression, peaked at 8 weeks and were absent by 24 weeks with concurrent neuronal loss and cortical thinning. Cortical synaptic loss has emerged as a consistent finding in neurodegenerative dementias, particularly in Alzheimer's disease. In human participants with FTLD-TDP, we have shown reductions in cortical levels of the dendritic spine protein spinophilin and the presynaptic protein synaptophysin, and a slight increase in the postsynaptic density protein of 95 KD (PSD- 95), likely due to reactive upregulation. This study investigated whether similar synaptic changes occur in conditional hTDP-43 transgenic mice. Western blot analysis was conducted using homogenized frontal and temporal cortex from 5 transgenic and 5 wild type mice following 14 days, 8 weeks, and 24 weeks of TDP-43 expression. Antibodies against spinophilin (Cell Signaling Technology; mAb; 1:1000), synaptophysin (Millipore Sigma; mAb; 1:10000), and PSD-95 (UC Davis/NIH Neuromab Facility; mAb, 1:3000) were used. Electron microscopy (EM) was performed on 11 transgenic and 9 wild type mice to quantify frontal cortical synapses.

Western blot analysis showed no consistent reductions in synaptic protein levels in transgenics. In some instances, levels were elevated; notably, PSD-95 was significantly increased in temporal cortex at 24 weeks of expression ($p = 0.0005$). However, quantitative analysis of EM images revealed significantly lower numbers of synapses in the frontal cortex of transgenic mice after 24 weeks. These findings suggest that hTDP-43 mice display synaptic loss despite stable or increased synaptic protein levels, likely due to compensatory upregulation. This mirrors observations in human FTLD-TDP and Alzheimer's disease and indicates that synaptic protein levels alone may not accurately reflect true synapse loss.

Lay Language: Frontotemporal lobar degeneration (FTLD) is a type of dementia that usually starts earlier in life. It is caused by problems with certain proteins in the brain, like tau or TDP-43. In this study, we used a special type of mouse that was made to produce human TDP-43 protein in its brain. We found that small clumps of this protein started to appear in brain cells after about 14 days. These clumps were most common at 8 weeks, but by 24 weeks they were gone. However, even though the clumps disappeared, the mice showed loss of brain cells and thinning of the brain's outer layer (cortex). Loss of connections between brain cells (called synapses) is often seen in diseases like Alzheimer's disease. In this study, we wanted to see if the same thing happens in our mice. To do this, we tested brain tissue from both modified mice and normal mice at 14 days, 8 weeks, and 24 weeks after TDP-43 was turned on.

Poster 36

Does Hearing Loss Promote the Onset and Progression of Alzheimer's Disease?

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Background: Numerous clinical studies have identified a significant correlation between hearing loss and the progression of Alzheimer's disease (AD). However, the causal relationship between the two remains inadequately understood. Amyloid-beta (Aβ), a hallmark of AD, may affect neurons responsible for hearing function. Conversely, impaired cochlear function might also play a role in advancing AD. APP/PS1 mice are among the most frequently used transgenic mouse models in AD research. However, this model is on the C57BL/6 background, which suffers from early-onset hearing loss due to a mutation in Cdh23 expressed in both the cochlea and brain. To exclude the influence of the Cdh23 mutation, we have "corrected" the Cdh23 mutant. We aim to use our modified model to investigate the relationship between hearing loss and memory impairment.

Methods: To eliminate the influence of the mutant Cdh23 (Cdh23753A) allele, we crossed APP/PS1 mice with the B6.CAST-Cdh23Ahl+/Kjn strain, which carries the WT allele of Cdh23 (Cdh23753G). We genotyped the offspring to confirm that the APP/PS1 mice carry one copy of the WT Cdh23 allele (Cdh23753G). Hearing and memory assessments of APP/PS1 mice and their WT littermates were conducted up to 15 months of age. Hearing was evaluated using ABR and DPOAE. Behavioral testing was performed using the open field test (OFT), novel object recognition (NOR) test, and Y-Maze.

Results: Between 3 and 15 months, there is no significant difference in hearing, as measured by ABR, between WT and APP/PS1 mice. However, APP/PS1 mice exhibit a statistically significant increase in DPOAE threshold at higher frequences, suggesting cochlear impairment in these mice. Behavioral assessments showed that significant differences in the NOR test between APP/PS1 and WT mice (n=11) did not appear until 15 months of age. Additionally, no discernible differences were observed in open-field and Y-maze tests.

Conclusion: Preliminary results indicate that we have successfully established a novel APP/PS1 mouse mode with delayed aged-related hearing loss. Contrary to expectations, APP/PS1 mice did not exhibit cognitive impairment until 15 months, while original APP/PS1 mice have the symptoms at 6-months. These findings highlight the crucial role of CDH23 and the significance of normal hearing in the progression of AD. Furthermore, the impaired cochlear function in APP/PS1 mice suggests that the overexpression of Aβ in the brain also affect cochlear function.

Lay Language: Hearing loss has long been associated with Alzheimer's disease onset but not fully understood as to what came first – it's a chicken or the egg situation. We set out to determine exactly how hearing loss progresses with Alzheimer's and whether hearing loss exacerbates the effects of the disease, mainly in memory and stress. Our data show some promising links between offsetting hearing loss and slowing the progression of Alzheimer's symptoms along with a possible new genetic link to the disease mechanism of hearing loss.

Poster 37

Neuroscience

Novel Mechanistic Roles of TMEM106B in Regulating Lysosomal Inter-Organelle Contact Sites and Misregulation in Frontotemporal Dementia

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Background: TMEM106B is an endo-lysosomal transmembrane protein known to be a risk factor for several neurological diseases, including frontal temporal lobar degeneration with TDP-43 pathology (FTLD-TDP). Frontal temporal lobar degeneration is the most common early age of onset dementia. Previous studies revealed TMEM106B loss-of-function as a cause for lysosomal biogenesis impairment, which further contributes to the molecular pathomechanisms of dysfunctional lysosome trafficking in disease. However, there is still very little known about the physiological functions of TMEM106B and its variants in the lysosome and how TMEM106B is associated with a wide range of neurodegenerative diseases at the molecular level. Inter-organelle contact sites are important hubs for organelles such as lysosomes to crosstalk with one another, but how TMEM106B regulates lysosomal contact sites has never been studied.

Design/Methods: Using Super-Resolution live microscopy, we modulated TMEM106B expression and analyzed the role of its disease-associated variants in human cell lines and examined its effects on lysosomal dynamics, and inter-organelle contact sites between lysosomes and other organelles.

Results: We found that TMEM106B can regulate lysosomal contact sites with other organelles and may play a key role in lysosomal contact site tethering, as well as lysosomal functional crosstalk with other organelles at contact sites. These findings have important consequences for understanding the role of TMEM106B in regulating lysosomal function, and the role of different disease-associated variants in TMEM106B.

Conclusions: This study suggests that TMEM106B may play a key role in mechanistically modulating lysosomal contact sites, and that mis-regulation of this pathway contributes to the disease etiology underlying FTLD-TDP. Moreover, targeting this pathway may modulate disease pathology and progression, and help to explain TMEM106B's contribution as a risk factor in FTLD-TDP.

Lay Language: Frontotemporal lobar dementia (FTLD) is a heterogeneous clinical syndrome characterized by the atrophy of frontal and temporal lobes, resulting in progressive changes in behavior, personality and/or language, with relative preservation of memory. Lysosomal dysfunction is one of the common pathogenic mechanisms in FTLD. Further studies into the normal function of lysosomal proteins are required to uncover mechanisms that cause diseases at the cellular level. This study examines novel functions of TMEM106B, a lysosomal protein, in physiological and pathological conditions. We found that TMEM106B may regulate lysosomal contact with its environment. This finding will help shed light on the molecular pathways that contribute to FTLD.

Poster 38

Neuroscience

Large-Scale Protein Analysis of the Relationship between FTD-Tau Pathology and Impaired Protein Turnover

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Tauopathies such as frontotemporal dementia (FTD-tau) are a diverse group of neurodegenerative disorders characterized by the hyperphosphorylation of the protein tau and formation of tau aggregates (neurofibrillary tangles; NFTs). Tau pathology causes synapse loss and neuronal death, which lead to symptoms such as dementia, personality changes, and movement disorders. My project aims to employ large-scale protein analysis of an FTD-tau model (PS19 mouse) to investigate the molecular mechanisms driving tau pathology

In healthy conditions, cells make new proteins to replace old or damaged proteins. However, in tauopathies like FTD-tau, this normal protein turnover is disrupted, allowing tau and other proteins to aggregate. My lab tracks the formation of new proteins through stable isotopes, which are atoms that have an extra neutron and act as molecular labels. I tracked protein synthesis in PS19 tau mice for 6 weeks starting at three, four, five, and six months. Newly synthesized proteins incorporate the heavier isotope while previously made proteins retain the lighter isotope. This allowed me to quantify protein turnover across four stages of tau pathology. To study changes, I analyzed different brain regions, isolated tau and tau-associated proteins, and performed biochemical isolations with the strong detergent N-Lauroylsarcosine.

Preliminary data of cortex from PS19 mice labeled from 3 and 4.5 months shows that many proteins have changes in protein turnover, compared to healthy controls. Mitochondrial dysfunction may be an early event in tau pathology, consistent with prior research. While total tau levels were elevated, there were no major differences in detergent-based soluble or insoluble isolations, compared to controls. Additionally, tau protein levels were increased compared to controls at synapses, a critical site of neurodegeneration.

Ongoing work will expand these findings to track changes across disease stages, providing unprecedented, large-scale protein stability analysis from early to late stages of tau pathology. This may uncover novel therapeutic targets to prevent or reverse the effects of tauopathies like FTD-tau. By elucidating the molecular underpinnings of tau pathology, my research has the potential to guide the development of more effective treatments for devastating neurodegenerative diseases.

Lay Language: My project seeks to understand how certain dementias develop and worsen over time. Tauopathies are a type of neurodegenerative disease in which the protein tau misfolds and aggregates into “tangles.” These tangles cause synapse loss, leading to symptoms including dementia, personality changes, and movement disorders. My project uses a mouse model of FTD-tau pathology and the powerful technology mass spectrometry (MS). I can measure thousands of proteins to see how they change as the disease progresses. To capture the complexities of the disease, I separate specific parts of brain cells from different brain regions and at distinct stages of disease. This allows me to identify which proteins are disrupted, where they originate, and when they are disturbed. This will clarify how tau pathology leads to neurodegeneration. Ultimately, my research will provide crucial insight into how tau-related diseases develop and may reveal new targets for treatments for these diseases.

Poster 39

Primary Progressive Aphasia Research Program at the Mesulam Institute for Cognitive Neurology and Alzheimer's Disease

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Primary progressive aphasia (PPA) is a neurodegenerative syndrome characterized by a progressive loss of language function. PPA has a low prevalence in clinical practice compared to Alzheimer's dementia. The Mesulam Institute for Cognitive Neurology and Alzheimer's Disease seeks to advance PPA research through a collaborative program aimed at studying, educating, and improving treatment for individuals living with PPA and their families.

Over the past decade, more than 250 participants from 39 US states, Canada, Singapore, and Spain have enrolled in PPA studies at the Mesulam Institute. Participants in the observational PPA Program visit Chicago every 2 years to complete neuropsychological assessments that precisely measure language, memory, and cognition. Additionally, participants undergo multiple brain imaging examinations with MRI and PET scanners in our state-of-the-art imaging facilities. Researchers combine neuropsychological testing with these advanced neuroimaging techniques to better understand the underlying mechanisms of language decline in the PPA brain. Additionally, functional imaging allows for the production of single-subject level functional maps of language networks. Most Mesulam Institute PPA research participants also agree to take part in our brain donation program to allow for further scientific investigation of the neuropathologic causes of the illness.

Some participants also take part in the Mesulam Institute's support groups, clinical trials, language treatment studies, and/or other educational research programs, which are tailored to the needs of people living with PPA. These life-enrichment interventions use innovative technology to improve access and the quality of specialized care.

Collectively, these studies allow us to improve the diagnosis, prognosis, and quality of life for individuals living with PPA, as well as understand the biological basis of language in the brain.

Funding from the National Institutes of Health, Illinois Department of Public Health, Run4Papa campaign, Association for Frontotemporal Degeneration, and generous personal donations have enabled the Mesulam Institute to research novel diagnostic and therapeutic initiatives in PPA. Through its multidisciplinary approach to both research and patient care, Northwestern University's Mesulam Institute remains one of the top referral centers in the world for PPA. We are grateful for the time and dedication of our research participants.

Poster 39 (continued)

Lay Language: Primary progressive aphasia (PPA) is a brain disease that slowly worsens a person's ability to speak, read, and understand language. Unlike more common memory disorders such as Alzheimer's disease, PPA mainly affects language rather than memory.

At Northwestern University's Mesulam Institute in Chicago, researchers have spent many years studying PPA with the help of more than 250 participants from across the United States and other countries. Every two years, participants complete language and memory assessments and undergo advanced brain scans. This information helps researchers better understand how language changes over time and what may be driving these changes.

In addition to research, the Institute provides support groups, language treatment studies, and clinical trials aimed at improving daily life for people living with PPA. Supported by government funding and generous donors, the Mesulam Institute is a leading center for PPA care and research, made possible by the dedication of its participants.

Poster 40

Neuroscience

Structural Diversity of Amyloid Aggregates Across Mouse Models and Human Brain Tissue Revealed by Vibrational Imaging

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Amyloid aggregation is a central hallmark of neurodegenerative diseases, yet increasing evidence indicates that amyloid assemblies are structurally heterogeneous. However, a critical gap remains in understanding how structural variability of amyloid relates to biological responses and which experimental mouse models best reflect the structural features observed in human disease. We hypothesized that commonly used transgenic mouse models capture only part of the structural spectrum of amyloid present in human Alzheimer's disease. The key research question was therefore which mouse models reproduce structural characteristics most similar to those found in human brain tissue.

To address this, we used sub-diffraction optical photothermal infrared (O-PTIR) spectroscopy to map amyloid secondary structure directly in brain sections. This label-free vibrational imaging approach enables detection of β-sheet-rich aggregates with spatial resolution sufficient to resolve structural heterogeneity within individual plaques.

We analyzed amyloid deposits from several transgenic mouse models with different pathological backgrounds and compared their spectroscopic signatures with those obtained from human Alzheimer's disease brain tissue. The results show that amyloid aggregates in mouse models display distinct structural signatures that differ between models and only partially overlap with those observed in human plaques. Variations in β-sheet organization and spectral heterogeneity were detected both between plaques and within individual deposits.

Our findings demonstrate that individual mouse models reproduce only subsets of the structural diversity observed in human amyloid pathology. Establishing direct links between amyloid structure and biological context is therefore essential for interpreting disease mechanisms and for selecting experimental models that better reflect human pathology. Vibrational spectroscopic imaging provides a platform for systematic cross-species comparison of pathological protein structures.

Lay Language: Some proteins can build up in the brain and damage it, causing memory problems such as in Alzheimer's disease. These build-ups are not all the same–they vary in structure, which makes the disease harder to treat. How to remove these deposits is still not fully understood.

Scientists often use transgenic mouse models to study specific diseases, such as Alzheimer's, but the models are only useful if they reflect what happens in humans. We hypothesized that common mouse models capture only part of the diversity seen in human amyloid. To test this, we used a high-resolution imaging method that allows us to see amyloid directly in brain tissue without adding labels or removing it, so we can study it in its natural environment. We compared several mouse models with human Alzheimer's brain tissue and found that amyloid structures differ between models and only partly match those in humans. This shows that each mouse model captures only part of the disease. Understanding these limits is important when choosing models and interpreting results, even though mouse models remain essential for research.

Poster 41

Cerebral Amyloid Burden Mediates the Pathway of Enlarged Perivascular Spaces to Cognition Decline

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Background: Enlarged perivascular spaces (ePVS) are fluid-filled cavities surrounding deep penetrating blood vessels in the white matter. Recent evidence indicates that ePVS may indicate glymphatic dysfunction and lead to amyloid plaque formation1. Although associations among ePVS diffusivity metrics, amyloid beta (Aß), and cognition have been reported in recent studies2,3, there are few studies addressing this pathway with anatomical MRI derived ePVS metrics and the Montreal Cognitive Assessment (MoCA). This work aims to explore mediation pathways linking ePVS, PET-Aß, and MoCA.

Methods:

- - PET-Aß, MRI images, and MoCA scores were obtained from the USC ADRC DVR database.
- - Anatomical segmentations were obtained from SynthSeg4. The ePVS regions of interest (ROIs) included (1) whole brain (total white matter), (2) Basal Ganglia (BG), and (3) Centrum Semiovale (CSO). PET-Aß was evaluated in 5 ROIs, including (1) anterior + posterior cingulate cortex, (2) frontal lobe, (3) lateral parietal cortex, (4) lateral temporal cortex, and (5) global.
- - EPVS was segmented with mcPVS-Net5 from MPRAGE images. The extracted ePVS metrics included volume, count, average length, average diameter, and average cross area.
- - Casual mediation analysis (CMA) was performed on 2 models. The evaluated pathways were from ePVS to MoCA with PET-Aß as the mediator. In model 1, Aß positivity was implemented as a moderator between ePVS and PET-Aß. In model 2, the Aß positivity was placed between PET-Aß and MoCA.

Results: Both models had statistically significant indirect pathways in the Aß+ group. There were no significant indirect pathways in the Aß- group. The indirect pathway effect sizes of model 2 were much greater than in model 1 (21-28% vs. 6-8% respectively). EPVS volume, count, and cross-area were the only metrics showing significant indirect pathways. In model 2, whole brain count and volume were both mediated by lateral temporal cortex PET-Aß. The CSO ePVS count and cross-area were both significantly mediated by PET-Aß in all PET-Aß ROIs.

Conclusion: Our result is the first quantitative evidence supporting the existence of a CSO ePVS-> PET-Aß-> MoCA pathway in the Aß+ group. CSO ePVS count showed the highest indirect effect sizes. This pathway is only present in the Aß+ cohort, hinting at possible compensatory and subsequent overburdened states for amyloid deposition based cognitive decline.

Lay Language: Enlarged perivascular spaces (ePVS) are fluid-filled spaces in the brain along the perforating arteries that show up in MRI images. EPVS are hypothesized as being a sign of impaired ability in the brain to clear neurotoxins. The accumulation of toxic proteins like amyloid beta is a major driver of Alzheimer's disease. This study provides the first quantitative evidence of a domino effect where these ePVS lead to amyloid beta buildup, and eventually to a decline in memory and thinking skills. We found that the number of ePVS in an area of the brain (centrum semiovale) accounted for up to 28% of the cognitive decline in patients with high amyloid beta levels. These spaces could serve as an early warning sign to identify at-risk individuals. In addition, this work provides a better understanding of how Alzheimer's disease progresses, which could pave the way for new treatment approaches.

Poster 42

Neuroscience

Northwestern University Alzheimer's Disease Research Center (NUADRC) Clinical Core

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Mesulam Institute for Cognitive Neurology and Alzheimer's Disease; Northwestern University

The Northwestern University Alzheimer's Disease Research Center (NUADRC) is entering its 31st year of funding from the National Institute on Aging (NIA). A national multi-site study, the NUADRC is one of 35 ADRCs across the country, all of which have a Clinical Core component. As an observational study, the main purpose of the Clinical Core is to establish a cohort of individuals across the cognitive aging spectrum to help support clinical and basic research on memory and aging. The Clinical Core follows research participants annually and collects, stores, and disseminates clinical data, brain imaging scans, and biological samples. The information collected by each ADRC (the Uniform Data Set, UDS) are contributed to the National Alzheimer Coordinating Center (NACC) to be available for largescale studies.

The Clinical Core recruits individuals with different forms of cognitive impairment and dementia (e.g. memory dementia, primary progressive aphasia, behavioral variant frontotemporal dementia, Lewy body dementia) and other disorders caused by neurodegenerative brain diseases such as Alzheimer's disease, Picks disease, and other forms of frontotemporal degeneration. Participants and designated study partners complete annual assessments (demographic information, health and family history, and neuropsychological tests). If eligible, participants also undergo MRI and PET scans so researchers can investigate brain structure, connectivity, and amyloid and tau proteins. Blood is also collected to support studies of disease process and biomarkers. Participants are asked to consider brain donation which provides researchers with a valuable resource for understanding brain changes with aging.

Since 1996, the NUADRC Clinical Core has enrolled more than 2,498 participants; 455 are active, with 26% of those followed for 10 or more years. Brain donations from our research participants increase our understanding of cognitive and brain aging. Researchers compare brains from healthy individuals to those with cognitive impairment and link disease-related brain changes with cognitive symptoms observed during life. Of our current active participants, 86% are committed to brain donation for our research, and another 14% are considering donation. Since our study began in 1996, our brain bank has received over 1,232 donations.

The Clinical Core is a valuable resource for researchers studying brain and cognitive aging. For many, participation is a lifelong, meaningful commitment and promotes national and international research efforts.

Lay Language: The Clinical Core is a longitudinal, observational study that collects information from research participants yearly, including demographic information, health and family history, neuropsychological tests, brain imaging, and blood biospecimens. Many commit to brain donation at the time of death to aid research efforts. Our research cohort includes participants across the cognitive aging spectrum from healthy to disease. Information collected from this study is shared across different collaborators associated with the National Alzheimer Coordinating Center.

Poster 43

The Northwestern University SuperAging Program (NUSAP)

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It is commonly assumed that memory and thinking abilities always decline with advancing age (e.g., so-called "normal aging"). The Northwestern University SuperAging Program (NUSAP) at the Mesulam Institute has shown that some individuals are able to maintain high levels of memory performance over age 80. Over the last 25+ years, NUSAP has followed a group of these individuals with exceptional episodic memory ability for age. The NUSAP cohort is thoroughly studied to identify factors associated with avoidance of age-related cognitive decline and memory loss.

NU SuperAgers are defined by being able to remember at least 9 of 15 words on a memory test 30 minutes after learning them; this score is considered "average" for 50- to 60-year-olds. NUSAP also enrolls and follows individuals 80+ years with memory scores that are average for their own age (i.e., Normal Agers). We have enrolled over 300 participants into SuperAging research over the history of NUSAP, 116 of whom continue to be actively followed. Participants visit our Institute every year to complete cognitive testing, blood collection, and questionnaires investigating emotional function, functional status, family history, and daily health habits. Many participants also undergo structural and functional brain imaging scans (e.g., MRI, PET). All participants are invited to take part in our Institute's brain donation program, providing researchers the opportunity to further investigate the biological mechanisms underlying SuperAging. To date, 87 NUSAP participants have donated their brains.

Findings suggest that the brains of SuperAgers resist the cortical atrophy that is typically associated with normal aging. They show significantly less of the proteins normally associated with Alzheimer's disease (i.e., amyloid, tau) in the entorhinal and anterior cingulate cortices compared to Normal Agers and those with cognitive decline. Their brains display a higher density of von Economo neurons, a specialized type of brain cell important for social intelligence, in the anterior cingulate cortex. A recent study found that SuperAgers generate significantly more new neurons in the hippocampus than Normal Agers and even much younger individuals, which suggests a "resilience signature" in SuperAger brains. Emerging findings highlight the heterogeneity within SuperAgers and show the importance of investigating both brain resistance (i.e., avoidance of pathology) and brain resilience (e.g., preserved cognition despite accumulating brain pathology) in this special cohort.

Lay Language: The Northwestern University SuperAging Program (NUSAP) studies individuals aged 80 or older whose memory is at least as sharp as people in their 50 and 60s and compares them with 80+ year olds whose memory scores are normal for their age. Over the past 20+ years, NUSAP has discovered a number of exciting facts about SuperAgers, including that there is a part of the brain related to social behaviors that is thicker than in Normal Agers, has fewer molecular markers of Alzheimer's disease, and has more of a certain type of neuron that supports social intelligence compared to their peers with normal-for-age memory. SuperAgers also have more new neurons in the memory center of the brain than Normal Agers. SuperAgers add a critical source of information about brain aging that does not follow the "normal aging" pattern.

Poster 44

Domain-Specific Transcriptomic Networks Underlying Neuropsychiatric symptoms in Alzheimer's Disease

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Background: Neuropsychiatric symptom (NPS), including apathy, affective symptoms, agitation, and psychosis, are common in Alzheimer's disease (AD) and contribute substantially to functional decline and caregiver burden. However, the mechanisms underlying these symptoms remain poorly understood. Our previous work suggested transcriptomic correlates of specific NPS domains within anterior cingulate cortex. However, whether similar changes also exist in the nucleus accumbens (NAc), a brain region involved in motivation, reward processing and behavioral regulation, has not been examined.

Methods: Bulk RNA sequencing from postmortem NAc tissue of 60 AD patients with NPS were analyzed. Differential expression and gene set enrichment analyses were conducted. Weighted gene co-expression network analysis (WGCNA) was used to identify transcriptional modules, and module-trait correlations were examined to determine associations with behavioral symptoms. Competitive domain modeling evaluated whether modules were uniquely associated with specific domains when symptoms were modeled simultaneously. Additional models incorporated estimated cell-type proportions to assess potential effects of cellular composition. Functional enrichment analyses were conducted using Gene Ontology biological process pathways.

Results: NPS domains are primarily associated with coordinated pathway-level transcriptional changes rather than large numbers of strongly differentially expressed genes. Co-expression network analysis identified 22 modules (ranging from 80–762 genes) associated with behavioral domains. Apathy was associated with modules enriched for immune and inflammatory pathways, including antigen presentation and complement signaling, with PIK3AP1, HCK, and C1QC as highly connected genes, as well as a separate module enriched for oxidative phosphorylation. Agitation was associated with neuronal modules enriched for synaptic signaling and membrane potential regulation, including genes such as MEF2C, GABRA3, HTR2A, and AMPH. Competitive modeling indicated that agitation explained the largest proportion of variance in neuronal modules ($\beta \approx -0.33$, LMG up to 0.20), whereas apathy showed the strongest associations with immune-related modules. Adjustment for estimated microglial abundance attenuated the apathy-associated immune module, suggesting that microglial activity contributes this signal. Psychosis-associated modules were detected but were fewer and less consistent, and Affective symptoms showed relatively modest transcriptional associations ($\beta \approx 0.09$–0.15).

Conclusion: Specific NPS domain in AD are associated with distinct transcriptional programs within the NAc. Immune and microglial-related pathways were most strongly linked to apathy, whereas neuronal and synaptic signaling pathways were associated with agitation. These transcriptional signatures may provide molecular targets for developing NPS-specific therapeutics.

Lay Language: Neuropsychiatric symptoms (NPS) such as apathy, mood changes, agitation, and psychosis are common in people with Alzheimer's disease (AD) and can affect quality of life for patients and caregivers, and accelerated disease progression. However, the biological causes of these symptoms are not well understood. In this study, we analyzed gene activity in brain region called nucleus accumbens, which plays an important role in motivation, reward, and behavior. Using brain tissue from 60 individuals of AD with NPS, we identified groups of genes that were linked to each NPS. For example, apathy was mainly associated with immune and inflammatory activity in the brain, including microglia, the brain's immune cells. In contrast, agitation was linked to genes involved in communication between brain cells. Psychosis, anxiety, and depression showed weaker gene signals at this brain region. These findings suggest that different NPS in AD may arise from distinct gene expression in the brain.

Poster 45

Neuroscience

Spatially Resolved Cell-Type-Specific Molecular Drivers of Anterior Temporal Pole Neuropathology in Frontotemporal Lobar Degeneration with TDP-43 Type C

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Background: Frontotemporal lobar degeneration with TDP-43 type C pathology (TDP-C) is a distinct FTLD subtype marked by pronounced unilateral anterior temporal lobe (ATL) atrophy and the accumulation of phosphorylated TDP-43 (pTDP-43) and annexin A11 (ANXA11) in long, tortuous dystrophic neurites within superficial cortical layers (II/III). Clinically, right ATL involvement presents with behavioral variant FTD, prosopagnosia, and social deficits, whereas left ATL involvement results in semantic variant primary progressive aphasia (svPPA). The mechanisms underlying selective ATL vulnerability and hemispheric asymmetry in TDP-C remain poorly understood.

Methods: Formalin-fixed paraffin-embedded tissue from paired left and right ATL, inferior frontal gyrus (IFG), and middle frontal gyrus (MFG) was obtained from six pathologically confirmed TDP-C svPPA cases and five non-neurological disease controls. Immunofluorescence staining for pTDP-43, ANXA11, IBA1, and MAP2 was performed to characterize pathology. Spatial transcriptomics (ST) was conducted using the 10X Genomics Visium platform. Single-cell RNA sequencing data from the ROSMAP cohort was used to deconvolve ST profiles, enabling cell-type-resolved transcriptomic analysis.

Results: The left ATL demonstrated the greatest transcriptomic dysregulation, encompassing nearly all differentially expressed genes (DEGs) observed in the right ATL. Minimal hemispheric asymmetry in NND controls suggests disease-specific left ATL vulnerability rather than inherent hemispheric differences. Compared to NND controls, the left ATL in TDP-C showed the strongest dysregulation in arterial endothelial cells, followed by astrocyte precursors, smooth muscle cells, and microglia. Within TDP-C, interneuron dysregulation in the left ATL most strongly distinguished the ATL from frontal regions. Transcriptomic changes decreased with distance from the ATL (IFG > MFG), consistent with a spatial disease gradient. In all regions except the left ATL, transcriptomic alterations correlated with pTDP-43/ANXA11 burden in layers II/III. Functional enrichment analyses highlighted neurovascular dysfunction and innate immune activation.

Conclusion: Dysregulation of ATL-specific interneurons that preferentially project to layers II/III may underlie both the characteristic pTDP-43-ANXA11 pathology and the selective vulnerability of the ATL in TDP-C. Distinct transcriptomic features of the left ATL likely contribute to its predisposition to svPPA. Widespread dysregulation across neurovascular cell types suggests blood-brain barrier impairment as a potential initiating factor, while concurrent innate immune activation implicates neuroinflammation in disease onset and propagation.

Lay Language: TDP-C is a rare brain disease that damages the language and speech centers of the brain, causing primary progressive aphasia. It is linked to abnormal protein buildup, but we do not yet know why it tends to affect one side of the brain more than the other or how it spreads from there.

We studied donated brain tissue from people with TDP-C and from people without brain disease. Using methods that measure where genes are more or less active, we found the largest changes in a key left-sided language area, with smaller changes in nearby regions, suggesting spread from an early "hot spot." The strongest changes involved blood-vessel support cells, inflammation-related cells, and specific nerve cells located near the protein buildup. These results highlight early problems with blood-brain barrier function and inflammation as possible disease drivers and treatment targets.

Poster 46

Clinical Improvisatory Music for Alzheimer's Disease Anxiety and Caregivers (CIMAC): Preliminary Behavioral and Network Modulation Findings from Ongoing Trials

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Background: Anxiety affects approximately 40% of individuals with Alzheimer's disease, diminishing quality of life and increasing caregiver stress. Anxiety medications can have negative side effects, prompting exploration of non-pharmacological interventions like music. Clinically Designed Improvisatory Music (CDIM) has previously shown efficacy in decreasing anxiety in healthy individuals. This study explores the feasibility of CDIM in reducing anxiety in individuals with Alzheimer's Disease (AD-A), decreasing caregiver burden, and modulating four brain networks crucial for emotional processing.

Methods: Fifteen individuals with AD-A and 12 caregivers participated in a delayed enrollment study with two pre- and one post-CDIM evaluation. CDIM involved eight 30-minute sessions of slow, meandering melodic improvisations delivered in 2-minute segments by a certified clinical music practitioner. Anxiety was assessed using the Rating Anxiety in Dementia (RAID), and caregiver burden was assessed using Neuropsychiatric Inventory – Caregiver Distress (NPI-CD) and Zarit Burden Interview (ZBI). Vital signs (blood pressure, respiratory rate, and heart rate) were recorded. Changes between pre- and post-CDIM phases were compared using the Mann-Whitney U-test. Functional MRI data were analyzed for connectivity changes in 4 brain networks: Default Mode Network (DMN), Salience Network (SN), Reward Network (RN), and Auditory Limbic Network (ALN) using the CONN toolbox.

Results: Pre- and post-CDIM comparisons using Mann-Whitney U test revealed RAID ($p=0.02$) and ZBI ($p=0.01$) reductions. Caregivers had a reduction in the systolic blood pressure (a trend in AD-A), heart rate, and respiratory rate (only caregivers). AD-A fMRI results revealed increased connectivity in SN, ALN, RN. Negative correlation between right ALN connectivity and heart rate was significant, and ALN connectivity and RAID trended towards significance. Decreased connectivity in anterior DMN positively correlated with RAID and trended towards a positive correlation with heart rate. Caregivers showed increased connectivity in SN, ALN, and RN, which negatively correlated with respiratory rate. Increased connectivity in ALN negatively correlated with ZBI and NPI-CD.

Conclusion: Our findings indicate CDIM appears feasible for reducing anxiety and caregiver burden, with symptomatic, physiological, and neural effects. In the AD-A group, autonomic dysfunction or cholinesterase inhibitors may interfere with evaluation of physiological measures. We believe CDIM transitions the autonomic and emotional networks to a calmer state through entrainment. fMRI findings suggest CDIM may modulate abnormal network connectivity, reducing anxiety. Recruitment and fMRI data collection are ongoing.

Lay Language: This ongoing study investigates Clinically Designed Improvisatory Music (CDIM) as a non-pharmacological intervention to induce calmness and relaxation in participants with Alzheimer's disease (AD) and caregivers who struggle with anxiety. Participants receive 30 minutes of calming viola music twice weekly for four weeks, both in person and virtually. We use standardized questionnaires and brain scans (fMRI) to measure anxiety and brain activity before and after the CDIM sessions. Fifteen AD patients and 12 caregivers completed the program. Initial results show an average decrease in reported anxiety and burden after CDIM. Brain scans reveal changes in brain areas linked to emotions, suggesting the music helps modulate these areas and promotes calmness. Caregivers and AD-A participants also experience lower blood pressure and heart rate, indicating relaxation. This suggests that CDIM is a promising non-pharmacological approach for reducing anxiety and improving well-being for both AD patients and their caregivers.

Poster 47

Graph theory analysis of network changes in Primary Progressive Aphasia due to underlying AD and TDP-43 Type C

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Introduction: Primary Progressive Aphasia (PPA) is a neurodegenerative syndrome characterized by progressive loss of language abilities due to disruption of left hemisphere language networks. This can be caused by different underlying diseases, including Alzheimer's Disease (AD) or TDP-43 Type C proteinopathy (TDP-C). Graph theory provides methods to study the functional organization of brain networks and how they change. In this study, we used these methods to examine how language-related brain networks are disrupted in PPA caused by AD versus TDP-C.

Methods: Resting-state fMRI data were analyzed from participants with PPA due to AD (n = 36), PPA due to TDP-C (n = 14), and healthy controls (n = 31). Brain connectivity was measured across 360 cortical regions and grouped into established functional networks. Graph-based measures were used to evaluate two aspects of brain organization: global efficiency, which reflects how easily information can be exchanged across the whole brain, and network segregation, which reflects how strongly regions within a network communicate with each other compared with regions outside the network. Segregation was measured separately for the language network and a control network (dorsal attention) in each hemisphere.

Group differences in global efficiency were evaluated using age-adjusted analysis of covariance. Network segregation was analyzed using linear mixed-effects models with fixed effects of group, hemisphere, and their interaction and corrected for age, and multiple comparisons were corrected with false discovery rate. Exploratory analyses examined relationships between network measures and clinical variables, including language performance, regional atrophy, and disease duration.

Results: Global efficiency was reduced in PPA-AD relative to controls, indicating reduced efficiency of whole-brain communication. No such reduction was observed in TDP-C. For language-network segregation, controls and AD showed greater left- than right-hemisphere segregation, consistent with the typical left-sided dominance of language networks. This pattern was not observed in the TDP-C group, suggesting reduced organization and specialization of left language network. This reduced left-hemisphere segregation was associated with longer disease duration in TDP-C.

Conclusion: PPA associated with underlying AD or TDP-C shows different patterns of brain network disruption. While PPA-AD displays more widespread network disruption, PPA-TDP-C shows selective loss of left-hemisphere language-network segregation. This pattern is consistent with the relatively focal language impairment and atrophy patterns that are typical of TDP-C.

Lay Language: Primary progressive aphasia (PPA) is a condition that gradually affects a person's ability to use and understand language. Different diseases can cause PPA, including Alzheimer's disease or the protein disorder TDP-43 type C. In this study, we examined brain scans from people with PPA to see how communication between different brain regions changes depending on the underlying disease. We found that when PPA is caused by Alzheimer's disease, communication across the brain becomes less efficient overall. In contrast, when PPA is caused by TDP-C, the main change is a loss of healthy organization of the language network. These results suggest that different diseases disrupt brain networks in different ways, helping explain why people with PPA can show different patterns of language and cognitive changes.

Poster 48

Neuroscience

Uncovering Interactions Between Vascular Components and Alzheimer Disease

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Background: Tau is a microtubule-associated protein that is a main hallmark of Alzheimer's disease and forms insoluble filaments that accumulate as neurofibrillary tangles in the diseased brain. ACE is a confirmed risk gene for Alzheimer's disease and known to impact the vascular system, but the mechanisms are incompletely understood. Our study aims to understand interactions between ACE1 and tau proteins and how they may contribute to neurodegeneration and vascular dysfunction.

Methods: We generated a mouse model expressing the high risk ACE1 mutation (R1284Q) and a well-characterized pathogenic tau mutation PS19. We used Morris Water Maze behavioral testing, immunohistochemistry, and single-cell RNA sequencing to assess cognition, neuropathology, vascular changes and transcriptomic alterations.

Results: We found that ACE1 R1284Q does not worsen hippocampal atrophy or tau levels in combination with PS19 genetics, surprisingly, ACE1 R1284Q improves cognitive performance, reduces gliosis, reduces tau-associated vascular dilation, and shows endothelial/pericyte transcriptional changes related to RAS signaling and BBB disruption.

Conclusions: While ACE1 R1284Q and PS19 genetic tau mutations are independently deleterious for cognitive processes and neurological function, when interacting together ACE1 R1284Q modifies tau mediated vascular and inflammatory responses in several beneficial ways. The ability for ACE RAS signaling and tauopathy to interact and affect these various brain functions supports the implications that vascular contributions are highly intertwined with Alzheimer's disease and other dementias. Our results show important insights into the brain RAS and its interaction with tauopathy in regard to BBB homeostasis, hippocampal health, cognitive impairment, and blood vessel organization.

Lay Language: There is rising interest in the Alzheimer's field for the vascular system and how it interacts to contribute to Alzheimer's disease. Tau is a commonly known protein involved in neurodegeneration and a hallmark of Alzheimer's disease. We crossed mice with a well-known tau mutation and our own mutation for a gene called ACE1 which is highly impactful in the vascular system and known to be linked to Alzheimer's disease. We assessed the resulting mice for memory, brain structure, and brain chemistry and found that these mutations act together in surprising ways such as improving cognitive performance and reducing signs of brain inflammation compared to the mice with tau mutation alone. Through these results we support the idea that Alzheimer's disease has a strong vascular component and hopefully opens the way to new paths of research.

Poster 49

Neuroscience

Sex-Specific Hypothalamic Pathology in Post-Mortem Tissue of Alzheimer's Disease Patients

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Aims: The hypothalamus is integral to regulating numerous physiological processes that are disrupted in Alzheimer's disease (AD). Yet despite its homeostatic importance, the hypothalamus remains critically understudied in AD. Additionally, nearly two thirds of AD cases are in females. However, mechanisms underlying this sex disparity remain unknown. We aim to investigate how hypothalamic pathology may contribute to both neuroinflammation and underlying sex differences in AD.

Methods: We performed single cell fixed RNA profiling (scFRP) on a cohort of post-mortem human hypothalamus tissues of from 64 AD donors (37% male, 63% female) with varying degrees of pathology and 21 controls (33% male, 66% female) without neurological disease. We also performed spatial transcriptomics using the Visium CytAssist protocol on matched hypothalamus FFPE tissue slides from 50 of the same donors in the scFRP dataset.

Results: We identify unique neuronal transcriptomic changes in females with dementia that are not present in males with dementia. Furthermore, we observe unique glial transcriptomic changes in males with high levels of AD pathology. We utilize spatial transcriptomics to locate transcriptional changes in the vicinity of hypothalamic AD pathology. Integrating these two modalities allows us to study transcriptomic changes and cell-cell interactions that associate with AD pathology in the hypothalamus of both sexes.

Conclusions: Our findings show a differential effect of AD that is sex dependent. More specifically, our findings elucidate putative female-specific neuronal dysregulation in individuals with dementia and male-specific pathology-induced glial dysregulation. Ultimately, this research enhances our understanding of how hypothalamic pathobiology may exacerbate neuroinflammation and potentially influence sex disparities in AD.

Lay Language: Alzheimer's disease (AD) is typically defined by the damage of brain cells, which leads to irreversible cognitive decline and memory loss. Importantly, many AD patients also experience non-cognitive symptoms that include disruptions in sleep, appetite, and hormonal signaling. Nearly two-thirds of all AD cases are in females, but the underlying reason for this sex difference remains unknown. The hypothalamus, a small region located deep within the brain, is responsible for maintaining many of the disrupted non-cognitive processes and produces sex-specific hormones. Currently, the hypothalamus is understudied in AD. As such, we aim to uncover changes in the hypothalamus in the AD brain. Furthermore, we investigate this deep-brain hub as a possible entry point for immune cells. Together, these findings work towards a mechanistic understanding of underlying sex differences in AD, and may help find treatments for AD.

Poster 50

Progress on Biobanking and Patient-Reported Outcomes in Anti-Amyloid Therapy at Northwestern

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Background: Anti-amyloid therapies (AAT) are a major advancement in Alzheimer's disease (AD) treatment. Amyloid-related imaging abnormalities (ARIA) is a common side-effect that has limited uptake of this new therapy due to safety and logistical concerns. While the cause of this novel condition is unknown, several groups speculate a mechanistic relationship with Cerebral Amyloid Angiopathy (CAA) and CAA-related inflammation (CAA-ri). Here, we report our progress building a biorepository with cerebrospinal fluid (CSF) and blood samples collected from patients with CAA, CAA-ri, and AD who are undergoing AAT. We are administering questionnaires to collect patient-reported outcomes (PROs) on their AAT satisfaction and burden levels.

Method: We are including patients on AAT, patients with CAA, and CAA-ri. Participants can elect to donate CSF from clinical lumbar punctures and blood on a research basis. AAT patients undergo baseline and repeat surveillance MRIs between infusions for ARIA detection. PROs assess AAT treatment satisfaction and perceived burden of infusions and MRI monitoring at each visit. Clinical Dementia Rating (CDR) and Montreal Cognitive Assessment (MoCA) scores are extracted from charts and study partners complete the Functional Activities Questionnaire (FAQ) and Neuropsychiatric Inventory Questionnaire (NPI-Q).

Result: We have enrolled 33 participants (n=26 AAT, n=1 CAA, n=5 CAA-ri). Of the 26 AAT participants enrolled, 4 have had ARIA. Of the ARIA cases, three participants were APOE ε3/ε4 carriers and one was APOE ε2/ε4. 70 blood samples and 5 CSF samples have been collected for eventual analysis. Preliminary PRO data from 41 assessments across 26 AAT patients demonstrated high satisfaction with infusions (38/41, 92.7%) and minimal infusion burden (38/41, 92.7% reporting no burden). While reported MRI surveillance burden was greater than infusions, the findings are not statistically significant.

Conclusion: We have established a biorepository for ARIA biomarker discovery. There is a trend suggesting MRI surveillance may be more burdensome for patients than infusions, but this was not significant. This trend highlights the importance of blood biomarker discovery in ARIA. Next steps include proteomic, transcriptomic, and further PRO analysis. We hope these advancements can improve the safe monitoring of AATs and advance understanding of potential immune mechanisms in ARIA and CAA-ri.

Lay Language: Anti-amyloid therapy (ATT) can slow cognitive decline in mild Alzheimer's disease (AD). However, this therapy carries a risk of side effects called ARIA (amyloid related imaging abnormalities), characterized by brain swelling and bleeding. In severe cases, ARIA can be deadly. The cause of ARIA is unknown, but our group suspects off-target effects on vascular amyloid. Because of this, we are studying outcomes in AD on AAT and individuals with vascular amyloid. Alongside outcome measurements, we are collecting blood and spinal fluid samples to search for ARIA mechanisms and diagnostic biomarkers. Recruitment and biospecimen testing is in early stages. It is too early to make firm conclusions about cognitive outcomes or ARIA rates. So far, patients report being satisfied with their infusions, but find frequent brain scan monitoring burdensome. We hope this research will help us elucidate the impacts of AAT, mechanism of ARIA, and improve ATT.

Poster 51

Machine Learning-Derived Structural Neuroimaging Signatures Discriminate Neuropathologies in Agrammatic Primary Progressive Aphasia

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Background: Agrammatic/non-fluent primary progressive aphasia (agPPA) is a clinical dementia syndrome characterized by morpho-syntactic impairment and motor speech abnormalities. AgPPA can arise from distinct underlying neuropathologies, most commonly tauopathy of four-repeat (4R-tau) or three-repeat (3R-tau; Pick's disease) subtypes, and Alzheimer's disease (AD). Identifying in vivo markers that distinguish these neuropathologic substrates remains a major challenge. Machine-learning (ML) approaches applied to neuroimaging data offer a principled framework for disentangling shared versus pathology-specific features of agPPA. The primary aim of this study was to identify structural neuroimaging features that best distinguish the neuropathologic causes of agPPA using an interpretable ML framework.

Methods: Longitudinal structural MRI data were derived from a cohort including 58 control scans and autopsy-confirmed agPPA patients: 18 with 4R-tau (30 scans), 10 with 3R-tau (16 scans), and 15 with AD (24 scans). Neuroimaging features included cortical volumes from the Schaefer 400 atlas, subcortical volumes from the Tian atlas, and brainstem structures derived from FreeSurfer. Regularized classification models were trained to discriminate each pathology from cognitively normal controls and from one another using repeated cross-validation, permutation testing, and bootstrap-based feature stability analyses.

Results: The models demonstrated strong classification performance for all pathology versus control comparisons (all AUCs > 0.90) and for direct pathology-to-pathology discrimination (all AUCs > 0.86). For 3R-tau, the most discriminative regions included the frontal operculum and temporopolar regions, whereas for 4R-tau, discriminative features were concentrated in putamen and thalamus. AD-related agPPA was distinguished by aspects of the posterior superior temporal gyrus.

Conclusions: Multivariate neuroimaging features effectively distinguish the underlying pathologies of agPPA. These findings suggest that while agPPA subtypes share a clinical phenotype, they are driven by distinct anatomical patterns and that automated MRI analysis offers a viable tool for predicting pathology in clinical settings.

Lay Language: Agrammatic primary progressive aphasia (agPPA) is a form of dementia that affects speech and grammar but can be caused by several different brain diseases. In this study, MRI scans analyzed using machine learning (a type of automated artificial intelligence) were able to distinguish the underlying disease causing agPPA by identifying distinct patterns of brain atrophy. These findings suggest that automated MRI analysis could help doctors better predict the specific disease driving language decline, even when patients show similar language symptoms.

Poster 52

Neuroscience

Associations of Carotid Pulse Wave Velocity and Damping Measured by a Rapid Oblique-Sagittal PC-MRI with Cognitive Function and Amyloid Burden

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Background: Contributions of cerebrovascular dysfunction in cognitive decline and Alzheimer's disease (AD) are well recognized1, while arterial stiffness plays a specific role in transmission of excessive pulsations into the downstream microvasculature and arterial wall impairment in AD pathogenesis2. This study used a fast MRI method to measure carotid stiffening by pulse wave velocity (PWV) and impaired damping of arterial pulsatility and their association with worse cognitive performance, greater dementia severity, and cortical amyloid-PET burden in elderly adults.

Methods: 68 Participants (mean age 72.3 ± 7.5 years) underwent a rapid single-slice oblique-sagittal phase-contrast MRI (OS PC-MRI)3 with retrospective cardiac gating to simultaneously acquire cardiac-induced blood flow waveforms along the common carotid artery (CCA) to the internal carotid artery (ICA). Carotid PWV (cPWV) along CCA-ICA using both muscular upstroke area method (PWV_musa) and time-to-foot method (PWV_ttf), pulsatility index (PI), and resistance index (RI) were calculated from multiple velocity waveforms acquired by OS PC-MRI to ensure high robustness. Damping factor (DFCCA-ICA) was also calculated by PICCA / PIICA, which quantified the damping of flow pulsatile energy along the cerebrovascular tree. Multiple linear regression models, correcting for age and sex, were used to assess associations of hemodynamic measures with global cognition (MoCA) and amyloid-PET SUVR (N = 34) from whole-brain and four brain regions, including anterior + posterior cingulate cortex, frontal lobe, lateral parietal cortex, and lateral temporal cortex. Group differences across subjects with CDR scores of 0, 0.5, and 1 or higher were assessed by one-way ANOVA.

Results: Higher cPWV was significantly associated with lower MoCA scores (PWV_musa: $\beta = -1.569$, $p = 0.029$; PWV_ttf: $\beta = -0.893$, $p = 0.018$). Both cPWV measures showed significantly positive associations with CDR scores ($p = 0.006$, 0.007). Lower DFCCA-ICA was associated with higher CDR scores ($p = 0.010$). PWV_musa was significantly associated with greater amyloid-PET SUVR in the anterior/posterior cingulate cortex ($\beta = 0.105$, $p = 0.042$), with positive trends in frontal and temporal regions.

Conclusion: Elevated cPWV was associated with worse cognition and higher cortical amyloid burden, especially in the anterior/posterior cingulate cortex. Reduced cerebrovascular pulsatility damping factor was associated with greater dementia severity. Together, these MRI-derived hemodynamic measures could be sensitive markers of cognitive impairment and be associated with amyloid pathology.

Refrence:

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2. Herzog, M. J. et al. Arterial stiffness and vascular aging: mechanisms, prevention, and therapy. Sig Transduct Target Ther 10, 282 (2025).

3. Pahlavian, S. H. et al. Assessment of Carotid Stiffness by measuring Carotid Pulse Wave Velocity using a Single-slice Oblique-sagittal Phase-Contrast MRI. Magn Reson Med 86, 442-455 (2021).

Lay Language: As people age, the carotid artery in the neck can become stiff and lose its flexibility. When this happens, each heartbeat sends stronger, less-controlled surges of blood energy into the brain's tiny vessels, instead of being gently cushioned. Over time, this can damage the vessel lining and trigger inflammation. This study advanced MRI to measure how fast blood waves travel through the arteries (a sign of stiffness) and how well the arteries can absorb and soften these surges. We found that people with stiffer arteries and weaker "shock-absorbing" ability performed worse on cognitive tests and showed more severe dementia, and also had more amyloid buildup in the brain, suggesting greater susceptibility to Alzheimer's disease. this disease. These findings suggest that natural ANXA11 expression may influence which brain regions are affected by TDP-C, opening new questions about its role in disease development and potential therapeutic targets.

Poster 53

Neuroscience

Epigenetic Signatures of Memory and Cognitive Resilience in SuperAgers and SuperAger-Like Mouse Models

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Background: Aging is the strongest risk factor for Alzheimer's disease (AD), yet some older adults known as SuperAgers (age≥80) maintain episodic memory comparable to individuals decades younger. Neuroimaging and neuropathological studies show preserved brain structure and reduced neurodegeneration in SuperAgers, but the molecular mechanisms underlying this resilience remain unclear. Progress is limited by the lack of experimental models that allow mechanistic testing of resilience pathways. Establishing a SuperAger-like animal model would enable investigation of molecular drivers of preserved memory and mechanisms of resilience to AD pathology.

Methods: To determine whether epigenetic regulation plays a role in memory and cognitive resilience, postmortem prefrontal cortex samples from SuperAgers (n=9), and age-matched normal elderly (n=10), were used to assess expression of key epigenetic regulatory genes. Quantitative PCR measured expression of CREBBP, HDAC1, HDAC2, DNMT1, DNMT3A, and DNMT3B. To establish a translational model of memory resilience, aged wild-type (n=32) and APP/PS1 mice (n=14) aged >24 months (equivalent age≥80 in human) underwent behavioral testing including Y-maze, novel object recognition, and social recognition tests. Composite Z-scores were calculated to stratify animals into impaired (percentile rank<30), intermediate, and Superager-like (percentile rank>70) groups followed by qPCR based expression analysis of the above mentioned genes in the cortex of these animals.

Results: Distinct expression patterns of epigenetic regulatory genes in SuperAgers compared with controls, including CREBBP, HDAC1, HDAC2, DNMT1, DNMT3A, and DNMT3B, and differential expression of these genes are associated with preserved cognitive status. For animal work, behavioral testing identified a subset of animals exhibiting preserved memory despite advanced age or amyloid pathology. Using composite Z-scores, 31% (n=10) of aged wild-type mice and 35% (n=5) of APP/PS1 mice were classified as SuperAger-like mouse models. These animals performed significantly better in all three selected memory tests. qPCR analysis found Dnmt3b and Crebbp as differentially expressed genes associated with preserved memory. These preliminary results support our hypothesis that epigenetic regulation may contribute to maintenance of memory function during aging. We are currently conducting DNA methylation analyses in human SuperAgers and animal models.

Conclusion: Our findings suggest epigenetic signatures are associated with preserved memory in SuperAgers and the identified mouse model provides a translational framework to study mechanisms of memory resilience and potential therapeutic targets for preventing age-related cognitive decline and neurodegeneration.

Lay Language: As people age, memory often declines, and aging is the biggest risk factor for Alzheimer's disease. However, some older adults, known as "SuperAgers," maintain memory abilities similar to younger people. Understanding what protects their brains from age-related decline could help prevent cognitive loss. In this study, we examined brain samples from SuperAgers and compared them with those from normal elderly. Our results suggest, several biological processes called epigenetic regulation involved in brain function behave differently in SuperAgers. To better understand these protective mechanisms, it is important to develop animal models that allow testing of how these processes influence memory. We therefore studied memory in very old mice using behavioral tests and identified animals that maintained strong memory despite aging or Alzheimer's related changes. These "SuperAger-like" mice provide an experimental model to study how the brain maintains memory during aging and may help guide strategies to prevent memory and cognitive decline.

Poster 54

Northwestern Alzheimer's Disease Research Center Neuroimaging Biomarker Core

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The Northwestern Alzheimer's Disease Research Center Neuroimaging Biomarker Core (IBC) at the Mesulam Institute for Cognitive Neurology and Alzheimer's Disease aims to enhance research activities on aging and dementia within and outside of Northwestern University. We seek to acquire multimodal data, enrich the projects of our collaborators, develop and apply quantitative and qualitative pipelines, train student researchers, and expand the boundaries of scientific knowledge. The IBC is responsible for acquiring imaging data and warehousing scans acquired through other studies at the Mesulam Institute. As such, the IBC is currently responsible for storing and organizing 1,751 MRI scans and 797 PET scans, which are available for viewing and collaboration through NURIPS (Northwestern University Research Image Processing System). Multimodal data collected from MR scans provide quantitative information on brain structure (MPRAGE), white matter properties (FLAIR), axonal pathways (diffusion MR), resting state hemodynamic fluctuations for establishing functional connectivity (rsfMRI), and cerebral blood flow (ASL). PET scans provide qualitative and quantitative measures of amyloid (Florbetaben PET) and tau (Flortaucipir PET) binding. The IBC has developed multiple pipelines to preprocess and postprocess structural, functional, and diffusion MRI, as well as PET imaging data. Standardized pipelines – including MRIQC, fMRIPrep, and FreeSurfer – are applied to assess scan quality and postprocess imaging data for downstream analysis. Customized analyses include TDI (Tract Density Imaging), which enhances white-matter visualization; ASL (Arterial Spin Labeling), which non-invasively quantifies cerebral blood flow; and PET Standardize Uptake Value ratio (SUVr), which quantifies uptake of a radiotracer in target brain regions to assess presence and severity of amyloid and tau pathology. Additionally, the IBC works with radiologists in the Nuclear Medicine department to provide visual reads of beta-amyloid plaque and tau neurofibrillary tangle accumulation in the brain, which aids in properly diagnosing dementia. Our data, pipelines, and expertise are also used to train the next generation of neuroscience students at Northwestern, while our staff members are applying generative artificial intelligence to explore linkages between neuroimaging and unstructured spontaneous speech.

Lay Language: The Northwestern Alzheimer's Disease Research Center's Neuroimaging Biomarker Core (IBC) studies brain changes related to aging and dementia at Northwestern and beyond through data collection and sharing, project collaboration, pipeline development, student training, and scientific exploration. Using advanced magnetic resonance imaging (MRI) and positron emission tomography (PET) scans, the IBC analyzes brain structures, white matter, neural pathways, blood flow, and proteins linked to Alzheimer's disease. Data collected and processed by the IBC and the Mesulam Institute are available for data sharing through NURIPS (Northwestern University Research Image Processing System). The IBC has also developed processing pipelines to enhance data quality and analysis and facilitate visual diagnostic reads of amyloid and tau accumulation in the brain. By providing high-quality neuroimaging data storage and results, the IBC helps advance our understanding of various aging trajectories while supporting efforts to discover causal links and develop early detection methods and treatments.

Poster 55

Quantitative Evaluation of Regional Tau Uptake: an Exploratory Application within Clinical Variants of Alzheimer's Disease Pathology

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Background: Positron emission tomography (PET) using radiolabeled tracers enables in vivo assessment of tau burden, a key pathological biomarker of Alzheimer's disease (AD). Building on our previous surface-based analysis of tau uptake, this study extends that work using a region-based approach to quantify standardized uptake value ratios (SUVR). Tau positivity in AD is typically determined using SUVR within a temporal meta-ROI. However, other clinical variants, such as primary progressive aphasia (PPA), involve vulnerability in language network regions, highlighting the need to explore alternative composite ROIs that better reflect variant-specific patterns of tau deposition.

Objective: To implement a tau-PET processing pipeline incorporating structural MRI segmentation, partial volume correction and region-based SUVR quantification, and to compare SUVR within the temporal meta-ROI and a temporoparietal ROI in amnestic AD and primary progressive aphasia associated with AD pathology (PPA-AD).

Methods: A total of 11 participants with amnestic AD and 22 with PPA-AD were included. Diagnoses were based on clinical evaluation, neuropsychological and language testing, and amyloid positivity. MRI scans were acquired on Siemens 3T Trio or Prisma scanners. Tau-PET scans were acquired on Siemens Biograph TruePoint/TrueV or Biograph Vision. Structural MRI scans were processed with FreeSurfer to generate anatomical parcellations and regional volumes. Using the ADNI protocol, tau-PET images were reconstructed into 5-minute frames and processed with PETSurfer, including motion correction, mean image generation, and co-registration to T1 MRI. Partial volume correction was applied using the Rousset geometric transfer matrix method (Baker et al., 2017).

Volume-weighted tau PET SUVR values normalized to the inferior cerebellar gray reference region were calculated within two composite ROIs: (1) a temporal meta-ROI (bilateral entorhinal, amygdala, fusiform, inferior and middle temporal cortices) and (2) a temporoparietal ROI (bilateral inferior, middle and superior temporal cortices, banks of the superior temporal sulcus, transverse temporal, supramarginal, and inferior parietal cortices). The SUVRs between amnestic and PPA-AD were compared using a linear mixed-effects model.

Results: Amnestic AD participants showed relatively higher SUVR within temporal regions, whereas PPA-AD participants demonstrated comparatively greater uptake in temporoparietal cortex. These observed differences did not reach statistical significance in the current sample.

Discussion: The observed trends in SUVR differences between amnestic AD and PPA-AD align with known phenotype-specific patterns and highlight that ROI selection may influence interpretation of tau positivity in AD variants.

Lay Langauge: Tau is a protein that accumulates in the brain in Alzheimer's disease and is linked to brain degeneration and cognitive decline. In this study, we implemented a PET processing pipeline to quantify tau levels across different brain regions. This approach may help improve understanding of how tau accumulation differs across clinical variants of Alzheimer's disease.

Poster 56

Neuroscience

HosPiCam: Continuous Video Monitoring System for Objective Behavioral Assessment in Hospitalized Patients

Ian George Sherrington

Principal Investigator: Eyal Kimchi

OBJECTIVE: To develop a compact video acquisition system for longitudinal inpatient behavioral monitoring and analysis.

BACKGROUND: Monitoring motor activity and behavior in hospitalized patients is crucial for the timely detection of conditions such as falls, delirium, and epilepsy. Prior work has suggested an objective continuous video monitor would help particularly in understanding delirium's fluctuating nature. However, variation in hospital rooms presents challenges in acquiring consistent video without impeding patient comfort or clinical care.

DESIGN/METHODS: We set out to develop HosPiCam: a discreet, compact, and lightweight infrared camera that can be attached to most surfaces for continuous video-based clinical monitoring. Various Raspberry Pi computer models (Zero & 5) were tested for their ability to record continuous video at 30 frames per second (fps). Multiple cameras were tested (RPI High Quality & Module v3), to determine appropriate lighting, field of view, and resolution. Custom 3D printed cases were designed to house all devices in a compact, mountable package.

RESULTS: Video recordings were attempted on 28 prospectively enrolled patients. Older generations of the Raspberry Pi were limited to low-resolution frames at 5-second intervals, while the newer Raspberry Pi 5 records continuously at 30 fps with a resolution of 2304x1296 pixels. In low-light conditions, the older HQ Camera was insensitive to IR lighting despite use multiple 850nm IR LED boards. The newer RPI module 3 NoIR camera achieved high-quality low-light recording, enabling 24-hour video recordings. An improved adhesive-based mounting system allowed the lightweight camera to be attached to the majority of room surfaces, minimizing impact on clinical care. Videos of 10,00-minute duration were recorded with excellent visual quality, facilitating the identification of behaviors relevant to delirium.

CONCLUSIONS: HosPiCam is a cost-effective, open-sourced device, facilitated by new advancements in small board computing, ~~for acquiring fluctuating behavioral and motoric symptoms in hospitalized patients, revealing complex fluctuating disorders like~~ delirium.

Lay Langauge: Limited staff availability has created a need to continuously monitor hospitalized patients for behaviors like falls, confusion (delirium), and seizures, but hospital rooms are difficult environments to set up cameras in without getting in the way of care.

We developed a small, lightweight camera, which can stick to any surface in a patient's room and provide round the clock monitoring. The camera utilizes tiny computers called Raspberry Pis and infrared lights to be able to record patients during the day and night when its dark. After testing different hardware combinations, we landed on a setup that records high-quality, continuous video at a smooth 30 frames per second. 28 patients have been prospectively recorded for 7,200-minute intervals, allowing for identification of key points to train models

Poster 57

Neuroscience

Amyloid-Beta Oligomers and Pro-inflammatory Cues Promote Microglial Tunneling Nanotubes and Synapse Targeting in Human Cocultures and the Aged Mouse Brain

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Background: Microglia survey synapses and maintain homeostasis, but become dysregulated in Alzheimer's disease (AD), contributing to chronic neuroinflammation and synapse loss. Tunneling nanotubes (TNTs) are ultrafine F-actin-based membrane bridges that support long-range intercellular communication, yet their regulation and functions in microglia-synapse crosstalk remain unknown due to their nanoscale and transient nature. Thus, we examined how microglia activation states influence TNT formation and their subcellular targets in AD-relevant systems using enhanced-resolution and super-resolution microscopy.

Methods: We developed a postmortem aged human microglia and iPSC-derived excitatory neuron (iEN) coculture model, then treated with pro-inflammatory oligomeric amyloid beta (oAβ)+interferon-gamma (IFN-γ), anti-inflammatory interleukin (IL)-4+IL-13, or control (PBS) cocktails. TNTs and their targets, i.e., sub-neuronal elements or other microglial processes, were quantified using live enhanced-resolution confocal images. In human microglia monocultures, we assessed localization of complement receptors (CRs), candidate tetraspanins, and pathological cargoes, oAβ and hTau, to TNTs versus corresponding cell bodies. Next, primary rat microglia monocultures were treated with pro-inflammatory and anti-inflammatory cocktails to assess TNTs. We performed 3D STED microscopy of aged microglia-reporter mouse brain slices after intracerebroventricular challenge with oAβ+IFN-γ or saline for three days to evaluate TNT-like structures and their synaptic targets in the cortex.

Results: In aged human microglia-iEN cocultures, AD-related pro-inflammatory conditions markedly increased TNT number and length, while preferentially directing TNTs toward axons, dendrites, and dendritic protrusions rather than neighboring microglia. Pro-inflammatory cues increased CR3 and CR4 localization to TNTs relative to cell bodies in human microglia monocultures, supporting synapse-related immune functions. The tetraspanin CD81 was enriched in TNTs across conditions, suggesting utility as a TNT-specific marker. During inflammation, oAβ, but not hTau, was enriched in TNTs, indicating selective pathological protein trafficking. Live imaging of primary rat microglia showed that pro-inflammatory stimulation significantly increased TNTs. 3D STED microscopy of aged microglia-reporter mouse brain slices revealed TNT-like networks that frequently targeted synapses and were most prominent in the oAβ+IFN-γ-challenged mouse cortex.

Conclusions: Microglial TNTs represent an environmentally regulated mode of neuroimmune communication that is amplified during inflammation. AD-relevant pro-inflammatory cues increase TNT formation, promote CR and oAβ enrichment at TNTs, and direct TNTs toward synapses. Our observation of TNT-like networks interacting with synapses in the aged pro-inflammatory-treated mouse cortex suggests a hidden microglial TNT-neuronal network that may facilitate synaptic changes in aging and AD.

Lay Language: In Alzheimer's disease (AD), the brain's immune cells called microglia become dysfunctional and contribute to chronic inflammation and disease progression. Microglia can form long, thin bridges called tunneling nanotubes (TNTs) that connect nearby cells, but what drives their formation and whether they interact with nerve cell connections is unclear. Thus, we assessed aged human microglia-neuron cocultures under AD-mimicking pro-inflammatory, anti-inflammatory, or control conditions. Pro-inflammatory cues promoted TNT formation and preferential interactions with nerve cell extensions and connection points, rather than neighboring microglia. Proteins that help microglia recognize immune-tagged nerve cell connections, along with amyloid-beta, concentrated at TNTs during inflammation. Strikingly, in aged mouse brain tissue, we observed microglial TNT-like networks that frequently targeted nerve cell connections and were most prominent in the pro-inflammatory-treated mouse cortex. These findings reveal TNTs as a hidden mode of microglia-neuron communication that may influence nerve cell connections and facilitate harmful protein spread in AD.

Poster 58

Mechanistic Analysis of AβO-Induced Neurotoxicity and Tau Pathology in an Inducible MC65 Cell Model

Poojak Patel

Principal Investigator: William L. Klein

Abstract: Alzheimer's disease is characterized by the buildup of amyloid-β oligomers (AβOs), tau pathology, and eventual neuronal loss. Yet, the mechanisms that link these processes remain incompletely understood. This project looks into whether induction of AβO in MC65 cells drives neurotoxicity through increased tau phosphorylation and other associated cellular stress pathways. The MC65 model allows for intracellular AβO accumulation through withdrawal of tetracycline (-Tet), while tetracycline presence (+Tet) suppresses Aβ production and serves to be a healthy baseline. To look into downstream tau pathology, we use the PHF1 antibody towards immunofluorescence staining to detect phosphorylated tau (p-Tau) under induced and uninduced conditions. Increased PHF1 fluorescence intensity in -Tet cells compared toTet controls indicated elevated tau phosphorylation following the buildup of AβOs. These observations support the link between amyloid toxicity and tau pathology in this model system. Comparably, cell viability, and oxidative stress were evaluated to assess the impact of induced toxicity from AβOs. We build a computational model, specifically a pipeline that measures p-Tau intensity per cell, quantifies the proportion of p-Tau positive cells, and relates these measures to cellular health. In short, this work clarifies the relationship of amyloid toxicity and neurodegeneration along with a framework for quantifying cellular relationships.

Lay Language: Alzheimer's disease is a brain disorder that slowly destroys memory and the ability to think. One of the main features of this disease is the buildup of small toxic protein clusters called amyloid-beta oligomers. These clusters can damage brain cells. Scientists work to understand exactly how this damage happens. In this project, we study a special human based cell model that allows us to turn amyloid buildup on or off. When amyloid builds up, we observe the changes in another important brain protein called tau and other stress signals which are linked to cell damage in Alzheimer's. By combining these laboratory experiments with computer-based analysis, this research clarifies how amyloid buildup leads to harmful changes in brain cells and can help with future strategies for developing treatments.

Lay Language: Alzheimer's disease is a brain disorder that slowly destroys memory and the ability to think. One of the main features of this disease is the buildup of small toxic protein clusters called amyloid-beta oligomers. These clusters can damage brain cells. Scientists work to understand exactly how this damage happens. In this project, we study a special human based cell model that allows us to turn amyloid buildup on or off. When amyloid builds up, we observe the changes in another important brain protein called tau and other stress signals which are linked to cell damage in Alzheimer's. By combining these laboratory experiments with computer-based analysis, this research clarifies how amyloid buildup leads to harmful changes in brain cells and can help with future strategies for developing treatments.

Poster 59

Advancing Alzheimer's Disease Molecular Diagnosis through NUsc1-Mediated Detection of CSF Amyloid-β Oligomers

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The single-chain fragment variable (scFv) NUsc1, which exhibits strong selectivity for AD-causing Aβ oligomers (AβOs), was previously delivered via AAV into the brains of animal models, demonstrating remarkable therapeutic efficacy. It not only prevented disease onset but also restored cognitive function in aged transgenic animals, demonstrating its promise as a novel intervention. Leveraging NUsc1's specificity toward disease-relevant AβO species, our group has developed a diagnostic strategy using the same antibody for non-invasive detection of AβOs: a supersensitive ELISA employing phage-bound NUsc1 (pbNUsc1). In this assay, the phage-based format amplifies the signal through secondary antibody binding, enabling detection at levels lower than those achievable with available assays. The pbNUsc1 ELISA enables sensitive measurement of synthetic AβOs, as well as oligomeric species derived from murine and human brain tissue and cerebrospinal fluid (CSF). The pbNUsc1 ELISA achieved remarkable picomolar sensitivity, detecting synthetic AβOs with a limit of detection of 0.65 pM and a limit of quantification of 2.0 pM. When applied to brain extracts from murine AD models, the assay detected significantly higher AβO signal intensity in transgenic animals compared to wild-type controls across three models: 3xTG, 5xFAD mice, and McGill AD rats. Notably, higher AβO levels were observed in demented human brain samples compared with non-demented samples. Application to CSF samples enabled clear separation between AD rat and wild-type samples. Strikingly, pbNUsc1 ELISA in human CSF demonstrated reliable distinction between AD-positive cases and controls, overcoming the inherently low abundance of secreted AβOs in this matrix. Ongoing studies are examining changes in CSF AβO levels throughout disease progression. These findings validate the potential use of NUsc1 in molecular diagnostics, providing a sensitive, non-invasive method with translational clinical significance.

Lay Language: Researchers have developed an antibody called NUsc1 that specifically targets toxic protein clumps causing Alzheimer's disease. In animal studies, delivering NUsc1 to the brain not only prevented memory problems but also restored lost cognitive function. Building on this, our team created a new, highly sensitive test called pbNUsc1 ELISA, which uses NUsc1 to detect tiny amounts of these harmful proteins in brain tissue and spinal fluid. This test can spot toxic proteins at levels far lower than existing methods, distinguishing between healthy and Alzheimer's-affected samples in mice, rats, and, most importantly, in humans. In human cerebrospinal fluid, the test reliably separates Alzheimer's patients from controls, despite the proteins being very scarce. These findings suggest NUsc1 could be a powerful tool not only for treatment but also for non-invasive diagnosis, offering hope for better detection and monitoring of Alzheimer's disease.

Poster 60

Neuroscience

Parallels between neurodevelopment and neurodegeneration in Alzheimer's disease: AD-type amyloid β oligomers and isoforms of pTau occur in extracellular vesicles in the developing CNS

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Amyloid beta oligomers (AbOs) are pathogenic in Alzheimer's Disease (AD) but have recently been found to occur physiologically in the embryonic chick retina, a widely used model for investigating CNS development. Intriguingly, both AbOs and Alzheimer's-associated forms of phospho-tau (pTau) are abundant during periods of robust differentiation after which they disappear. Since these molecules have profound impact on cells in the course of Alzheimer's disease, it raises the hypothesis that they participate transiently in cell-cell interactions during neural differentiation. As a first step toward investigating this idea, we determined the subcellular localization of AbOs using super-resolution fluorescence microscopy and fluorescence-activated cell sorting (FACS). In situ and in cell culture, AbOs were found to localize to vesicles. AbO-containing vesicles occurred in the nucleus as well as the cytoplasm, with subcellular distributions shifting as cells matured. AbO subtypes, recognized by different AbO-selective antibodies, typically were not found in the same vesicles. Although virtually no cytoplasmic vesicles with AbOs stained for lysosomes, a substantial fraction (~35%) co-labeled for amyloid precursor protein, consistent with the possibility these vesicles were involved in AbO formation. Another possibility is that the AbO-containing vesicles might connect with the extracellular milieu, playing a role in internalizing or releasing AbOs. This possibility was strongly supported by high levels of co-localization between AbOs and a marker for exosomes (CD81). Further support came from findings that extracellular vesicles (EVs) isolated from chick retina tissue contained AbOs and isoforms of pTau. Treatment of retinal cell cultures with the tissue-derived EVs (marked with a membrane stain) resulted in the EVs selectively associating with the membranes of certain cells in large clumps while being absent from other cells. Imaging of intact EVs after FACS indicated AbOs occurred on ~5% of EV surfaces, suggesting that AbOs in EVs could interact directly with receptors on cell membranes, recruiting proteins after contact. Results are in harmony with the hypothesis that mechanisms are in place during neurodevelopment for AbOs and pTau to influence in tandem the developmental status of nearby cells, as occurs pathologically in Alzheimer's Disease. Further investigation of these relationships could shed light on similar mechanisms in Alzheimer's Disease that can be targeted for therapeutics.

Lay Language: Alzheimer's Disease research has traditionally focused on amyloid beta plaques, but in recent years attention has shifted toward smaller forms of amyloid beta called oligomers. Oligomers are harmful to brain cells, linked to memory problems in experimental models, and are commonly found in people with Alzheimer's. Interestingly, they have also been observed during brain development in chickens. Our work shows that these molecules are not only present during development but also interact with cell components involved in communication. This suggests they may play a role in how brain cells organize and form connections, possibly by influencing the removal of unnecessary connections or the programmed death of certain cells. Understanding why these molecules appear during development could provide insight into similar processes in Alzheimer's disease and help identify new treatment targets.

Poster 61

Neuroscience

A Two-Dimensional Western Blot Approach for Reliable Detection of Amyloid-β Oligomers in Alzheimer's Research

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Abstract: Western blotting (WB) remains a widely used first-line method for detecting the presence and apparent molecular weight of antibody-recognized species. In Alzheimer's disease (AD), accurate characterization of metastable, toxic amyloid-β oligomers (AβOs) is crucial for guiding therapeutic development and advancing diagnostics. However, conventional WB presents limitations when applied to AβOs. Beyond the limited resolution, the detergent sodium dodecyl sulfate (SDS) used during electrophoresis can disrupt oligomeric assemblies, altering their aggregation state and native size distribution. These detergent effects, together with limited resolving power, have led to the underutilization of WB in AβO studies despite its sensitivity and accessibility. To overcome these limitations, we applied two-dimensional electrophoresis (2D) followed by WB to elucidate AβO size and aggregation state. This strategy reduces detergent-induced artifacts and improves the resolution of complex protein mixtures by separating molecules first by isoelectric point (pH) and then by size. We hypothesized that 2D-WB could provide a more detailed characterization of toxic oligomers by capturing both apparent size and pH. In synthetic AβO preparations, 2D-WB revealed predominantly slightly acidic species centered at pH 5-6, consistent with the acidic residues of $A\beta_{1-42}$. Monomers and low-order oligomers were observed, while a diffuse smear indicated higher-molecular-weight assemblies ranging from 50 to 250 kDa, particularly in cross-linked preparations. In the chick retina model, AβOs initially focused around pH 7.1, and higher sample amounts revealed additional species at pH 5-6. Across all pH values, oligomers consistently measured ~50 kDa, corresponding roughly to a 10-mer aggregation state. In human brain extracts from mild cognitive impairment (MCI) subjects, a strong 50 kDa band appeared with an additional 35 kDa species and a faint smear up to 250 kDa, all near pH 7.1, similar to chick retina. In advanced AD brain extracts, the 50 kDa band remained but shifted to pH 5-6. Across stages, 50 kDa assemblies were consistently detected, suggesting 10-mer oligomers may represent structural motifs relevant to disease. Investigations into whether these pH shifts reflect post-translational modifications are ongoing. In summary, these findings support 2D-WB as an effective, accessible method for initial assessment of AβO size. Future studies using more conformational antibodies could expand these observations and enable broader characterization of toxic species in a technically approachable way

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Lay Language: Alzheimer's disease is linked to small, toxic protein clusters called amyloid-β oligomers (AβOs). Studying them is tricky because common lab methods can break them apart, hiding their true size. We used a two-step lab method that separates proteins by charge and size before detection, preserving these clusters. In lab samples, chick retinas, and human brains, we consistently found ~50 kDa AβOs—about 10 protein units in total. This approach offers a simple, accessible way to study these harmful molecules and better understand Alzheimer's disease.

Poster 62

Synthetic Data-driven 2.5D Diffusion Model for Brain MRI Motion Correction

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Background: Magnetic Resonance Imaging (MRI) is a widely used clinical imaging modality, but it is highly sensitive to patient motion during acquisition. Even subtle head motion can introduce blurring, ghosting, and structural distortion effects. High-quality structural MRI is especially important in neurodegenerative disorders such as Alzheimer's disease, where subtle anatomical changes may be clinically meaningful. Although conventional retrospective correction and CNN-based image restoration methods have shown some success, they often struggle to recover fine anatomical details and generalize to real clinical data. Recently, diffusion models have emerged as a powerful framework for image restoration and translation. However, directly applying diffusion models to 3D MRI volumes remains challenging due to their high computational cost and memory burden. In addition, supervised training for motion correction is limited by the scarcity of paired motion-corrupted and motion-free MRI data in real clinical settings.

Method: To address these challenges, we developed a synthetic data-driven 2.5D diffusion-based framework for brain MRI motion correction. First, we built a synthetic data generation pipeline with a motion simulation engine to create paired clean and motion-corrupted MRI data from clean scans, helping overcome the lack of real paired datasets. We then trained a 2.5D diffusion model that operates on multi-slice inputs in the sagittal plane, allowing the model to leverage through-plane contextual information while maintaining feasible computational cost. The framework was evaluated on both synthetically corrupted data and real clinical scans that were not seen during training to assess restoration quality and generalization under realistic conditions.

Results: Experimental results showed that the proposed framework effectively reduced motion artifacts and restored clearer anatomical structures in both synthetic and real MRI data. On simulated datasets, the diffusion-based model outperformed conventional CNN-based restoration methods, producing cleaner images with better preservation of structural boundaries and fine details. Importantly, qualitative evaluation on unseen real clinical scans suggested that the model also generalized well beyond the synthetic training setting and remained effective for real-world motion correction.

Conclusion: This work shows that combining a synthetic paired-data pipeline with a 2.5D diffusion model is a practical and promising approach for brain MRI motion correction. The framework balances image quality and computational cost, and it may help reduce repeat scans while supporting more reliable clinical image analysis.

Lay Language: MRI scans can become blurry when a patient moves, even slightly, during the exam. Our project develops an AI-based method to clean up these motion-corrupted images and recover clearer brain structures. This could help doctors read scans more confidently and may reduce the need to repeat long and uncomfortable MRI exams.

Poster 63

Traumatic injury causes selective degeneration and TDP-43 mislocalization in human iPSC-derived C9orf72-associated ALS/FTD motor neurons

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A hexanucleotide repeat expansion (HRE) in C9orf72 is the most common genetic cause of ALS/FTD. However, the wide disparity between age of disease onset and disease severity within patients suggests an interplay between genetic background and environmental stressors. Neurotrauma as a result of traumatic brain or spinal cord injury has been shown to increase the risk of ALS/FTD in epidemiological studies. Here, we combined patient-specific induced pluripotent stem cells (iPSCs) with a custom-built device to deliver biofidelic stretch trauma to C9orf72 patient and isogenic control motor neurons (MNs) in vitro. We find that mutant motor neurons exhibit selective degeneration after a single incident of severe trauma, which can be partially rescued by pretreatment with a C9orf72 antisense oligonucleotide (ASO). A single incident of mild trauma does not cause degeneration but leads to extended cytoplasmic accumulation of TDP-43 in C9orf72 motor neurons. This mislocalization, which only occurs briefly in isogenic controls, is restored in patient cells after 6 days. Lastly, repeated mild trauma ablates the ability of patient motor neurons to recover. These findings highlight alterations in TDP-43 dynamics in C9orf72 patient motor neurons following traumatic injury, and demonstrate that neurotrauma compounds neuropathology in C9orf72 ALS/FTD. More broadly, our work establishes an in vitro platform that can be used to interrogate the mechanistic interactions between ALS/FTD and neurotrauma.

Lay Language: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that causes the progressive loss of motor neurons controlling movement, while frontotemporal dementia (FTD) leads to the degeneration of brain regions involved in behavior and language. Both conditions are linked to a genetic change in a gene called C9orf72, although patients with this mutation can develop symptoms at very different ages and with varying severity. Previous studies have shown that traumatic injuries to the brain or spinal cord may increase the risk of developing ALS or FTD. In this study, we used patient-derived stem cells and used a device to simulate mechanical injury, modeling traumatic brain or spinal cord injury. We found that neurons carrying the C9orf72 mutation were more vulnerable to trauma and showed abnormal changes in TDP-43, a key protein linked to ALS/FTD, suggesting that head or spinal injuries may worsen disease processes in people with this genetic risk.

Poster 64

Pharmacology

Differential Autophagy-Related Protein 9 Localization Suggests Distinct Mechanisms of Autophagy Activation by NU-9 and Torin-1

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Background: Alzheimer's disease lacks effective therapies that directly target neurotoxic amyloid-β oligomers (AβOs), small protein aggregates believed to contribute to early neurodegeneration. NU-9, a small molecule drug candidate developed by Northwestern's Silverman Laboratory, has been shown to reduce the buildup of AβOs and improve upper motor neuron health, including increased axon growth and branching. The Klein Lab demonstrated that NU-9 reduces AβO buildup via a cell-mediated mechanism involving autophagy, a process in which cells break down unwanted components; however, its precise target within the autophagic pathway has yet to be identified. This project investigated whether NU-9 engages Autophagy-Related Protein 9 (ATG9), a protein involved in autophagosome formation and trafficking, in a manner distinct from other autophagy inducers.

Methodology: HT22 mouse hippocampal cells were cultured and treated with NU-9, Torin-1 (a known autophagy activator via mTORC1 inhibition), or vehicle control. Cells were fixed with paraformaldehyde and stained using a fluorescent autophagosome marker and a selective ATG9 antibody. Imaging was performed using a Nikon SoRa super-resolution microscope.

Results: Both NU-9 and Torin-1 treatment groups showed increased autophagosome fluorescent signal compared to vehicle and secondary-only controls, consistent with autophagy activation. ATG9 signal intensity was also elevated in both treatment groups relative to control. Phenotypic differences in ATG9 localization were observed between treatments: NU-9-treated cells appeared to exhibit increased nuclear and perinuclear ATG9 signal, along with a more dispersed cytosolic distribution, compared to Torin-1-treated cells. These spatial differences suggest potentially distinct patterns of ATG9 engagement.

Conclusions: NU-9 treatment is associated with differences in ATG9 localization compared to Torin-1, indicating a potentially distinct mode of autophagy activation. These findings provide preliminary insight into NU-9's mechanism of action and support further investigation into its interaction with the autophagy pathway.

Lay Language: Abnormal protein aggregation is a common cause of many neurodegenerative diseases, such as Alzheimer's disease, causing damage to cells and impairing communication between neurons. Amyloid-β oligomers are small protein clusters that are shown to cause Alzheimer's disease. NU-9 is a novel drug candidate created by researchers at Northwestern's Silverman Laboratory that has been shown to reduce the buildup of neurotoxic amyloid-β oligomers. NU-9 has been shown to activate a cellular pathway known as autophagy, which breaks down unwanted aggregates in the cell, but it is not known how NU-9 activates the autophagy pathway. This project investigates NU-9's engagement of the ATG-9 protein, a specific protein in the autophagy pathway. NU-9's potential selective engagement of ATG-9 in a different way than the traditional autophagy activation pathway provides valuable insight into how the drug works and supports its continued advancement toward clinical evaluation.

Poster 65

Pharamcology

Novel Small-Molecule Strategies Targeting AβO Pathology: Autophagy Activation and nNOS Inhibition

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Soluble amyloid-β oligomers (AβOs) are key neurotoxic drivers of synaptic dysfunction, tau hyperphosphorylation, and neuronal loss in Alzheimer's disease (AD). Small molecule therapeutic strategies that address its downstream signaling cascades remain limited. Here, we present two novel small-molecule approaches that target AβO pathology through innovative mechanistic pathways. We first characterized NU-9, a novel small molecule that enhances autophagic clearance of AβOs. Our recent data shows that NU-9 engages autophagy through a non-canonical mechanism primarily targeting autophagic degradation. In live neuronal cells, DALGreen-based imaging revealed a significant increase in acidic autolysosomal compartments following NU-9 treatment, indicating enhanced autolysosomal activity and degradative capacity. Unlike classical autophagy inducers, NU-9 promotes more efficient degradation and more pronounced redistribution of ATG9A-positive vesicles, suggesting modulation of vesicle trafficking as a key regulatory step. This enhanced autophagic engagement is associated with a reduction in intracellular AβO burden and other toxic proteins, supporting a role for NU-9 in restoring proteostasis under AβO-induced stress. In parallel, we investigated HD-3-86, a selective neuronal nitric oxide synthase (nNOS) inhibitor, as a strategy to disrupt AβO-mediated neurotoxic signaling. Using DAF-FM live-cell imaging, we demonstrate that AβOs induce a robust increase in intracellular nitric oxide (NO) levels in neuronal cells, consistent with activation of nNOS-dependent pathways. Treatment with HD-3-86 significantly suppresses AβO-induced NO production and attenuates pathological tau phosphorylation in both HT22 cells and primary hippocampal neurons. These findings identify nNOS as a critical molecular link connecting AβO exposure to tauopathy. Collectively, our results establish an innovative therapeutic framework targeting AβO-mediated proteotoxic stress and downstream signaling in Alzheimer's disease. These strategies provide new mechanistic insight into AβO-driven pathology and highlights small-molecule modulation of autophagy and NO signaling as promising avenues for disease-modifying interventions in Alzheimer's disease.

Lay Language: Alzheimer's disease is caused by toxic protein clumps called amyloid-beta oligomers and ptau that damage brain cells and lead to memory loss. In this work, we studied two new potential drugs that help protect brain cells in different ways. The first, NU-9, helps cells clean out harmful proteins by boosting their natural "recycling and clearance" system. We used live-cell imaging to show that NU-9 increases the number of active recycling compartments inside cells, helping remove toxic buildup. The second molecule, HD-3-86, blocks a harmful signal called nitric oxide that is triggered by these toxic proteins. Using another live-cell method, we showed that this drug reduces this damaging signal and lowers tau-related damage. Together, these approaches offer promising new ways to treat Alzheimer's disease.

Poster 66

Associations of Choroid Plexus Perfusion Measured by pCASL MRI with Amyloid Burden and Cognition in elderly adults

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Background: The choroid plexus (ChP) is a complex network of capillaries in the ventricles of the brain, which produces cerebrospinal fluid (CSF) and plays a key role in glymphatic clearance. Adequate cerebral blood flow (CBF) is required to maintain ChP function, and impaired ChP perfusion may promote the accumulation of neurotoxic proteins such as amyloid-β (Aβ), a pathological hallmark of Alzheimer's disease (AD). Although age-related reductions in ChP CBF have been reported, its relationship with amyloid burden and cognition remains unclear. This study investigates the associations between ChP CBF, amyloid deposition, and cognition in elderly adults.

Method: MRI acquisition: 131 elderly participants (73.74 ± 8.03 years, 68 males) were scanned on 3T MRI systems. High-resolution T1-weighted structural images were acquired using a 3D MPRAGE sequence. Perfusion imaging was performed using a single-delay pCASL sequence with 3D GRASE readout.

Data processing: Motion-corrected pCASL images were used to generate mean CBF maps using a single-compartment model and were co-registered to MPRAGE images in SPM12. A 3D U-Net model was used to segment the ChP from structural images, while grey matter (GM) masks were obtained from SPM12. Mean ChP CBF and GM CBF were extracted using these masks with a threshold of 10 ml/100g/min. Global and regional amyloid burden (SUVR) were derived from amyloid PET.

Statistical Analysis: Linear mixed-effects models were used to examine associations of ChP CBF with amyloid SUVR and cognitive function assessed by MoCA, adjusting for age and gender. Two-sample t-tests and ANCOVA assessed group differences in ChP CBF across demographic and clinical variables.

Results: ChP CBF showed a significant negative association with global amyloid SUVR ($p = 0.0219$) and regional SUVR values of the lateral temporal cortex ($p = 0.0187$) in all subjects and the frontal cortex in normal cognition (NC) ($p = 0.0345$). No significant correlation was observed between ChP CBF and MoCA scores ($p=0.424$). Consistently, no significant difference in ChP CBF was observed across three cognitive groups, including NC, MCI, and dementia, or between APOE4 carriers and non-carriers.

Conclusion: Decreased ChP perfusion was significantly associated with increased global and regional amyloid burden, whereas no association was observed with cognitive function or APOE status. These findings suggest that ChP perfusion reduction may be closely linked to cerebral amyloid accumulation.

Lay Language: The brain contains a small structure called the choroid plexus located within the ventricles to produce the fluid surrounding the brain and spinal cord. This fluid helps deliver nutrients and remove waste from the brain. When this system does not function properly, harmful proteins may build up and contribute to diseases such as Alzheimer's disease. In this study, we used a noninvasive MRI technique to measure blood flow in the choroid plexus and examined whether it is related to cerebral amyloid accumulation, a protein linked to Alzheimer's disease. We found that lower blood flow in this structure was associated with higher amyloid levels in the whole brain and certain regions. Interestingly, this relationship was observed regardless of whether individuals showed clear clinical symptoms. These findings suggest that changes in blood flow in this brain structure may reflect early biological processes and be related to amyloid pathology.

Poster 67

Physiology

Aortic Stiffness, Cerebral Hemodynamics, and White Matter Hyperintensities in Vascular Territories: A Heart-Brain MRI Study

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Background: Arterial stiffening has been linked with age, hypertension, markers of brain injury, including white matter hyperintensities (WMHs), and cognitive decline. However, the hemodynamic relationships along the heart-brain pathway remain unclear. 4D flow MRI enables quantification of hemodynamic parameters (e.g., peak velocity and pulsatility) in major blood vessels. We developed a comprehensive heart-brain MRI protocol and analysis workflow using 4D flow MRI and brain MR imaging to concurrently analyze aortic stiffness by pulse wave velocity (PWV), hemodynamics in the main cerebral arteries, and WMHs in distinct territories supplied by those arteries.

Methods: Heart-brain MRI was acquired in 44 cognitively asymptomatic adults (63.6±8.0[49-78] years; 14 males; 19 hypertensive; Telephone-MoCA≥17) at 3T (MAGNETOM Prisma, Siemens Healthineers, Forchheim, Germany), including whole-chest and intracranial 4D flow MRI research sequences, T1-MPRAGE, and T2-FLAIR. Aortic PWV was quantified from whole-chest 4D flow using cross-correlation analysis. Hemodynamic parameters in arteries of the Circle of Willis (CoW), including pulsatility and resistivity indices PI=(flowmax-flowmin)/flowmean and RI=(flowmax-flowmin)/flowmax, were quantified from intracranial 4D flow MRI using analysis planes. WMH volumes were derived from T2-FLAIR and T1-MPRAGE using an automated segmentation tool with manual refinement and a vascular territory atlas and were quantified as a percentage of intracranial volume.

Results: Hypertensive participants were older than non-hypertensives (66.4±8.4 vs 61.5±7.2 years, p=0.04) and had higher CoW PI (1.21±0.22 vs 1.03±0.14, p=0.003[age-adjusted p=0.02]) and RI (0.72±0.08 vs 0.66±0.06, p=0.01[age-adjusted p=0.08]). Aortic PWV increased with age among hypertensives (r=0.52, p=0.02) and all participants (r=0.35, p=0.02). Total WMH volume correlated with age in non-hypertensives (r=0.41, p=0.04) and the entire sample (r=0.42, p=0.005). Notably, aortic PWV correlated with total WMH volume in the full sample (r=0.30, p=0.046[age-adjusted p=0.24]), with a correlation among hypertensives (r=0.62, p=0.005[age-adjusted p=0.02]) and consistent associations within most vascular territories. Aortic PWV also correlated with CoW RI (r=0.32, p=0.03[age-adjusted p=0.34]); CoW RI with WMH approached significance among all participants (r=0.27, p=0.08).

Conclusion: Aortic PWV was associated with WMHs in CoW vascular territories among hypertensive participants, suggesting a potential hemodynamic coupling mechanism along the heart-brain pathway in hypertension. The observed relationships between aortic PWV, cerebral resistivity, and WMH support the powerful utility of this approach for investigating vascular mechanisms of brain injury in larger cohorts, with cardiovascular risk factors and cognitive impairment. Funding: NIH NIA P30AG059988, K01AG080070

Lay Language: Arteries in the body can become stiffer with age and high blood pressure (hypertension). Arterial stiffening has been linked to a higher risk of brain injury and memory problems. However, the mechanisms underlying this relationship are unclear. To address this, we developed a heart-brain imaging protocol using advanced MRI flow techniques. We used this approach to capture blood flow dynamics in the aorta (the body's main artery) and brain vessels, as well as white matter hyperintensities (WMH, a marker of brain injury) in 44 middle-aged to older adults, both with and without hypertension. We found that higher aortic stiffness was associated with greater vascular resistance in the brain's main arteries. It was also associated with more WMH in brain regions supplied by those arteries, particularly in individuals with hypertension. This study provides an integrated framework for larger future studies investigating how vascular changes relate to brain injury and memory problems.

Poster 68

Physiology

Wearable EEG recordings show dysregulated sleep-wake and circadian rhythms in hospitalized patients with delirium

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Objective: To identify specific differences in sleep architecture and circadian rhythms between older hospitalized patients with and without delirium.

Background: Delirium is an acute and fluctuating state of confusion, often accompanied by disturbances in attention and cognitive function. Delirium affects over 20% of hospitalized older adults and is associated with poorer clinical outcomes, including increased mortality. More than 90% of patients with delirium experience disturbances in sleep-wake activity. However, the ways in which circadian rhythms are disrupted in delirium remain unclear.

Method: In this prospective cohort study, we collected and analyzed 513 single-channel electroencephalogram (EEG) recordings, each approximately 24 hours in duration, from 208 hospitalized patients aged 50 years and older (n = 208; 134 non-delirious, 74 delirious). We defined delirium using the 3-minute diagnostic interview for the Confusion Assessment Method (3D-CAM). Sleep-wake activity was assessed in 30-second epochs using multiple automated sleep staging models.

Results: Across both automated sleep staging models, patients with delirium exhibited significantly greater total sleep duration compared to patients without delirium (linear mixed effects model (LMEM); U-Sleep: t=6.58, p<0.001; Luna: t=6.04, p< 0.001). Patients with delirium also spent significantly more time in N2 sleep (Estimated Marginal Means; U-Sleep: t=8.10, p<0.001; Luna: t=19.80, p<0.001), had more N2-to-REM transitions (LMEM U-Sleep: t = 6.03, p < 0.001; LMEM Luna: t = 4.76, p < 0.001), and had greater intervals of uninterrupted sleep (LMEM U-Sleep: t = 4.17, p < 0.001; LMEM Luna: t = 5.95, p < 0.001).

Conclusion: Delirium status is associated with changes in sleep quantity, quality, and structure. Ongoing work aims to examine specific circadian patterns to determine how the timing and distribution of sleep across the day may differ between delirious and non-delirious patients. Identifying specific circadian disruptions in sleep architecture may guide targeted interventions for improving sleep onset and quality, potentially improving outcomes in patients with delirium.

Lay Language: Delirium is a sudden state of confusion that commonly affects older adults in the hospital and is closely associated with disrupted sleep. While it is known that patients with delirium often experience difficulty sleeping, it is still unclear exactly how their sleep patterns differ and how this relates to delirium. Studying sleep in the hospital is also challenging because traditional methods can be complex and disruptive. In our study, we used a small, comfortable device to continuously track sleep in hospitalized patients with and without delirium. We found that patients with delirium slept more overall, spent more time in certain stages of sleep, and had longer uninterrupted periods of sleep compared to those without delirium. These results suggest that delirium is associated with changes in how sleep is structured, not just “poor” sleep. Better understanding these patterns may help improve how delirium is identified and treated in hospitalized patients.

Poster 69

Facilitated or Self-Guided Positive Emotion Regulation for Alzheimer's Disease Caregivers: Results from the LEAF 2.0 Randomized Controlled Trial

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Background: Alzheimer's disease caregivers face high levels of stress that place them at risk for depression, anxiety, and burden. Positive psychological interventions that build positive emotion may offer benefits beyond traditional stress reduction approaches. LEAF 2.0 is an evidence-based positive emotion regulation program that teaches eight core skills: noticing positive events, savoring, gratitude, everyday mindfulness, positive reappraisal, self-compassion, identifying personal strengths, and setting attainable goals. These skills have shown efficacy in improving well-being across stressed populations and may help counter the emotional toll of caregiving while offering a scalable approach to caregiver support.

Methods: In this three-arm randomized controlled trial, 387 Alzheimer's caregivers across the United States were allocated to (1) a facilitator-delivered LEAF intervention, (2) a self-guided online version, or (3) a daily emotion reporting waitlist control. Participants completed assessments at baseline and 3, 5, and 7 months. Primary outcomes included positive affect, depression, anxiety, perceived stress, caregiving burden, and positive aspects of caregiving. Mixed effects regression models tested differences in change over time. Moderator analyses examined effects of caregiver age, gender, relationship to the person with dementia, and baseline dementia severity.

Results: Participants were on average 63 years old and primarily spouse caregivers. Intervention adherence and retention were higher in the facilitated condition. Compared to control, facilitated LEAF produced significant benefits across outcomes, including improvements in depression at 3, 5, and 7 months, and improvements in positive affect, perceived stress, caregiving burden, and positive aspects of caregiving at later follow-ups. Self-guided LEAF produced significant improvements in perceived stress and depression at 3 months and in positive affect at 5 months. Moderator analyses identified that gender and baseline dementia severity influenced the effect of delivery mode on anxiety: men showed greater improvement with self-guided delivery, while caregivers supporting persons with more severe dementia showed greater improvement with facilitated delivery.

Conclusion: Both facilitated and self-guided versions of LEAF 2.0 improved caregiver psychological well-being, although effects were more consistent and broader for the facilitated delivery. Findings support the scalability of positive emotion regulation training for Alzheimer's caregivers.

Lay Language: Caring for a loved one with Alzheimer's disease is stressful and can harm caregivers' emotional and physical health. This study tested two online programs that teach skills for increasing positive emotions such as gratitude, mindfulness, and noticing small good moments. One program involved weekly sessions with a trained facilitator. The other was fully self-guided. Both versions helped caregivers feel less stressed and more positive over time, although the facilitated program showed the strongest and most consistent benefits. Caregivers' characteristics mattered too. For example, men benefited more from the self-guided version, while caregivers supporting someone with more severe dementia benefited more from the facilitated version. These findings show that positive emotion skills can support caregiver well-being, and that different caregivers may prefer or benefit from different program formats.

Poster 70

Associations between modifiable risk factors for dementia and cognitive SuperAging

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Background: Research suggests that a substantial portion of the risk for developing all-cause dementia can be attributed to potentially modifiable environmental and lifestyle factors, including certain medical comorbidities and health behaviors. However, less is known about whether lower rates or lesser severity of these risk factors are associated with exceptionally successful cognitive aging. The current project determined differences in modifiable risk factors for dementia between cognitive SuperAgers, who are persons aged 80 and above with exceptional memory performance, and age-matched controls with normal-for-age memory performance.

Method: 284 healthy control participants enrolled in the Northwestern University Alzheimer's Disease Research Center (NUADRC) were included. SuperAgers (SAs; n = 206) performed at least within the normal range at baseline for persons 20-30 years younger on the Rey Auditory Verbal Learning Test (RAVLT) delayed recall, whereas Normal Agers (NAs; n = 78) performed within the normal range for their own age group. Data were derived from the first annual NUADRC visit above age 80 with available data related to selected health comorbidities (i.e., hypertension, hypercholesterolemia, heart attack, diabetes, TBI, obesity, hearing loss, vision loss, depression) and health behaviors (i.e., smoking, alcohol use). Independent samples t-tests and chi-square tests were used to compare extent and/or presence of each risk factor between groups for continuous and categorical variables, respectively.

Results: SAs and NAs did not differ in age, years of education, race, or ethnicity; there was a significantly higher proportion of female participants in the SA group. SuperAgers were significantly less likely to have had a heart attack compared to Normal Agers, though frequency was low in both groups. There were not significant differences between groups across any other health factors or health behaviors.

Conclusion: The current findings suggest that SAs are not simply more physically healthy, or less likely to engage in behaviors thought to be harmful to health, than their peers with normal-for-age memory. These findings, in the context of prior findings of greater anterior cingulate cortex integrity and lesser Alzheimer's tangle pathology in SAs compared to NAs, support the idea of a largely neurobiological underpinning of SuperAging. That is, whereas potentially modifiable health factors play a significant role in risk for development of dementia, such factors may be less impactful than genetic/biological factors in determining exceptional cognitive aging.

Lay Language: Research has reliably found links between certain health factors, such as high blood pressure, diabetes, and smoking, and higher risk for dementia. Modifying these factors could thus reduce risk for dementia, but it remains unclear whether this would also promote preservation of memory. This study looked at whether SuperAgers, who are persons age 80 and above whose memory is as good as those in their 50s-60s, have lower rates of health risk factors than same-age controls. Other than a slightly lower rate of heart attack, SuperAgers did not differ from controls on any of the selected risk factors for dementia. This suggests that, whereas modifiable health risk factors play a large role in risk for dementia, such factors may be less important than biological factors in determining exceptional cognitive aging.

Poster 71

Social & Behavioral Sciences

Stories for Dementia Justice: Creating a Storytelling Workshop for Children of a Parent Living with Young-Onset Dementia

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INTRODUCTION: While prevalence studies of young-onset dementia [YOD] – those younger than 65 - in the U.S. are limited and data varies, there is an estimated 200,000 – 600,000 Americans who have younger-onset dementia. Support options for these families are few and tend to focus on the care partner who is often the spouse or partner. Due to the young age of YOD, children may also be involved and have even fewer support options. Lorenzo's House was founded in 2021 as a global non-profit supporting families of YOD. LH's mission is to "Heal in community, Educate for a YOD-informed society and Advocate for Dementia Justice" which includes the NEXTGEN movement inviting young leaders – sons, daughters and children - of YOD to raise awareness, end stigma and meet dementia without silence, shame or invisibility. LH leadership sought out an ally to develop and facilitate a storytelling workshop for LH young leaders helping to create, shape and share their chosen stories for Dementia Justice.

METHODS: Social worker/storyteller instructor met with LH leaders to learn about NEXTGEN goals and discuss how storytelling could be a vehicle for their mission. The workshop proposal was introduced at a NEXTGEN online meeting with young leaders inviting those interested. The 5-week workshop met once a month for 1.5 hours with the support of an LH coordinator. Each week included a "3 Good Thing" check-in, sharing assignments, feedback from witnesses, reflection on the process, storytelling craft lessons, writing prompts and homework assignments. The group consisted of 4 children of a parent living with YOD [n=4].

RESULTS: Participants expressed positivity with sharing their stories about their parent living with YOD in a supportive environment and hearing other's accounts. The storytellers shared value in looking at times in their life with their parent before the diagnosis and benefited from using touchstones [e.g. photos, music, clothing, objects] to assist with unearthing stories. Participants revealed that the monthly meetings were something they looked forward to attending and expressed interest in continuing.

CONCLUSION: This storytelling workshop revealed a process that invites children of a parent with YOD to explore the potential benefit of creating and sharing stories with others in a similar lived experience within a supportive environment. The potential psychosocial intervention would benefit from research to evaluate its value with the intention to be replicated.

Lay Language: Younger-onset dementia (YOD) affects people under age 65. Many with YOD have children who are impacted and have few support resources. Lorenzo's House [LH] supports families affected by YOD through community, education, and advocacy. LH created the NEXTGEN movement, inviting young leaders who are children of an individual with YOD to raise awareness and reduce stigma. A five-week storytelling workshop was created to assist with creating stories of their experience. Four participants met once a month for 90 minutes and sessions included check-ins, writing prompts, storytelling lessons, sharing stories, and supportive feedback. Participants reported that sharing their stories in a safe and understanding space was meaningful and valued reflecting on memories from before their parent's diagnosis. The workshop suggests storytelling may help young people process their experiences with YOD and connect with others in a similar situation.

Poster 72

An Integrated Language Intervention in Primary Progressive Aphasia: Preliminary Results

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Purpose: Primary progressive aphasia (PPA) is a younger-onset, language-based dementia for which no pharmacological treatments are currently available. Research has shown that speech therapy is the most effective tool for helping people affected by this syndrome sustain language abilities as long as possible. Existing restitutive approaches, which focus on target specific language deficits, yield variable generalization to everyday communication, underscoring the need for treatment models that integrate restitutive approaches with functional communication training. This study presents preliminary data from an 8-week, remotely delivered integrated intervention combining Lexical Retrieval Cascade Treatment (LRCT) with Communication Partner Training (CPT).

Methodology: Two individuals with early-stage PPA (one with semantic variant, one with logopenic variant) completed the integrated LRT-CPT protocol, with twice-weekly sessions via Zoom. Sessions included 45-60 minutes of LRT followed by 15-25 minutes of CPT every other session. Outcomes were assessed across four domains: picture naming accuracy (50-item personalized probe set; 40 trained, 10 untrained), narrative discourse (Cinderella story re-tell task), quality of life (Aphasia Impact Questionnaire; AIQ), and dyadic communication efficacy (Measures of Skills and Participation in Conversation; MSC-MPC).

Findings: On items trained in sessions, both participants' naming accuracy improved significantly ($p=.001$ for both, McNemar's test). Gains were also noted on untrained items, indicating generalization beyond directly trained stimuli. Analysis of narrative data showed that both participants' sentence construction had improved, with one participant also demonstrating improved word choice specificity. Quality of life scores improved significantly for both participants on the AIQ (P1: $p=.012$; P2: $p=.022$), reflecting meaningful gains in perceived communicative participation and emotional well-being. Dyadic communication scores showed improvement in both participant efficacy and communication partner competence from pre- to post-intervention.

Conclusion: Based on these initial results, LRT-CPT appears to be a promising combined restitutive and functional communication intervention that may improve word-finding, discourse, quality of life, and conversational involvement in people with early-stage PPA.

Lay Language: Primary progressive aphasia (PPA) is a neurodegenerative disorder that gradually affects a person's ability to speak, find words, and communicate. There is currently no medication to treat PPA. Our team developed a new 8-week communication program, delivered remotely via Zoom, which combines targeted word-finding treatment with conversation training for both the person with PPA and their communication partner. In our early results with two participants, both showed meaningful improvements in word-finding, sentence formation, quality of life, and conversational abilities. These finding suggest that integrating both approaches into treatment may be key to improving daily communication and quality of life.

Poster 73

Behavioral Treatment of Insomnia to Improve Memory in Older Adults: A Pilot Study

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Background: Insomnia affects up to 48% of older adults and is a well-established risk factor for memory decline in later life. Sleep fragmentation and reduced slow-wave activity (SWA), both hallmarks of insomnia, have been linked to impaired declarative memory and reduced hippocampal function. Behavioral therapy for insomnia is the AASM-recommended first-line treatment and has been shown to reduce sleep fragmentation and increase SWA. Yet, whether this treatment leads to memory benefits in older adults remains unknown. Prior studies have found no memory benefit for brief behavioral therapy for insomnia (BBTI) but may have been limited by insensitive memory tasks and assessment windows too narrow to capture delayed treatment effects. Further research is needed to examine whether behavioral insomnia treatment benefits memory in older adults, using robust memory tasks and adequate follow-up assessment.

This proposed pilot study will test whether BBTI improves memory immediately following treatment and at 3 months post-treatment (when effects are most likely to be pronounced). In addition, we will examine sleep architecture (e.g., sleep fragmentation), which may implicate specific aspects of sleep physiology in predicted memory gains.

Methods: Thirty older adults aged 60–85 with insomnia will be enrolled. BBTI will be administered by a trained clinician and last four weeks. Memory will be assessed using the Mnemonic Similarity Task (MST) which is sensitive to sleep disruption and age-related memory change. Subjective insomnia symptoms will be assessed with the Insomnia Severity Index. At-home sleep EEG will be collected across three nights per timepoint using the Muse-S wireless device (Toronto, ON, Canada). Daily sleep diaries will supplement objective data. Memory, insomnia severity and sleep will be assessed at baseline, post-treatment, and 3-month follow-up. Linear mixed-effects models will be used to examine changes in memory performance over time. Sleep parameters will be added as time-varying predictors.

Implications: This study will generate preliminary data for future large-scale study. Findings will provide proof-of-concept for BBTI as a nonpharmacological strategy to benefit memory in later life.

Lay Language: Memory decline is one of the most feared consequences of aging. Poor memory and poor sleep often occur together. Luckily, behavioral therapy for insomnia is a highly effective treatment. But does better sleep in later life lead to better memory? This study explores that question by testing memory before treatment, right after treatment ends, and 3 months later, when we expect benefits to be most apparent. We will use highly sensitive memory assessments to detect subtle changes that previous studies might have missed. Our results may identify ways we can protect brain health in later life through better sleep.

Poster 74

Distinct Cognitive Trajectories in SuperAgers Identified by Repeated-Measures Latent Class Analysis

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Background: SuperAgers are individuals aged 80 and older with exceptional episodic memory performance comparable to individuals 20–30 years younger. Whereas some SuperAgers maintain stable memory over time, others exhibit longitudinal decline, potentially reflecting accumulation of neurodegenerative pathology. Characterizing heterogeneity in longitudinal cognitive trajectories may illuminate mechanisms of cognitive resilience. This study applied repeated-measures latent class analysis (RMLCA) to identify memory trajectory subtypes among SuperAgers and same-age controls and examined demographic predictors of class membership.

Methods: 262 participants enrolled in the Northwestern Alzheimer's Disease Research Center Clinical Core who completed the Rey Auditory Verbal Learning Test (RAVLT) at a minimum of three annual visits were included. RMLCA is a person-centered statistical approach that identifies hidden subgroups sharing similar longitudinal patterns of change; models with one to four classes were compared using the Bayesian Information Criterion (BIC) and convergence, with time since baseline as the longitudinal metric. Age, education, sex, race, and ethnicity were incorporated as class-membership covariates. Individual RAVLT slopes were classified empirically as Decliner or Stable; agreement with RMLCA was assessed via Cohen's kappa.

Results: The 2-class solution achieved full convergence and best fit (BIC = 3938.33). Class 1 (n = 134, 51.1%) exhibited a flat trajectory (slope ≈ +0.004 SD/year) with a mean baseline RAVLT score approximately 0.84 SD above the sample mean and a mean baseline age of 81.8 years. Class 2 (n = 128, 48.9%) showed loss of approximately one word recalled per year on the raw RAVLT (slope = −0.193 SD/year; $p < 0.001$), with lower baseline performance and a mean enrollment age of 83.1 years. Older baseline age predicted reduced probability of Class 1 membership ($\beta = -0.145$, $p = .032$). Concordance with empirical classification was moderate ($\kappa = 0.391$, $p < .001$): 81% of Decliners were assigned to Class 2 and 65% of Stables to Class 1.

Conclusion: RMLCA identified two distinct longitudinal memory trajectory subtypes among SuperAgers and cognitively-average peers: a stable class and a declining class differing in both baseline level and rate of change. Older age at enrollment predicted declining-class membership. These findings highlight meaningful heterogeneity in the pace of cognitive aging in very old adults and establish a foundation for investigating the neurobiological correlates of cognitive resilience.

Lay Language: SuperAgers are people aged 80 and older with memory as sharp as people 20-30 years younger. Though many maintain exceptional memory for years, others show gradual decline. Using repeated-measures latent class analysis, a method that groups individuals by how their memory changes over time, we classified 262 participants based on up to 21 years of annual testing. We identified two groups: a stable group (51%) whose memory scores remained largely consistent, and a declining group (49%) whose memory scores meaningfully worsened over time. Participants who enrolled at older ages were more likely to belong to the declining group. These findings show that even older adults with exceptionally preserved memory vary meaningfully in how memory changes with age, providing a foundation for identifying the factors that help some individuals resist memory loss.

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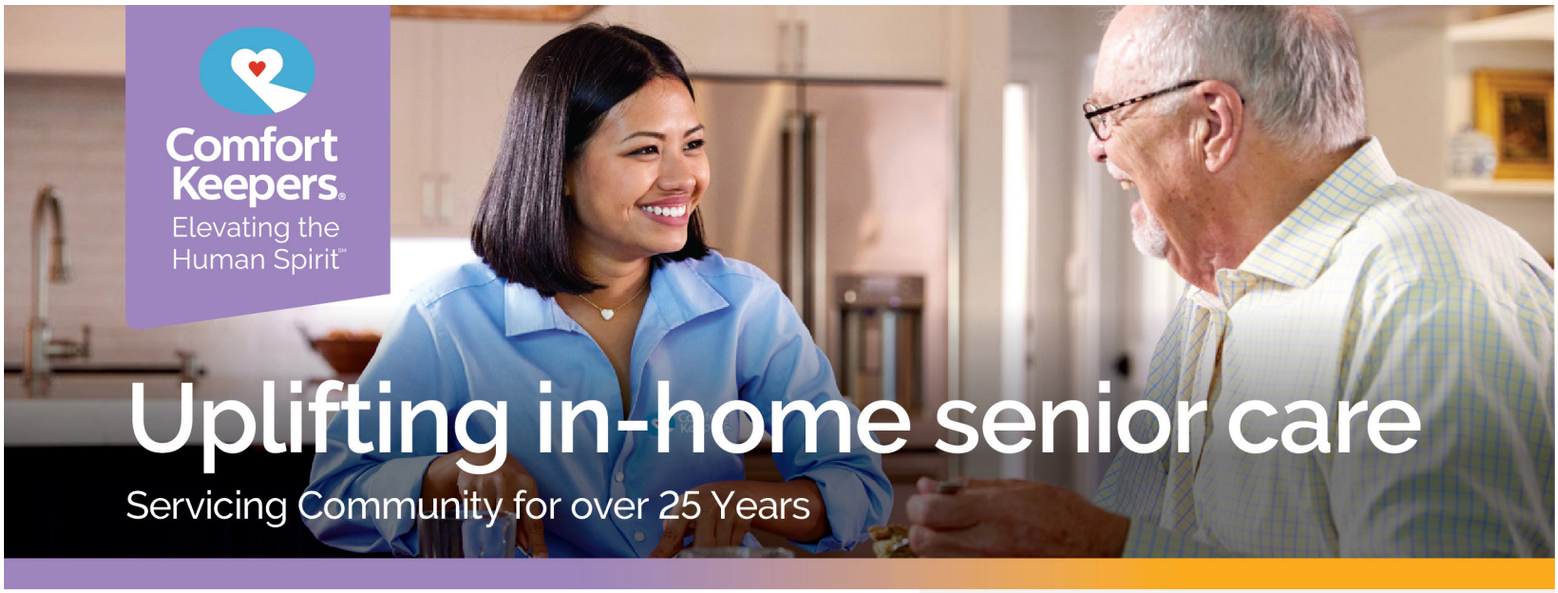

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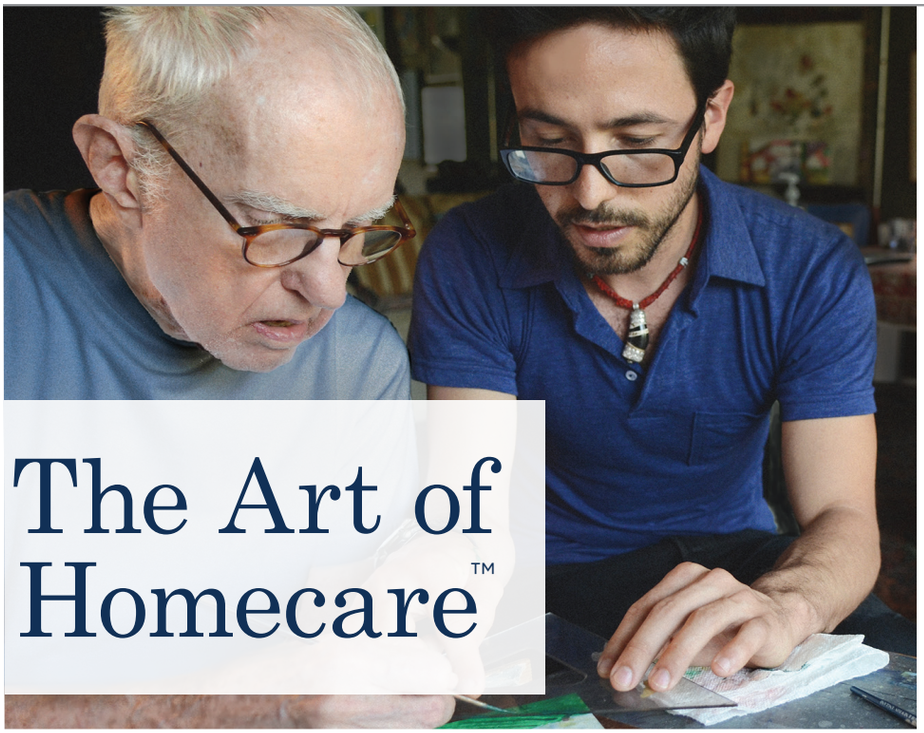

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- Escorts to doctor's appointments
- Meal preparation, errands, & light housekeeping
- Assistance with organization & technology
- Personal care support, including all activities of daily living (ADLs)

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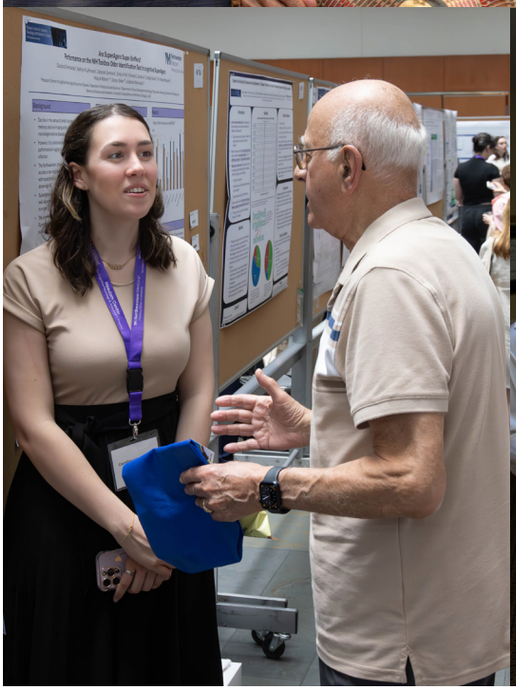

Join Us at the Mesulam Institute

Whether virtual or in-person, we offer a variety of events, including conferences and seminars for our community.

Learn more at brain.northwestern.edu.

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