Mesulam Center
for Cognitive Neurology & Alzheimer's Disease

30th Annual Alzheimer Day

Friday, May 3, 2024 | 9:00 AM - 2:30 PM CT

Abstract Book

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Thank you to all Mesulam Center staff and faculty who have made this day a success!

The Mesulam Center appreciates your dedication and commitment to making this day possible.

Schedule of Events

30th Annual Alzheimer Day | Friday, May 3, 2024

Robert Feinberg Pavilion Conference Center
251 E. Huron St, 3rd Floor

9:00 - 10:00 AM	**Registration and Vendor Fair**
10:00 - 10:25 AM	**Welcome and Center Update**
	Robert Vassar, PhD *Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease; Davee Professor of Alzheimer Research, Northwestern University Feinberg School of Medicine*
10:25 - 10:30 AM	**Presentation of Marie and Carl Duncan Prize in Memory Research**
	John Disterhoft, PhD *Associate Director, Ernest J. and Hattie H. Magerstadt Memorial Research Professor Emeritus in Neuroscience, Northwestern University Feinberg School of Medicine*
10:30 - 11:30 AM	**Mendelson Lecture: "The Molecular Era of Alzheimer's Disease Diagnosis and Treatment"**
	Gil Rabinovici, MD *Edward Fein & Pearl Landrith Distinguished Professor and Director, UCSF Alzheimer's Disease Research Center, University of California, San Francisco (UCSF)*
11:30 - 11:45 AM	**Break**
11:45 AM - 1:00 PM	**Quality of Life Symposium: "Through the Lens of Younger Onset Dementia: Forging a New Path"**
	Sponsored by the Glen and Wendy Miller Family Foundation.
1:00 - 2:30 PM	**Lunch, Research Poster Session, and Vendor Fair**

Welcome

Dear Friends and Colleagues:

It is my great pleasure to welcome you to the 30th annual Alzheimer Day. This year marks the 30th anniversary of the Mesulam Center for Cognitive Neurology and Alzheimer's Disease (formerly the Cognitive Neurology and Alzheimer's Disease Center). Drs. Marsel Mesulam and Sandra Weintraub established the Center in 1994, and it has been going strong ever since. Their vision for the Center was to create a multi-departmental, multi-disciplinary academic unit integrating basic and clinical research under one roof to understand dementia and cognition, a mission that continues unabated to this day. One year and four months ago, I transitioned to Director of the Mesulam Center, following in the footsteps of Dr. Mesulam. He is a giant of the dementia field, and it is my great honor to lead this extraordinary treasure that he, Dr. Weintraub, and their colleagues have built over the course of three decades. Our programs on the understanding of dementia, primary progressive aphasia, and SuperAging have prospered and enjoy international leadership in these fields of research. Although Dr. Mesulam has stepped down as Director, he remains very active in the Center, conducting his many research, clinical, and teaching activities. I look forward to my continued work with him and our dedicated faculty, staff, trainees, study participants, patients, families, community partners, and you all, as we spur the Mesulam Center on to new heights and achievements..

Mesulam Center Update

You will be pleased to know that the current year has witnessed exceptional growth and progress. Components of the Mesulam Center, including the Alzheimer's Disease Research Center (ADRC), the Northwestern SuperAging Program (NUSAP), the Primary Progressive Aphasia (PPA) 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), which Dr. Mesulam established at the Center a quarter century ago, is advancing our knowledge of superior cognitive aging in "SuperAgers", individuals over the age of 80 with memory performance equivalent to those at least 20-30 years younger (please visit poster #44). Northwestern continues to lead research on SuperAgers and is making discoveries on how SuperAgers may have achieved their exceptional cognitive status. For example, research led by Dr. Changiz Geula indicates that the cholinergic neurotransmitter system, which is important for cognition and degenerates early in Alzheimer's disease (AD), has fewer abnormalities in the SuperAger brain compared to the normal-ager brain. In addition, work by graduate student Alyssa Macomber in the lab of Dr. Tamar Gefen has determined that a biomarker of AD, p-tau181, is reduced in the blood of SuperAgers compared to normal agers. The Mesulam Center is humbled and grateful to have amassed the largest collection of post-mortem SuperAger brains in the world, which is propelling new research in this fascinating area of science. These and other advances in NUSAP, too many to mention here, promise to reveal the secrets of SuperAgers in the hope that this knowledge will benefit normal agers and those with AD and other dementias.

PPA, a clinical syndrome which initially affects speech and language, has been a major focus of the Mesulam Center since its inception. Although not as well known as its more infamous cousin, AD, PPA has received more press lately with the recent diagnoses of celebrities Wendy Williams and Bruce Willis, both of whom have a form of primary progressive aphasia. As Dr. Elena Barbieri puts it, PPA is a special window into the brain that enables us to both gain insight into the causes of this devastating neurodegenerative disorder as well as understand how language is represented in the brain. For example, Dr. Mesulam recently published that PPA caused by a pathology named TDP-C revealed the function of a brain region called the temporal pole. He and his team made the fascinating discovery that not only does the temporal pole subserve language, i.e., word comprehension, but it also is important for face recognition and the regulation of behavior. Through these detailed clinical-pathological correlation studies, the Center is making progress elucidating the underpinnings of dementia and normal brain function. To support those caring for individuals living with PPA, Dr. Darby Morhardt and her team, completed the second pilot of PPA Tele-Savvy, an online psychoeducation program offering disease education, care strategies and other tools addressing the unique psychosocial needs of this complex disease.

The Glen and Wendy Miller Family Buddy Program, that matches persons living with dementia with students and fellows, continues to flourish and expand under the leadership of Dr. Darby Morhardt and her team. This very popular program was initiated at the Mesulam Center 27 years ago and has been replicated by other institutions

around the country. Buddies enjoy mutual benefits: those living with a dementia diagnosis have the opportunity to mentor a first-year medical student and engage socially while students obtain valuable first-hand experience around the lived experience of dementia. We look forward to supporting the Buddy Program for another successful year.

The soothing power of music is being studied in the Center by Dr. Borna Bonakdarpour, who was awarded a grant from the National Endowment for the Arts. In a recent publication, Dr. Bonakdarpour found that improvisatory music increased calmer and slower brain waves and reduced blood pressure in patients and caregivers. His research will enable us to measure the effects of music in more objective and scientific ways that may be valuable for alleviating anxiety.

The Research Education Component of our ADRC, led by Dr. Geula, has continued its mission of training and education. Dr. Geula's Brain Scholars Program has the goal of training the future research workforce with a concentration on underrepresented groups. In partnership with schools on the South Side of Chicago, this program provides exposure to research and clinical aspects of aging and dementia, and in its short period of operation, has engaged over 200 high school and middle school students from underrepresented groups in activities related to this field. Engaging young people from underrepresented groups in research at an early stage of their education is one of our most important missions. The Mesulam Center will continue vigorous efforts to expand diversity at all levels of dementia training and research.

Recruitments, promotions, and awards are central to academic life. I am delighted to report that Dr. Todd Parrish was named as Imaging Biomarker Core Leader of our ADRC. This role is critical for the Center's research on the causes of dementia. In addition, we have recruited five new faculty to the Mesulam Center. Dr. Pouya Jamshidi was promoted to Assistant Professor of Pathology and was appointed ADRC Assistant Neuropathology Core Leader. Dr. Molly Mather, Assistant Professor of Psychiatry and Behavioral Sciences, has assumed a leadership role in the Northwestern SuperAging Program. Dr. Elena Barbieri joined the Mesulam Center as Research Assistant Professor of Physical Medicine and Rehabilitation on the PPA team. Dr. Allison Lapins, Assistant Professor of Neurology, Dr. Malik Nassan, Assistant Professor of Psychiatry and Behavioral Sciences, treat patients in the Neurobehavior and Memory Clinic and conduct research in the Center and Lauren Dowden, MSW, LCSW was promoted to Assistant Director, Outreach, Recruitment and Engagement Core. Last but not least, Dr. Mesulam received a Distinguished Lifetime Contribution to Neuropsychology Award from the National Academy of Neuropsychology.

The Mesulam Center 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 care and support. The Neurobehavior and Memory Clinic will enable new and expanded clinical programs to continue its dedication to serve those who seek care for neurodegenerative diseases.

The future of dementia research and care is bright, and the Mesulam Center will continue to work diligently to advance the understanding of dementia and how to mitigate the effects of these devastating neurodegenerative disorders. New hope for Alzheimer's disease has recently come from the successful clinical trials of the amyloid immunotherapies called lecanemab (Leqembi) and donanemab. Lecanamab was approved by the FDA last July and we are now prescribing it in our Neurobehavior and Memory Clinic. Donanemab is expected to be approved in the near future. Although there are possible side effects associated with these immunotherapies, they represent the first disease-modifying drugs for Alzheimer's disease that slow progression of the disorder. These amyloid immunotherapies are not the end, but just the beginning of disease-modifying treatments that are in development for Alzheimer's. Much work in the years ahead will be required to test different therapies that attack targets besides amyloid. We must also understand the basis of side effects and learn who would benefit the most from these new therapies.

There is much work left to be done in therapeutic testing for dementia, and the Mesulam Center will continue to be leading the way. Our clinical trials team led by Dr. Ian Grant has been expanding the number of interventional trials conducted by the Center. For example, we are enrolling patients to test the drug verdiperstat for the first ever semantic PPA trial. In addition, we are testing whether lecanemab can prevent AD in asymptomatic individuals with amyloid pathology. We are conducting many other trials and I encourage you to go the Mesulam Center website (www.brain.northwestern.edu) for further information about them and how to enroll.

Alzheimer Day 2024

As in years past, we have organized an action-packed Alzheimer Day event for you. 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 then will be honored by Dr. Gil Rabinovici from the University of California San Francisco, who will be giving the Mendelson Lecture entitled "The Molecular Era of Alzheimer's Disease Diagnosis and Treatment". Dr. Rabinovici is a world-leading Alzheimer researcher who uses neuroimaging technologies to understand the changes in the brain that occur during Alzheimer's disease. We are very fortunate to have him with us today to provide his deep insights into this critical question.

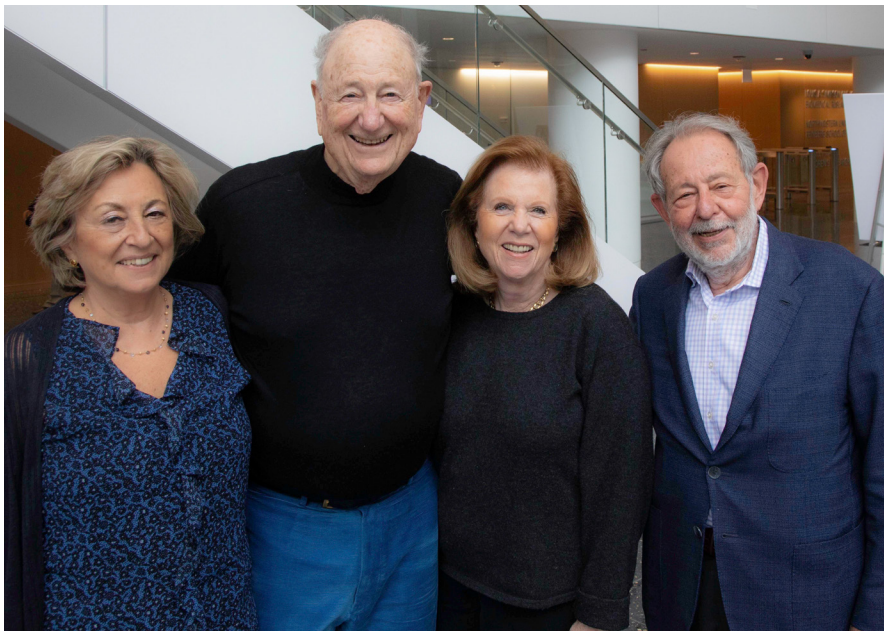
Following Dr. Rabinovici's lecture, we will have our Quality of Life Symposium, "Through the Lens of Younger Onset Dementia: Forging a New Path", sponsored by the Glen and Wendy Miller Family Foundation, featuring a distinguished panel to discuss topics related to this important subject affecting both those living with younger onset dementia and care partners alike.

Next, we invite you to enjoy lunch while you peruse the many posters that describe the exciting research that is being conducted at the Mesulam Center. 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 vendor fair and our many sponsors who are represented there. We thank them for their generous support.

I look forward to seeing you in-person at the 30th Alzheimer Day festivities!

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

Thank You



(Left to Right): Sandra Weintraub, PhD, Robert Mendelson, Linda Mendelson, Marsel Mesulam, MD

Mendelson Family

The Mesulam Center 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 Center's annual Alzheimer Day.

Miller Family

The Mesulam Center 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.

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

Thank You

We would like to thank our Platinum, Gold, Silver, and Bronze Sponsors for their support of this event.

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List of Vendors by Number

The numbers of each vendor correspond to the Map of Vendor Fair on the next page.

1. **Peck Ritchey, LLC**
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5. **Memory and Aphasia Care**
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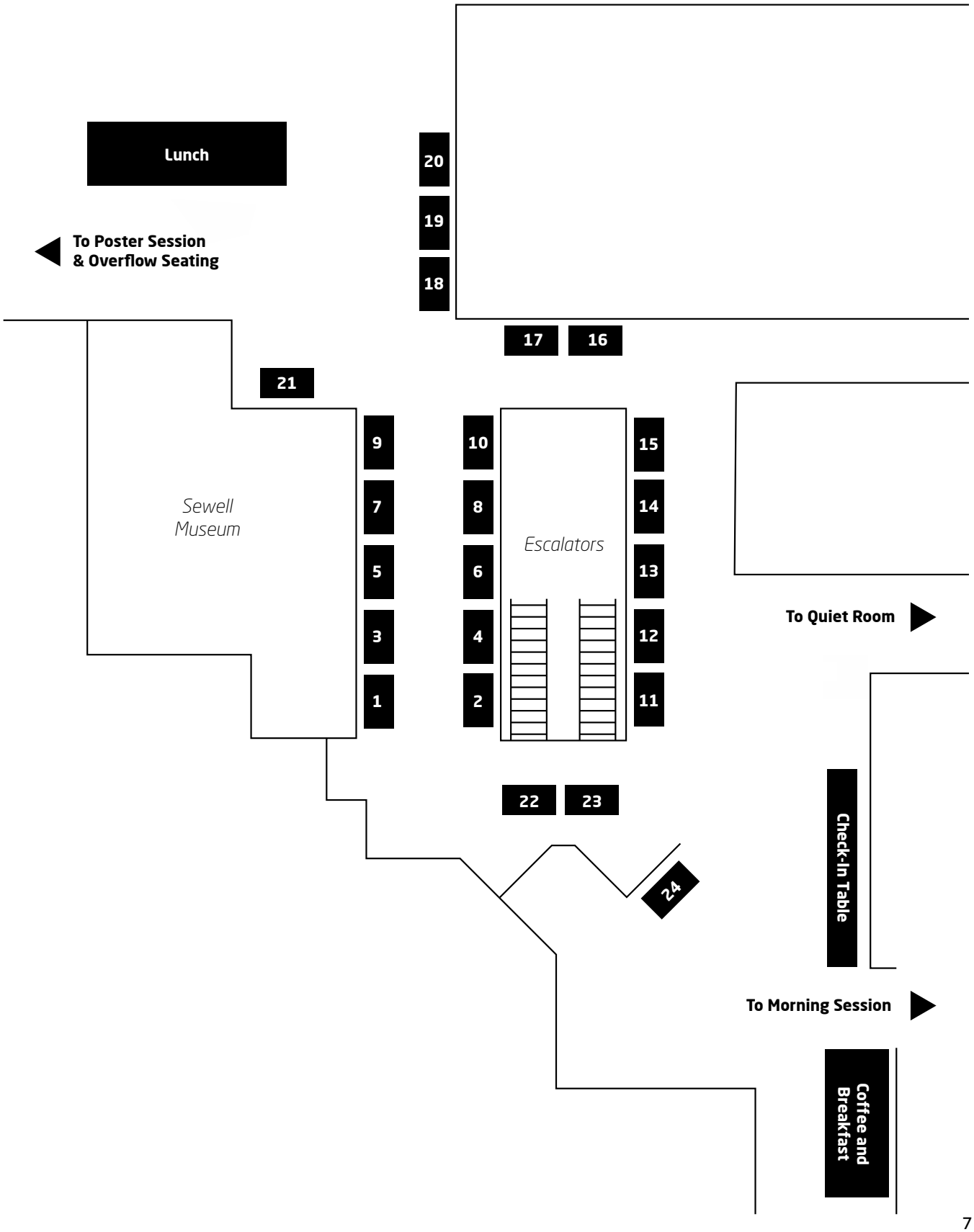
8. **Centers for Cognitive Wellness**
9. **CJE SeniorLife**
10. **Freedom Home Care and Medical Staffing**
11. **Home Instead Senior Care**
12. **Movement Revolution**
13. **Renewal Memory Partners**
14. **Senior Living Specialists Chicago**
15. **Zinnia Technologies**
16. **Hyde Park Village and Village Chicago**
17. **South Loop Village and Skyline Village**
18. **Osher Lifelong Learning Institute (OLLI)**
19. **Dementia Friendly Illinois**
20. **Lorenzo's House**
21. **Northwestern Music and Medicine Program**
22. **Northwestern Mesulam Center for Cognitive Neurology and Alzheimer’s Disease**
23. **Northwestern Mesulam Center Research Information**
24. **Poster Presenter Check-In and CEU Information**

Map of Vendor Fair



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Welcome & Center Update

Robert Vassar, PhD

Director of the Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Davee Professor of Alzheimer Research

Director of the Northwestern Alzheimer's Disease Research Center

Scientific Director of Behavioral Neurology, Department of Neurology, Northwestern University

Robert Vassar is the Davee Professor of Alzheimer Research, Departments of Neurology and Cell and Developmental Biology at the Feinberg School of Medicine, Northwestern University. He is Director of the Mesulam Center for Cognitive Neurology and Alzheimer's Disease, Scientific Director of the Division of Behavioral Neurology, and Director of the Northwestern NIH-funded P30 Alzheimer's Disease Research Center. He serves on the Cure Alzheimer's Fund Research Strategy Planning Committee, the Board of Directors of the International Society of Molecular Neurodegeneration, the Dominantly Inherited Alzheimer's Network Trials Unit Therapy Evaluation Committee, and he is a member of the Cure Alzheimer's Fund Research Leadership Group.

He has received the MetLife Foundation Award for Medical Research in Alzheimer's Disease, the Potamkin Prize from the American Academy of Neurology, and the Zenith Fellows Award from the Alzheimer's Association. He is a Fellow of the American Association of the Academy of Science and a member of the Dana Alliance for Brain Initiatives. He is an associate editor of the journal *Molecular Neurodegeneration*.

Dr. Vassar received his PhD in 1992 in molecular genetics and cell biology in the lab of Dr. Elaine Fuchs at the University of Chicago studying transgenic mouse models of human epidermal disease. He did his postdoctoral fellowship in the lab of Dr. Richard Axel at Columbia University, New York, where he investigated the molecular neurobiology of olfaction. His scientific discoveries in Dr. Axel's lab contributed to the Nobel Prize in Physiology or Medicine in 2004 to Dr. Axel.

Dr. Vassar's mother had Alzheimer's disease. Wanting to contribute to the understanding of this devastating disorder, after his postdoc he joined the biotechnology company Amgen to start a research group to identify novel drug targets for Alzheimer's disease. Using an expression cloning approach, he and his team co-discovered the beta-secretase enzyme, beta-site amyloid precursor protein cleaving enzyme-1 (BACE1) that is essential for generating the Abeta peptide that makes amyloid plaques, a primary lesion of the Alzheimer's brain.

In 2001, Dr. Vassar moved to the Northwestern University Feinberg School of Medicine, where he invented the 5XFAD transgenic mouse model of amyloid pathology in the Alzheimer's brain. He continues to explore molecular and cellular mechanisms of Alzheimer's disease using genetic, biochemical, and physiological approaches. His trainees in basic neuroscience and neurodegeneration research lead major research academic and industrial programs in the United States and abroad.

Presentation of Duncan Prize

John Disterhoft, PhD

Associate Director, Ernest J. and Hattie H. Magerstadt Memorial

Research Professor Emeritus in Neuroscience, Feinberg School of Medicine

John Disterhoft and his laboratory group are studying the neurobiology of associative learning in the young and aging mammalian brain with in vivo and in vitro techniques using eyeblink conditioning and spatial learning as behavioral model systems.

Many of their ongoing experiments focus on the hippocampus, a paleocortical region involved in transferring information during learning from short- to long-term memory storage. Single-neuron ensemble recording in the conscious animal is used to localize and functionally characterize the cell types involved in laying down the "memory trace" in the hippocampus and associated medial temporal lobe regions. In parallel experiments, biophysical measurements are made from brain slices taken from trained animals to define ionic mechanisms for the conditioning-specific alterations in postsynaptic intrinsic currents that have been observed. Synaptic alterations related to conditioning are also being explored in brain slices. Cellular and systems alterations in aging brain that may underlie learning deficits and agents which may be useful in enhancing learning rates in aging are being studied.

An overall goal of their studies is to understand both the mechanisms of learning and of memory storage and how those mechanisms are altered in cognitively intact "SuperAger" rats as compared to cognitively impaired aging animals. Hippocampus is especially involved in the initial acquisition of associative tasks. More permanent memory storage occurs in other brain regions after a process called memory consolidation. Some of their recent experiments are focusing on the manner that lateral entorhinal cortex and dentate gyrus change during both initial learning and after longer term storage of the eyeblink conditioned response. After regions are defined that store memories of the conditioned response after consolidation, more focused cellular and molecular studies can be done to characterize how this storage occurs at the subcellular level. Collaborative experiments are being done with mass spectroscopy to determine if cognitively intact aging animals show a different pattern of protein expression from cognitively impaired aging animals, as well as from a transgenic rat model of Alzheimer's disease.

The portion of Dr. Disterhoft's research program investigating slow outward currents during learning in aging received two consecutive MERIT award designations from the National Institute on Aging (NIA). His laboratory is collaborating with Dr. Joel Voss' laboratory at the University of Chicago to investigate the mechanisms of learning enhancement after transcranial magnetic stimulation in both humans and a preclinical animal model.

Dr. Disterhoft is associate director of the Northwestern University Alzheimer's Disease Research Center, executive director of the Northwestern University Behavioral Phenotyping Core and director of the Northwestern University Postbaccalaureate Research Education Program (PREP).

Mendelson Lecture

"The Molecular Era of Alzheimer's Disease Diagnosis and Treatment"

Gil Rabinovici, MD

Edward Fein & Pearl Landrith Distinguished Professor and Director, UCSF Alzheimer's Disease Research Center, University of California, San Francisco (UCSF)

Dr. Gil Rabinovici is the Edward Fein and Pearl Landrith Distinguished Professor in the University of California San Francisco (UCSF) Departments of Neurology, Radiology & Biomedical Imaging. He received his BS degree from Stanford University and MD from the Northwestern University Feinberg School of Medicine. He completed neurology residency (and chief residency) at UCSF and a behavioral neurology fellowship at the UCSF Memory and Aging Center. Dr. Rabinovici's work investigates how structural, functional and molecular brain imaging techniques can be used to improve diagnostic accuracy in dementia and to study the biology of neurodegenerative diseases, with the goal of accelerating drug development.

He is director of the NIH-funded UCSF Alzheimer's Disease Research Center, study chair of the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) and New IDEAS studies (~25,000 total participants), co-PI and PET Core lead of the Longitudinal Evaluation of Alzheimer's Disease Study (LEADS), co-PI of a Weill Neurohub sponsored project on novel PET ligand development, and PI on several additional national and local clinical, imaging and translational studies focused on AD and related disorders. Dr. Rabinovici's research is supported by NIH, Alzheimer's Association, American College of Radiology, Rainwater Charitable Foundation, Weill Neurohub Alliance for Therapies in Neuroscience, additional foundations and industry partners.

Previous awards include the 2022 Kuhl-Lassen Award from the Society for Nuclear Medicine and Molecular Imaging, 2015 Christopher Clark Award in Amyloid Imaging, the 2012 American Academy of Neurology Research Award in Geriatric Neurology and the 2010 deLeon Prize from the Alzheimer's Association.

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Quality of Life Symposium

"Through the Lens of Younger Onset Dementia: Forging a New Path"

Welcome and Introduction

Lauren Dowden, MSW, LCSW

Presentations

Differential Diagnosis in Younger Onset Dementia: *Sandra Weintraub, PhD*

The Unique Challenges of Families Living with Younger Onset Dementia: *Darby Morhardt, PhD, LCSW*

Lorenzos House: A Place for Families to Find Connection & Light: *Diana Cose*

Panel Discussion

Moderator: *Lauren Dowden, MSW, LCSW*

Panelists: *Sandra Weintraub, PhD; Darby Morhardt, PhD; LCSW, Diana Cose; Rachel Kaplan, JD; Vickie Johnson; Robert Johnson*

Community Conversation

Vickie (left) and Robert (right) Johnson with their son (center).

Vickie and Robert Johnson

Vickie and Robert Johnson have been married for 26 years. They have six children (one deceased). Vickie relocated from Grand Rapids/Kalamazoo, MI, to Chicago where she met Robert. Robert is retired from Chicago Transportation Authority as rail supervisor. Since moving to Chicago, Vickie has worked for two non-profit organizations: Evangelical Lutheran Church in America (10 yrs.) and Feeding America (15 yrs).

Vickie was diagnosed with Early Onset Alzheimer's (EOA), June 2023. Since her diagnosis, she has been involved in two ALZ studies: TACCO (Tracking and Characterization of Cognition Over Time (Massachusetts General Hospital), and Viva-Mind (NWMH). She is also a mentor in the Glen and Wendy Miller Family Buddy Program.

Quality of Life Symposium

Diana Shulla Cose

Founding Executive Director, Lorenzo's House

Diana Cose is a former primary care partner to her husband, mom of two sons, entrepreneur, visionary, strategist, innovator, and proven fundraiser. After her husband was diagnosed with younger-onset Alzheimer's, Diana recognized a massive connection and resource gap for younger families affected by dementia. She set out to solve this societal problem and founded Lorenzo's House in 2021, a virtual non-profit social impact organization designed to empower younger families walking with dementia.

With a focus on young carers, Lorenzo's House aims to *shift the narrative and cure isolation, build community and drive forward dementia justice*.

Diana leveraged her past career as an educator, school leader, and for 24 years, founder and president of a network of public schools in Chicago. Diana led the scaling of an idea from a single classroom of two teachers with 35 students - to over 250 staff, 2,300 students across ive campuses.

Diana brings passion, experience, sincerity and insight to her new venture.

Lauren Dowden, MSW, LCSW

Clinical Social Worker and Assistant Director of the Outreach, Recruitment, and Engagement Core, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Lauren Dowden is a clinical social worker and the assistant director of the Outreach, Recruitment and Engagement Core at the Mesulam Center for Cognitive Neurology and Alzheimer's Disease at the Northwestern University Feinberg School of Medicine. Lauren provides clinical care to individuals and families who are navigating a dementia diagnosis and supports the research, coordination and facilitation of ongoing quality of life programs – the Miller Family Buddy Program, PPA Tele-Savvy, and care partner support groups. Lauren co-developed the Mesulam Center storytelling workshop, *Don't Look Away: Using Storytelling to Give Voice, Find Connections, and Change Perceptions*, which invited individuals with a dementia diagnosis and their care partner to co-create a story about their lived experience that were shared across the Chicagoland area.

Lauren holds a master's of social work degree from Loyola University Chicago, specializing in mental health with a gerontology sub-specialization and a BA in theater arts from Pennsylvania State University. She is a medical improv instructor working with medical students, physicians, and healthcare professionals at Northwestern University Feinberg School of Medicine, Northwestern Medicine, Indiana University-Purdue University Indianapolis, and University of California Los Angeles.

Quality of Life Symposium

Rachel Kaplan, JD

Chief Attorney, Chicago Transit Authority

Rachel Kaplan has worked as a lawyer in the public sector for almost three decades. Her previous positions were in the Chicago Transit Authority's (CTA) legal department, the City of Chicago's Office of Corporation Counsel, and the Minnesota Attorney General's office.

Rachel has served on the boards of several social service/social justice organizations, including the Ark and Avodah. **She has also served on the Civic Leadership Council of Constitutional Rights Foundation Chicago, which promotes civic and political engagement among K-12 students.** She is currently a volunteer with Lorenzo's House, Jewish United Fund's Uptown Cafe, and the Common Pantry.

Rachel graduated from the University of Pennsylvania and Boston University School of Law.

Darby Morhardt, PhD, LCSW

Research Professor, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Darby Morhardt, PhD, LCSW is a research professor at the Mesulam Center 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 Center'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

Sandra Weintraub, PhD, ABCN/ABPP, FAAN

Professor of Psychiatry and Behavioral Sciences, Psychology, and Neurology, Northwestern University Feinberg School of Medicine

Sandra Weintraub, PhD, is professor of psychiatry and behavioral sciences, neurology and psychology at Northwestern University Feinberg School of Medicine. She has been the director of the Clinical Core at the Mesulam Center for Cognitive Neurology and Alzheimer's Disease, and now also associate director of the Alzheimer Disease Research Center (ADRC), funded since 1996 by the National Institute on Aging (NIA). The NIA-funded ADRC is a component of the Mesulam Center where she is also a researcher and clinician.

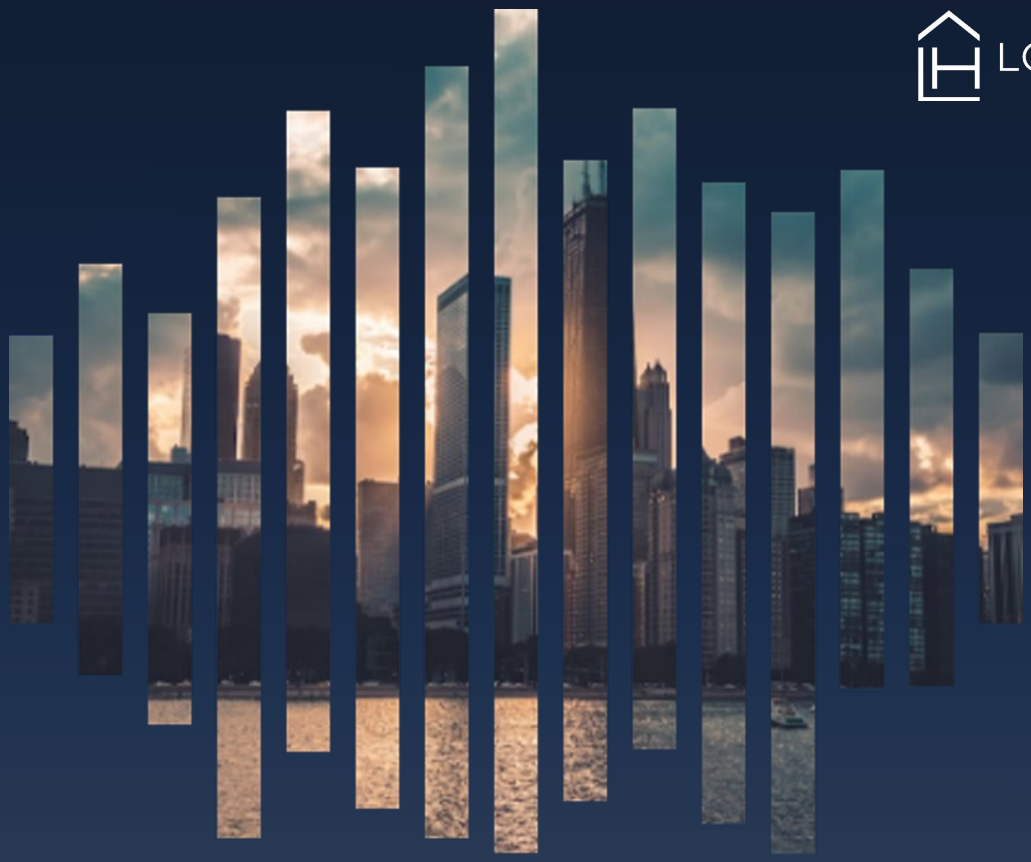
Sandra was one of the two Scientific Honorees recognized at the Rita Hayworth Gala of the Alzheimer's Association in 1997. She serves on the Alzheimer's Disease Clinical Task Force, a special advisory committee to the NIA, to create a method for standardizing data collection at all 30 centers funded by the NIA across the US, including specialized tests for disorders related to frontotemporal lobar degeneration. She was a member of three special work groups to redefine criteria for the clinical diagnosis of dementia of the Alzheimer type, the clinical diagnosis of behavioral variant frontotemporal dementia, and the clinical diagnosis of primary progressive aphasia.

Dr. Weintraub was the Cognition Domain Team leader for the NIH Toolbox, a compendium of computerized measures of neurological health. She is a past President of the International Neuropsychological Society.

Dr. Weintraub received her bachelor's degree from McGill University and PhD from Boston University and was on the faculty at Harvard Medical School before joining the Northwestern Feinberg School of Medicine in Chicago. 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, including those with early onset dementia.

Dr. Weintraub has authored over 300 publications on the neuropsychology of dementia, aging and aphasia. Her main research interest lies in the clinical, genetic and neuropathological heterogeneity of dementia and aging factors that influence individual differences in dementia and in cognitive aging.

LORENZO'S HOUSE



Lorenzo's House presents

Music Movement & Community

An in-person interactive experience where music and expression ignite joy. This is in an exclusive and stimulating learning environment of personal connection and fun. Our sessions are led by a Chicago-based musician and educator ***- designed for families walking with younger-onset dementia.***

Starting January 2024
1st and 3rd Wednesday of the month 10:30am-12pm
735 East 44th Street, Chicago, IL 60653

Email mmc@lorenzoshouse.org

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

M. Marsel Mesulam, MD
Founding Director Emeritus, Mesulam Center 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
Assistant Professor of Neurology

Joshua Cahan, MD
Assistant Professor of Neurology

Rudolph Castellani, MD
Professor of Pathology

Maureen Daly, PhD
Assistant Professor of Psychiatry and Behavioral Sciences

John Disterhoft, PhD
Research Professor Emeritus in Neuroscience, Feinberg School of Medicine
Ernest J. and Hattie H. Magerstadt Memorial Research Professor of Physiology

Tamar Gefen, PhD
Assistant Professor of Psychiatry and Behavioral Sciences

Nathan Gill, PhD
Assistant Professor of Preventive Medicine

Changiz Geula, PhD
Research Professor, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Ian Grant, MD
Assistant Professor of Neurology

Pouya Jamshidi, MD
Assistant Professor of Pathology

Allison Lapins, MD
Assistant Professor of Neurology

Molly Mather, PhD
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Research Professor, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Malik Nassan, MD
Assistant Professor of Psychiatry and Behavioral Sciences

Fred Osview, MD
Clinical Professor of Psychiatry and Behavioral Sciences

Todd Parrish, PhD
Professor of Radiology

Alfred Rademaker, PhD
Professor Emeritus of Preventive Medicine

Deborah Reed, MD
Assistant Professor of Psychiatry and Behavioral Sciences

Sandra Weintraub, PhD
Professor of Psychiatry and Behavioral Sciences, Psychology, and Neurology

Jana Wingo, PhD
Assistant Professor of Psychiatry and Behavioral Sciences

Hui Zhang, PhD
Professor of Preventive Medicine

Executive Committee

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Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease
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Founding Director Emeritus, Mesulam Center for Cognitive Neurology and Alzheimer's Disease
Ruth Dunbar Davee Professor in Neuroscience and Neurology

Eskedar Yirga Alem, BS, MSC
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Professor of Psychiatry and Behavioral Sciences, Psychology, and Neurology

Hui Zhang, PhD
Professor of Preventive Medicine

Advisory Board

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

Terry Chapman, Co-Chair
Craig C. Grannon, Co-Chair
David Moscow, Past Chair (2014-2016)

Honorary Members

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Susan Spier Chapman
Carole Feiger
Bill Goldberg
David Mendelson
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Ronald Vander Weele
Adrienne Drell
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Gloria LaGrassa
Linda Mendelson
Bob Mendelson

In Memoriam

Ken Davee
Ruth Davee
Ivan Himmel
Carl LaGrassa
Jerome Rosenstone
Kay Van Cleave
John Van Cleave

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

If you are interested in learning more about the Mesulam Center 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.**

2023: **Ivan Ayala**
Cognitive SuperAgers are Protected from Phosphorylated Tau Accumulation in Basal Forebrain Cholinergic Neurons

2022: **Allegra Kawles**
Concordance between Neocortical Distribution of Pick's Disease and the Salience of Distinct Dementia Phenotypes

Rachel Keszycki
Characterization of Distinct Neuropsychiatric Trajectories in FTLD-tauopathies

2021: **Erfan Taefi**
Cultured Microglia from Cognitive SuperAgers Show High Rates of Proliferation

2020: **Chloe Parker**
The role of astrocytes in the propagation of tau45-230-induced neuronal degeneration.

Adam Martersteck
Age prediction and amyloid deposition in SuperAgers

2019: **Kyla Guillaume**
Impaired Turnover of Synamptic Vesicle Machinery Contributes to Amyloid Pathology in Mouse Models of Alzheimer's Disease

Timothy J Hark
Decreased Resting Connectivity of Language Network with Extrasylvian Regi

2018: **Melvin Thompson & Darby Morhardt**
REACH to Faith 2.0: Building the Dementia Friendly Woodson Library

2017: **Borna Bonakdarpour**
Altered Language Network Connectivity in Primary Progressive Aphasia

2016: **Ashlee E. Rubino**
Internalized Tau45-230 Aggregates Can Spread Tau Pathology and Neuronal Degeneration in Alzheimer's Disease and Related Disorders

2015: **Dina Simkin**
Calbindin-D28K Restores the Intrinsic Excitability Properties of Aged CA1 Pyramidal Neurons to Young-Like State

2014: **Daniel M. Curlik II**
Ameliorating Age-Related Cognitive Impairments by Reducing Expression of L-Type Calcium Channels in Area CA1 of the Hippocampus

2013: **Diana Schwab Himmelstein**
Characterization of the Oligomeric Form of Tau

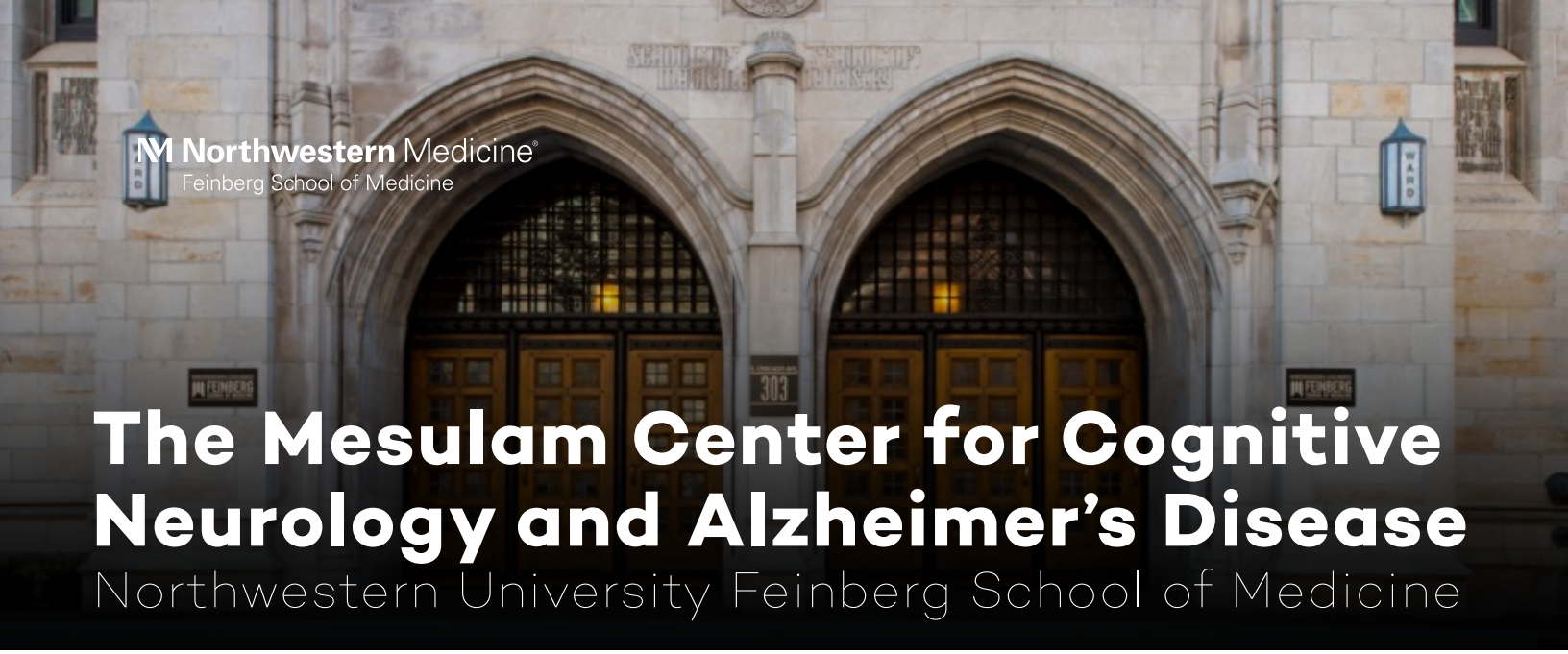
2012: **Tharinda Rajapaksha**
The Alzheimer's β-Secretase Enzyme BACE1 is Required for Accurate Olfactory Sensory Neuron Axon Guidance and Normal Glomerulus Formation in the Olfactory Bulb

2011: **Carmen Westerberg**
Electrically Enhancing Memory Consolidation During Sleep: A Novel Method for Reducing Age-Related Memory Decline

2010: **Nicolas Kanaan**
Phosphorylation in the N-Terminal Region of Tau Can Regulate Tau-Mediated Inhibition of Anterograde Fast Axonal Transport in the Squid Axoplasm

2009: **Katherine Sadleir**
The Role of EIF2-α Phosphorylation in Aβ42 Induced BACE1 Elevation

2008: **Carmen Westerberg**
Relationships Between Poor Sleep and Poor Memory in Mild Cognitive Impairmen



The Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Northwestern University Feinberg School of Medicine

Who We Are

Mission

The Mesulam Center for Cognitive Neurology and Alzheimer's Disease (Mesulam Center) 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

The Mesulam Center 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**

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Tarry 8th Floor
Chicago, IL 60611
Phone: 312.908.9339
Fax: 312.908.8789
mesulam-center@northwestern.edu

The Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Northwestern University Feinberg School of Medicine

Neurobehavior and Memory Clinic

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

Our dedicated clinical team includes behavioral neurologists, neuropsychiatrists, neuropsychologists, and social workers.

Call for an appointment:
312.695.9627

676 North Saint Clair Street
Suite 1310
Chicago, Illinois 60611
Phone: 312.695.9627
Fax: 312.695.6072

Learn more at: **brain.northwestern.edu/care-and-support**

Neurobehavior and Memory Clinic

A dedicated clinical team

Behavioral Neurologists

Marsel Mesulam, MD, Director
Borna Bonakdarpour, MD
Joshua Cahan, MD
Ian Grant, MD
Allison Lapins, MD
Malik Nassan, MD

Neuropsychiatrists

Fred Ovsiew, MD
Deborah Reed, MD

Neuropsychologists

Sandra Weintraub, PhD
Maureen Daly, PhD
Tamar Gefen, PhD
Molly Mather, PhD
Jana Wingo, PhD

Clinical Social Workers

Darby Morhardt, PhD, LCSW
Lauren Dowden, MSW, LCSW
Kate Lucca, MSW, LCSW

Nurses

Carly Liebst, RN
Brianna Lee, MPAS

Clinic Manager

Kevin Reyes, BA

Resource Coordinator

Nicole Wright, BA, CSP

Admin Team

Anthony Nowaske
Sandra Zuniga, AA

Neuropsychology Technicians

Gregory Tesnar
Connor Morfoot

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A LIFE WELL EARNED.

Since 1998, Belmont Village has safely delivered an unparalleled senior living experience for thousands of families. Collaborations with experts from the nation's top healthcare institutions and universities, including Northwestern, have established our national leadership in demonstrably effective cognitive health and wellness programs. Combining the highest levels of hospitality and care, our communities make life worth living.

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BELMONT Village

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Memory and Aphasia Care

Memory and Aphasia Care is a pioneer in providing person-centered therapy for individuals and families coping with different forms of dementia and cognitive impairments

- Primary progressive aphasia
- Mild Cognitive Impairment (MCI)
- Parkinson's disease & other movement disorders
- Alzheimer's dementia
- Lewy Body dementia
- Vascular dementia
- Behavioral frontotemporal dementia

Our Services

Speech and Cognitive Therapy

Focuses on developing tools and strategies that will help individuals to compensate for difficulty with: memory, orientation, word-finding, comprehension, sequencing tasks and swallowing.

States of licensure for telehealth: IL, IN, CA, MA, CT, FL

Occupational Therapy

Focuses on increasing independence and safety in daily life related to: attention, memory and organization strategies for schedule, and medication management, cooking, managing household activities, bathing, dressing and low vision.

States of licensure for telehealth: IL, IN, CA

Virtual Cognitive Classes

Our cognitive classes provide a unique opportunity for life-long learning in an environment that is supportive of memory and language difficulties. Each course immerses participants in a topic that promotes engagement and socialization.
The class format includes oral reading, videos, class discussion and printable home activities.

Our Locations

Outpatient Clinics	Communities	In The Home	Telehealth
Lincoln Park, Oakbrook Terrace, and Hyde Park	Assisted Living and Memory Care	Chicagoland area	IL, IN, CA, MA, CT, FL

Frequently Asked Questions

Will Medicare pay for services?

Yes, Medicare will pay for medically necessary services for individuals who have recently experienced a functional decline.

Do I need a doctor's order?

Yes, a doctor's order is required to evaluate and provide treatment. Our office can request the orders from your physician.

For More Information Contact:
(630) 800-2444 or contact@memorycarecorp.com

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.

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:

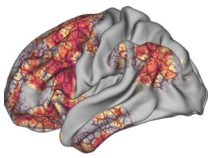
More information at www.allftd.org/sites.
Contact us at info@allftd.org.
IRB00227492 Drs. Boeve, Boxer, and Rosen.

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)

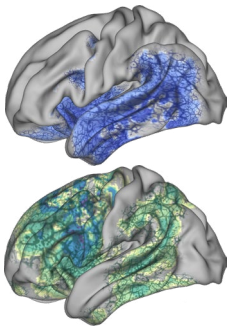


Behavioral Variant of Frontotemporal Dementia (bvFTD)

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)

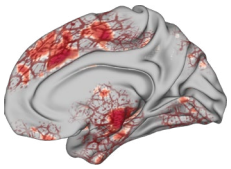
Non-Fluent Variant of Primary Progressive Aphasia (nfvPPA)



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.

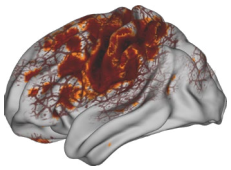
Progressive Supranuclear Palsy (PSP)



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.

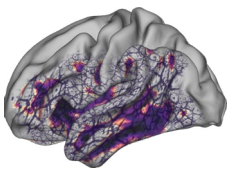
Corticobasal Syndrome (CBS)



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.

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

Northwestern Medicine®
Feinberg School of Medicine

Mesulam Center for Cognitive Neurology and 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:

Seyi Adeolu, Research Coordinator
PPA.Research@northwestern.edu
312-503-2398
www.brain.northwestern.edu

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 Center every year
- Pen and paper cognitive tests
- Surveys and questionnaires.
- MRI/PET brain scans (optional)

Compensation will be offered for your time. Travel to the Mesulam Center will be covered.

Interested? Please contact us for more information:

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

Northwestern Medicine®
Feinberg School of Medicine

Mesulam Center for Cognitive Neurology and Alzheimer's Disease

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

ALZHEIMER'S DISEASE ADCS COOPERATIVE STUDY

VIVA MIND

vivoryon therapeutics

The VIVA-MIND trial is designed to determine if the study drug, varoglutamstat, can stabilize or slow memory and thinking problems that increase in early AD.

The VIVA-MIND clinical research trial is designed specifically 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 disease, is also known as early AD.

Basic Eligibility Criteria

- Age 50-89
- Diagnosed Mild Cognitive Impairment (MCI) due to AD or probable Mild AD
- Taking the following Alzheimer's medication(s) for at least four months: Donepezil (Aricept®) or rivastigmine (Exelon®) or galantamine (Razadyne®) with or without memantine (Namenda®)
- Have a study partner who can accompany the participant to clinic visits
- Willing to participate in the VIVA-MIND study for up to 20 months

What happens during the VIVA-MIND Study?

Participation in the study will take up to 20 months. A potential participant will first go through a screening process to see if they are eligible to take part in the clinical trial. Half of the participants are given the study drug, Varoglutamstat, and half are given an inactive pill (called a placebo), which is taken orally two times daily.

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

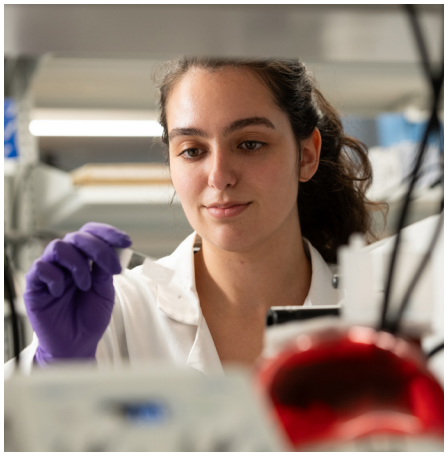
For more information or to volunteer, please contact:

NORTHWESTERN UNIVERSITY

Caila Ryan
Study Coordinator
Phone: (312) 503-5674
Email: clinicaltrials.mesulam@northwestern.edu

www.VIVA-MIND.org

The Importance of Brain Donation to our Research



Brain donation helps researchers understand cognitive aging.

Brain donation at an individual's time of death is the ultimate gift from someone who has been studied in our research for several years prior to death. Brain donation is important because it helps us understand how the brains of those who have maintained their cognitive abilities even into their 90's differ from the brains of those who have suffered cognitive decline in later years.

Some loss of cognitive efficiency typically is felt by adults over the age of 65. However, there are individual differences in the extent to which these changes occur. The relationship between what we see in the aging brain and how well a person ages cognitively turns out not to be so simple. The Northwestern Mesulam Center has been dedicated for over 30 years to study individuals who during their lifetime experience "normal" age-related cognitive change, as well as those who are affected by dementia. But Northwestern has created excitement about a unique group of individuals, who we call "SuperAgers," whose memories are better than expected for their age.

Researchers now know that some SuperAgers have healthier, bigger brain cells (neurons) than their peers with typical age-related memory loss. Some of those individuals' brains do not contain the age-related accumulation of Alzheimer proteins we find in most people over 80, especially those with cognitive decline. However, some of them contain a proliferation of those proteins but without cognitive decline! Research is being conducted to determine why some people are resistant to producing Alzheimer protein, why some people produce them but show no cognitive impairment, and why some people have these proteins and develop cognitive impairment and dementia. Although major advances have already been made possible through the generosity of brain donation, there is still much more to be learned.

Brain donation provides valuable information to families

A comprehensive autopsy is performed on the brain of donors. In the case of those with cognitive impairment, a donor's family receives a full report detailing the neuropathologist's findings and the opportunity to discuss the findings with one of our faculty. Such information is useful if other family members develop dementia in the future or if there is a known strong family history. Making this generous donation provides the family with a way to potentially help others, which can create a sense of hope and power over the illness that affected their loved one. In the case of those who have not had cognitive impairment during life, this gift stretches into the future, permitting researchers to study healthy brain aging.

Northwestern Medicine®
Feinberg School of Medicine

Mesulam Center for Cognitive Neurology and Alzheimer's Disease

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

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

The Mesulam Center Presents

The Glen and Wendy Miller Family 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**

Contact

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

Learn more at: **brain.northwestern.edu/buddy**

The Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Northwestern University Feinberg School of Medicine

Care Partner Support Groups

The Mesulam Center 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

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

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

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

Care Partners of Individuals Living with FTD

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

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

Contact: Lauren Dowden, LCSW, lauren.dowden@northwestern.edu, 312.503.5559

Care Partners of Individuals Living with Younger-Onset Dementia

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

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

Contact: Kate Lucca, MSW, LCSW, kaitlyn.lucca@northwestern.edu, 312.503.5764

Learn more at: **brain.northwestern.edu /SupportGroups**

Northwestern Music and Medicine Program (NMMP)

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.

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.

To join our research or program as a participant, or a member, please contact us:

Website: bornacogneurology.com
Email: nmmp@northwestern.edu
Phone: (312) 908-9339

Learn more at: **bornacogneurology.com/music-and-medicine-program**

Clinical Social Work Consultation:

A Customized Approach to Care

The Northwestern Neurobehavior and Memory Clinic offers a multidisciplinary team approach. Your care team includes neurologists, psychiatrists, neuropsychologists and social workers. Clinical social workers are available to discuss your questions and work with you to develop a personal and customized approach to care. Following are some questions you may have:

- **"Do I understand the diagnosis?"**

  Your social worker will:

  - Review the diagnosis and provide the opportunity to ask questions and get up-to-date disease information.
  - Discuss changing behaviors and other diagnosis-related symptoms, and offer helpful communication strategies.

- **"How do I cope with this now and as it progresses?"**

  Your social worker can:

  - Provide counseling regarding changing roles as the disease progresses.
  - Help you to assure your own self-care and to strengthen your support network.
  - Provide referrals for individual, couples, and/or family counseling.

- **"How can I plan for future care?"**

  Your social worker can:

  - Connect you to trusted elder law attorneys for estate planning and to establish powers of attorney for health care and finances.
  - Provide counseling regarding advance directives.
  - Help you to explore long-term care options and funding sources.

- **"What services are available at Northwestern or in my own neighborhood?"**

  Your social worker can guide you to:

  - Specialized support and education groups for newly diagnosed individuals and families.
  - Quality-of-life programs designed to offer meaningful and purposeful activity.
  - Other community programs in which you can find enriching opportunities.

Please call the Northwestern Neurobehavior and Memory Clinic,
312-695-9627 or ask your doctor for a referral for a clinical social work consultation.

Dementia Friends USA

A Dementia Friendly America initiative

Become a Dementia Friend

Dementia Friends USA is part of a global movement that is changing the way people think, act, and talk about dementia. Anyone can be a Dementia Friend – we all have a part to play in creating dementia friendly communities!

A Dementia Friend is someone who, through viewing a series of online videos or attending a live interactive session, learns about what it's like to live with dementia and then turns that understanding into action. From telling friends about the Dementia Friends program to visiting someone who is living with dementia, every action counts.

Get started today at **www.DementiaFriendsUSA.org**! From there you can become a Dementia Friend by committing to an activity that will help someone in your community with dementia.

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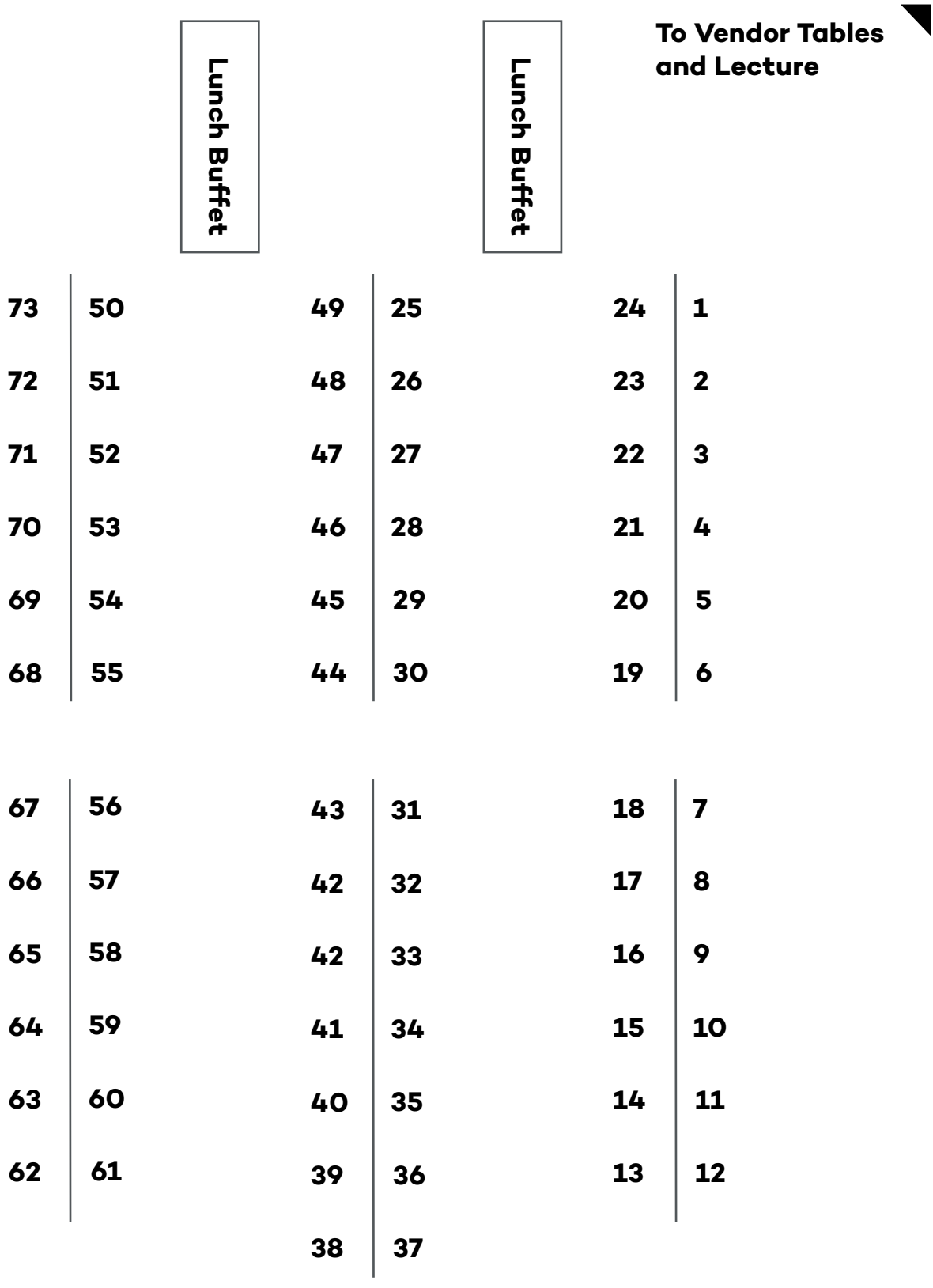
Dementia Friendly QR CODE

Poster Session Map



Poster Session

Cell & Molecular Biology

1. **Investigating the role of rare genetic variants in angiotensin-1-converting enzyme in Alzheimer's Disease pathogenesis.**
   Miranda A Salvo, BS; Leah K Cuddy, PhD; Dmitry Prokopenko, PhD; Rudolph E Tanzi, PhD; Robert J Vassar, PhD
2. **Super-resolution microscopy of lysosome contact sites in human microglia and Alzheimer's disease patient microglia**
   Kevin Shen, Erfan Taefi, Atousa Bahrami, Changiz Geula, Yvette C. Wong
3. **Distinct microglia characteristics distinguish cognitive SuperAgers from their cognitively normal peers**
   Erfan Taefi, Atousa Bahrami, Donte Garcia, Ivan Ayala, Suzanne E. Hickman, Tamar Gefen, Matt Huentelman, M-Marsel Mesulam, Emily Rogalski, Joseph El Khoury, Changiz Geula
4. **Spatial transcriptomics reveals neuroimmune mechanisms of Aβ clearance in immunized Alzheimer's disease patients**
   Lynn van Olst, Brooke Simonton, Alex J Edwards, Anne V Forsyth, Pouya Jamshidi, Mengwei Li, Nate Shepard, Talia Krainc, Benney Argue, Charles Zhang, Hang Xu, Jeanette Norman, Rudolph J Castellani, Thomas J Watson, Jinmiao Chen, James AR Nicoll, Delphine Boche, David Gate
5. **Elucidating the Role of Cis-regulatory Elements in Alzheimer's Disease via Single-cell Multi-Omics Profiling**
   Li Wang, Yaping Liu
6. **The late-onset Alzheimer's disease (LOAD) risk factor Bin1-mediated alterations of mitochondrial morphology**
   Sehyoun Yoon, Britta Schürmann, Peter Penzes
7. **Putative Cellular Identity of Dystrophic Neurites in FTLD-TDP Type C**
   Allegra Kawles, Grace Minogue, Rachel Keszycki, Antonia Zouridakis, Alyssa Macomber, Sandra Weintraub, Rudolph Castellani, M-Marsel Mesulam, Changiz Geula, Tamar Gefen

Clinical Best Practices

10. **Evaluation and Modification of the 10-Item Short Form Communicative Participation Item Bank for Persons with Primary Progressive Aphasia and their Communication Partners**
    Ollie Fegter, MA, Sara Shaunfield, PhD, Matthew Bona, MPH, Angela Roberts, PhD, Emily Rogalski, PhD
11. **Occurrence of Delirium or Encephalopathy in Pneumonia: Systematic Review and Meta-Analysis**
    Erika L. Juarez-Martinez, Aida Araia, Dilan Prasad, Shreya Dhar, Khizar Nandoliya, Ian Sherrington, Catherine Zhao, Annie Wescott, Eyal Kimchi
12. **A diagnostic tool for Alzheimer's disease: on-chip simultaneous detection of biomolecules via molecular pendulum approach**
    Vuslat B Juska, Shana O Kelley
13. **Streamlining Missing Data Identification Across REDCap Databases Through Automation**
    Deborah Zemlock, MSDS
14. **Northwestern University Alzheimer's Disease Research Center (NUADRC) Data Management Team**
    Deborah Zemlock, MSDS, Nina Reiser, MSDS, Sandra Weintraub, PhD

Poster Session

Clinicopathologic Studies

8. Stathmin-2 (STMN2) as a Potential Substrate of Cytoskeletal Integrity in Cognitive SuperAgers
Allegra Kawles, Christopher Mazurek, Antonia Zouridakis, Grace Minogue, Alyssa Macomber, Rachel Keszycki, Sarat Vatsavayai, Benayahu Elbaz-Eilon, Rudolph Castellani, M-Marsel Mesulam, William Seeley, Emily Rogalski, Changiz Geula, Tamar Gefen

15. The AHEAD 3-45 Study
Kailey Basham; Aaliyah Korkoyah; Leena Lukose; Nathaniel Houghtaling; Loreece Haddad, MS; Caila Ryan, MS; Joshua Cahan, MD; Allison Lapins, MD; Malik Nassan, MD; Ian Grant, MD

16. Veri-T
Loreece Haddad, MS; Leena Lukose; Kailey Basham; Nathaniel Houghtaling; Aaliyah Korkoyah; Caila Ryan, MS; Joshua Cahan, MD; Allison Lapins, MD; Malik Nassan, MD; Ian Grant, MD

17. ALLFTD
Nathaniel Houghtaling; Aaliyah Korkoyah; Leena Lukose; Loreece Haddad, MS; Kailey Basham; Caila Ryan, MS; Joshua Cahan, MD; Allison Lapins, MD; Malik Nassan, MD; Sandra Weintraub, MD; Ian Grant, MD

18. Disease-Specific Severity of Amygdalar Inflammation and Tau Burden in 3R vs 4R FTLD-tauopathies
Keszycki, R., Kawles, A., Minogue, G., Zouridakis, A., Macomber, A., Lubbat, V., Weintraub, S., Gill, N., Castellani, R., Mesulam, M., Geula, C., and Gefen, T.

19. The VIVA-MIND Study
Aaliyah Korkoyah; Loreece Haddad, MS; Nathaniel Houghtaling; Kailey Basham; Leena Lukose; Caila Ryan, MS; Joshua Cahan, MD; Allison Lapins, MD; Malik Nassan, MD; Ian Grant, MD

20. Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4)
Leena Lukose; Loreece Haddad, MS; Nathaniel Houghtaling; Kailey Basham; Aaliyah Korkoyah; Caila Ryan, MS; Joshua Cahan, MD; Allison Lapins, MD; Malik Nassan, MD; Darby Morhardt, PhD; Ian Grant, MD and for The Alzheimer's Disease Neuroimaging Initiative

21. Differential Vulnerability of Von Economo Neurons to FTLD-tau Species
Alyssa Macomber, Antonia Zouridakis, Vivienne Lubbat, Grace Minogue, Rachel Keszycki, Allegra Kawles, Nathan Gill, Eileen H. Bigio, Rudolph J. Castellani, M-Marsel Mesulam, Changiz Geula, Tamar Gefen

22. Alzheimer Plasma Biomarkers Distinguish SuperAgers from their Cognitively Average Peers
Alyssa Macomber, Tamar Gefen, Ivan Ayala, Sandra Weintraub, Marsel Mesulam, Emily Rogalski, Changiz Geula

23. Resistance and resilience to neuropathology in cognitive SuperAgers
Molly A. Mather, Elizabeth A. Haynes, Kathryn LaFroscia, Autumn E. Frater, Daniela Mashoudy, Pouya Jamshidi, Sandra Weintraub, Tamar D. Gefen, M.-Marsel Mesulam, Changiz Geula, & Rudolph J. Castellani

25. Utility of the Frontotemporal Lobar Degeneration Module (FTLD-MOD) to Distinguish Underlying Neurodegenerative Neuropathology in behavioral variant Frontotemporal Dementia
Janelli Rodriguez, Allegra Kawles, Miranda Gurra, Rachel Keszycki, Antonia Zouridakis, Grace Minogue, Alyssa Macomber, Vivienne Lubbat, Sandra Weintraub, Nathan Gill, Tamar Gefen

Poster Session

Community Engagement

26. Mesulam Center Brain Scholars Program: Empowering Diverse Next Generation of Neurologists and Neuroscientists
Paige Barenthin, Antonia Zouridakis, Grace Minogue, Ivan Ayala, Janelli Rodriguez, Sarah Simon, Vivienne Lubbat, Kaitlyn Lucca, Melvin Thompson, Eskedar Alem, Darby Morhardt, Tamar Gefen, Changiz Geula

27. Can People Living with Dementia Read? What Studies Show
Mary Beth Riedner

Health Services

28. Cannabis for treatment of agitation in Alzheimer's dementia - a case report
Ryan Buck, MD, Rebecca Abraham, RN, BSN

Neuroanatomy

29. Spatial and Temporal Progression of Right Hemisphere Atrophy in Primary Progressive Aphasia due to TDP-43 Type C Pathology
Jane Stocks, Jordan Behn, Sarah Simon, Elena Barbieri, Marsel Mesulam

Neuroscience

69. Relatedness effects in Primary Progressive Aphasia
Lauren Ables-Torres, Elena Barbieri, Sandra Weintraub, Marek-Marsel Mesulam

30. Age-dependent expression and accumulation of TDP-43 in a conditional wild-type human TDP-43 transgenic mouse model on the C57BL/6 genetic background
Yekaterina Taylor, Amber Chiodini, Atousa Bahrami, Ivan Ayala, Katherine R. Sadleir, Robert Vassar, Hongxin Dong, M.-Marsel Mesulam, and Changiz Geula

31. Exosomes isolated from human cortex with TDP-43 proteinopathy, TDP-43 transgenic mice and media from cultured human microglia contain human TDP-43
Ivan A. Ayala, Atousa Bahrami, Erfan Taefi, Donte Garcia, Tamar Gefen, M.-Marsel Mesulam, Changiz Geula

32. Progressive Oral Apraxia of Reading
Elena Barbieri, Joseph J Salvo, Nathan L Anderson, Sarah Simon, Lauren Ables-Torres, Jordan Behn, Borna Bonakdarpour, Ania Holubecki, Rodrigo M Braga, Marek-Marsel Mesulam

33. Semantic blurring and atrophy progression in individuals with PPA due to Frontotemporal Lobar Degeneration TDP-43 Type C.
Elena Barbieri, Allegra Sheppard Kawles, Michelle Los, Jordan Behn, Sandra Weintraub, Marsel Mesulam

34. Comparison of Atrophy Measures in Primary Progressive Aphasia
Jordan Q. Behn, Daniel Gutstein, Eunbi Kwon, Ajay Kurani, Marsel Mesulam, Todd Parrish, Elena Barbieri

35. Elucidating neurophysiological mechanisms of human brain development and aging-related memory resilience using invasive electrophysiology.
Zachariah R. Cross, Samantha M. Gray, Adam J. O. Dede, Qin Yin, Parisa Vahidi, Elias M. B. Rau, Christopher Cyr, Ania M. Holubecki, Eishi Asano, Jack J. Lin, Olivia Kim McManus, Shifteh Sattar, Ignacio Saez, Fady Girgis, David King-Stephens, Peter B. Weber, Kenneth D. Laxer, Stephan U. Schuele, Joshua M. Rosenow, Joyce Y. Wu, Sandi K. Lam, Jeffrey S. Raskin, Kurtis I. Auguste, Edward F. Chang, Ammar Shaikhouni, Peter Brunner, Jarod L. Roland, Rodrigo M. Braga, Robert T. Knight, Noa Ofen, Elizabeth L. Johnson

36. Within-network Functional Connectivity of Intrinsic Networks in SuperAgers
Bram Diamond, Adam Martersteck, Jaiashre Sridhar, Jess Wood, Nathan Gill, Sandra Weintraub, M-Marsel Mesulam, Emily Rogalski

Poster Session

37. Spatial Transcriptomic Characterization of FTLD-TDP Type C Pathology
Brian Druciak, Thomas Watson, Joshua Kuruvilla, Changiz Geula, David Gate

38. Transcriptomic Signatures of Neurotransmitter Dysfunction in the Alzheimer's Disease Nucleus Accumbens
Jeffrey T. Dunn, Guadalupe Rodriguez, David A. Bennett, Robert S. Wilson, Hongxin Dong

39. Utilizing imaging techniques in conjunction with spatial transcriptomics to investigate neuroimmune response in Alzheimer's disease patients.
Alex J Edwards, Lynn van Olst, David Gate

40. Redefining Alzheimer's Disease Therapeutics by Anti-Amyloid Monoclonal Antibodies
Kritika Goyal, Jeffrey N Savas

41. Northwestern Alzheimer's Disease Research Center Imaging Biomarker Core
Daniel Gutstein, Eunbi Kwon, Joshua Pasaye, Jaiashre Sridhar, Sarah Nicole Simon, Shruti Chandra, Jordan Behn, Megan Dorn, Malik Nassan, Allison Lapins, Ryan Avery, Emily Rogalski, Adam Martersteck, Sandra Weintraub, Elena Barbieri, M-Marsel Mesulam, Robert Vassar, Ajay Kurani, Todd Parrish

42. The Northwestern University SuperAging Program (NUSAP): 25 Years of Progress
Elizabeth Haynes, Kathryn LaFroscia, Janelli Rodriguez, Christopher Mazurek, Shruti Chandra, Antonia Zouridakis, Joshua Pasaye, Deborah Zemlock, Rudolph Castellani, Darby Morhardt, Todd Parrish, Daniel Gutstein, Bram Diamond, Nathan Gill, Hui Zhang, Molly Mather, Tamar Gefen, Changiz Geula, M-Marsel Mesulam, Sandra Weintraub

43. Fiber tract profiles of community dwelling older adults and associations with postmortem TDP-43
Ashley Heywood, Julie A. Schneider, Konstantinos Arfanakis, David A. Bennett, Lei Wang

44. High Levels of the Dendritic Spine Protein Spinophilin in Cognitive SuperAgers
Tiarra Hill, Regina Taefi, Kenton Haynes, Ivan Ayala, Atousa Bahrami, Margaret E. Flanagan, Tamar Gefen, Emily Rogalski, M.-Marsel Mesulam, Changiz Geula

45. Characterizing Motor Neuron Metabolism in ALS
Evan Kaspi, Navdeep Chandel, Evangelos Kiskinis

46. Young CSF restores oligodendrogenesis and memory in aged mice via Fgf17
Achint Kaur, Tal Iram, Fabian Kern, Saket Myneni, Heather Shin, Andreas Keller, Bradley Zuchero, Tony Wyss-Coray

47. Advancing Alzheimer's Research: An End-to-End PET Workflow Implementation using the Northwestern University Research Image Processing System (NURIPS)
Ajay S. Kurani, Jaiashre Sridhar, Elena Barbieri, Daniel B. Gutstein, Todd B. Parrish

48. Northwestern University Alzheimer's Disease Research Center (NUADRC) Clinical Core
Kathryn LaFroscia MPH, Janelli Rodriguez BS, Christopher Mazurek BS, Elizabeth Haynes BS, Shruti Chandra BS, Antonia Zouridakis BS, Joshua Pasaye BS, Deborah Zemlock MSDS, Borna Bonakdarpour MD, Rudolph Castellani MD, Changiz Geula PhD, Ian Grant MD, Molly Mather PhD, M-Marsel Mesulam MD, Darby Morhardt PhD, Todd Parrish PhD, Robert Vassar PhD, Hui Zhang PhD, Tamar Gefen PhD, Sandra Weintraub PhD

49. Music Therapy Protocol for Loss of Empathy in behavioral variant Frontotemporal Dementia
Grace Lee, Jeffrey Wolfe, MT-BC Borna Bonakdarpour, MD, Kaitlin Seibert, MD

50. Unc5C T835M mutation-mediated neurodegeneration in late-onset Alzheimer's disease in a novel mouse model
Makenna Ley, Devi Krishna, Priya Karunakaran, Joanna Guo, Jasvinder Atwal, Ryan J Watts, Robert Vassar

51. Increased resting brain connectivity in individuals with Primary Progressive Aphasia in the absence of cortical atrophy
Li, K., Behn J., Mesulam, M., Bonakdarpour, B.

Poster Session

52. Evaluating the causal association between resting state intrinsic functional networks and the risk for neurodegeneration
Malik Nassan, Iyas Daghlas, Bram R. Diamond, Adam Martersteck, Emily Rogalski

53. Comparison of Different Hippocampal Subfield Segmentation Software on Normal Controls & Mild Cognitively Impaired Patients
Joshua Pasaye, Daniel Gutstein, Jaiashre Sridhar, Ajay Kurani, Todd Parrish

54. Assessing the Effectiveness of Noise Reduction with Distribution Corrected (NORDIC) PCA Framework in Improving MRI Imaging Quality
Eunbi Kwon, Joshua Pasaye, Daniel Gutstein, Ajay Kurani, Shruti Chandra, Jordan Behn, Borna Bonakdarpour, Todd Parrish

55. Role of Brain Estrogen Deficiency in Memory Deficits in Female Aromatase Knockout Mouse Models
Tanvi Potluri, Caroline Haywood, Guadalupe Rodriguez, John Coon V, Tianming You, Hongxin Dong, Serdar E. Bulun, Hong Zhao

56. Levetiracetam prevents Aβ42 production and synapse loss in Alzheimer's disease models through SV2a-dependent modulation of App processing.
Nalini R. Rao, Olivia DeGulis, SeungEun Lee, Arun Upadhyay, Timothy J. Hark, Justin C. Dynes, Jeffrey Savas

57. Within-Individual Mapping of Language Regions in the Posterior Cerebellum
Joseph J. Salvo, Nathan L. Anderson, Elena Barbieri, M. Marsel Mesulam, Rodrigo M. Braga

58. The effect of non-pathological aging on behavior, genetics, and epigenetics in mice
Sarah B. Scheinman, Bryan McClarty, Guadalupe Rodriguez, Gemma L. Carvill, Hongxin Dong

59. Oligodendrocyte-derived Carnosine Protects the Central Nervous System from Neuroinflammation
Gwen Schulz, Tanya Klein, Benayahu Elbaz

72. Primary Progressive Aphasia Asymmetry as a Predictor of Neuropathological Diagnosis
Sarah Simon, Daniel Gutstein, Elena Barbieri, Jane Stocks, Eunbi Kwon, M.-Marsel Mesulam, Todd Parrish

73. Primary Progressive Aphasia Research Program at the Mesulam Center for Cognitive Neurology and Alzheimer Disease
Sarah Simon, Michelle Los, Lauren Ables-Torres, Oluwaseyi Adeolu, Hayley Olson, Christina Coventry, Jaiashre Sridhar, Daniel Gutstein, Eunbi Kwon, Joshua Pasaye, Adam Martersteck, Emily Rogalski, Darby Morhardt, Cynthia Thompson, Borna Bonakdarpour, Rodrigo Braga, Elena Barbieri, Todd Parrish, Sandra Weintraub, M.-Marsel Mesulam

60. Investigating sex-specific hypothalamic pathology and immune infiltration in Alzheimer's Disease
Brooke Simonton, Alex Edwards, Lynn van Olst, Jared Ahrendsen, David Gate

61. Clinical Improvisatory Music for Alzheimer's Disease Anxiety and Caregivers (CIMAC): Preliminary Results from Ongoing Trials
Vidano, K., Behn J., Takarabe, C., Bonakdarpour, B.

62. Anatomic Selectivity of Cortical Neuronal and Glial Tau in Behavioral Variant Frontotemporal Dementia with 4R FTLD-tau
Antonia Zouridakis, Grace Minogue, Allegra Kawles, Rachel Keszycki, Alyssa Macomber, Vivienne Lubbat, Nathan Gill, Sandra Weintraub, Rudolph J. Castellani, M-Marsel Mesulam, Changiz Geula, Tamar Gefen

Poster Session

Pharmacology

63. PREVENTABLE: Pragmatic Evaluation of Events and Benefits of Lipid-lowering in Older Adults
Carla Salazar Marchan, Tiffany Brown, Amanda Venables, Ji Young Lee, Manisha Cherupally, Jeffrey A. Linder

Social & Behavioral Sciences

9. Cognitive Function at Midlife by Sexual Orientation and Gender Identity in the CARDIA Cohort
Allegra Kawles, B. R. Slone, Grace V. Avila, Molly A. Mather, Ankeet S. Bhatt, James Shikany, Beth Lewis, Pamela J. Schreiner, Farzaneh Sorond, Kristine Yaffe, Patrick Janulis, Tamar Gefen, Lauren B. Beach

24. Incidental Delayed Recall of a Picture Scene as a Marker of Memory Preservation in Primary Progressive Aphasia: A Multiple Case Study
Molly A. Mather, Maureen P. Daly, Sandra Weintraub

64. PPA Tele-Savvy: Results of an Online Pilot Intervention with Caregivers of Persons with Primary Progressive Aphasia
Darby Morhardt, Kate Maley, Lauren Dowden, Kaitlyn Lucca, Bridget Moran-McCabe, Allison Lindauer, Tamar Gefen, Sandra Weintraub, Kenneth Hepburn

65. Protocol & Preliminary Results for a Multi-Domain Scoping Review to Identify Measures of Decision-Making Ability
Emily H Ho, Berivan Ece, Miriam Novack, Sarah Pila, Tatiana Karpouzian-Rogers, Molly Mather, Elizabeth M. Dworak, Zahra Hosseinian, Aaron J. Kaat, S. Duke Han, Peter Lichtenberg, Janel Hanmer, Corinne H. Miller, Richard Gershon, Sandra Weintraub

66. Anti-Amyloid Treatments for Alzheimer's Disease: Patients' and Families' Perception and Experience with Drug Consultation
Kate Lucca, LCSW, Allison Lapins, MD, Sarah Welch, MPH, Darby Morhardt, PhD, LCSW

67. 20 Years of Friendship and Understanding The Buddy Program's Legacy: Introducing Medical Students to the Lived Experience of Cognitive Impairment and Dementia.
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68. Mediterranean Eating Patterns Amongst Cognitive SuperAgers
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Investigating the role of rare genetic variants in angiotensin-1-converting enzyme in Alzheimer's Disease pathogenesis.

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Background: Recent genome-wide association studies discovered angiotensin-converting enzyme (*ACE*) as a risk locus for developing late-onset Alzheimer's disease (LOAD). ACE1 is known for its role as a blood pressure regulating enzyme in the renin-angiotensin system (RAS); however, it is also present in the brain and has other substrates, including amyloid-beta peptide. Hypertension is associated with increased risk for developing AD, and people taking select RAS-targeting therapeutics have a reduced incidence of AD. Recent whole genome sequencing (WGS) of LOAD families revealed rare *ACE* coding variants that alter the risk for LOAD. Previous work from our lab demonstrated that one such variant, rs4980, caused hippocampal neurodegeneration, which was exacerbated by amyloid pathology in a knock-in mouse model. In an effort to better understand the role of *ACE* in LOAD, other AD-risk and AD-protective *ACE* variants were selected for analysis. This project seeks to characterize these rare variants in a cellular model system in order to understand the mechanisms by which they could alter ACE1 processing, expression, function, and cell viability.

Methods: SH-SY5Y neuroblastoma cell lines stably expressing each *ACE* variant were used in the following experiments. Cell lines were differentiated for 5 days in retinoic acid, then subjected to experimental procedures to determine ACE1 expression and function as well as markers of apoptosis.

Results: AD-risk variants increased ACE1 catalytic activity while AD-protective variants altered ACE1 membrane expression and ectodomain shedding. Some mutations had altered ACE mRNA-protein relationships, which may suggest differences in ACE1 stability and turnover. No mutations caused overt cell death, indicating the potential involvement of other cell types in AD pathogenic mechanisms.

Conclusions: Thus far, this study shows that the AD-risk *ACE* variants increase ACE1 protein activity, which is consistent with other studies that have found brain ACE1 activity to correlate with AD Braak staging progression. Furthermore, this study showed that ACE1 ectodomain shedding from the cell membrane may be a protective characteristic in this culture model. Future directions include investigating these AD-associated ACE1 mutants for ACE1 protein stability and the cleavage of pathogenic ACE1 substrates such as amyloid-beta42 and angiotensin I.

Lay Language: Alzheimer's disease (AD) is the most common form of dementia and there are factors which are known to increase one's risk of developing AD including genetics, sex, and lifestyle choices. My project focuses on how the genetics of angiotensin-1-converting enzyme (ACE1) contribute to AD development. I've discovered that certain changes to ACE1 cause more of a bad protein, angiotensin II (Ang II), to be created by brain cells, which may cause those cells to die. Luckily, there are drugs that block the creation of Ang II, which may be beneficial therapeutics to prescribe to AD patients.

Poster 2

Super-resolution microscopy of lysosome contact sites in human microglia and Alzheimer's disease patient microglia

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Alzheimer's disease (AD) is the most common neurodegenerative disorder, resulting in dementia with significant cognitive decline. Recent studies have highlighted microglia as a key player in AD pathogenesis and have also pointed to lysosomal dysfunction as a contributing mechanism underlying AD etiology. Lysosomes have been shown to form dynamic membrane contact sites with one another at inter-lysosomal contact sites, as well as with mitochondria at mitochondria-lysosome contacts, which together act as important hubs for regulating lysosomal network dynamics and function. However, whether lysosomal contact sites form and how lysosomes crosstalk with amyloid-beta over time at nanoscale resolutions in human microglia, and in microglia from AD patients, is still not well understood. In this study, we used super-resolution live imaging with SIM (structured illumination microscopy) to investigate lysosomal contact site dynamics in microglia derived from post-mortem human brains. Lysosomes were found to dynamically form inter-lysosomal contact sites in these microglia, and transiently tethered at these membrane contact sites. In addition, the dynamic formation of mitochondria-lysosome contact sites between mitochondria and lysosomes was also identified using high temporal resolution imaging in human microglia. Of note, inter-lysosomal contacts and mitochondria-lysosome contacts could still undergo tethering events in sporadic AD patient post-mortem microglia. Finally, we also investigated the dynamics of amyloid-beta inside human microglia over time and were able to visualize amyloid-beta trafficking to lysosomes using live super-resolution imaging. Thus, further understanding the highly dynamic role of lysosomal contact sites in human microglia may shed light on the contributions of this pathway to AD pathogenesis.

Lay Language: Microglia are immune cells within the brain that are activated in Alzheimer's disease (AD) to eat up and degrade pathological proteins and dead cells. Understanding how this cargo is packaged and moved around inside these cells is critical to understanding how AD progresses and may reveal new targets for therapy. However, previous efforts to do so have been limited to low-resolution images or in static images of non-living cells. By using a new super-resolution microscopy technique, we are able to study the movement of cargo over time inside cellular structures known as lysosomes within living human microglia and to begin teasing apart differences in these dynamics brought about by AD.

Poster 3

Distinct microglia characteristics distinguish cognitive SuperAgers from their cognitively normal peers

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Background: SuperAgers are individuals ≥80 years with exceptional episodic memory equal to or better than individuals 20 to 30 years their junior, and display resistance to age-related neurofibrillary degeneration. Qualitative observations suggested that SuperAger cultured microglia display higher rates of proliferation compared to age-matched controls. The purpose of this study was a comprehensive and quantitative investigation of potential differences between SuperAger and control microglia.

Methods: Approximately 6.6X103 microglia from the frontal cortex of 5 SuperAgers and 5 controls were seeded and allowed to proliferate to 80% confluence prior to passage (P). Number of cells at confluence, number of days to confluence, and highest passage reached were recorded. Gene expression profiles were investigated in P4 cultures. RNASeq libraries were prepared using the Lexogen QuantSeq 3' RNA Library kit and assessed using the Agilent High Sensitivity DNA chip. Bioinformatic analysis was performed using the BlueBee integrated data analysis pipeline. Microglia function was assayed through uptake of fluorescently tagged oligomeric and fibrillar amyloid-β (Aβ42) and production of reactive oxygen species (ROS) in response to the two Aβ conformations.

Results: At each passage, SuperAger cultures contained greater numbers of microglia when compared with controls (by 150% at P5, $p<0.01$) and reached 80% confluent faster (by 108%). Control microglia ceased proliferating at P10, while SuperAger microglia proliferated up to and beyond P13. RNAseq analysis identified 434 genes differentially expressed in the two groups ($p<0.05$). Upregulated genes in SuperAgers included genes involved in DNA repair and in membrane trafficking. SuperAgers exhibited downregulation of several transcripts involved in age-related disease pathogenesis, including Adap2, MAP2, RBM20, CNTN3, and genes that regulate mitochondrial oxidative burst. Preliminary functional analysis revealed more efficient uptake and response to oligomeric when compared with fibrillar Aβ. SuperAger microglia displayed greater ROS production when compared with controls. No differences were observed in Aβ uptake.

Conclusions: These results point to distinct characteristics of microglia that may contribute to the biological bases of the SuperAging phenotype. Upregulation of genes involved in DNA repair is likely to slow microglia senescence, allowing increased proliferation in SuperAgers. Additional studies are needed to validate and extend these findings.

Lay Language: SuperAgers are identified as individuals 80 years of age or older, with superior memory compared to individuals 20-30 years their junior. To examine this population, we focused our study on the immune cells of the brain, known as microglia, to determine their potential role in superior cognitive performance. We analyzed specific characteristics of human microglia from SuperAgers and compared them with same aged cognitively normal participants. Our findings suggests that SuperAgers have an enhaced inflamatory response to abnormal proteins in the brain. Additionally, microglia in SuperAgers may be better able to repair their DNA, preventing damage to the cells. The results of our findings point to distinct characteristics of microglia that may contribute to the biological basis of SuperAging.

Poster 4

Spatial transcriptomics reveals neuroimmune mechanisms of Aβ clearance in immunized Alzheimer's disease patients

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Recent advances in Alzheimer's disease (AD) therapeutics involve immunization against amyloid-β (Aβ). Post-mortem brain analysis from the first active Aβ immunotherapy trial indicated clearance of Aβ in some AD patients. Yet, the mechanisms regulating Aβ clearance following immunization remain unknown. Here, we utilized a novel spatial proteogenomics approach to study brain tissues from 13 AD patients immunized with Aβ. We compared these actively immunized patient brains to tissues from non-immunized AD patients and non-neurologic disease controls. Additionally, we used spatial proteogenomics and single-cell RNA sequencing technologies to investigate the effects of lecanemab, a passive anti-Aβ drug. We reveal the transcriptomic neuroimmune response in the Aβ plaque microenvironment following anti-Aβ immunization. This response is characterized by an increase in genes associated with the TREM2-APOE axis in microglia of the immunized AD cortex. Furthermore, we found genes associated with neuroprotection in actively vaccinated patient brains cleared of Aβ. Altogether, our data uncover immediate and lasting neuroimmune responses in the AD brain induced by active and passive Aβ vaccination.

Lay Language: Recent advances in Alzheimer's disease (AD) therapeutics involve immunization against a protein called amyloid-β (Aβ), which is associated with the disease. Post-mortem brain analysis from the first active Aβ immunotherapy trial indicated clearance of Aβ, yet the patients still developed dementia. To investigate the mechanisms regulating Aβ clearance, we use a new technique to analyze brain tissue from patients who had been immunized against Aβ. This technique enables us to identify and localize the expression of genes within the brain tissue. We found genetic signatures in areas of the brain where Aβ had been cleared that show brain immune cell-mediated clearance and suggest the repair of nerve cells. Overall, these findings show mechanisms of Aβ clearance and long-term effects of Aβ immunization in the AD brain.

Elucidating the Role of Cis-regulatory Elements in Alzheimer's Disease via Single-cell Multi-Omics Profiling

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AD poses a significant challenge within the field of neurodegenerative disorders, progressing from Mild Cognitive Impairment (MCI) to severe dementia and impacting millions globally. While extensive research has identified numerous genetic loci, predominantly in non-coding regions, linked to AD risk, the underlying molecular mechanisms at the transcriptional, epigenomic, and cellular levels remain largely unexplored. Growing evidence suggests that a substantial fraction of these variants may affect the binding of transcription factors to cis-regulatory elements(CREs), regulating target gene expression in a cell-type-specific way. AD is also marked by notable disturbances in regulatory elements across neuronal and non-neuronal cells, complicating its study in heterogeneous tissue contexts. To address the above challenges, we propose to implement an innovative single-cell multi-omics profiling technique from our laboratory, designed to simultaneously profile the 3D genome, DNA methylation, chromatin accessibility, and transcriptome in postmortem frontal cortex samples across different stages of AD, including MCI and controls matched by age and gender. We will further utilize the hypermatrix model to computationally integrate multi-omics within the same cells by considering their spatial genomic coordination and variations in replicates. The research is expected to reveal distinct epigenetic patterns, 3D genomic structures, and integrated gene-regulatory programs in AD, delineating the functional consequences of non-coding Cis-regulatory Elements implicated in AD progression.

Lay Language: Our research is focused on understanding Alzheimer's Disease (AD), a condition that affects memory and can lead to severe brain problems. Scientists have found many genetic factors that increase the risk of AD, but there's still a lot we don't understand about how these factors actually lead to the disease. We've come up with a new way to study the disease by examining individual cells from the brains of people with AD and comparing them to healthy brains. This innovative method allows us to see multiple layers of information in the genome simultaneously in the same single cell. The information will give us a holistic picture of how genes are altered in the disease. This could help us find new ways to prevent the disease or slow down its progression, making a big difference in the lives of millions of people and their families.

Poster 6

The late-onset Alzheimer's disease (LOAD) risk factor Bin1-mediated alterations of mitochondrial morphology

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Background: Recent large GWAS identified the BIN1 gene locus as one of the most important late-onset Alzheimer's disease (LOAD) genetic susceptibility loci. However, its neuronal functions are only beginning to be understood.

Method: To determine the localization of Bin1 in neuronal mitochondria, immuno-electron scanning and structured illumination microscopy were utilized. To identify the domain of the protein interacting with Bin1, immunoprecipitation and proximity ligation assay were performed to specify the intracellular interaction site.

Results: Bin1 is highly expressed in both axons and dendrites of primary cultured cortical neurons, and interestingly, it localized in the dendritic-residing mitochondria of the mouse brain. Remarkably, the knockdown of Bin1 leads to the elongation of mitochondria in the dendritic shafts, whereas the overexpression shows no significant change. Finally, Drp1, which participates in mitochondrial fission, is identified as a Bin1 interactor by immunoprecipitation, and proximity ligation assay reveals that both interactions are positioned at the mitochondria located in the soma and dendrite.

Conclusion: A new function for Bin1 in regulating mitochondrial dynamics in neuronal dendrites is identified. It provides new insights into the biology of the LOAD risk and mitochondrial dynamics. Further investigations may suggest that Bin1 and Drp1 interaction may be a potential therapeutic target to prevent mitochondrial fragmentation and AD.

Lay Language: Research is being conducted to provide insight into exploring and discovering potential therapeutics through understanding the mechanisms of the Alzheimer's risk factor in the brain and neuronal cells.

Putative Cellular Identity of Dystrophic Neurites in FTLD-TDP Type C

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Background: Approximately 90% of individuals diagnosed with the clinical syndrome of semantic variant of primary progressive aphasia (PPA-S) will present at autopsy with the TDP-43 type C pathologic form of frontotemporal lobar degeneration (FTLD-TDP-C). FTLD-TDP-C is primarily characterized by the presence of TDP-43-immunoreactive long, thick dystrophic neurites (DNs); however, the cellular identity of long DNs is not yet known. This study aims to understand the neuronal origin of DNs via co-localization of pathologic TDP with axonal and dendritic markers.

Method: Three right-handed cases with FTLD-TDP-C as the sole pathologic diagnosis and a clinical diagnosis of PPA-S were identified from the Northwestern University Alzheimer's Disease Research Center (NU-ADRC) brain bank. Participants were co-enrolled in the NU PPA program, a longitudinal study of individuals with this dementia syndrome. Paraffin-embedded sections of right inferior frontal gyrus (IFG) were fluorescently double stained immunohistochemically with an antibody to TDP-43 phosphorylated at Ser 409/ 410 (pTDP) and antibodies to either phosphorylated neurofilament (SMI-31) or non-phosphorylated neurofilament (SMI-32) to visualize axons or proximal dendrites, respectively. Sections of right IFG were then fluorescently double stained immunohistochemically with a pTDP and microtubule-associated protein 2 (MAP2) antibody to better visualize neuronal processes, including distal dendrites. A digital image of each slide was obtained at 20X magnification using the Olympus VS200 Slide Scanner and analyzed using QuPath software (v.0.4.3).

Result: An estimated 2% of DNs showed true co-localization with dendritic protein antibody SMI-32. Qualitatively, no DNs were found to colocalize with the SMI-31. MAP2 immunostaining successfully visualized proximal and distal dendritic processes, and double staining revealed that about 50-99% of DNs co-localized with the MAP2 antibody. Both long and short DNs, the latter of which are commonly apparent in other pathologic TDP subtypes (e.g., type A), also demonstrated colocalization with SMI-32 and MAP2.

Conclusion: Preliminary findings showed that DNs in FTLD-TDP-C may be remnants of dystrophic dendrites. Greater co-localization with MAP2 antibody provides evidence for DNs as fragments of damaged distal dendrites. DNs that did not colocalize with any cellular protein may reflect loss of dendritic protein in affected neurons. While it is difficult to determine the pathogenic history of the DN through postmortem tissue, the observed co-localization, particularly that with the MAP2 antibody, is promising. Future studies will include more regions and analyze other pathologic markers to further elucidate the pathogenesis of TDP-C.

Lay Language: This study investigates the underlying causes of a dementia syndrome known as the semantic variant of primary progressive aphasia (PPA-S), which is often associated with a specific brain pathology called the TDP-43 type C pathologic form of frontotemporal lobar degeneration (TDP-C). TDP-C is primarily characterized by the presence of long, thick TDP-43-positive dystrophic neurites (DNs); however, what these long DNs are (damaged dendrites or axons) is not yet known. Using brain tissue from individuals diagnosed with TDP-C, we found DNs were associated with dendritic structures, not axonal structures. As a follow-up, we utilized additional markers to visualize distal dendrites, and findings suggest that DNs are likely remnants of distal dendrites damaged by TDP-43. These results provide exciting clues into the mechanisms that lead to TDP-C and hold potential to promote the development of future interventions for this disease.

Stathmin-2 (STMN2) as a Potential Substrate of Cytoskeletal Integrity in Cognitive SuperAgers

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Objective: SuperAgers are individuals aged 80 or older with memory performance similar to those 20-30 years their junior. Previous studies have found several unique neurobiological features of SuperAgers compared to their cognitively average same-aged peers (Normal Old), including less Alzheimer's pathology and larger, healthier neurons in the entorhinal cortex (ERC), a core memory-related limbic region. Stathmin-2 (STMN2) is a microtubule-associated protein expressed in neurons and required for cytoskeletal stabilization and axon outgrowth and maintenance. Decreased STMN2 expression has been linked to the presence of several age-related neurodegenerative diseases, including Alzheimer's disease. Increased STMN2 expression is thought to play a protective role in neuronal health, while excessive expression has been shown to have detrimental effects on neuronal health. Our objective was to explore whether STMN2 expression in the entorhinal cortex is a potential substrate of neuronal integrity across the successful cognitive aging spectrum.

Participants and Methods: Specimens from SuperAgers and Normal Old (N=4 per group) were acquired from the Northwestern University Alzheimer's Disease Research Center (ADRC) Brain Bank and the SuperAging Research Program. Paraffin-embedded anterior hippocampal sections that included the ERC were immunohistochemically stained with STMN2 antibody to visualize STMN2 expression. A digital image of each slide was obtained at 20X magnification using the Olympus VS200 Slide Scanner for analysis. Using QuPath software (v.0.4.3), the ERC was traced as a guide at 0.5x magnification. A 500 μ m x 500μ m grid was superimposed on the image, and perikarya of ~2 STMN2-positive neurons per grid square were traced. Traced neurons were analyzed for optical density (OD) due to STMN2 immunopositivity. Unpaired t-tests were used to compare age at death and Braak stage (a measure of neurofibrillary tangle burden) between groups. A nonparametric Mann-Whitney t-test was utilized to compare STMN2 OD between groups, and a Spearman correlation was used to analyze the relationship between STMN2 OD and age at death.

Results: There was no significant difference in age at death (range, 82-101) or Braak stage between groups. Normal Old showed significantly higher average STMN2 OD per neuron in the ERC (M=0.136, SD=0.075) compared to SuperAgers (M=0.078, SD=0.041) ($p<0.001$). There was a positive correlation between age and STMN2 OD across all participants that trended towards significance ($r=0.57$, $p=0.076$).

Conclusion: Preliminary findings indicate that SuperAgers may express less STMN2 than Normal Old in ERC neurons, despite comparable Braak stage, reflecting a possible substrate for superior memory. Lower STMN2 expression in SuperAgers may be due to healthier neuronal cytoskeleton in these individuals, obviating the need for increased STMN2. The positive relationship between age at death and STMN2 suggests that preserved cognition in the oldest-old may be supported by STMN2-mediated cytoprotection in pyramidal neurons. Future studies are needed to corroborate findings by examining additional limbic and neocortical regions in a larger cohort of successful agers and those with memory impairment due to Alzheimer's disease.

Lay Language: This study aims to understand why SuperAgers, aged 80 or older, maintain memory performance similar to people 20-30 years younger. Previous research identified unique neurobiological features in SuperAgers, such as less Alzheimer's pathology and healthier neurons in the entorhinal cortex (ERC), a memory-related brain region. The study focused on a protein called Stathmin-2 (STMN2), known for its role in neuron health. We examined STMN2 expression in ERC neurons in brain specimen from SuperAgers and normally aging individuals (Normal Old). Surprisingly, we found that SuperAgers expressed less STMN2 in ERC neurons compared to Normal Old. This suggests that SuperAgers may have healthier neurons, reducing the need for increased STMN2. We also found a positive relationship between age and STMN2 expression, which implies that preserving cognition in the oldest individuals may involve STMN2-mediated neuron protection.

Cognitive Function at Midlife by Sexual Orientation and Gender Identity in the CARDIA Cohort

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Introduction: Sexual and gender minority (SGM) individuals have higher prevalence of dementia risk factors compared to non-SGM individuals. However, it is not known whether SGM individuals show differences in cognitive function during midlife given limitations in comprehensive sex, sexual orientation, and gender identity (SSOGI) measures or standardized cognitive assessments in prior studies. We utilized Coronary Artery Risk Development in Young Adults (CARDIA) study data to describe midlife cognitive function by SSOGI.

Hypothesis: We hypothesize that middle-aged sexual minority (SM) and transgender and non-binary (TGNB) participants demonstrate worse cognitive test scores compared to non-SM and non-TGNB participants, respectively.

Methods: A total of 1,978 CARDIA participants completed cognitive assessments at Y25 and self-reported SSOGI measures at Y35. Participants with a history of brain cancer, kidney failure, or stroke prior to Y25 were excluded. Y25 examination included administration of standardized cognitive assessments that tested verbal memory (Rey Auditory Verbal Learning Test; RAVLT), processing speed (Digit Symbol Substitution Test; DSST), and executive function (Stroop Test). The Y35 SSOGI variables are listed in Table 1. Wilcoxon t-tests were employed to compare cognitive test scores between analytic subgroups.

Results: Mean age of the overall cohort at Y25 was 45 (SD = 3.6) years and 43% identified as Black. TGNB individuals performed significantly worse on a memory recall portion of the RAVLT ($p<0.001$) and DSST ($p<0.05$) compared to non-TGNB individuals. There was no significant difference in cognitive test scores between SM and non-SM and gay/lesbian and bisexual individuals. See Table 1 for statistical results.

Conclusions: Preliminary findings suggest TGNB individuals may demonstrate lower midlife cognitive performance related to verbal memory and processing speed compared to non-TGNB individuals. Future studies will analyze effects of depression and chronic conditions of cognitive scores and expand to later CARDIA time points.

Lay Language: Sexual and gender minority individuals face higher dementia risk factors, but it is unclear if this population show differences in midlife cognitive function. This study investigates midlife cognitive function of sexual and gender minority individuals using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study. 1,978 CARDIA participants completed comprehensive identity questionnaires and standardized cognitive assessments that tested verbal memory (Rey Auditory Verbal Learning Test), processing speed (Digit Symbol Substitution Test), and executive attention (Stroop Test). Cognitive performance was compared between: (1) transgender and non-binary (TGNB) vs. non-TGNB participants; (2) sexual minority (SM) vs. non-SM participants; and (3) gay/lesbian and bisexual individuals. Mean age of this cohort was 45 years. Preliminary findings show that TGNB individuals performed worse on verbal memory and processing speed measures compared to non-TGNB individuals. There was no significant difference in cognitive test scores between SM and non-SM and gay/lesbian and bisexual individuals. Additional study is needed to explore whether lower scores are related to differences in demographic status between groups, and to expand to all cognitive domains in a larger sample across the lifespan.

Evaluation and Modification of the 10-Item Short Form Communicative Participation Item Bank for Persons with Primary Progressive Aphasia and their Communication Partners

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Background: Primary progressive aphasia (PPA) is a dementia syndrome characterized by language and communication impairments, with relative sparing of other cognitive domains. As a relatively rare dementia syndrome, there are few measures developed and validated for individuals with PPA. Development of outcome measures tailored to the communication experiences of persons with PPA (PwPPA) is critical for the accurate assessment of interventions success. The 10-item Communicative Participation Item Bank (CPIB) has been used as a measure for communication participation in PPA. However, the CPIB was validated as a disorder-agnostic measure and its content validity for PPA has not been evaluated. This study aims to evaluate the face and content validity of the 10-item CPIB for PwPPA and their communication partners (CP).

Method: Cognitive interviews were conducted with participants (N=12) who had previously completed the CPIB during the Communication Bridge 2 randomized controlled trial (NCT03371706) and with four participants unfamiliar with the CPIB. PwPPAs and CPs completed the CPIB during a semi-structured interview assessing measure format, instructions, response options, item comprehension, and item relevance. To evaluate content validity, participants were asked open-ended questions to elicit relevant communication participation experiences missing from the questionnaire. Closed-ended responses (e.g., clarity, relevance) were tabulated, and open-ended responses (e.g., item comprehension, missing content) were thematically analyzed. Summaries of measure format, instructions, and response options were generated, as well as item-level findings regarding comprehension, relevance, and missing content.

Results: Both PwPPAs and CPs: a) considered the instructions to be clear (n=16, 100%); b) recommended adding a fifth response option (e.g., "Somewhat; n=11) to better represent the range of communication situations; c) reported all items except one ("persuade...to see a different point of view") were relevant (n≥13; ≥81%, for 9 items); and d) talking on the phone was the most reported missing communicative participation situation (n=12; 75%). Further, 3 participants reported talking over videochat, and 4 participants reported email/texting as missing. Results were similar between CPIB-experienced and CPIB-naïve participants.

Conclusion: Findings indicate that modifications to the 10-item CPIB short form may be needed for use with PwPPA and their CPs to more fulsomely capture communication participation in PPA.

Lay Language: Primary progressive aphasia (PPA) is a dementia syndrome that impairs language functions such as speaking and understanding. It is important to measure how much PPA interferes with people's ability to participate in communication activities, such as communicating in a small group of people, asking a question, or having a long conversation about a book or movie. The 10-item Communicative Participation Item Bank (CPIB) is a survey commonly used by speech-language pathologists to measure how much a condition interferes with communication activities but has not yet been evaluated rigorously in persons with PPA. In this study we interviewed people with PPA and their communication partners as they complete the CPIB, to gather their impressions regarding its clarity, relevance to their experiences with PPA, and if important communication experiences are captured by this survey. This research will help us develop a better questionnaire for individuals living with PPA and their families.

Occurrence of Delirium or Encephalopathy in Pneumonia: Systematic Review and Meta-Analysis

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Background: Delirium is a serious neuropsychiatric condition frequently observed in patients hospitalized with pneumonia. Comorbidities such as Alzheimer's disease and other dementias increase the risk of developing delirium1,2. Importantly, it is associated with increased length of hospitalization and mortality and a strong predictor of adverse outcomes3. Here, we report the occurrence of delirium in patients hospitalized with pneumonia.

Methods: We systematically searched for studies across five electronic databases from inception to February 2023. Eligible studies described adult patients hospitalized with pneumonia with rates of occurrence of delirium or encephalopathy. We compared delirium occurrence using random-effects models to describe summary estimates. Study quality and risk of bias was assessed using the JBI manual for evidence synthesis that includes a critical appraisal checklist for analytical cross-sectional studies. We incorporated this in sensitivity analyses. We performed subgroup analyses for age (<65, >65), infection setting (community-acquired, hospital-acquired, and ventilation-associated pneumonia), microbiological agent (bacterial, viral, and COVID), care setting (intensive care, emergency department or medical floor), mechanical ventilation status, clinical severity, delirium diagnostic method (confusion assessment method scoring, clinical diagnosis, other) and clinical comorbidities (dementia, stroke, respiratory and heart disease).

Results: Of 3396 titles, we included 98 papers (n = 8,349,120) in the quantitative analysis. Delirium occurred in 93,439 participants. Summary estimate for occurrence of delirium was 21.93% (95% CI [17.3%; 27.4%]). Limiting to studies at low risk of bias with ascertainment for pneumonia based on standardized diagnostic tools (43 studies, 30862 participants) the occurrence rate was 20.51% (n = 4327, 95% CI [15.4%; 26.8%]). When standardized diagnostic tools to ascertain delirium were used (11 studies, 3558 participants), the occurrence of delirium was higher 29.89 % (n = 884, 95% CI [16.2%; 48.4%]). Only 8 studies met a strong quality-criteria that included both standardized pneumonia and delirium ascertainment (2208 participants). Based on these, the reported occurrence of delirium increased to 36.88% (n = 666, 95% CI [17.1%; 62.3%]).

Conclusions: Delirium is common in patients suffering with pneumonia. Reported rates of delirium increase when standardized diagnostic tools are used indicating their relevance in accurately detecting the condition and its high prevalence in a hospital setting.

Impact statement: Our estimate of delirium occurrence can raise awareness of delirium in hospital settings and aid in establishing early intervention plans.

Clinical Trial Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023385571

Lay Language: Delirium is a serious neuropsychiatric condition frequently observed in patients hospitalized with pneumonia. Comorbidities such as Alzheimer's disease and other dementias increase the risk of developing delirium. Importantly, this is associated with increased length of hospitalization and mortality. Here, we report the occurrence of delirium in patients hospitalized with pneumonia and its association with age, different comorbidities, and care settings. Our estimate of delirium occurrence can raise awareness of delirium in the hospital and aid in establishing early intervention plans.

Poster 12

A diagnostic tool for Alzheimer's disease: on-chip simultaneous detection of biomolecules via molecular pendulum approach

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Background: Alzheimer's disease (AD) is the most prevalent and profoundly impactful neurodegenerative disorder, accounting for 60-70% of dementia cases. The current diagnosis of AD involves medical imaging, cognitive tests, and cerebrospinal fluid (CSF) analysis. Over the past years, there has been a surge in literature demonstrating the development of biosensors for AD to address the need for an AD diagnostic tool. However, existing examples often involve large experimental setups with numerous components for a single measurement or encounter challenges related to bio-fouling which affect the performance of the sensor. Our project aims to overcome these limitations by developing miniaturised electrochemical on-chip technology capable of simultaneously determining concentrations of key clinical biomarkers for AD on a single device.

Method: We combine silicon microtechnologies with electrochemistry and "molecular pendulum (MP)" for rapid diagnostics development (milliseconds of detection time).

Results: We have designed and manufactured silicon based chips with several electroactive areas. The device fabrication flow is characterized with critical analysis methods such as electrochemistry and scanning electron microscopy. We have shown the reproducibility of the devices. Each electroactive area has 2 µ m diameter disk/band shape electrodes, which serve as microelectrodes. We also focused on the aptamers selection with high specificity towards amyloids. The chosen aptamers were used to integrate with the MP approach. Currently we investigate the electroanalytical performance of the sensing surfaces.

Conclusion: We introduce a new perspective for the next generation precision diagnostics dedicated for AD. Our research is well-focused on reliable, user-friendly and accessible detection platform development for AD biomarkers. (This project started in September 2023 at Northwestern University.)

Lay Language: We're working on the development of a simple and rapid blood testing device to help detect Alzheimer's disease (AD) as early as possible. A device like the home-use blood sugar testing devices for diabetes, but instead of measuring sugar levels, ours will measure biomarkers of Alzheimer's using a tiny electronic probe. This probe, made with advanced technology, will be incredibly precise and small, making it more sensitive for detection of the fingerprint of Alzheimer's disease in the blood. Ultimately, our goal is to add accurate technology for Alzheimer's disease diagnosis protocols, which directly test the blood. The global value of a statistical life based economic burden of AD and related dementias was an estimated $2.8 trillion (2019) and it is projected to increase to $8.5 trillion in 20401. Clearly this probe may have societal and economic impact by providing the opportunity of timely and early diagnosis.

Poster 13

Streamlining Missing Data Identification Across REDCap Databases Through Automation

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In research, effective data management is critical to ensure the production of accurate and high-quality outcomes. However, the meticulous task of evaluating data quality demands significant time and effort to establish robust protocols (Houston et al., 2018; Jones, 2018; Liu et al., 2017). This project aims to streamline data quality checks by developing an automated program designed to identify and categorize missing data values stored in REDCap (Research Electronic Data Capture) databases.

Despite REDCap offering a built-in tool for identifying missing data, its effectiveness is limited by size constraints, thereby reducing its reliability. To address this challenge, the current project extracts data from REDCap and assesses missingness using R programming, thereby enhancing the capacity to process larger datasets more efficiently. The R program employs branching logic derived from REDCap metadata and translates it into R code to discern whether blank values represent genuine omissions or non-applicable data, thus hidden during collection.

Validation of this program against the built-in tool confirms its reliability and functionality. Essentially, the R data completion check replicates the features of the REDCap data check while enhancing speed, detail, and scalability to larger database sizes. This automated process empowers research teams to conduct regular, thorough data completion checks, ultimately elevating the overall quality of research data.

Lay Language: Imagine you're doing important research. You know that managing your data well is key to getting accurate results. But checking data quality takes a lot of time and effort. That's where this project comes in. We've developed a smart tool to make data quality checks a breeze, specifically for REDCap databases, widely used by researchers around the world. REDCap does have a tool for spotting missing data, but it's not always reliable because of its size limitation. The solution? We've created a program that digs deep into REDCap data using R programming. It's like giving the data a thorough health chNoeck. The program replicates the features of the REDCap tool while enhancing speed, detail, and scalability to larger database sizes. In short, the automated tool makes sure research data is complete and accurate without all the hassle. So, researchers can focus on what matters—getting meaningful results and advancing research.

Northwestern University Alzheimer's Disease Research Center (NUADRC) Data Management Team

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The Data Management team within the Data Management and Statistics (DMS) Core at the Northwestern ADRC plays a central role in the research efforts of the Mesulam Center by ensuring the organization, integration, and accessibility of all research data. Through substantial investments in data management, we have enhanced our impact on internal activities and collaborations with NACC and other partners.

Our initiatives have streamlined interactions across ADRC cores, benefiting clinical research, neuropathology, and outreach and recruitment activities. We have automated reporting processes, saving significant staff time and improving data review processes. Additionally, we have innovated the consenting process for the clinical core, making it entirely virtual for improved efficiency and tracking.

Revamping recruitment processes has led to better participant tracking and study eligibility assessments, resulting in more efficient recruitment practices and improved data management. Furthermore, we have undertaken projects to enhance efficiency and accuracy within the neuropathology core, including database creation and data harmonization efforts.

Overall, we have handled 153 data requests, focusing on internal pulls, database management, reports, data quality checks, and collaborations. Our efforts are tailored to the nature and complexity of each request, optimizing our workflow. We are committed to enhancing data quality across all collected data, aiming to centralize all digital data within REDCap by the end of 2024. Additionally, we have developed standard operating procedures to streamline interactions with ADRC databases, ensuring efficient workflows and data management practices.

Lay Language: The goal of the data management team is to ultimately liberate researchers from the burdens of data management, allowing them to concentrate on discovering answers to crucial research questions. We've heavily invested in refining our processes, resulting in increased efficiency in our internal operations and fortified partnerships with other research bodies. Whether it's transforming participant consent procedures or enhancing research subject tracking, we're perpetually refining our methods. Looking ahead, our objectives include refining the quality of our historic research data, optimizing research practices, and centralizing research data for improved accessibility and accelerated analysis. By achieving these goals, we envision speeding up research processes and enhancing effectiveness.

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The AHEAD 3-45 Study

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The AHEAD 3-45 trial is a phase III, multi-center, placebo-controlled, double-blind, parallel-treatment arm study evaluating the safety and efficacy of the investigational drug BAN2401 (also known as lecanemab or Leqembi) at reducing the risk of Alzheimer's Disease (AD) in preclinical populations. BAN2401 is an intravenous amyloid targeting monoclonal antibody therapy that slowed the decline in cognition in some people in a previous study. In June of 2023, the FDA approved the use of BAN2401 for those clinically diagnosed with mild cognitive impairment due to AD or mild dementia due to AD and has approved the investigational use of BAN2401 for this trial. The study will enroll approximately 1,400 participants across 100 research sites globally into 2 cohorts: elevated levels of amyloid (A45 cohort) and intermediate levels of amyloid (A3 cohort). Amyloid levels are determined via amyloid PET imaging during the screening process. Participation involves biweekly (A45) or monthly (A3) infusions, clinical and cognitive assessments, brain imaging including PET scans and MRIs, biomarker and genetic testing, and optional cerebrospinal fluid analysis. This trial will last over a duration of 4.5 years with an option to continue participating in an open label extension period. Northwestern enrollment for this trial is open and currently screening for participants between the ages of 55 and 80. Those who are not eligible for AHEAD 3-45 may be eligible to enroll in the observational Alzheimer's plasma extension sister study (APEX).

Lay Language: The AHEAD 3-45 trial is a phase III, multi-center, placebo-controlled study evaluating whether an investigational drug called lecanemab will reduce the risk of developing Alzheimer's Disease (AD) dementia. This drug works by reducing an abnormal form of a protein called "amyloid" that builds up in the brains of people with Alzheimer's disease. Participants in this study receive intravenous infusions of lecanemab or placebo every 2 or 4 weeks, depending on study cohort over a course of 4 years with an option to continue participating in an open label extension period.

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Veri-T

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The Veri-T trial is a Phase I multi-center, randomized, double-blind, placebo-controlled treatment study testing the safety, tolerability, and efficacy of an oral drug, Verdiperstat (BHV-3241), in patients with semantic variant primary progressive aphasia (svPPA) due to frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP). Verdiperstat is a known drug that has been shown to reduce oxidative stress in patients diagnosed with Parkinson's disease, multiple system atrophy (MSA), and amyotrophic lateral sclerosis (ALS). Oxidative stress from brain inflammation is a common occurrence in individuals diagnosed with neurodegenerative diseases, such as svPPA, a subtype of frontotemporal dementia affecting the temporal lobe of the brain. svPPA is a progressive neurodegenerative syndrome characterized by the build-up of a protein called TDP-43 (transactive response DNA-binding protein 43) in the areas of the brain that control language and speech. Those affected by the disease often experience gradual difficulty in finding words, comprehending words, or finding names of objects and people. The Veri-T study hopes to determine whether Verdiperstat will reduce oxidative stress in people with svPPA to slow down the progression of these symptoms. The study is approximately 8 months long with a 6-week screening period, 24-week study drug treatment period, and a final safety follow-up visit 4 weeks after end of treatment. Assessments required as part of involvement in the study include general health assessments, paper and digitalized cognitive tests, blood and urine collection, magnetic resonance imaging (MRI) scans, and lumbar punctures for cerebrospinal fluid (CSF) collection. Eligible participant will be randomized 3:1 to receive either Verdiperstat or placebo. The Veri-T study is actively recruiting subjects between the ages of 18 and 85 with a diagnosis of svPPA due to FTLD-TDP.

Lay Language: Semantic variant primary progressive aphasia (svPPA) is a progressive neurodegenerative syndrome characterized by the build-up of a protein called TDP-43 (transactive response DNA-binding protein 43) in the areas of the brain that control language and speech. Those diagnosed with svPPA often experience gradual difficulty in finding words, comprehending words, or finding names of objects and people. The Veri-T trial is a Phase I multi-center, placebo-controlled study that will evaluate whether an oral drug, Verdiperstat, will slow down the progression of these symptoms.

ALLFTD

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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. Recruitment at Northwestern University is currently paused and limited to an active study waitlist.

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 an annual 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.

Disease-Specific Severity of Amygdalar Inflammation and Tau Burden in 3R vs 4R FTLD-tauopathies

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Objective: Primary progressive aphasia (PPA) and behavioral variant frontotemporal dementia (bvFTD) are dementia syndromes characterized by primary language impairment and changes in personality and comportment, respectively. Frontotemporal lobar degeneration (FTLD) with tau pathology (FTLD-tau) is a neurodegenerative disease that can underly both syndromes. There are several subtypes of FTLD-tau characterized by distinct pathologic inclusion morphology and areas of peak atrophy, including Pick's disease (PiD), a 3R tauopathy, and corticobasal degeneration (CBD), a 4R tauopathy. Prior research suggests that limbic regions such as the amygdala may be differentially affected across neurodegenerative diseases and may be implicated in distinct neuropsychiatric presentations in dementia. This study examined activated microglia as a marker of inflammation in the amygdala of individuals with antemortem diagnosis of PPA or bvFTD and postmortem PiD or CBD neuropathology. The goal was to determine whether amygdalar pathology contributes to clinical symptoms unique to dementias due to 3R vs 4R FTLD-tau.

Participants and Methods: Autopsied cases (N=35) with PPA (PiD N=9, CBD N=11) or bvFTD (PiD N=9, CBD N=6) were identified from the Northwestern Alzheimer's Disease Research Center brain bank. Paraffin embedded unilateral amygdala sections (27 left, 8 right) were stained with antibodies to visualize phosphorylated tau (AT-8) or activated microglia (HLA-DR). We quantified the percent area AT-8 and HLA-DR immunopositivity and the number of activated microglia per mm2 via HALO software (Indica Labs). Outliers >3 SDs outside of the mean were removed. Multiple linear regressions covarying for dementia syndrome, tauopathy, and amygdala hemisphere were performed for each pathologic marker.

Results: Across all cases, those with PiD showed significantly more pathology than CBD, including AT8 % area (PiD M = 8.13, CBD M = 3.09, $p<0.01$), HLA-DR % area (PiD M = 3.62, CBD M = 1.33, $p<0.05$), and number of activated microglia per mm2 (PiD M = 103.19, CBD M = 41.47, $p<0.05$). Regarding clinical groups, AT-8 % area was similar between PPA (M = 6.13) and bvFTD (M = 5.49). Relative to PPA, bvFTD had a higher neuroinflammation, characterized by a higher HLA-DR % area (PPA M = 1.40, bvFTD M = 3.32, $p<0.05$) and more activated microglia per mm2 (PPA M = 38.20, bvFTD M = 99.28, $p<0.05$).

Conclusions: Our findings indicate that the amygdala is differentially vulnerable to FTLD-tauopathies, with more severe tau burden and neuroinflammation in PiD than in CBD. Furthermore, microglial activation in the amygdala may play a particularly salient role in personality and comportment disruption in patients with an underlying 3R-FTLD tauopathy.

Lay Language: Primary progressive aphasia (PPA) is a language-based dementia, whereas behavioral variant frontotemporal dementia (bvFTD) is characterized by personality/behavior changes. PPA and bvFTD are caused by brain pathologies discovered at autopsy. This includes "tauopathies," which contain either three repeats (3R) or four repeats (4R) of a portion of tau protein. "Pick's disease" is a 3R tauopathy, and "corticobasal degeneration" 4R tauopathy.

We examined tau and inflammation in the amygdala in the brain, which influences emotions and behavior, in participants with PPA or bvFTD due to tauopathies who committed to brain donation. Pick's disease showed more tau and inflammation in the amygdala than corticobasal degeneration. PPA and bvFTD had similar tau burden, but inflammation was higher in bvFTD.

Findings suggest that tauopathies show distinct levels of brain pathology and related disease processes like inflammation in the amygdala, representing a potential treatment target for patients with severe personality/behavior changes.

The VIVA-MIND Study

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The VIVA-MIND Study is a Phase II multi-center, randomized, double-blind, placebo-controlled trial that will evaluate the efficacy, safety, and tolerability of an oral investigational product, Varoglutamstat (PQ912), in its ability to delay or slow the progression of symptoms of early Alzheimer's Disease (AD). Varoglutamstat prevents the formation of a specific toxic form of the amyloid protein that is linked to proinflammatory mechanisms and neurotoxicity found in AD pathology. This study aims to enroll approximately 414 participants across all sites with Mild Cognitive Impairment (MCI) and Mild probable AD. Participants will be randomized 1:1 to either Varoglutamstat or placebo. The duration of the study is approximately 20.5 months and involves clinical and cognitive assessments, biomarker and genetic tests, magnetic resonance imaging (MRI) scans, electrocardiograms (ECG), electroencephalograms (EEG), and cerebrospinal fluid (CSF) analysis. Northwestern University is currently screening and enrolling individuals ages 50 to 89 with MCI or Mild probable AD who are on a stable dose of an AD medication or memantine.

Lay Language: The VIVA-MIND Study is a Phase II multi-center, placebo-controlled trial that will evaluate the safety and potential benefit of an investigational drug, Varoglutamstat (PQ912), which aims to prevent formation of a specific toxic form of the amyloid protein. Abnormal forms of the amyloid protein is linked to the proinflammatory mechanisms and neurotoxicity in Alzheimer's Disease (AD).

Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4)

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The Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4) is a 5-year longitudinal study that seeks to correlate clinical biomarkers to the detection and progression of Alzheimer's Disease (AD). This study is a continuation of work collected since 2004. ADNI has had multiple initiatives leading up to ADNI4 including: ADNI1, ADNI-GO, ANDI2, and ADNI3. It is a non-randomized, natural history, non-treatment study that aims to gather data from 1500 participants between the ages of 55 to 90 years old. Participants will be enrolled into one of three cohorts: Cognitively Normal (CN), Mild Cognitive Impairment (MCI), and Dementia (DEM). The study aims to determine the relationship between AD and associated clinical indicators through routine blood collection, cognitive and neuropsychological assessments, brain imaging, genetic analysis, and optional lumbar punctures for cerebrospinal fluid (CSF) analysis. It is designed to increase participation of underrepresented populations (URPs) to allow for generalizable results, identify and validate biomarkers that can accurately predict cognitive decline, and discover genes associated with AD. Northwestern University is one of the 65 sites conducting this study across the United States and Canada, and as an ADNI Diversity Hub site, we aim to enhance diversity, equity, and inclusion in AD research. Recruitment, screening, and continued visits are anticipated to begin Spring of 2024.

Lay Language: The Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4) study intends to advance the clinical design of Alzheimer's Disease (AD) research by increasing enrollment of underrepresented populations and determining the validity between clinical, cognitive, imaging, genetic, and biochemical biomarkers for the detection of AD. ADNI4 aims to better understand Alzheimer's disease and how clinical measures can be utilized to predict disease development amongst participants of varying stages of cognitive decline.

Differential Vulnerability of Von Economo Neurons to FTLD-tau Species

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Objective. Von Economo Neurons (VENs) are spindle-shaped bipolar projection neurons that are uniquely situated in the anterior cingulate cortex (ACC) and the fronto-insular cortex (FI) of the human brain. VENs are speculated to be involved in complex social-emotional functions and studies have shown a significant reduction of VENs in the ACC and FI in brain specimens from individuals diagnosed with behavioral variant frontotemporaementia (bvFTD), a dementia syndrome characterized by changes in personality and socially inappropriate behavior. In particular, ACC VEN loss has been shown to be selectively vulnerable to the TDP-43 pathologic subtype of frontotemporal lobar degeneration (FTLD-TDP) which gives rise to the bvFTD phenotype (Nana et al., 2020). This study investigated the density of VENs in two distinct tauopathy subtypes of FTLD: the 4R tauopathies of corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) and the 3R tauopathy of Pick's disease (PiD).

Participants and Methods. Density of VENs and total neurons were quantitated using unbiased stereological methods in the ACC of postmortem samples from 12 right-handed participants from the Northwestern Alzheimer's Disease Research Center, all of whom carried a clinical diagnosis of bvFTD and FTLD-tau as the primary pathological diagnosis (PiD, N = 4; CBD, N = 4; PSP, N = 4). Five sections of the ACC were stained for Nissl substance to visualize neurons including VENs. Modified stereological methods (Microbrightfield StereoInvestigator) were used to determine the density of neurons. Statistical analyses included ANOVAs and non-parametric t-tests to compare 1) Mean VEN density; 2) Mean neuronal density; and 3) the ratio of VEN/total neuronal density across groups.

Results. There were no significant differences in age between the 3R vs 4R FTLD-tau groups. Analyses demonstrated a decrease in VENs relative to total neuronal density in 3R (PiD) versus 4R (CBD and PSP) which trended toward significance ($p=0.15$). Though VEN densities were lowest in the PiD group compared to CBD and PSP, results did not reach statistical significance. Additionally, total density of neurons was significantly higher in the group with PiD pathology when compared with the groups with CBD or PSP pathology ($p<0.05$).

Conclusions. Preliminary results suggest that VENs in the human ACC may be differentially vulnerable to the 3R FTLD-tau species of PiD compared to 4R FTLD-tau species (PSP and CBD). Additional cases are necessary to confirm clinicopathologic concordance between the bvFTD phenotype and selective loss of VENs to specific FTLD-tau species. Findings will ultimately help clarify the role of this unique cell population in normal human behavior and its susceptibility to neurodegenerative disease.

Lay Language: Behavioral variant frontotemporal dementia (bvFTD) is a type of dementia that affects behavior, personality, and language skills. Unlike other forms of dementia, such as Alzheimer's disease, which primarily impacts memory, bvFTD primarily affects the frontal and temporal lobes of the brain, leading to changes in behavior and personality. Tau is a protein that can become abnormal in bvFTD, leading to damage to brain cells and the development of symptoms. In this study, researchers investigated a special type of brain cell called Von Economo Neurons (VENs), believed to play a role in complex social and emotional functions, in three distinct subtypes of tau, known as corticobasal degeneration and progressive supranuclear palsy (4R tauopathies) and Pick's disease (3R) tauopathy. The results showed that individuals who had Picks disease had less VENs compared to those with corticobasal degeneration and progressive supranuclear palsy.

Alzheimer Plasma Biomarkers Distinguish SuperAgers from their Cognitively Average Peers

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Background. SuperAgers are individuals ≥80 years old who were selected for having episodic memory performance that is at least as good as individuals 20-30 years their junior. We have previously shown that on average SuperAgers show lower neurofibrillary tangle density in the entorhinal cortex than cognitively average controls, which may be one biological factor contributing to superior memory beyond the 8th decade. This preliminary study investigated whether plasma concentrations of Alzheimer and related neurodegenerative biomarkers differ between SuperAgers and their cognitively average peers.

Methods. SuperAgers (N=61) and Cognitively Average Controls (N=28) were enrolled through the SuperAging Research Program. The plasma biomarkers amyloid β peptide 40 (Aβ40), amyloid β peptide 42 (Aβ42), neurofilament light (NFL), phosphorylated tau-181 (pTau-181), and glial fibrillary acidic protein (GFAP) were measured in SuperAgers and Cognitively Average participants using the Quanterix single molecule protein detection (SIMOA) platform. Independent samples t-tests were used for statistical analyses (significance was set at $p<0.05$, uncorrected).

Results. There were no significant differences in mean age between SuperAgers and Cognitively Average Controls. Concentrations of Aβ42, Aβ40, the ratio of Aβ42/Aβ40, NFL or GFAP did not significantly differ between groups. On average, SuperAgers and Controls showed pTau-181 levels that were <16.5 pg/mL, falling within the "Unlikely Alzheimer's" designation according to Quanterix guidelines. SuperAgers showed significantly lower pTau-181 levels compared to Cognitively Average Controls [M=5.42 pg/mL (SD=2.60) vs M=7.10 pg/mL (SD=3.14), respectively].

Conclusions. Plasma phosphotau biomarkers are promising for the assessment of brain integrity versus degeneration across the age-Alzheimer continuum. The current results provide preliminary support for the contention that the SuperAger brain may be even more removed from the Alzheimer side of the continuum than neurotypical controls.

Changiz Geula and Emily Rogalski contributed equally to this study.

Lay Language: SuperAgers are individuals ≥80 years old who were selected for having episodic memory performance that is at least as good as individuals 20-30 years their junior. Blood-based biomarkers are promising for the assessment of brain integrity versus degeneration across the age-Alzheimer continuum. Our study investigated plasma differences in SuperAgers versus cognitively older adults. Our results demonstrated that SuperAgers have less phosphorylated tau compared to normal controls. The current results provide preliminary support for the contention that the SuperAger brain may be even more removed from the Alzheimer side of the continuum than neurotypical controls.

Resistance and resilience to neuropathology in cognitive SuperAgers

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Background: SuperAgers are persons over 80 years with at least normal-for-age global cognition and who perform as well as persons 20-30 years younger on tests of episodic memory. The Northwestern University SuperAging program was initiated in 2001 and follows SuperAgers with serial annual neuropsychological testing. Brain donation at time of death allows for correlations between cognitive performance during life and neuropathological findings on autopsy. The goal of this study was to examine neuropathologic features of SuperAging participants with a focus on those who showed relative cognitive stability versus decline.

Methods: Thirty-eight SuperAging participants underwent annual study visits as part of a longitudinal research program at the Northwestern University Alzheimer's Disease Research Center. Study visits consisted of neurocognitive tests, questionnaires, and interviews with study partners; cognitive and functional status at each visit were determined in consensus meetings. Average age at death was 91.63 years (range 82-101 years). Average length of neuropsychological follow-up was 12.6 years (range, 3 to 25 years). The average time interval between the last cognitive evaluation and death was 1.72 years (range, 1 month-10 years); trajectory designations (i.e., "stable" vs "decliner") were supplemented with informant reports for subjects with longer than 2 years between last testing and death. Autopsy examination consisted of standard sampling throughout the neuraxis, with assessment of macroscopic atrophy and vascular disease, and assessment of neurodegenerative disease using routine histopathology, thioflavin S fluorescent staining, and immunohistochemistry for amyloid-β (4G8), phosphorylated-tau (AT8), phospho-TDP 43 (Ser409-410), α-synuclein, and p62. Assessment was performed according to 2012 NIA-AA recommendations.

Results: Of the 38 SuperAging participants, 20 showed relative cognitive stability (52.6%) and 18 showed evidence of cognitive decline (47.4%). Overall, there was a general tendency for stable SuperAgers to show less proteinopathy. Stable SuperAgers (26.3%) were significantly more likely to be rated a 'B1' score (Braak I-II) according to the 2012 NIA-AA criteria compared to those who declined (0%; OR=0.737, $p<0.05$). Of those who declined, two-thirds had intermediate or greater Alzheimer's disease neuropathologic changes (ADNC; 66.7%); interestingly, 45% of stable SuperAgers met criteria for intermediate ADNC. Those who declined also tended to be rated as "A3" (50%), as CERAD "frequent" by Thioflavin S (38.9%), showed Tau positive neuritic plaques (23.5%), and ARTAG (66.7%); though present in a higher number of decliners, these features did not differ significantly from stable SuperAgers.

Conclusions: Initial and preliminary clinicopathological analysis of SuperAgers indicates both resistance to proteinopathy and cognitive resilience despite proteinopathy. "High" ADNC was entirely absent from this SuperAger cohort, while nearly half of stable SuperAgers met criteria for "intermediate" ADNC. Although there was, not surprisingly, a trend toward stable SuperAgers demonstrating less proteinopathy, neuropathology was not uniformly predictive of antemortem cognitive trajectory. More studies are needed to explore the biological basis for resistance and resilience in this population, as well as the biological drivers of cognitive decline with age.

Lay Language: SuperAgers are persons over 80 years old with at least normal-for-age cognitive abilities and who perform as well as persons 20-30 years younger on tests of memory. This study examined the postmortem brains of SuperAgers to determine differences between SuperAgers that maintained stable cognitive performance and those that experienced decline prior to death. The goal of this study was to examine neuropathologic features of SuperAging participants with a focus on those who showed relative cognitive stability versus decline. Though SuperAgers that declined did show a tendency to have more abnormal proteins than SuperAgers that stayed stable, postmortem brain findings were not uniformly predictive of cognitive trajectory during life. These findings support there being many pathways to SuperAging and demonstrate the possibility of both brain reserve (e.g., resistance to typical age-related brain changes) and cognitive reserve (e.g., stable cognition despite build-up of age-related brain changes).

Incidental Delayed Recall of a Picture Scene as a Marker of Memory Preservation in Primary Progressive Aphasia: A Multiple Case Study

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Objective: Primary progressive aphasia (PPA) is a dementia syndrome defined by initial focal progressive language deficits without evidence of impairment in other domains. Assessment of memory abilities is difficult in this population due to interference from language disturbance, especially for tests that require auditory verbal encoding and recall. Alternate, and at times creative, approaches are needed to accurately establish memory preservation in PPA. We present an informal method of assessing retentive memory preservation in three PPA cases using incidental delayed recall of the Western Aphasia Battery – Revised picture description.

Participants and Methods: We present a series of three patients diagnosed with PPA who underwent clinical neuropsychological evaluation at a memory clinic. Cases 1 and 2 (ages 56 and 62) were diagnosed with logopenic variant PPA and both had positive CSF biomarkers for Alzheimer's disease. Case 3 (age 53) was diagnosed with non-fluent/agrammatic PPA, likely due to FTLD given negative research amyloid PET scan. All cases were right-handed white women with at least 16 years of education. As part of a broader neurocognitive battery, all patients were administered standardized tests of verbal and visual memory (e.g., RBANS, BVMT-R, HVLT-R). The WAB-R was administered to assess language functions, including the ability to tell a story from a drawing of a picnic scene. After a delay of 20-30 minutes, patients were asked to recall details of the picture they had described even though not asked to remember it (i.e., incidental recall).

Results: Neurocognitive profiles of all three cases were predominantly notable for language difficulties with additional frontal-networks weaknesses. MoCA scores were significantly lower than expectation (range: 16-22/30), largely due to interference from aphasia. In each case, performance on tests of verbal memory was below expectation for age. However, all patients were able to recall all or nearly all details previously described of the picnic scene in the WAB-R after a delay of at least 20 minutes.

Conclusion: The current multiple case study provides evidence of preserved contextual verbal memory in early stages of PPA as assessed by recall of a previously described picnic scene. This is consistent with evidence of relatively better performance on tasks of memory with visually based encoding (e.g., Three Words Three Shapes) than auditory based encoding for word lists and stories in PPA. Poor performance on standard tests of verbal memory in PPA is not a reliable marker of retentive memory impairment. Recall of a visual picture scene may serve as a useful alternative task to standard auditory story memory tasks to establish preservation of contextual verbal memory.

Lay Language: Primary progressive aphasia (PPA) is a type of dementia defined by decline in language abilities. It can be difficult to accurately measure memory in PPA because most common tests of memory rely heavily on language abilities. This project describes an alternative way to show that memory is intact in persons with PPA. Specifically, three persons with PPA were asked to recall the details of a picnic scene that they had described about 20 minutes before as part of a standard neuropsychological evaluation. Each of the three cases included in this study scored below expectation on standard tests of memory but were able to remember almost all of the details of the picnic scene. This strategy for measuring memory may be useful to support accurate assessment of cognitive abilities in PPA.

Utility of the Frontotemporal Lobar Degeneration Module (FTLD-MOD) to Distinguish Underlying Neurodegenerative Neuropathology in behavioral variant Frontotemporal Dementia

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Objective: The Frontotemporal Lobar Degeneration Module (FTLD-MOD) was designed by the National Institute of Aging as a specialized neuropsychological battery to evaluate symptoms unique to FTLD-related clinical dementia syndromes including behavioral variant frontotemporal dementia (bvFTD). BvFTD is characterized by progressive decline in social comportment and behavioral changes at initial stages. Different neuropathological diseases can be found at autopsy in individuals diagnosed antemortem with bvFTD, including FTLD (due to either tau, which can be further categorized into 3 repeat (3R) or 4 repeat (4R) tauopathies, or TDP-43 species) or, though less common, Alzheimer's disease (AD) pathology. Prior research has shown that while bvFTD due to FTLD pathology leads to disinhibited behaviors (e.g., impulsivity), the same syndrome due to AD often presents with more affective symptoms (e.g., withdrawal or anxiety). The current study investigated whether performance on FTLD-MOD measures could differentiate between multiple neuropathologic diagnoses (i.e., FTLD-tau vs FTLD-TDP vs AD) that lead to a single clinical dementia syndrome (i.e., bvFTD).

Participants and Methods: Fifty-five participants from the National Alzheimer's Coordinating Center (NACC) database with clinically diagnosed bvFTD and postmortem data available were included in the retrospective analysis. All participants had a global CDR of 0.5 or higher. Autopsy-confirmed neuropathological diagnosis further classified participants into three groups; those with underlying Alzheimer's Disease (AD; N = 16), the tau form of FTLD (FTLD-tau; N = 22), and the TDP form of FTLD (FTLD-TDP; N = 17). Group performance scores on FTLD-MOD questionnaires from the initial visit were analyzed. Logistic and multinomial regression models controlling for visit age and education were used to test the ability of the FTLD-MOD to distinguish between underlying pathologic diagnoses.

Results: The Behavioral Inhibition Scale (BIS; Form C4F), a 7-item informant questionnaire that measures withdrawal-related behavior such as self-criticism and social anxiety, demonstrated a potential ability to distinguish between pathologic groups; a unit increase in total score was associated with an increase in the odds of AD pathology compared to FTLD-tau or TDP (OR=1.26, p=0.04). No significant differences were found in the other FTLD-MOD questionnaires.

Conclusions: Among individuals diagnosed with bvFTD during life, higher scores on the Behavioral Inhibition Scale of the FTLD-MOD appear to be associated with an increase in likelihood of AD pathology at autopsy relative to FTLD. Findings show that BIS may be clinically beneficial to help distinguish between underlying pathologic diagnoses that lead to bvFTD.

Lay Language: The Frontotemporal Lobar Degeneration Module (FTLD-MOD) was created as a set of specialized neuropsychological tests and questionnaires for patients with dementia syndromes associated with FTLD such as behavioral variant frontotemporal dementia (bvFTD). BvFTD is marked with behavioral and social changes during the beginning stages of clinical diagnosis and patients can show various types of neuropathologic diseases during post-mortem autopsy. The current study looked into how the FTLD-MOD can be used with patients diagnosed with bvFTD to differentiate the pathology present at autopsy.

Poster 26

Mesulam Center Brain Scholars Program: Empowering Diverse Next Generation of Neurologists and Neuroscientists

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The Brain Scholars Program is an initiative of the Mesulam Center for Cognitive Neurology and Alzheimer's Disease committed to providing meaningful scientific and professional experiences in brain sciences for students from underrepresented groups. To date, the Brain Scholars Program has forged partnerships with St. John de la Salle Catholic Academy (a K-8 school), as well as Butler College Prep (a high school). We are also working on partnering with a four-year university on the South Side of Chicago. Our program has hosted six visits at our center with students ranging from 4th graders to 12th graders. At these visits students are exposed to various aspects of brain function and health, including manifestations of cognitive decline in dementias. These visits include a tour of facilities, mentoring by Center staff in brain sciences, professional development activities such as shadowing scientists and researchers, and visits to laboratories for exposure to scientific experiments and examination of human brains. Mesulam Center staff have also conducted two satellite visits to St. John de la Salle school. During these visits students learned about brain function and health, dementia and Alzheimer's Disease, and neuropsychological testing. Overall, over 230 students have participated in activities offered by the Brain Scholars Program. Last summer, seven of these students who showed interest to further their understanding of brain sciences were invited to participate in our 5-week summer internship program. Over the course of this program students were further immersed into brain function and health, participated in various laboratory experiments, shadowed Mesulam Center staff and faculty, and were exposed to a diversity of careers within brain sciences.

Continuing and expanding its efforts, the Brain Scholars Program hopes to empower increasing numbers of students from underrepresented groups 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 Center for Cognitive Neurology and Alzheimer's Disease committed to providing meaningful, scientific and professional experiences in the health sciences for students from underrepresented groups at all levels, with a focus on brain health. So far over 230 students have participated in activities offered by this program through visits hosted and/or conducted by the Mesulam Center. Continuing and expanding its efforts, the Brain Scholars Program hopes to empower increasing numbers of students from underrepresented 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 27

Can People Living with Dementia Read? What Studies Show

Mary Beth Riedner

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

Purpose: To conduct a literature review to determine the state of research on the topic of whether reading is preserved among people living with dementia and its impact on their lives.

Methods: While not a systematic review, articles on this topic have been accumulated by the author for over 15 years. Search strategies included searching databases such as Medline and Pub Med, conducting Internet searches, extracting citations from reference lists of identified articles, and seeking recommendations from colleagues/experts in the field.

Results: From over 70 resources identified, seventeen were chosen to demonstrate:

- the fact that reading skills can be preserved,
- the impact of reading on those living with dementia,
- the identification of the most appropriate types of reading materials,
- the success of several book and reading programs designed for this population.

Conclusion: While those living with dementia may be reading in a different way and for different purposes than before diagnosis, research shows that there are still valuable and important benefits from offering them literacy opportunities. While some studies that investigate the objective posed by this poster do exist, their number is limited. Many were conducted over a decade ago. Additional research needs to be conducted to evaluate how reading can be used to improve the quality of life for this population cognitively, socially and behaviorally. Also, more precise instruments to measure the preserved reading abilities need to be developed in order to obtain the most accurate results.

Lay Language: People living with dementia often feel stigmatized and excluded from the larger society. One common misconception is that they can no longer read or benefit from print materials. This poster will present findings from academic research studies that demonstrate just the opposite. While those living with dementia may be reading in a different way and for different purposes, research shows that there are still valuable and important benefits from offering them literacy opportunities. Literacy activities can include reading out loud, browsing through books, singing using printed lyrics, choral reading of poetry, and storytelling. Efforts from across the globe will be highlighted and suggestions for practical applications in libraries will be offered.

Cannabis for treatment of agitation in Alzheimer's dementia - a case report

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Introduction: Alzheimer's disease (AD) is a common neurodegenerative disease and afflicts 6 million adults in the US. Neuropsychiatric symptoms (NPS) are common, with agitation affecting more than 40% of patients - leading to patient distress, worsening cognitive function, caregiver burden, poor quality of life, increased institutionalization, and increased cost of care. For more severe agitation that doesn't respond to non-pharmacologic interventions, treatment may include medications such as antidepressants, anxiolytics, antipsychotics and sedative hypnotics. However, only one of these medications (Brexpiprazole) is FDA approved for treating agitation - and generally these medications have poor evidence for efficacy and come with risks for significant side effects including falls, cerebrovascular accidents, and death. There is growing evidence that cannabinoids are safe and effective at improving the NPS seen with Alzheimer's dementia. We present a patient with severe agitation and anxiety related to her Alzheimer's that did not improve with typical pharmacologic intervention, but had dramatic improvement in symptoms after starting a regimen of cannabinoids.

Case: The patient is an 80-year-old Caucasian woman with chronic back pain and dementia from Alzheimer's disease. Family reports that her long-term memory was good, but with a significant decline in short term memory over recent years. She would sleep for large portions of the day, and then wake up at night with great difficulty returning to sleep. She would struggle with feeling worried and scared - which could happen throughout the day, but mornings were the most difficult time. Family also noted worsening agitation - especially if the patient was triggered by being reminded of her memory problems, dementia diagnosis, or physical limitations such as needing assistance to transfer from bed or help with toileting and hygiene. The agitation behaviors escalated over time - including yelling and berating family, becoming physically aggressive, refusing medications, refusing to eat, and throwing objects (including bodily fluids) at caregivers. Family described many attempts at distraction and redirection, but reported that ultimately it was only the passing of time that would eventually lead to her calming down.

Medications tried included donepezil, alprazolam, and mirtazapine - none of which seemed to help these symptoms significantly. The family reported that the Mirtazapine initially did help some with sleep, but after several weeks she began to wake at night with more frequent nightmares.

Family sought care from a nurse certified by the American Cannabis Nurse Associate. They received education and guidance on different cannabinoids, routes of administration, typical doses and titration, side effects, and important drug-drug interactions to monitor for. They decided to start a regimen of gummies with 1:1 THC and CBD twice daily, a tincture of CBDa daily, and a tincture of CBG daily. They would also use an edible with CBD/THC in a 20:1 ratio as needed for acute pain, anxiety, or agitation.

After starting this regimen, the family reported that she was now sleeping through the night for 8 hours nearly every night without nightmares or waking. She did continue to nap frequently during the day, but no differently than before. The family also reported no worsening confusion or euphoric "high" while awake. The only side effect that they noted was dry eyes that was successfully treated with artificial tears. Most importantly to them - they reported no further episodes of agitation and aggression, and that her anxiety was "90% better," and described a much improved quality of life for both the patient and the caregivers.

Discussion: The endocannabinoid system (ECS) is a vitally important physiologic system that is involved in regulating homeostasis and cell to cell signaling. Endogenous cannabinoids Anandamide (AEA) and 2-AG interact with CB1 and CB2 receptors throughout the entire body, with CB1 being the main form and one of the most frequent G-protein coupled receptors in the CNS. CB1 is found concentrated in the basal ganglia, amygdala, hippocampus, cerebellum, hypothalamus, and the prefrontal cortex - areas associated with higher level functions such as executive decision making, memory, and emotional response. Post-synaptic neurons release endocannabinoids in a retrograde fashion, where they interact with CB1 receptors on the presynaptic neuron,

modulating neurotransmitter release. The phytocannabinoid delta-9-tetrahydrocannabinol (THC) interacts with CB1 and CB2 receptors in a similar manner to the endogenous cannabinoids. Cannabidiol (CBD) has less direct effect on the CB1 and CB2 receptors, and interacts more with the transient receptor potential vanilloid (TRPV) channels - where they modulate a variety of body processes including inflammation, pain communication, and temperature regulation. CBD and THC have also been shown to act as an agonist at serotonin 5HT1A receptors. Further, endogenous cannabinoids like AEA are broken down via fatty acid amide hydrolase (FAAH), and several cannabinoids such as CBD and cannabigerol (CBG) inhibit FAAH leading to higher levels of AEA. Cannabinoids have also been shown to have neuroprotective effects - reducing oxidative stress and decreasing the burden of beta amyloid plaques in AD specifically. Cannabinoids can successfully help maintain normal circadian rhythm function and sleep/wake cycles.

While more robust studies are needed, studies have shown cannabinoids to be safe and well tolerated, with few short term side effects in patients with AD. We have a patient with severe agitation who found significant symptom relief after beginning a regimen of cannabinoids. Current literature is limited by primary studies that often include low quality evidence or uncontrolled trials. Many studies also often look at a single synthetic cannabinoid. The use of cannabinoids in a setting where patients are educated and guided through cannabis titration with a trained cannabis clinician has not been looked at. Further research with controlled studies and larger cohorts is needed to evaluate the role for cannabinoids and education provided from an experienced cannabis clinician in this fragile population with limited safe and effective treatments.

Lay Language: An 80 year old woman with Alzheimer's disease had been experiencing severe anxiety and agitation, which did not respond to multiple prescription treatments. The family sought education and guidance from a trained cannabis nurse - then started a regimen of delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), cannabidiolic acid (CBDa), and cannabigerol (CBG) daily. She subsequently had dramatic improvement in her symptoms - and improved quality of life for both her and the caregivers with minimal side effects. Agitation with dementia is a very common problem and one with few safe and effective treatments. Cannabis use guided by trained clinicians may be an effective method to help manage this difficult problem.

Spatial and Temporal Progression of Right Hemisphere Atrophy in Primary Progressive Aphasia due to TDP-43 Type C Pathology

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Objective: The objective of this study was to investigate the spatial and temporal progression of right hemisphere atrophy in individuals with Primary Progressive Aphasia due to TDP-43 Type C pathology (PPA-TDPC). PPA-TDPC subjects often present to clinic with substantial left-hemisphere atrophy, impeding the ability to pinpoint the regions of initial volume loss and discern the spatial progression of atrophy. Here, we aimed to characterize the distribution of abnormally decreased brain volume in specific regions of interest (ROIs) within the right hemisphere over three time points.

Participants & Methods: Forty-two right-handed participants with PPA-TDPC were included in the analyses. Pathological diagnoses were made based on autopsy in 16 participants and on patterns of left-sided anterior temporal lobe atrophy in 26 living participants. 42 structural MRI scans available for subjects at Visit A, 28 scans at Visit B, and 13 scans at Visit C. Visits were performed at 2-year intervals. At baseline, participants had a mean age of 63.0 years (SD = 6.6), with an average age of reported symptom onset of 58.5 years (SD = 6.9); 52.4% were male. Structural MRIs were preprocessed using the computational anatomy toolbox (CAT12), a software that performs voxel-based morphometry (VBM) and provides an estimate of brain volume at each voxel. Brain volume was then parcellated into 400 cortical and 32 subcortical ROIs based on well-validated atlases. Next, we computed W-scores at each ROI to determine abnormally decreased volume in PPA-TDPC subjects. W-scores were calculated by fitting a general linear model against age in a set of cognitively normal reference participants, and taking the standardized residuals generated from this model for all participants (i.e., W = ([raw value] – [expected value])/(standard deviation of the residuals of reference)). For each visit and in each ROI of the right hemisphere, we determined the percentage of participants with W-scores less than -1.5.

Results: At Visit A, the largest percentage of PPA-TDPC subjects with W-scores under -1.5 was noted in the temporal pole, with highest percentages (88%-71%) in the anteriormost regions, with relatively lower proportions of participants with volume loss extending posteriorly. Subcortically, 71% of subjects had W-scores below -1.5 in both the lateral and medial amygdala. At Visits B and C, similar spatial distributions of W-scores were observed, with greater proportions of subjects with volume loss in the anterior portions of temporal lobe, extending posteriorly along the temporal lobe and additionally including portions of the frontal operculum/insula. Subcortically, areas of significant volume loss remain relatively confined to the lateral and medial amygdala, with 51-69% of participants additionally demonstrating volume loss in the nucleus accumbens, anterior putamen, and the anterior and posterior hippocampus.

Conclusions: The study concludes that individuals with PPA-TDPC exhibit a distinct spatial and temporal progression of right hemisphere atrophy. Areas of initial volume loss include the anteriormost portions of the temporal pole and the amygdala. These findings underscore the importance of characterizing the progression of atrophy in PPA-TDPC, providing valuable insights into the nature of disease onset and progression due to TDP-C pathology.

Lay Language: Our research focused on understanding how the brain changes in individuals with a specific type of language-related disorder called Primary Progressive Aphasia due to TDP-43 Type C pathology (PPA-TDPC). People with this condition often show significant changes in the left side of their brain before symptoms even develop, making it challenging to identify where these changes start and how they spread over time. By using advanced brain imaging techniques, we found that areas like the front part of the temporal pole and the amygdala are particularly affected early on.

Poster 30

Age-dependent expression and accumulation of TDP-43 in a conditional wild-type human TDP-43 transgenic mouse model on the C57BL/6 genetic background

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Frontotemporal lobar degeneration (FTLD) is among the most prevalent dementias of early onset. Pathologically, FTLD presents with tauopathy or TAR DNA-binding protein 43 (TDP-43) proteinopathy. A biallelic mouse model of FTLD was produced on a mixed FVB/129SVE background overexpressing wild-type human TDP-43 (hTDP-43) employing tetracycline transactivator (tTA) which activates the hTDP-43 gene, placed downstream of the tetracycline response element (TRE). We backcrossed the tTA and hTDP-43 transgenic mice to the C57BL/6 background and investigated age-dependent expression and accumulation of TDP-43 in cortical neurons. TDP-43 expression was turned on at 21 days postpartum by taking animals off doxycycline in diet. Mouse brain tissue from bigenic and wild-type animals harvested at 14 days through 24 months of expression of human TDP-43 was analyzed using immunohistochemistry with an antibody against wild-type human TDP-43. After 14 days of expression, lightly stained human TDP-34-positive cortical neuronal nuclei were visible in bigenic animals, whereas no staining was observed in wild-type animals. The number and staining intensity of nuclear TDP-43 immunoreactivity gradually increased and was at a peak at 24 months of expression. We also observed gradual age-dependent accumulation of cytoplasmic TDP-43 in some cortical neurons. At the peak of expression and accumulation, positive neurons were most abundant in superficial and deep cortical layers and were primarily present in frontal and temporal cortical regions. Few and small punctate TDP-43 immunoreactive inclusion-like structures were visible in cortical neurons at 10 months of expression and thereafter. Large Iba1 immunoreactive microglia were observed in areas with high TDP-43 nuclear and cytoplasmic immunoreactivity. In summary, our findings reveal a gradual increase in human TDP-43 in neurons with age, accompanied with large (activated) microglia. Greater expression and accumulation of TDP-43 in frontal and temporal cortices are consistent with the pattern of atrophy seen in FTLD.

Lay Language: Our research seeks to illuminate the disease progression of frontotemporal dementia in a mouse model. These mice have a human protein in their brains which, in humans, plays an important role with DNA in the nucleus of the cell. However, it can relocate outside the nucleus and accumulate in the cell, disrupting normal cell processes. We are looking at how, in mice, the presence of this human protein is quantified and visualized in different strains and ages, and what effects this has on specific areas of the brain. Over time this will help illustrate how frontotemporal dementia progresses so we can better understand it and treat it effectively.

Poster 31

Exosomes isolated from human cortex with TDP-43 proteinopathy, TDP-43 transgenic mice and media from cultured human microglia contain human TDP-43

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Exosomes are extracellular vesicles produced in the endosomal compartment and released by most eukaryotic cells. They are the smallest extracellular vesicle and have been implicated in cell-to-cell communication under normal conditions and propagation of pathology in neurodegenerative disorders. In particular, microglia-derived exosomes have been implicated in pathologic tau propagation in Alzheimer's disease. It is not known whether exosomes, including those derived from microglia, contribute to propagation of pathology in other neurodegenerative disorders. As a first step in this process, we isolated and characterized exosomes from various sources, with the eventual aim of investigating their involvement in propagation of TDP-43 proteinopathy in frontotemporal lobar degeneration (FTLD-TDP) Frozen postmortem human tissue from the middle frontal gyrus of four participants with FTLD-TDP and one cognitively-normal control, frozen fontal cortex from two wild-type and three human TDP-43 transgenic C57/Bl6 mice, and pooled media from primary human microglia cultures with exosome depleted serum in media were used and exosomes were prepared employing established high speed ultracentrifugation and fractionation protocols. Western blot analyses were used to determine the presence of exosome markers flotillin-1 and CD63, microglia marker CD68, and human TDP-43 in isolated exosomes. Successful isolation of exosomes was confirmed through electron microscopy. All isolated exosome preparations contained the exosome markers flotillin-1 and CD63. Exosomes isolated from cultured human microglia and human brain contained CD68. Human TDP-43 was present in exosomes isolated from frozen human brain with FTLD pathology, human microglia cultures, and TDP-34 transgenic mice. Weak bands were detected in wild-type mice, most likely due to partial homology of TDP-34 protein in the mouse and human. In conclusion, exosomes can be successfully isolated from various sources of brain tissue and cells, a proportion originating from microglia, and they contain human TDP-43. It remains to be seen whether exosomes isolated from FTLD-TDP or TDP-34 transgenic mice can seed or propagate pathology when injected into wild-type or transgenic mice.

Lay Language: Exosomes are extracellular microvesicles that carry proteins from cell to cell. Their role in the propagation of pathologic TDP43 is not well understood. In this study we investigate the presence of TDP43 in exosomes originating from different cells and derived from human and mouse brains as well as microglia cell culture.

Poster 32

Progressive Oral Apraxia of Reading

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Background: We identified a syndrome characterized by a relatively isolated progressive impairment of reading words that the patient was able to understand and repeat but without other components of apraxia of speech. This cluster of symptoms fits a new syndrome designated Progressive Oral Apraxia of Reading.

Methods: A right-handed man (AB) came with a 2.5-year history of increasing difficulties in reading aloud. He was evaluated twice, 2 years apart, using multimodal neuroimaging techniques and quantitative neurolinguistic assessment.

Results: AB showed significant difficulties in reading aloud, which arose in the context of intact ability to visually recognize, understand and repeat words he was unable to read aloud. The unique feature was the absence of dysarthria or speech apraxia in tasks other than reading. Initial imaging did not reveal statistically significant atrophy. Structural magnetic resonance and FDG-PET imaging at the second assessment revealed isolated atrophy and hypometabolism in the right posterior cerebellum, in areas shown to be part of his language network by task-based functional neuroimaging at initial assessment.

Discussion: This syndromic cluster can be designated Progressive Oral Apraxia of Reading, an entity that has not been reported previously to the best of our knowledge. We hypothesize a selective disconnection of the visual word area from the otherwise intact articulatory apparatus, a disconnection that appears to reflect the disruption of multisynaptic cerebello-cortical circuits.

Lay Language: We describe an individual with progressive and isolated difficulty in reading words aloud, which occurs in the absence of difficulties visually recognizing, understanding, or repeating the same words. By illustrating a new syndrome that has so far never been reported, we aim to increase awareness and improve the clinical diagnosis of atypical neurodegenerative disorders.

Semantic blurring and atrophy progression in individuals with PPA due to Frontotemporal Lobar Degeneration TDP-43 Type C.

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Background: Individuals with the semantic subtype of Primary Progressive Aphasia (PPA-S), which is most commonly associated with a type of neuropathology called Frontotemporal Lobar Degeneration TDP-43 Type C (FTLD-TDP-C), display profound impairment of picture naming and word comprehension, with naming preceding word comprehension impairment. Word comprehension impairment in these participants takes the shape of a progressive dissolution ("blurring") of the distinction in meaning between members of the same category (e.g., participants point to "apple" when they hear "pear"), hereafter "intra-category blurring", or between different semantic categories (e.g., participants point to "scissors" when they hear "lion"), hereafter "inter-category blurring".

Methods: Twenty-four participants with diagnosis of PPA-S (mean age: 60.8 ± 6.0, 15 female) and autopsy-confirmed neuropathology of FTLD-TDP-C were included in the study. Individuals were asked to name 20 common pictures (displaying animals, tools, food, or clothing) and then perform a written word definition and a word-to-picture matching task on the same items. Participants were assigned to 1) the "anomic" stage, if their performance was lower than 80% correct on the naming task and greater than 80% on the word-to-picture naming task; 2) the "intra-category blurring" stage, if performance on the word-to-picture matching task was lower than 80% and errors exclusively consisted of pointing to animals other than the target; 3) the "inter-category blurring" stage, if performance on the word-to-picture matching task was lower than 80% and errors mostly consisted of pointing to items from other semantic categories. Individual atrophy maps were generated using Voxel-Based Morphometry (VBM), by comparing gray matter volume maps obtained from each participant to those obtained from a group of healthy age-matched individuals. For each stage (anomic, intra-category blurring, inter-category blurring), maps obtained from each participant were binarized and overlaid onto each other to identify brain regions in which all participants within a stage had significant atrophy.

Results: In the anomic stage, all participants showed atrophy in the left temporopolar region (area TG), the anterior inferior lateral temporal cortex, the parainsular region and the perirhinal enthorhinal cortex, with no evidence of subcortical involvement. In the intra-category blurring stage, in all participants, atrophy further encompassed the most anterior portions of the middle and superior temporal gyri, parts of the parahippocampal and entorhinal cortex, the head of the left hippocampus and the amygdala. In the inter-category blurring stage, atrophy encompassed the entire middle and part of the posterior portion of the left middle temporal gyrus, as well as part of the posterior fusiform gyrus.

Discussion: The results of this study offer a description of atrophy progression in individuals with PPA due to FTLD-TDP-C neuropathology that is based on the symptoms, namely on the progressive disruption of semantic knowledge that is typical of PPA-S. Left Area TG, which is considered a "coordinating hub" in the temporal lobe, appears to be atrophic in the earliest stages of the disease, even before semantic blurring is detected. While disruption of the boundaries between members of the same semantic category appears to be linked to anterior lateral temporal atrophy, involvement of extrastriate regions (i.e., the posterior portion of the fusiform gyrus) becomes apparent only when the boundaries between separate semantic categories begin to dissolve.

Lay Language: Primary Progressive Aphasia (PPA) is a dementia syndrome caused by neurodegenerative brain disease. The semantic subtype (PPA-S) shows a progressive impairment in understanding the meaning of common words (e.g., "lion"), which in the initial stages of the illness tend to be confused with other words within the same category (e.g., "camel") and later on can be confused with any other word (e.g., "apple"). This study identifies areas of the brain that are associated with this progressive loss of word meaning, thereby identifying possible targets for interventions in PPA.

Comparison of Atrophy Measures in Primary Progressive Aphasia

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Background: Primary Progressive Aphasia (PPA) is a syndrome distinguished by predominant language decline and progressive brain atrophy, which is a reduction of cortical thickness or loss of gray matter volume. Accurate measurement of both cortical and subcortical brain atrophy is essential for early and accurate diagnosis of PPA. FreeSurfer and CAT12 are current neuroimaging software packages that use distinct, validated methods for estimating atrophy measures. Understanding the strengths and limitations of these methods can expand knowledge of PPA and improve diagnostic accuracy. Therefore, comparative analyses of FreeSurfer and CAT12 are warranted to elucidate their individual utility and complementary information in assessing neurodegeneration in PPA.

Methods: Structural MRIs were acquired from 2 right-handed individuals with PPA (3 times, once every two years) and from 40 healthy controls (once). MRI images were separately run through 2 distinct processing pipelines. First, using FreeSurfer, individual MRIs underwent automated surface reconstruction followed by manual correction of errors. Cortical thickness maps were then estimated by measuring distances between white-gray and pial-CSF boundaries at each point on the surface. Structural MRIs were then separately preprocessed using the computational anatomy toolbox (CAT12), a software that performs a fully automated measurement of cortical thickness and surface reconstruction using surface-based morphometry. CAT12 also performs voxel-based morphometry, which provides an estimate of the volume of specific types of tissue in each voxel, allowing for the creation of whole-brain gray matter maps.

Single subject cortical thickness and gray matter volume maps for the two participants with PPA were then statistically compared to the maps of healthy controls via nonparametric 2-sample T-Test using the Permutation Analysis of Linear Models (PALM) toolbox. Resultant T-statistic atrophy maps were transformed using threshold free cluster enhancement (TFCE) and then corrected for familywise error at $P < 0.05$.

Results: For both participants with PPA, three atrophy maps were generated for each visit (FreeSurfer cortical thickness, CAT12 cortical thickness, and CAT12 gray matter volume). The FreeSurfer and CAT12 generated cortical thickness maps were similar, with the greatest thinning in the left temporal pole for the semantic PPA brain and left superior frontal gyrus for the agrammatic PPA. Volume measures were less sensitive to cortical atrophy; however, they detected decreases in subcortical regions: left amygdala, fusiform gyrus, and hippocampus in the first participant, and left putamen and thalamus in the other.

Discussion: The comparison between FreeSurfer and CAT12 in assessing brain atrophy in Primary Progressive Aphasia (PPA) reveals complementary strengths and limitations of each method.

The precise surface reconstruction afforded by manual correction in FreeSurfer increases its sensitivity, especially in areas of moderate to severe atrophy. However, it does not offer a voxel-wise analysis of subcortical volume changes. Additionally, in areas with extreme atrophy such as the final semantic PPA MRI, manual editing can become prohibitively difficult. CAT12's measure of subcortical gray matter volume provides more detailed insight into the neurodegeneration of deep brain structures. CAT12's fully automated surface reconstruction is less sensitive to changes in cortical thickness, but it allows for atrophy estimations even in the presence of very severe cortical thinning. Further research will explore these methods in larger cohorts and diverse disease states to validate their generalizability across neurodegenerative disorders.

Lay Language: Primary progressive aphasia (PPA) is a condition where people gradually lose their language ability. This is in part due to the loss of neurons in their brain, which can be observed as the brain shrinking over time. Being able to accurately measure this shrinking is crucial for early and accurate diagnosing of PPA and other related diseases. This study compared two different analysis programs that can be used to measure brain shrinking (FreeSurfer and CAT12), and found that they both offered unique advantages, offering the possibility of combining both techniques to get a fuller picture of brain changes in PPA.

Poster 35

Elucidating neurophysiological mechanisms of human brain development and aging-related memory resilience using invasive electrophysiology. .

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Background: The prefrontal cortex (PFC) is central to higher-order cognition, undergoes protracted development, and demonstrates aging-related structural and functional changes that make it susceptible to neurodegenerative disease. To date, research examining aging-related differences in PFC function have focused on older adults (e.g., > 50 years old), and employed methods with low spatial (i.e., scalp electroencephalography [EEG]) or low temporal (i.e., [functional] magnetic resonance imaging) resolution. Consequently, it is not known how age affects PFC physiology from development through early aging, and whether aging-related PFC differences have distinct spatio-temporal profiles that predict aging-related memory differences. Addressing this fundamental unknown carries significant clinical relevance for the early detection and management of aging-related memory decline and neurodegenerative disease.

Method: Intracranial EEG (iEEG) affords uniquely high spatio-temporal resolution in human neuroscience. Leveraging an exceptionally large iEEG cohort (n = 101, n artifact-free channels = 5691; age range = 5.93 – 54 years, 63 males), we isolated signals from each channel that have been linked to higher-order cognition and aging: slow (~1.5 – 4.5 Hz) and fast theta (~4.5 – 8 Hz) frequencies and the aperiodic slope. We analyzed aperiodic slopes and theta frequencies in PFC subregions during memory-based (i.e., visual memory recognition task) and memory-free (i.e., rest) states, mapped effects by age, and related effects to aging-related memory resilience.

Results: In caudal middle frontal gyrus (cMFG), slower slow theta frequencies during memory task performance predicted higher memory recognition irrespective of age ($p = .03$). By contrast, cMFG fast theta slowed with age irrespective of task state (memory-based, memory-free; $p = .005$) and did not significantly predict memory recognition. The aperiodic slope flattened with age in cMFG and rostral MFG (rMFG), with more pronounced effects for memory-free compared to memory-based states (age ´ task interaction, cMFG: $p < .001$, rMFG: $p = .004$). In relating the aperiodic slope to memory recognition, we revealed significant age ´ slope interactions in rMFG for memory-based ($p = .03$) and memory-free recordings ($p = .03$). In both instances, memory performance improved with advancing age and a steepening of the aperiodic slope. Whereas steeper slopes predicted inferior memory recognition in children, they predicted superior memory recognition with advancing age.

Poster 35 cont.

Conclusion: Prior efforts to characterize the neurophysiological dynamics of brain development and aging have been hampered by spatiotemporally imprecise measures, limited age ranges, and relatively small sample sizes. In our large iEEG cohort, we revealed that PFC-derived slow theta frequencies predict memory performance irrespective of age. By contrast, PFC-derived aperiodic slopes vary by task state and predict aging-related memory resilience. PFC theta oscillations and aperiodic activity reflect distinct neurophysiological mechanisms, each of which may be targeted with brain stimulation to slow down or ameliorate age-related memory decline characteristic of many neurodegenerative diseases.

Lay Language: Our brains and behaviors change considerably across our lifetime. Understanding how aging shapes the processes by which our brains function in health and disease is fundamental to understanding memory resilience in the aging human brain, particularly in preventing the onset of neurodegenerative disease, such as Alzheimer's disease. To better understand the aging brain, we focused on a key brain region involved in many cognitive processes, the prefrontal cortex (PFC). The PFC is one of the last brain regions to develop, and is often affected by neurodegeneration, leading to significant cognitive decline. Using direct brain recordings of PFC in a large cohort of neurosurgical patients, we found that specific patterns of brain activity differed from approximately 5 to 55 years of age and were associated with age-related differences in memory. Our findings help understand the underlying mechanisms of brain development and aging, which could be targeted in future work to detect and manage memory loss characteristic of many neurodegenerative diseases.

Poster 36

Within-network Functional Connectivity of Intrinsic Networks in SuperAgers

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Background: Memory decline in late life is a hallmark of aging, yet SuperAgers are individuals 80 or older with episodic memory performances at least as good as cognitively average 50-to-60-year-olds. Neuroimaging analyses have found SuperAgers to have thicker cortices and slower atrophy rates compared to similarly aged controls (Controls). This project extended the anatomical findings by examining the functional integrity of seven intrinsic networks spanning the entire cortex and two memory-specific systems identified from task-based and resting state studies.

Methods: Within-network functional connectivity (FC) of seven large-scale networks and two memory systems were compared between 25 SuperAgers and 16 Controls using resting state functional MRI (rs-fMRI). Classification of SuperAgers/Controls was determined based on measures of episodic memory, executive functioning, verbal fluency, and picture naming (Harrison et al., 2012). Inclusion criteria required stable cognitive status across two visits. T1-weighted structural and rs-fMRI scans from a single visit were used in the analysis. The seven networks were identified from a common resting-state atlas (Schaefer et al., 2018) while memory systems included the anterior temporal (AT) and posterior medial (PM) systems. Within-network FCs for all networks were defined as the average FCs between all within-network regions from a predefined resting-state atlas. AT and PM cortical maps were identified from prior research (de Flores et al., 2022). Within-network FC of the AT and PM systems were defined as the FC between AT-to-anterior-hippocampus and PM-to-posterior-hippocampus, respectively. Within-network FCs were compared across groups using two-sample independent t-tests and corrected for multiple comparisons.

Results: We found no significant between-group differences in demographic characteristics including age, sex, and education. Performance on neuropsychological measures were significantly different for episodic memory, verbal fluency, and picture naming. Group differences in within-network FCs for large-scale networks and memory systems were nonsignificant.

Conclusion: At the group-level within-network FC of large-scale networks and memory-specific systems were not a primary differentiator between cognitively average aging and SuperAgering phenotypes. Person-specific functional connectome approaches may be important for understanding organizational features of SuperAgers.

Lay Language: Memory decline is common as people age, but there are some remarkable individuals known as SuperAgers who maintain memory abilities similar to much younger adults. Previous studies have shown that SuperAgers have thicker brain cortices and slower brain shrinkage compared to typical older adults. In this study, researchers used brain imaging to explore the functional connections within different brain networks of SuperAgers compared to typical older adults. They found that while there were differences in memory and other cognitive abilities between the groups, there were no significant differences in the integrity of brain networks. This suggests that the topography of SuperAgers' brain networks may be unique and future research should apply high-precision techniques to detect more subtle group differences.

Poster 37

Spatial Transcriptomic Characterization of FTLD-TDP Type C Pathology

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Frontotemporal lobar dementia (FTLD) is a heterogeneous group of disorders characterized by the degeneration of the neurons in the frontal and temporal lobes of the brain. It is the most common form of dementia in patients under the age of 60 years old. A hallmark feature of approximately half of FTLD cases is the presence of TAR DNA-binding protein 43 (TDP-43) aggregates. These aggregates are associated with greater pathological burden and clinical symptom severity. This group of FTLD with TDP-43 aggregates, dubbed FTLD-TDP, can be further subdivided into five distinct subtypes: A, B, C, D, and E. Amongst these, Type C is the least studied subtype of FTLD-TDP. Post-mortem samples obtained from patients with confirmed TDP-43 Type C pathology reveal TDP-43 aggregates in long dystrophic neurites and asymmetric cortical atrophy primarily of the left anterior temporal lobe (ATL). In later disease stages, TDP-43 pathology spreads to the right ATL and eventually the middle frontal gyrus (MFG). Clinically, FTLD-TDP Type C presents with the semantic variant of primary progressive aphasia (svPPA). The molecular mechanism underlying the ATL's vulnerability to FTLD-TDP Type C and the preferential lateralization of the disease to the left hemisphere remains largely unknown. To address this, we utilize the 10X Genomics Visium platform to define the spatial transcriptomic profiles of the left and right ATL and MFG in both FTLD-TDP Type C and control (CT) human brain tissue. We identify localized cell populations and cortical layer-specific differentially expressed genes (DEGs) in FTLD-TDP Type C cases compared to control. Moreover, we demonstrate the capacity for this platform to detect unique disease gene markers and uncover the genetic risk factors promoting disease development. Our results may help further understanding of the complex architecture and genetic changes underlying the development of FTLD-TDP Type C in this vulnerable brain region.

Lay Language: Frontotemporal lobar dementia (FTLD) Type C is a rare brain disorder that slowly damages the parts of the brain that control speech and language. There has not been much research studying how this disease develops or why it specifically targets the parts of the brain that it does. By uncovering the structural and genetic changes underlying FTLD Type C, we aim to gain a better understanding of the causes and potential treatments for this disease.

Poster 38

Transcriptomic Signatures of Neurotransmitter Dysfunction in the Alzheimer's Disease Nucleus Accumbens

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Background: The nucleus accumbens (NAc) is a component of the ventral striatum, which historically has not been heavily studied in the field of Alzheimer's disease (AD). However, recent work intriguingly indicates that the NAc is one of the earliest regions in which changes in brain volume are detectable in individuals with high genetic risk for AD. Further, the NAc has been implicated in hippocampal formation-dependent learning and memory, as well as neuropsychiatric symptoms such as apathy and depression that are commonly experienced by individuals with AD. The present investigation seeks to improve understanding of the NAc in AD through a transcriptomic characterization of human postmortem tissue.

Method: RNA-sequencing was performed on postmortem NAc samples from 5 cognitively normal individuals and 14 individuals with AD from the Rush Alzheimer's Disease Center. All sequenced RNA samples possessed a RIN score ≥ 8.0. Differential gene expression was called at FDR < 0.05. Metascape was used to perform pathway analysis on differentially expressed genes (DEGs) identified as protein coding with ≥ 50% change in expression level. Significantly enriched pathways were clustered by similarity score. The unique DEGs annotated to all pathways of a given cluster were treated as a single network to facilitate the identification of specific gene/gene product interactions between clusters conceptualized as broader biological processes.

Results: RNA-seq differential expression analysis indicated significantly different expression levels of 9,239 genes in the AD NAc compared to cognitively normal controls (FDR < 0.05). Of the 9,239 detected DEGs, 2,924 were protein coding genes with at least a 50% change in expression level, from which 156 pathways were determined to be significantly enriched. Notable enriched pathways included GO:0099536 – synaptic signaling (log10q = -29.35), GO:0007610 – behavior (log10q = -24.78), R-HAS-372790 – signaling by GPCR (log10q = -22.11), GO:0050804 – modulation of chemical synaptic transmission (log10q = -16.34), GO:0050808 – synapse organization (log10q = -15.42), and WP58 – monoamine GPCRs (log10q = -13.22). At the level of individual genes, notable DEGs vastly spanned the receptors, transporters, and biosynthesis enzymes of several neurotransmitters including GABA, glutamate, acetylcholine, dopamine, norepinephrine, epinephrine, serotonin, adenosine, and histamine.

Conclusion: Our results indicate that the NAc is heavily impacted by AD at the transcript level, with evidence pointing to several neurotransmitter systems being affected. Interestingly, our results more specifically indicate that such neurotransmitter aberrations may be the consequence of faulty biosynthesis or signaling mechanisms rather than cell death (e.g., lack of change in tyrosine hydroxylase combined with several-fold changes in all downstream catecholamine synthesis enzymes). We are following up the described NAc RNA-seq results with measurement of nine neurotransmitter levels via mass spectrometry to contextualize the consequences of our detected changes in gene expression.

Lay Language: The nucleus accumbens (NAc) is a brain region that is known to play a role in symptoms experienced by people with Alzheimer's disease (AD) such as cognitive decline, apathy, and depression. However, the NAc has been relatively understudied in brains with AD, and as a result the molecular changes that occur in the NAc of brains with AD are not well understood. This project used a technique called RNA sequencing to identify thousands of genes that are altered in the NAc of individuals with AD, and then identified the specific brain processes that those genes are involved in. Our results indicate that several processes related to neurotransmission, which is the way that many cells in the brain communicate with each other, are likely atypical in the NAc of those with AD.

Poster 39

Utilizing imaging techniques in conjunction with spatial transcriptomics to investigate neuroimmune response in Alzheimer's disease patients.

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The mechanisms involved in the neuroimmune response to abnormal amyloid-β (Aβ) aggregation in the Alzheimer's disease (AD) brain remain unknown. Immunofluorescence image analysis in conjunction with spatial transcriptomics allows for unprecedented insight into the spatial organization and genomic dysregulation of cells in tissue. Here, we present a comprehensive image analysis pipeline for formalin-fixed paraffin-embedded tissues processed for spatial transcriptomics using the 10X Genomics Visium platform. Our pipeline includes preprocessing steps for background subtraction, thresholding, and filtering to establish a ground truth for all immunofluorescence (IF) stains. We also demonstrate creation of a distance map to ensure the detection of Aβ located between Visium spots, and advanced machine learning algorithms to localize vascular versus cortical Aβ pathology, as well as microglia-neuronal interactions. Processed channels are then compiled and passed through SpaceRanger to provide the spatial context for transcriptomic data. Additionally, 3D reconstructions of IF images can be generated to determine synaptic density and pruning based on interactions with microglia. We demonstrate that this integrated image analysis pipeline can be used to quantify the microglial immune response to AD pathology.

Lay Language: The mechanisms involved in the neuroimmune response to abnormal amyloid-β (Aβ) aggregation in the Alzheimer's disease (AD) brain remain unknown. To investigate this, we present a comprehensive analysis pipeline that combines two well-established methods of investigating gene and protein dysregulation in brain tissue: immunohistochemistry (IHC) and spatial transcriptomics. Our pipeline includes preprocessing steps to prepare IHC images for analysis, distance map creation to establish the complete Aβ plaque niche, and advanced machine learning to identify different types of Aβ aggregation, as well as interactions between neurons and microglia, the immune cells in the brain. By combining these two experimental methods, we can molecularly define the immune response facilitated by microglia in the AD brain.

Redefining Alzheimer's Disease Therapeutics by Anti-Amyloid Monoclonal Antibodies

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Alzheimer's disease (AD) represents a significant public health challenge with limited therapeutic options. Amyloid accumulation is the key initiating event of AD and is followed by downstream effects which include formation of neurofibrillary tangles, neuroinflammation, cell death, synapse loss and neurotransmitter deficits. This hypothesis has been instrumental in guiding therapeutic strategies and clinical trials for Alzheimer's Disease. Two anti-amyloid monoclonal antibodies (MABs)—lecanemab (Leqembi®) and aducanumab (Aduhelm®)—have been approved in the USA for the treatment of Alzheimer's disease (AD). Lecanemab, formerly known as BAN2401, has emerged as a promising monoclonal antibody targeting amyloid beta (Aβ) aggregates, a hallmark pathology of AD. This abstract provides an overview of lecanemab, including its mechanism of action, preclinical and clinical findings, safety profile, and ongoing research. Lecanemab specifically targets protofibril forms of Aβ, thereby potentially halting disease progression. Clinical trials have demonstrated promising results in reducing amyloid plaque accumulation and slowing cognitive decline in individuals with early AD. Furthermore, lecanemab has shown a favorable safety profile, with manageable adverse effects. Ongoing research aims to elucidate its long-term efficacy, safety and explore its potential in different stages of AD. To investigate the mechanism by which murine version of BAN2401, mAb158, lowers the levels of pathogenic Aβ and prevents Aβ deposition, we injected mAB158 in APP knock in animal model of Alzheimer's disease (AD). We observed mAB158 inhibited protofibrils in the animals which were treated with mAB158. The Aβ levels in the cortical homogenates also reduced significantly. Anti-amyloid monoclonal antibodies are the first disease-modifying therapies for AD that achieve slowing of clinical decline by intervening in the basic biological processes of the disease. These are breakthrough agents that can slow the inevitable progression of AD into more severe cognitive impairment.

Lay Language: Alzheimer's disease (AD) is a devastating neurodegenerative disease. People suffering from AD lose their ability to learn and memorize. Clinically AD is characterized by the progressive loss of neurons, which further leads to severe impairments in cognition and behavior. Lecanemab (Leqembi®) represents a novel therapeutic avenue in the treatment of AD, offering hope for improving outcomes and addressing the unmet medical needs in this devastating neurodegenerative disorder The outcomes of anti-amyloid MAB trials showed significant reduction in the rate of clinical decline as measured by cognitive and functional outcome measures.

Poster 41

Northwestern Alzheimer's Disease Research Center Imaging Biomarker Core

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The Northwestern Alzheimer's Disease Research Center Imaging Biomarker Core (IBC) at the Mesulam Center 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 enhance diagnostic characterization of participants and to enrich the projects of our collaborators. Neuroimaging is focused on the full spectrum of aging: from extraordinary cognitive SuperAging to dementia. The IBC contains multimodal data from MR scans that 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 (PASL). PET scans provide quantitative measures of amyloid (Florbetaben PET) and tau (Flortaucipir PET) binding. Since inception, the IBC has acquired 121 MR scans and 170 PET scans. Raw neuroimaging data from the IBC along with MR scans and PET scans acquired through collaborative studies at the Mesulam Center are made available for data sharing and collaboration through NURIPS (Northwestern University Research Image Processing System). Structural MRI scans undergo 3D reconstruction in FreeSurfer. All MRI sequences are also preprocessed into BIDS (Brain Imaging Data Structure) on the Quest High Performance Computing Cluster for pipeline usage and further analysis.

Lay Language: The Northwestern Alzheimer's Disease Research Center Imaging Biomarker Core at the Mesulam Center 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 enhance diagnostic characterization of participants and to enrich the projects of our collaborators. Neuroimaging is focused on the full spectrum of aging: from extraordinary cognitive aging to dementia. Since inception, the Imaging Biomarker Core has acquired 291 scans. Raw neuroimaging data from the Imaging Biomarker Core, as well as scans acquired through other studies at the Mesulam Center, are made available for data sharing and collaboration via the Northwestern University Research Image Processing System. Imaging data are appropriately organized and stored to facilitate pipeline implementation and downstream analysis.

Poster 42

The Northwestern University SuperAging Program (NUSAP): 25 Years of Progress

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It is commonly assumed that memory and thinking abilities always decline with advancing age. Though this can define the "typical" aging trajectory, the Northwestern University SuperAging Program (NUSAP) at the Mesulam Center for Cognitive Neurology and Alzheimer's Disease has shown that some individuals are able to maintain high levels of cognitive function, especially memory, despite older age. Our conceptualization of a uniquely preserved cognitive aging trajectory dates to the 1980s, with the term "SuperAging" coined in the late 1990s. Over the last 25 years, NUSAP has followed a group of individuals over the age of 80 with exceptional episodic memory ability and overall preserved cognitive function. The NUSAP cohort is thoroughly studied to identify factors associated with avoidance of age-related cognitive decline and memory loss.

NU SuperAgers are defined as "individuals that perform at or above average normative values for individuals in their 50s and 60s on tests of episodic memory and at least within the average range for their age and education on non-memory cognitive domains according to published normative values." NUSAP also enrolls and follows individuals with normal-for-age memory. We have enrolled 205 participants into SuperAging research over the history of NUSAP, over 100 of whom continue to be actively followed. Participants visit our Center 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 Center's brain donation program, providing researchers the opportunity to further investigate the biological mechanisms underlying SuperAging. To date, almost 50 NUSAP participants have donated their brains, allowing for expansion of investigations into the unique biological characteristics of the brains of SuperAgers.

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 in the entorhinal and anterior cingulate cortices of older individuals and of those with cognitive decline. Their brains display a higher density of von Economo neurons, a specialized brain cell population implicated in social intelligence, in the anterior cingulate cortex. Emerging findings highlight the heterogeneity within SuperAgers and show the importance of investigating both brain resistance (i.e., avoidance of pathology) and cognitive resilience (e.g., preserved cognition despite accumulating brain pathology) in this special cohort.

Lay Language: The Northwestern University SuperAging Program (NUSAP) studies individuals in their 80s and 90s whose memory is at least as sharp as people in their 50s and 60s. Over the past 25 years, NUSAP has discovered a number of exciting facts about SuperAgers, including that they have thicker brains, fewer markers of Alzheimer's disease, and more of a certain type of neuron that supports social intelligence compared to their peers with normal-for-age memory. SuperAgers add a critical source of information about brain aging that does not follow the "normal aging" pattern.

Poster 43

Fiber tract profiles of community dwelling older adults and associations with postmortem TDP-43

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Background: TAR DNA-binding protein 43 (TDP-43), has been shown to be involved in various neurodegenerative disorders involving axonal damage including movement disorders and dementias. Studying the relationships between postmortem TDP-43 and antemortem white matter (WM) structural integrity can allow for a better understanding of the disease, rather than exploring clinical presentations alone. Traditional measures of white matter integrity assume the entire tract to maintain similar characteristics, however, advanced computational research has identified that white matter integrity varies in stereotyped patterns along the tract.

Methods: In-vivo diffusion-weighted images were gathered on a 1.5T scanner from subjects from the Religious Orders Study and the Rush Memory and Aging Project. Tractography was conducted for each subject using Mrtrix and Automated Fiber Quantification was used to calculate fractional anisotropy (FA) along fiber tracts. A semi-quantitative rating of TDP-43 severity was assessed in 5 brain regions. We utilized regression models to relate postmortem disease and antemortem FA at 200 nodes along each fiber tract. Coexisting disease including β-amyloid plaques, tau tangles, and cerebrovascular disease were used as covariates, along with demographic variables.

Results: The 47 subjects were 91.5 (SD=5.4) [range: 77.7-100.9] years old at death. Fifty-one percent had TDP-43 pathology and 55% had cognitive changes before death. Results revealed a significant negative relationship ($p<0.05$) between postmortem TDP-43 and FA at unique regions of numerous tracts, specifically the right arcuate fasciculus, left corticospinal tract, left cingulum, and corpus callosum minor.

Conclusion: Findings support current literature indicating white matter integrity does not follow a uniform pattern along fiber tracts. Pathology relationships reveal unique portions of tracts which are vulnerable to disease. Understanding the relationship between disease and these vulnerable regions will be critical in elucidating the effect of TDP-43 on white matter integrity, leading to cognitive decline.

Lay Language: TDP-43 is a common disease of the brain which results in cognitive changes and dementia. We were interested in exploring the integrity of structural connectivity of the brain as related to TDP-43 to better understand how this disease affects the brain. To do this, we mapped structural connections within the brain using brain scans. We saw unique patterns of reduced white matter integrity related to the disease in multiple brain fibers which connect different brain regions. From these findings we can better explore how this disease impacts certain vulnerable regions of the brain that give rise to clinical symptoms including changes in cognition.

High Levels of the Dendritic Spine Protein Spinophilin in Cognitive SuperAgers

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Although memory decline is typically observed throughout the aging process, the Northwestern SuperAging Research Program has identified individuals who maintain superior memory in old age. "SuperAgers" (SA) are selected for having episodic memory at age 80 or older that is at least equivalent to those 20-30 years younger. Initial studies show SAs generally have larger cortical volumes, less ApoE4, more von Economo neurons, and less prevalence of Alzheimer's disease (AD) pathology compared to their cognitively average peers. Loss of synapses commonly occurs with aging and AD as a feature of cognitive decline. Spinophilin is a protein found in dendritic spines, dynamic structures that form the postsynaptic element of most synapses in the CNS. Spinophilin displays distinct localization to the heads of dendritic spines in all brain regions, making it an excellent marker for quantitative assessment of dendritic spine and synaptic integrity. Previously, we observed overall higher cortical levels of the pre-synaptic protein synaptophysin, and the post-synaptic density 95 (PSD-95) protein in SuperAgers. In the current study, we examined cortical levels of spinophilin using fresh frozen post-mortem human tissue from the middle frontal gyrus (MFG), hippocampus (HPC), middle temporal gyrus (MTG), and visual cortex (VIS) in SuperAgers (n=10), normal cognitive elderly (n=5), and AD patients (n=5). Western blot analysis was carried out and results were expressed as a percentage of the housekeeping protein GAPDH. In all regions studied, spinophilin levels were higher in SuperAgers when compared with normal controls (12-41%, $p<0.05$), while in most regions, levels were lower in AD when compared with controls (5-46%). These preliminary results indicate a potential relationship between the SuperAging phenotype and integrity of dendritic spines/synapses as indicated by spinophilin levels. Initial findings will be extended by determining levels of spinophilin and other synaptic proteins in cortical tissue from additional participants to allow rigorous statistical analyses.

Lay Language: The Northwestern University Mesulam Center has identified a group of older adults, dubbed "SuperAgers", who maintain excellent memory even in their 80s and 90s. These SuperAgers have bigger brains, fewer signs of Alzheimer's disease, and more intact neurons compared to their peers who have aged normally. As people age, they tend to lose brain connections, especially in diseases such as Alzheimer's disease. Spinophilin, a protein in the brain, indicates the health of these connections. Previous research showed SuperAgers have high levels of certain proteins related to brain connections. In this study, we found that SuperAgers have more spinophilin than normal older adults, while those with Alzheimer's disease have less. This suggests a link between good memory and healthy brain connections.

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Characterizing Motor Neuron Metabolism in ALS

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Amyotrophic Lateral Sclerosis (ALS) is a debilitating neurodegenerative disease which selectively targets upper and lower motor neurons (MNs) of the brain and spinal cord. Mislocalization of RNA-binding protein TDP-43 and mitochondrial dysfunction are two common pathologic hallmarks degenerating ALS MNs. However limited emphasis has been placed on accurately modeling human MN metabolism in vitro, and thus investigating the causal relationship between mitochondrial metabolism, the aberrant action of TDP-43, and neurodegeneration. Traditional cell culture media utilized to maintain neurons is specifically formulated to reduce metabolic stress and is not physiologic. Little is known about how a physiologic metabolic milieu affects MN mitochondrial metabolism, and what metabolic mechanisms in this context contribute to disease. Here, we aim to address this fundamental limitation by utilizing Human Plasma-Like Media (HPLM), which closely approximates the extracellular glucose and small metabolite composition of human plasma & cerebrospinal fluid. In preliminary experiments, we find HPLM can support iPSC-derived MNs, the maintenance of MN cell identity, and typical patterns of electrophysiologic activity. Using mass spectrometry analysis, we show HPLM remodels the intracellular polar metabolome of healthy MNs, and increases the relative abundance of mitochondrial metabolites. Additionally, we show that Phosphofructokinase-P (PFKP), a rate-limiting glycolytic enzyme, is pathologically mis-spliced in the context of TDP-43 knock down. Together, these results provide a promising platform for further investigation into novel metabolic mechanisms of MN vulnerability in ALS.

Lay Language: Neurodegenerative disorders are broadly characterized by metabolic dysfunction within diseased neurons. However, it remains unknown if metabolic pathology is a bona-fide driver of neurodegeneration, or a late-stage correlate of distressed neurons. In the context of Amyotrophic Lateral Sclerosis (also known as Lou Gehrig's Disease), we propose utilizing Human Plasma-Like Media (HPLM), in combination with patient stem cell-derived neurons, to study metabolic mechanisms of motor neuron vulnerability and degeneration.

Poster 46

Young CSF restores oligodendrogenesis and memory in aged mice via Fgf17

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Background: Brain aging underlies dementia and neurodegenerative diseases, imposing an immense societal burden. Systemic interventions in model organisms have shown great promise in reversing ageing-related decline of various tissues, including the brain. For example, heterochronic parabiosis and young plasma transfer rejuvenated the aged brain and restored memory function. Nevertheless, the brain is protected with barriers, which may limit access to these factors, presumably impeding their rejuvenation potential. However, there is a previously unexplored alternative to plasma, the cerebrospinal fluid (CSF). CSF has tremendous potential for brain therapeutics as it is already in direct contact with the brain and its contents are unencumbered by the blood brain barrier. We theorize that intracerebroventricular (ICV) administration of young CSF to aged mice would have rejuvenating effects on the brain.

Methods: Young CSF from 10-week-old mice, was collected and administered to 20-month-old mice. These aged mice with young CSF were then tested at the behavioral, cellular, and transcriptomic levels.

Results: We discovered that infusing young CSF directly into aged brains improves memory function. Unbiased transcriptome analysis of the hippocampus identified oligodendrocytes to be most responsive to this rejuvenated CSF environment. We further showed that young CSF boosts oligodendrocyte progenitor cell (OPC) proliferation and differentiation in the aged hippocampus and in primary OPC cultures. Using SLAMseq to metabolically label nascent mRNA, we identified serum response factor (SRF), a transcription factor that drives actin cytoskeleton rearrangement, as a mediator of OPC proliferation following exposure to young CSF. With age, SRF expression decreases in hippocampal OPCs, and the pathway is induced by acute injection with young CSF. We screened for potential SRF activators in CSF and found that fibroblast growth factor 17 (Fgf17) infusion is sufficient to induce OPC proliferation and long-term memory consolidation in aged mice while Fgf17 blockade impairs cognition in young mice.

Conclusion: These findings demonstrate the rejuvenating power of young CSF and identify Fgf17 as a key target to restore oligodendrocyte function in the ageing brain.

Lay Language: Aging is the main risk factor for neurodegenerative disorders and dementia. This is a major issue for society, affecting millions of people and their families. Our research is looking at new ways to potentially slow down or even reverse this decline. Previous studies showed success with using young blood to improve other organs, but the brain has a special barrier that prevents this approach from working. We believe a fluid called cerebrospinal fluid (CSF), which naturally bathes the brain, could be a better option because it already bypasses this barrier. In our study, we gave young CSF to older mice and saw signs of improvement in their memory. We were even able to isolate a protein, Fgf17, that lead to these memory improvements in mice. If this holds true in future studies, it could lead to new treatments to help people maintain healthy brains as they age.

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Advancing Alzheimer's Research: An End-to-End PET Workflow Implementation using the Northwestern University Research Image Processing System (NURIPS)

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Background: Positron Emission Tomography (PET) imaging, especially with the use of specific radioligands like amyloid and tau tracers, plays a crucial role in Alzheimer's disease (AD) research, enabling researchers and clinicians to visualize and quantify the presence of amyloid plaques and tau tangles in the brain, aid in the diagnosis, staging of disease progression, and identification of affected brain regions. However, one of the challenges with large-scale multimodal imaging studies is having validated PET reads from trained clinicians alongside other imaging modalities as part of a seamless workflow that is easily accessible to both researchers and clinicians. The current Tau PET workflow is as follows: 1) Install the Medical Image Merge (MIM) software locally, 2) download PET datasets locally, 3) draw contours of a control cerebellum slice using the PET images locally, 4) save contours locally for future review, 5) rescale color bar thresholds based on the cerebellar standardized uptake value (SUV), 6) make a clinical read, and 7) upload patient status based on the clinical read to REDCAP database.

Method: NURIPS is a browser-accessible data management, visualization, and analysis platform designed using the XNAT framework to support imaging research, with a focus on streamlining end-to-end workflows. Using the integrated open health integrated foundation (OHIF) viewer (v3.6.1) in NURIPS, we simplify the current Tau PET workflow to the following steps: 1) Draw and save the cerebellum contour using the integrated OHIF viewer, with access to both the CT and PET images, 2) rescale the OHIF viewer color bar thresholds based on the cerebellar SUV, 3) make a clinical read, and 4) Add patient status to a custom variable in the PET session within NURIPS.

Results: We were able to successfully replicate the core Tau PET workflow using the integrated OHIF viewer that is built into NURIPS. Using the integrated viewer allows one to perform the same workflow without the need to install custom software, download data, store files locally for preservation of contours, or accessing other databases to upload the final patient status based on the clinical read. All contours are stored with the PET session and can be viewed and edited in the future. More importantly, all data associated with the PET session is accessible to both the researcher and the clinician.

Conclusion: Using the integrated OHIF viewer built into NURIPS not only simplifies the PET screening workflow but enables a seamless workflow for both researchers and clinicians to view, process and upload results to a centralized data management system to accelerate the pace of research.

Lay Language: Leveraging the Northwestern University Research and Image Processing System (NURIPS), we have been able to create an end-to-end PET workflow to facilitate clinical reads of PET scans that seamlessly integrates with our centralized data management and analytics infrastructure. This browser-friendly platform allows for faster clinical reads, better data management and improved transparency with the end goal of accelerating Alzheimer's disease research.

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

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The Northwestern University Alzheimer's Disease Research Center (NUADRC) is entering its 29th year of funding from the National Institute on Aging (NIA). The NUADRC is one of 33 ADRCs across the country, all of which have a Clinical Core component. The purpose of the Clinical Core is to establish a cohort of individuals across the cognitive aging spectrum to support clinical and basic research on memory and aging. The Clinical Core is an observational study that follows research participants annually and collects, stores, and disseminates clinical data, brain imaging scans, and biological samples. The data collected by each ADRC (the Uniform Data Set, UDS) are contributed to the National Alzheimer Coordinating Center to all largescale, multicenter research collaborations. Over the past year, the Clinical Core has worked closely with the NUADRC's Education, Neuropathology, and Imaging Cores to recruit and enroll participants, facilitate brain donations, obtain Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) scans, and educate the public on effectively coping with cognitive aging and dementia.

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 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 2,400 participants; 416 are currently active with 21% 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, 80% are committed to brain donation for our research, and another 15% are considering donation. Since our study began in 1996, our brain bank has received over 1,100 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. 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 49

Music Therapy Protocol for Loss of Empathy in behavioral variant Frontotemporal Dementia

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Background: Behavioral variant frontotemporal dementia (bvFTD) often presents with social cognition and behavior changes out of proportion to cognitive changes. BvFTD has the highest caregiver burden of any dementia, presents challenges in nearly interpersonal relationships, and poses significant marital problems not infrequently ending in divorce (Hsieh et al., 2013). One factor in such social cognition deficits is a lack of empathy, a core diagnostic feature in bvFTD (Mendez et al., 2021). Empathy is defined as the ability to recognize and/or adopt another person's emotional state while maintaining self-other distinction (Decety and Jackson et al., 2004). While several interventions have attempted to target a lack of empathy, none have adequately alleviated the emotional burden of families with bvFTD (Finger et al, 2015). Music intervention in autism has successfully led to increased neural activity in brain regions responsible for empathy, improving social communication (He et al., 2018). Similarly to autism, we wonder if impairment of emotions in bvFTD may be stimulus-specific and reliant on social cognition (Molnar-Szakacs and Heaton, 2012). Therefore, we propose that a music intervention protocol may be an effective treatment for improving empathy in bvFTD.

Objective: The purpose of this study is to demonstrate that a strategically planned music therapy curriculum can improve empathy in individuals with bvFTD and burden for caregivers of bvFTD individuals.

Methods: Five participants with bvFTD will be part of our initial pilot program. We will implement a 5-step program that addresses emotional competence, imitating and demonstrating emotions, affect modulation, affect discrimination, emotional expression, and identifying differences in emotional expression. Each step of the intervention will be conducted by a music therapist through interventions such as music listening, song creation and recreation, lyric and song analysis, breathing, and singing techniques. Sessions will be 60 minutes and occur every week for a period of 6 months.

Outcome Measures and Result Predictions: Empathy will be assessed with questionnaires using the Interpersonal Reactivity Index (IRI) and Socioemotional Dysfunction Scale (SDS). Caregiver Burden and Patient-Caregiver Relationship will be assessed using the Zarit Burden Interview (ZBI) and Intimate Bond Measure (IBM), respectively.

Discussion: After the conclusion of our pilot program, we will assess whether the intervention is clinically feasible. If it is proven to be feasible, we plan to proceed with a clinical trial to measure the efficacy of the intervention using the assessments above. We plan to enroll patients in collaboration with the Institute of Music Therapy for the Arts and the University of Chicago.

Lay Language: Behavioral variant frontotemporal dementia (bvFTD) is a neurological condition that often presents with social cognition, behavior, and cognitive changes. One core diagnostic feature of bvFTD is a lack of empathy. Empathy is defined as the ability to recognize another person's emotional state while maintaining self-other distinction. While several interventions have attempted to target a lack of empathy, none have improved the emotional burden on the families of bvFTD patients. In this study, we propose a music therapy protocol that may be an effective treatment for improving empathy in bvFTD.

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Unc5C T835M mutation-mediated neurodegeneration in late-onset Alzheimer's disease in a novel mouse model

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Background: A rare T835M missense mutation in the Un-coordinated 5C (UNC5C) netrin receptor gene has been shown to increase the risk of late-onset Alzheimer's disease (LOAD). The Unc5c receptor contains an intracellular hinge region that, when in its open conformation, gets cleaved and signals for cell death through activation of its death domain. The T835M mutation alters a conserved amino acid in the hinge region of UNC5C death domain which makes it favor an open conformation, suggesting that the mutation may increase cell death through apoptosis. However, the cellular mechanisms of how this mutation leads to AD pathogenesis are unexplored. We hypothesize that the T835M mutation predisposes to LOAD by exacerbating neuronal death via increased sensitivity to beta-amyloid (Aβ) induced neurotoxicity and UNC5C death domain activation.

Method: We generated a double knock-in (dKI) mouse model by crossing a T835M Unc5c knock-in (KI) mouse model to an amyloid mouse model of AD pathology, NLGF. We harvested brains from cohorts of mice at time points of 6 months and 12 months. Hemibrains were fixed for histological and biochemical analyses.

Results: In the dKI mouse model, we see increased cell death by 6 months of age through increased cleaved caspase-3 activity, increased hippocampal area loss, and decreased NeuN levels compared to the NLGF mice. Amyloid pathology is worsened in the dKI mice compared to NLGF mice by showing a significant change in the nature of the plaques and dystrophies with decreased GFAP levels and increased BACE1 and LAMP1 levels.

Conclusion: By adding the additional cellular stress of Aβ, the implications of the T835M Unc5C mutation are further exacerbated in the dKI mouse model through increased neuronal loss and increased AD pathology compared to the NLGF mouse model, suggesting that the mutation exacerbated the amyloid pathology and aided the neuronal cell death in these dKI mice. Our findings could bring valuable insight into potential therapeutic targets to prevent neuronal loss in AD.

Lay Language: The purpose of this investigation is to understand the cellular mechanisms behind a rare mutation in the Unc5C receptor gene that has been linked to late-onset Alzheimer's disease (LOAD). We created a mouse model that knocked in this specific mutation to see the progression of Unc5C-mediated neuronal cell death in the aging mouse brain. In addition to this, we wanted to see how this mutation is affected in the presence of beta-amyloid (Aβ), a protein that aggregates in the brain and is a hallmark in AD pathology. For this, we cross-bred our mutant mouse to an amyloid mouse model and further looked at cellular mechanisms and the pathology of Aβ to better understand how the mutation may affect AD brains.

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Increased resting brain connectivity in individuals with Primary Progressive Aphasia in the absence of cortical atrophy

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Background: Primary Progressive Aphasia (PPA) is a syndrome of progressive language decline secondary to neurodegenerative disease including Frontotemporal lobar degeneration (PPA-FTLD) & Alzheimer's Disease (PPA-AD). The underlying pathology causes network disruption and subsequent shrinking in the brain (atrophy). In a previous report, we showed disrupted network connectivity in the absence of brain atrophy. However, the limited number of participants prevented generalization of results. In this follow-up study, we report results from more PPA participants and investigated possible increase in connectivity within major brain language regions.

Methods: Eighteen right-handed individuals with PPA with no evidence of significant cortical atrophy, and 32 cognitively healthy persons were included in this study. The underlying cause of PPA was Alzheimer's disease (PPA-AD) in 8 and (PPA-FTLD) in 10 participants. Participants underwent structural magnetic resonance imaging (MRI), and scans were preprocessed through SPM12. Three regions of interest (ROIs) within the left and right hemispheres were selected: Inferior Frontal Gyrus (IFG), Middle Temporal Gyrus (MTG), and Anterior Temporal Lobe (ATL). Pairwise resting state functional connectivity (RSFC) values between the 6 ROIs were calculated using the CONN toolbox for each subject. These RSFC values for the PPA groups were compared to those of controls via two-sample t-tests corrected at false discovery rate (FDR) < 0.05 thresholds. Results were also compared in the PPA-AD and PPA-FTLD subgroups and again divided by severity of object naming deficit as measured by the Boston Naming Test (BNT).

Results: Pair-wise ROI analysis showed resting connectivity was significantly decreased between the left and right MTG regions, and significantly increased between the left and right ATL regions in the group containing all PPA participants, compared to controls. Subgroup analysis showed increased left and right ATL connectivity in PPA-AD and not in PPA-FTLD as compared to controls. When compared based on severity of object naming, increased left/right ATL and decreased left/right MTG connectivity was seen in PPA participants with moderate, but not in mild anomia.

Discussion: Individuals with PPA and no significant atrophy showed a decreased connectivity within the left/right MTG and increased connectivity in the left/right ATL regions. Decreased connectivity between the MTG regions suggests that resting connectivity can be used as a leading indicator or PPA pathophysiology as we reported in a smaller group of PPA participants previously. Increased connectivity between the ATLs could be a compensatory mechanism to adjust to progressive decline in naming. This finding was shown mostly in moderately anomic PPA and in PPA caused by AD suggesting a clinicopathologic specificity. The compensatory role of ATL could be a target for future studies of PPA treatment using neuromodulatory interventions such as transcranial direct current stimulation.

Lay Language: Primary Progressive Aphasia (PPA) is a syndrome in which language abilities decline over time due to underlying diseases in the brain. This study looked at changes in brain connectivity in people with PPA whose brain had not shown a reduction in size. Within that group, this study found an increase in connection between certain regions in the brains of participants with Alzheimer's Disease and those who have difficulty naming objects. These results suggest that these brain regions may play an important role in language function, warranting future studies into the ability of these areas to help compensate when language is impaired.

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Evaluating the causal association between resting state intrinsic functional networks and the risk for neurodegeneration

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Background and Objectives: Alterations of resting state intrinsic functional networks have been associated with neurodegenerative diseases risk even before the onset of cognitive symptoms. Emerging hypotheses propose a role of intrinsic functional networks alterations in the risk or vulnerability to neurodegeneration. It is unknown whether intrinsic functional networks alterations can be causal for neurodegenerative diseases. We sought to answer this question using two-sample Mendelian randomization, a method able to assess causal relationships.

Methods: Using the largest genome wide association study of resting state intrinsic functional networks (n=47,276), we generated genetic instruments (at the significance level 2.8 × 10-11) to proxy resting state intrinsic functional networks features. Based on the known brain regions implicated in neurodegenerative diseases, we selected 26 genetically proxied resting state intrinsic functional features and tested their association with their paired neurodegenerative outcomes Alzheimer dementia (111,326 cases, 677,663 controls); frontotemporal dementia (2,154 cases, 4,308 controls); semantic dementia (308 cases, 616 controls), and Lewy body dementia (2,591 cases, 4,027 controls). Major depressive disorder outcome (170,756 cases, 329,443 controls) was included as a positive control. Power and sensitivity analyses were completed to assess the robustness of the results.

Results: None of the genetically proxied resting state intrinsic functional networks features were significantly associated with neurodegenerative disease outcomes (adjusted P value >0.05), despite sufficient power. However, two resting state exposures in the visual cortex showed nominal level of association with Lewy body dementia (P= 0.01), a finding that was supported using separate visual cortex connectivity exposure (P=0.03). As a positive control, global connectivity pattern in the default mode network was associated with risk of major depressive disorder (P=0.024), supporting the validity of the selected genetic instruments. Sensitivity analyses were supportive of the main results.

Discussion: This is the first study to comprehensively assess the causal effect of resting state intrinsic functional networks features on risk of neurodegenerative diseases. Our results overall do not support a causal role for intrinsic functional networks connectivity in the pathogenesis of neurodegenerative disorders. However, we report a suggestive association between visual network connectivity and risk of Lewy body dementia which requires further evaluation.

Lay Language: It has been proposed that abnormal brain connectivity could make the relevant brain regions more vulnerable to degeneration. We tried to study this question using genomic data. We found that in general this is not the case for most dementias. However, abnormal connectivity in the vision cortex areas could increase the chance of Lewy body dementia, but this finding needs further evaluation. This study is important because brain connectivity can be modulated by multiple interventions such as brain magnetic or electrical stimulation and thus (if this hypothesis is proven) we could have a way to modulate a risk factor for dementia.

Poster 53

Comparison of Different Hippocampal Subfield Segmentation Software on Normal Controls & Mild Cognitively Impaired Patients

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Objective: The hippocampus plays a major role in learning and memory. Hippocampal atrophy is a hallmark for Alzheimer's Disease (AD) pathology. The hippocampus is segmented into different subregions which play a role in episodic memory. Accurately identifying the boundaries and the volume of the hippocampal subregions may be used as a biomarker for developing AD. Moreover, monitoring changes in volume in different diagnostic groups such as mild cognitive impairment (MCI) and AD patients can be used to more accurately determine disease progression. The aim of this study is to determine the usefulness of different software that automate segmentation of the hippocampal subfields to better understand AD pathology.

Methods: Twenty-three subjects with varying clinical diagnoses (13 Cognitively Normal (CN), 10 MCI) who have completed the Magnetic Resonance Imaging (MRI) T1w MPRAGE sequence and T2w High Resolution Hippocampus sequence were selected from the Alzheimer's Disease Research Center Neuroimaging Biomarker Core study. Images were processed through the Penn Image Computing and Science Laboratory (PICSL) Automated Segmentation of Hippocampal Subfields (ASHS) software and the Laboratory of Computational Neuroimaging Freesurfer software to obtain hippocampus segmentation volumes. Both ASHS and Freesurfer software use a training pipeline and a segmentation pipeline to calculate the subfield volumetric outputs. The training pipeline creates an atlas package that registers the sequence to an unbiased template and constructs left and right region of interests (ROIs) that are used in the segmentation pipeline. The segmentation pipeline registers the T1w sequence to the template and regional registration of T2w to the atlases which labels subfields based on manual segmentation and outputs volumetric sizes. Volume outputs were compared between diagnostic groups using a one-way ANCOVA in IBM SPSS.

Results: The ANCOVA showed that there was a statistically significant difference between diagnostic group and certain regions of the hippocampus. For the Freesurfer software, the head of the CA1 region ($p = .049$, $F = 3.87$), whole body of the hippocampus ($p < .001$, $F = 12.89$), whole head of the hippocampus ($p < .001$, $F = 37.67$), and the whole hippocampus ($p < .001$, $F = 120.05$) was significantly different between CNs and MCI patients. For the ASHS software, the CA1 region ($p = .018$, $F = 5.66$), Brodmann area 36 ($p = .038$, $F = 4.34$), and the parahippocampal cortex ($p = .036$, $F = 4.43$) were significantly different between CNs and MCI patients. The CA1 head and tail volumetric sizes in the Freesurfer software segmentation were combined to create a composite value of the whole CA1 subregion to compare with the ASHS software segmentation. The same analysis was performed on the composite value, and it was significantly different between diagnostic groups ($p = .024$, $F = 5.15$).

Conclusions: Our results showed that there was a significant difference between CN and MCI subjects in each hippocampus segmentation software. For the Freesurfer software, the head of the CA1 region, entire CA1 region, whole body of the hippocampus, whole head of the hippocampus, and the whole hippocampus were found to have differences between diagnostic groups. This makes sense as hippocampal atrophy is first seen in patients with MCI in the form of memory loss. For the ASHS software, the CA1 region, Brodmann area 36 (BA36), and parahippocampal cortex (PHC) were found to have differences between diagnostic groups. The study results provide valuable clinical implications of neurodegenerative patients by using hippocampus atrophy as a biomarker for AD pathology. Furthermore, utilizing the subregions of the hippocampus can help clinicians determine a treatment plan for their patients. The future direction of this study is to look at atrophy in specific subregions to better understand the decline in clinical symptoms. This would provide clinicians with more knowledge regarding disease progression that could lead to the development of more precise treatment plans for their patients.

Poster 53 cont.

Lay Language: The hippocampus is an important structure for learning and memory, and it is segmented into different regions that encode, process, and retrieve memory information. Identifying the different subregions of the hippocampus can help clinicians more accurately determine disease progression and can help with treatment of Alzheimer's Disease (AD). Two different software automatically label the different subregions, Automated Segmented Hippocampal Subfields (ASHS) and Freesurfer between normal control and Mild Cognitively Impaired (MCI) participants. In this sample, the CA1 region, head of the hippocampus, body of the hippocampus, and whole hippocampus was significantly different between groups for the Freesurfer software; and the CA1 region, Brodmann area 36 (BA36), and parahippocampal cortex (PHC) was significantly different between groups for the ASHS software. The next step is to look at specific subregions to better understand the decline in clinical symptoms.

Assessing the Effectiveness of Noise Reduction with Distribution Corrected (NORDIC) PCA Framework in Improving MRI Imaging Quality

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Background: The use of high (3-7 Tesla) and the ultrahigh magnetic field (UHF) of 7 Tesla has improved the spatiotemporal resolutions of Magnetic Resonance Imaging (MRI) data. However, higher spatiotemporal resolutions are often associated with reduced signal-to-noise ratio (SNR), as smaller voxels or faster acquisition times reduce the signal level relative to the noise level. To overcome this challenge, advanced denoising techniques, such as the Noise Reduction with Distribution Corrected (NORDIC) PCA framework, are utilized to effectively suppress noise while preserving spatial precision. NORDIC is designed to specifically target thermal noise using deep learning methodologies directly on the data rather than estimating parameters that is typically done in other denoising methods. This study aims to evaluate the effectiveness of NORDIC in improving the imaging quality of resting state scans in Primary Progressive Aphasia (PPA) participants.

Methods: Participants of this study are identical to the participants used in Bonakdarpour et al., 2019, which included 33 healthy controls and 73 PPA participants enrolled in Language in PPA observational study. All 73 PPA participants were evaluated by a comprehensive neuropsychological and language test battery and the diagnosis and subtypes of PPA were determined based on a group consensus: 36 participants were in the agrammatic group (PPA-G), 20 in the logopenic group (PPA-L), and 17 in the semantic group (PPA-S). The raw resting state fMRI (rsfMRI) data were first processed on Matlab version 2017b using NIFTI_NORDIC.m developed at the University of Minnesota. The original rsfMRI data and NORDIC-processed data were stored in Brain Imaging Data Structure (BIDS) format and image quality metrics were calculated by the MRI Quality Control toolbox (MRIQC). The same methods for processing the resting state data will follow the Bonakdarpour paper.

Results: MRIQC outputs the Image Quality Metrics, including framewise displacement (FD), static signal-to-noise ratio (SNR), temporal SNR (tSNR), etc. As expected, there was not a statistically significant difference in FD between the orginal and the NORDIC-processed groups since NORDIC does not correct motion. Further, tSNR of NORDIC-processed group was statistically higher than that of original group, indicating that NORDIC effectively targeted thermal noise and improved tSNR ($p < 0.001$, $t = -21.15$). Surprisingly, there was not a statistically significant difference in static SNR between the two groups contrary to the expectation that NORDIC-processed group would have higher SNR. It could be due to how MRIQC calculates the SNR of the image, where it takes the mean/standard deviation of the image mask rather than taking the brain signal/standard deviation of the background noise. The resting state results will be reported following the processing of the data.

Conclusion: NORDIC framework seems to be effective in reducing thermal noise in rsfMRI, as evidenced by higher tSNR in NORDIC-processed group when compared to the original data. Building upon the observed enhancement in imaging quality with NORDIC, the next step is to conduct the same analyses in the Bonakdarpour paper to investigate if these corrected data lead to more robust results and conclusions drawn from the previous study.

Lay Language: Noise Reduction with Distribution Corrected (NORDIC) PCA framework is a new method to improve the quality of Magnetic Resonance Imaging (MRI) data by reducing noise in the images. The original resting state fMRI data of participants with Primary Progressive Aphasia (PPA) and normal control participants were processed with NORDIC. In this sample, NORDIC-processed group had significantly higher temporal signal-to-noise ratio (tSNR), indicating that NORDIC effectively reduced noise. Building upon the observed improvement in imaging quality with NORDIC, the next step is to explore if improved imaging quality can lead to robust conclusions drawn from the previous study.

Poster 55

Role of Brain Estrogen Deficiency in Memory Deficits in Female Aromatase Knockout Mouse Models

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Background: Almost two-thirds of Americans living with Alzheimer's disease (AD) are women, however, the molecular mechanisms underlying this sex difference in AD vulnerability remain unclear. AD is more common in women after menopause with drastically reduced blood estrogen levels due to ceasing estrogen production in ovaries. Aromatase, the key enzyme for estrogen biosynthesis, is expressed in the ovary and brain in female mice. To explore the role of estrogen deficiency in sex-specific AD vulnerability, we generated mouse models with brain-specific aromatase knockout (bArKO) and whole-body total aromatase knockout (tArKO).

Method: We performed a series of memory and behavior tests including spontaneous alternation, social interaction, and tail suspension tests on 6- and 19-month-old bArKO and tArKO mice with both sexes (n=10/group). Serum and tissue estrogen was measured using liquid chromatography-mass spectrometry.

Results: Aromatase deletion decreased brain but not serum estrogen levels in bArKO mice. As expected, circulating and brain estrogen levels were significantly decreased in tArKO mice. Impairments of spatial working memory and social interaction behavior were found in 19-month-old female bArKO and tArKO mice. Female tArKO mice also displayed depression-like behavior at the age of 6 and 19 months. At 6 months old, tArKO female mice showed impaired working memory whereas bArKO female mice had normal working memory. Male bArKO and tArKO mice had normal working memory and social interaction and did not show depression-like behavior at both 6 and 19 months of age.

Conclusion: Our findings show estrogen deficiency in the brain and the entire body contributes to sex-specific memory loss in aged female mice. Future studies will focus on defining the underlying molecular mechanisms linking estrogen deficiency and memory loss and identifying druggable targets to inform the development of new therapeutic strategies for the prevention and treatment of AD.

Lay Language: Women are disproportionately affected by Alzheimer's disease (AD), comprising approximately two-thirds of all AD patients. AD is more common in women after menopause with drastically reduced estrogen levels due to ceasing estrogen production in ovaries. This study focuses on the role of estrogen deficiency in the brain vs. in the whole body (the brain and the ovary) of female mice at both young (6 months) and old age (19 months). We found estrogen loss highly impacted working memory, social interaction, and depression-like behavior in female but not male mice in old age. Future studies will define the related underlying molecular mechanisms and identify druggable targets to inform the development of new therapeutic strategies for the prevention and treatment of AD.

Poster 56

Levetiracetam prevents Aβ42 production and synapse loss in Alzheimer's disease models through SV2a-dependent modulation of App processing.

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Current Alzheimer's disease (AD) therapeutics predominantly target the clearance of existing $A\beta_{42}$ deposits rather than addressing its production. Aβ production requires synaptic vesicle (SV)-cycling at the presynapse, but how this process can be targeted therapeutically remains unclear. First, we followed up on our previous findings that presynaptic protein turnover leads to elevated levels of presynaptic proteins during the early stage of Aβ pathology. To determine whether this resulted from impaired proteostasis or compensatory mechanisms, we utilized a proteostasis reporter in App KI mice, which revealed proteostasis dysfunction at excitatory presynaptic sites. Biochemical analyses of SVs isolated from App-KI mice revealed the App ectodomain and $A\beta_{42}$ in the SV lumen. Next, we investigated the mechanism of action for the presynapse targeting small-molecule drug, Levetiracetam (Lev). We discovered that Lev modulates App proteolytic processing preference by correcting SV protein levels and decreasing SV-cycling. As a result, App is preferentially retained at the plasma membrane, where it is more likely to cleaved by α-secretase, thereby reducing $A\beta_{42}$ levels. Notably, Lev prevented $A\beta_{42}$ production and rescued synapse loss in vivo. To address whether these findings are relevant to humans, we performed quantitative proteomic analyses of pre-amyloid human Down syndrome brains. Our results revealed elevated levels of presynaptic proteins prior to significant $A\beta_{42}$ accumulation in patient brains that will inevitably develop AD. Taken together, our discoveries highlight the therapeutic mechanism of action for Lev in targeting the presynapse to prevent the production of $A\beta_{42}$ and consequently downstream irreversible pathologies.

Lay Language: Current Alzheimer's disease (AD) therapeutics predominantly target the clearance of existing toxic amyloid beta ($A\beta_{42}$) protein deposits rather than preventing its production. $A\beta_{42}$ is produced through the amyloidogenic processing pathway of the amyloid precursor protein (App) during synaptic vesicle (SV) cycling at presynapses, but how to target this process therapeutically remains unknown. Here, we investigated repurposing the FDA-approved presynaptic targeting drug levetiracetam (Lev) for AD, which has shown promise in slowing cognitive decline. However, the mechanism of action for Lev's therapeutic effect remains unknown. In this work, we discovered that Lev decreases SV-cycling which reduces $A\beta_{42}$ production by altering the location of App such that it avoids the amyloidogenic processing pathway. In addition, we show that Lev prevents $A\beta_{42}$ production and synapse loss in AD-mouse models. This study uncovers Lev's therapeutic mechanism of action and demonstrates that Lev prevents the production of $A\beta_{42}$, and consequently, downstream irreversible pathologies.

Poster 57

Within-Individual Mapping of Language Regions in the Posterior Cerebellum

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The cerebellum's role in language is often overlooked. Yet the cerebellum is active during language tasks (Petersen et al., 1989; Ashida et al. 2019). Functional connectivity estimates suggest that classic language regions of the cerebrum connect to specific regions of the cerebellum (Xue et al., 2021; King et al., 2019). We tested the functional properties of these cerebellar language regions across visual and auditory language tasks and asked whether viewing orthographic forms recruits the same portions of cerebellum. We collected functional magnetic resonance imaging data (8h per person) at 3T from neurotypical adults across 8 sessions, using a multi-echo sequence to boost signal (Lynch et al., 2020). Participants were shown text or played audio clips of speech, alongside control conditions of text pseudo-words or distorted speech. Participants also viewed an unfamiliar foreign script. For functional connectivity analysis, participants completed resting state runs while fixating a crosshair. We created individualized maps of resting state functional connectivity using two approaches. First, we chose seeds in known language regions of the cerebrum to identify reproducible correlation patterns. Next, we defined networks using data-driven clustering performed on the same resting state data. These estimates were compared to activity evoked by visual and auditory language tasks. This procedure led to a map of the higher-order language network for each subject, defined from the clustering solution (value of k) that best matched the seed-based correlation and task-based maps on the cerebrum. A winner-take-all approach sorted cerebellar vertices into clusters based on correlation with the cerebral cortex (Xue et al. 2021). Participants demonstrated language regions in the right cerebellum, particularly in Lobules VII, VIII. The cerebellar network regions overlapped with activity during both visual and auditory language tasks. Auditory language activity was more bilateral than visual language activity, consistent with the cerebral cortex. Language activity in Lobules VII, VIII juxtaposed or partially overlapped activity evoked by viewing orthographic forms. These lobules could represent a critical site for the translation of visual inputs into comprehensible language. Accordingly, we describe a patient with a progressive, isolated reading impairment that arose in the context of otherwise preserved language and cognitive functions. Applying the same functional mapping methods, we observed selective atrophy in the language regions of right Lobules VII, VIII, supporting a causal role for this nexus in reading and language processing.

Lay Language: The cerebellum is often overlooked in brain imaging studies, but evidence suggests its organization parallels that of the cerebral cortex. We studied which parts of the cerebellum are active during reading and general language (i.e., speech and reading) processing, and found that reading and general language regions were positioned next to each other in the cerebellum, just as they are in the cerebrum. Further, we observed a patient in whom neurodegeneration selectively affected this cerebellar region, leading to difficulties specifically in reading words aloud.

Poster 58

The effect of non-pathological aging on behavior, genetics, and epigenetics in mice

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Background: Aging is a time-dependent deterioration of physiological functions that occurs in both humans and animals. Within the brain, aging cells gradually become dysfunctional through a complex interplay of intrinsic and extrinsic factors, ultimately leading to behavioral deficits and enhanced risk of neurodegenerative diseases such as Alzheimer's disease (AD). The characteristics of normal aging are distinct from those associated with age-related diseases and it is important to understand the processes that contribute to this pathological divergence. The identification of behavioral, genetic, and epigenetic biomarkers associated with normal aging is key in determining the mechanisms of underlying pathological aging and how these impact AD.

Methods: We conducted a comprehensive behavioral assessment of young (3-month-old) and aged (18-month-old) C57/BL6 mice including locomotion, memory-relevant, and anxiety-like behavior to elucidate the cognitive and behavioral phenotypes of aging. We subsequently employed RT-qPCR to determine synapse-related gene expression in the prefrontal cortex of mice at both ages, and ChIP to assess age-related differences in histone acetylation (H3K9ac) at the same genes. Finally, we conducted CUT&RUN sequencing to analyze the relative abundancy of H3K27ac, a histone marker that associates with promoters and enhancers of active genes to determine age-related changes in epigenomic profiles.

Results: Compared to young mice, aged mice displayed decreased locomotion in the open field ($p<0.0001$), enhanced anxiety in the elevated plus maze ($p=0.0003$), and deficits in the novel object recognition task ($p=0.0011$) and novel arm entry task ($p=0.0155$). These age-related behavioral changes occurred in tandem with lower abundancy of H3K9ac at synapse-related gene promotors nr2a ($p=0.001$), glur1 ($p<0.0001$), glur2 ($p<0.0001$), and PSD-95 ($p<0.0001$), and lower mRNA expression levels of nr2a ($p=0.028$), glur1 ($p=0.016$), glur2 ($p=0.038$), and PSD-95 ($p=0.0037$) in 18-month-old mice. CUT&RUN analysis also revealed significant age-related differences in H3K27ac genome occupancy, including sites associated with synaptic plasticity and neuron function.

Conclusions: These data suggest that non-pathological aging induces a unique behavioral phenotype that's associated with alterations in epigenetic markers and gene expression. Future studies will be focused on disentangling epigenetic and behavioral alterations that occur during normal aging from those that occur during pathological aging and aging-related diseases such as AD.

Lay Language: This research suggests that normal aging in mice leads to unique changes in behavior, genetics, and epigenetics. Understanding these changes is crucial for distinguishing them from those linked to diseases like Alzheimer's. Future studies will delve into unraveling the specific alterations that happen during normal aging and how they differ from those seen in diseases like Alzheimer's.

Poster 59

Oligodendrocyte-derived Carnosine Protects the Central Nervous System from Neuroinflammation

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Background: Acrolein (systematic name: propenal) is a highly toxic aldehyde that exerts strong toxic effects by covalently binding to surrounding macromolecules, such as proteins, RNA, DNA, and lipids. Among the byproducts of lipid peroxidation, acrolein is by far the most toxic. Elevated levels of acrolein were found in the brains of Alzheimer Disease (AD) patients at the preclinical stage, suggesting that acrolein accumulation contributes to the early stages of disease pathogenesis.

Due to its toxicity, cellular mechanisms evolved to detoxify acrolein by quenching acrolein and turning it into a non-toxic compound. In the central nervous system (CNS), acrolein is quenched by carnosine, which turns acrolein into a non-toxic compound (carnosine-propanol) that is secreted in the urine. The enzyme Carnosine synthase 1 (Carns1) catalyzes the formation of carnosine (beta-alanyl-L-histidine) from beta-alanine and histidine. We found in our preliminary studies that in the CNS, Carns1 is expressed solely by oligodendrocytes. Nevertheless, the role of oligodendrocyte-derived carnosine in protection of the CNS remains unknown, in part, due to lack of appropriate experimental models. We hypothesize here that oligodendrocyte-derived carnosine plays a fundamental role in protection of CNS from neuroinflammation and AD.

Methods: We developed mice with a Carns1 conditional allele that enabled us to ablate carns1 specifically in oligodendrocytes, thereby reducing carnosine levels in the CNS. Carns1 expression was explored by IHC, and carnosine (the metabolite) levels were examined by LC-MS. We utilized the EAE model to explore the role of Carns1 in neuroinflammation.

Results: Oligodendrocyte-specific ablation of Carns1 resulted in a reduction in carnosine in the CNS. Using the EAE model we found the ablation of oligodendrocyte-derived carnosine caused an increase in damaged areas marked by acrolein adducts.

Conclusions: Our data suggest that oligodendrocytes are the sole source of carnosine in the CNS. Furthermore, our preliminary results show the protective ability of carnosine in neuroinflammation. In our current work we are using the 5XFAD and the APPNL-G-F mice to explore the role of oligodendrocyte-derived carnosine in AD.

Lay Language: Our research aimed to evaluate new ways to protect the brain from the effects of aging, specifically neuroinflammation. Our results showed that the brain-produced molecule, carnosine, has protective abilities in neuroinflammation. This suggests that carnosine could be protective against neuroinflammation in the brain, an important finding in identifying ways to slow the negative effect of aging. The next step will be to expand our research of carnosine to models of Alzheimer's disease and aging to further characterize carnosine's protective abilities.

Poster 60

Investigating sex-specific hypothalamic pathology and immune infiltration in Alzheimer's Disease

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The hypothalamus is integral to regulating numerous physiological processes that are disrupted in Alzheimer's disease (AD). Yet, the hypothalamus remains critically understudied in AD. We hypothesize that blood-cerebrospinal fluid-barrier (BCSFB) dysfunction in the hypothalamus results in increased peripheral immune infiltration and subsequent neuroinflammation in AD. Here, we performed single-cell fixed RNA profiling (scFRP) and spatial transcriptomics on post-mortem human hypothalamus tissues with and without AD pathology. We show that scFRP can identify all primary cell types in the hypothalamus, and that spatial transcriptomics can be used to locate transcriptional changes in the vicinity of hypothalamic AD pathology. By integrating these two modalities, we will study transcriptomic changes and cell-cell interactions that associate with AD pathology in the hypothalamus and at the BCSFB. Together, these results work towards establishing a mechanistic link between peripheral immunity and AD pathobiology in the hypothalamus. They will further provide a deeper understanding about how BCSFB function may exacerbate neuroinflammation in AD to promote sex disparities. In turn, this will inform future design of therapeutic approaches, potentially targeting the BCSFB, for a disease that currently lacks an effective treatment.

Lay Language: Alzheimer's disease (AD) is typically characterized by the degradation of neurons, which leads to irreversible cognitive impairment and memory loss. Importantly, many AD patients also experience non-cognitive symptoms that include sleep disruption, metabolic dysfunction, and disturbances in hormonal signaling. Nearly two-thirds of all AD cases are females, but the underlying reason for this sex discrepancy 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 the context of AD. As such, we aim to uncover hypothalamic changes occurring in the AD brain. Furthermore, we investigate this deep-brain hub as a possible entry point for immune cells. Together, these findings work towards establishing a mechanistic understanding of underlying sex differences in AD, and eventually may aid with therapeutic target identification.

Poster 61

Clinical Improvisatory Music for Alzheimer's Disease Anxiety and Caregivers (CIMAC): Preliminary Results from Ongoing Trials

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Background: Approximately 40% of individuals with Alzheimer's disease (AD) experience anxiety symptoms including irritability and agitation. Anxiety and neuropsychiatric symptoms of AD also cause a significant amount of burden on their caregivers. Since the management of AD anxiety (AD-A) with medication can be limited by negative side effects, polypharmacy, and high mortality, non-pharmacological interventions are increasingly being studied, including music interventions. Previous studies of music interventions for anxiety in AD (AD-A), had less than 60 participants and mostly used familiar music (Ting et al., 2023). To utilize the physiologic effects of music regardless of familiarity effect we have created Clinically Designed Improvisatory Music (CIDIM), which has been shown to be effective in cognitively healthy individuals (Bonakdarpour et al., 2021 & 2022). The purpose of this ongoing study is to provide preliminary results, demonstrating that CDIM brings relief and reduces anxiety in individuals with AD-A and their care partners. Here we report preliminary results for 2 AD-A and 2 caregiver participants.

Methodology: Two participants with Alzheimer's disease and 2 care partners have completed the study so far, using a delayed enrollment design with two evaluations before and one evaluation after CDIM. Evaluations were a month apart. CDIM consisted of 30 minutes of meandering melodic lines in slow tempos (around 60 beats per minutes), utilizing a pitch range one octave below and one octave above middle C, presented in multiple 2-minute statements interspersed by 10 second pauses, and was played by a certified clinical music practitioner (CMP) on viola for 8 sessions (4 in person and 4 virtual). Anxiety in AD was measured using Rating Anxiety for in Dementia (RAID) and Beck Anxiety Inventory (BAI), and care burden in care partners using Zarit Burden Interview (ZBI). Participants' blood pressure (BP), respiratory rate (RR), and heart rate (HR) were also measured.

Results: Participants self-reported that the level of anxiety or burden decreased at each session, and cumulatively after 8 CDIM sessions. One participant mentioned being able to "think" more clearly. Pre- and post-intervention anxiety questionnaires revealed average RAID and average ZBI scores decreased from 20 to 11 and 40 to 16.5 respectively after CDIM. For participants with AD-A systolic BP decreased from 134.5 to 122 mmHg, and HR decreased from 95.5 to 76 bpm after 8 CDIM sessions. For caregivers, average systolic BP decreased from 148.5 to 131.5 mmHg, and average HR decreased from 105 to 78.5 beats per minute (bpm) following CDIM. RR values remained unchanged.

Discussion: In these preliminary results, we found positive effects of CDIM measured by standardized tests which suggest feasibility and potential effectiveness of CDIM. The decreased BP and HR in both groups during each session and cumulatively after 8 intervention sessions suggest immediate and cumulative physiologic entrainment induced by CDIM. At this stage of the study, we have collected resting state functional magnetic resonance imaging (rsf-MRI) data; however, we are underpowered to report any results. This study provides preliminary data, which suggests that live and virtual CDIM can reduce anxiety and care burden with physiological correlations for participants with AD-A and their caregivers. Based on our current funding, our goal is to run 40 individuals with AD-A and 18 caregiver participants.

Lay Language: In this ongoing study, we investigate Clinically Designed Improvisatory Music (CDIM) as a non-medicinal intervention to induce calmness in participants with Alzheimer's disease and anxiety (AD-A) and burdened caregivers. During the CDIM intervention, a certified clinical music practitioner performed 30 minutes of CDIM on the viola twice a week (in-person and virtually) for four weeks. Anxiety and care burden were measured before and after CDIM. Our preliminary results from 2 AD-A and 2 caregivers indicate a decrease in average anxiety and burden levels after CDIM sessions, which is supported by decreased average blood pressure and heart rate. While these studies are still in their preliminary stages, these initial results highlight the potential effectiveness of CDIM as a calming intervention for anxiety in AD-A and caregiver burden.

Poster 62

Anatomic Selectivity of Cortical Neuronal and Glial Tau in Behavioral Variant Frontotemporal Dementia with 4R FTLD-tau

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Objective: Behavioral variant frontotemporal dementia (bvFTD) is an early-onset clinical dementia syndrome characterized by progressive worsening of behavior and personality at initial stages, with peak areas of focal atrophy typically isolated to bilateral frontotemporal brain regions. Various underlying pathologies can be present, including the 4R tauopathies of Corticobasal Degeneration (CBD) or Progressive Supranuclear Palsy (PSP) pathological subtypes. This study investigated clinicopathologic concordance between bvFTD and cortical distributions of 4R-FTLD neuronal and glial markers of pathology.

Participants and Methods: Right-handed cases with antemortem diagnoses of bvFTD and autopsy-confirmed PSP (N=5) or CBD (N=4) as the sole pathologic diagnosis were identified from the Northwestern University Alzheimer's Disease Research Center brain bank. Paraffin-embedded sections were stained immunohistochemically with AT8 to visualize neuronal inclusions, tufted astrocytes, and coiled bodies in PSP, and neuronal inclusions, astrocytic plaques, and coiled bodies in CBD. Modified stereological analysis (MicroBrightField, MBF Bioscience) was performed on 3 regions bilaterally [middle frontal gyrus (MFG), inferior parietal lobule (IPL), and superior temporal gyrus (STG)]. One-way nonparametric ANOVAs and students' t-tests were used to compare regional distributions of pathology.

Results: In both PSP and CBD pathological subgroups, there was relatively symmetric predominance of cortical pathology, with highest burden in MFG (compared to STG and IPL, ~2-fold on average). Cases with CBD pathology had significantly more neuronal inclusions than cases with PSP pathology in all regions ($p<0.05$), whereas cases with PSP pathology displayed more glial pathology—particularly coiled bodies—compared to CBD ($p<0.05$).

Conclusions: Preliminary findings of middle-frontal, and relatively symmetric, predominance of pathology in FTLD-PSP and FTLD-CBD are concordant with the bvFTD clinical phenotype. In bvFTD, CBD pathologic burden appears to be primarily neuronal, while in cases with PSP pathology it is characterized by considerably higher glial tau in cortex, offering insights into the selective vulnerability of distinct cell populations within 4R-tauopathies.

Lay Language: Our lab studies the relationship between clinical symptoms of dementia during life and the underlying pathologic disease in the brain found at death. One clinical syndrome can be caused by multiple diseases, so there is no direct correlation between pathology and clinical disorder. To better characterize these complex relationships, we examine the amount and location of specific misfolded proteins in various diseases to see how location of pathology may correlate to clinical presentation.

In this project, we analyzed the brains of people presenting with behavioral variant frontotemporal dementia (bvFTD), a clinical dementia syndrome characterized by progressive worsening of behavior and personality. These people also showed either a disease known as Progressive Supranuclear Palsy (PSP) or Corticobasal Degeneration (CBD), both of which are characterized by abnormalities in the protein ""tau."" We examined the distribution of PSP and CBD disease markers in neurons as well as non-neuronal cell populations in several brain regions to distinguish cases with bvFTD due to PSP versus CBD. In summary, we found that cases with bvFTD-CBD there is a higher presence of abnormally-folded tau in neurons in several regions, whereas in bvFTD-PSP there is higher burden of tau in non-neuronal cell types, such as astrocytes and oligodendrocytes. Further distinction of the pathologic fingerprint of these two tauopathies and the clinicopathologic relationship will lead to earlier and more accurate diagnoses of these diseases.

Poster 63

PREVENTABLE: Pragmatic Evaluation of Events and Benefits of Lipid-lowering in Older Adults

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Background: Statins lower cholesterol and reduce cardiovascular risk in adults under 75 years old. In older adults, it is unknown if statins reduce the risk of dementia, disability, or heart disease.

Methods: Northwestern is participating in PREVENTABLE, a pragmatic, placebo-controlled trial of atorvastatin 40 mg in community-dwelling, English, or Spanish-speaking adults, aged 75 years or older, who do not have clinically evident cardiovascular disease, significant disability, or dementia. PREVENTABLE will follow up to 20,000 older adults from 100 US sites for up to 5 years.

Discussion: Northwestern is applying a study-specific cohort assessment query to the electronic health record to generate a list of potential participants. We screen participants to confirm eligibility, consent and enroll those interested in joining the study via phone or in-person. Enrolled participants complete a baseline visit with Northwestern staff via phone or in-person. We can perform a short physical performance battery for subjects who make in-person visits. Follow-up calls, including Cognitive and Disability assessments, are performed by a call center at 3 months, 12 months, 24 months, 36 months, and a final visit call. The primary outcome is survival free of new dementia or permanent disability. Secondary outcomes include a composite of CV death, hospitalization for unstable angina or myocardial infarction (MI), heart failure, stroke, or coronary revascularization, and a composite of mild cognitive impairment or probable dementia.

As of March 2024, PREVENTABLE has enrolled 7,260 subjects and Northwestern has screened 2,000 patients and enrolled 30 since January 2023. Enrollment has been challenging because most healthy older adults are hesitant to start a new medication, and other older adults, dealing with other health issues, do not want to add more medications to their regimen. PREVENTABLE also has ancillary studies to assess clinical atherosclerotic cardiovascular disease (ASCVD) as reflected by coronary artery calcium (CAC), the longitudinal effect of statins in physical performance (SPPB), and the association between sedentary, standing, and stepping durations and risk of cognitive impairment or dementia (STAND).

Future Directions: Although recruitment has been challenging across the entire network of participating sites, including at Northwestern, PREVENTABLE will assess the efficacy of statins to reduce dementia, disability, or cardiovascular disease in older adults.

Lay Language: Statins lower cholesterol and reduce cardiovascular risk in adults under 75 years old. In older adults, it is unknown if statins reduce the risk of dementia, disability, or heart disease. The PREVENTABLE study wants to learn if taking an Atorvastatin, commonly known as Lipitor, could help older adults live well for longer by preventing dementia, disability, or heart disease.

PPA Tele-Savvy: Results of an Online Pilot Intervention with Caregivers of Persons with Primary Progressive Aphasia

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Background: Understanding the nature of Primary Progressive Aphasia (PPA) and the underlying disease process is difficult due to limited information and support from health care professionals. At the time of onset, PPA presents as a language-based impairment, but persons with PPA and their caregivers may not identify PPA as a progressive dementia, eventually impacting other areas of cognition. Persons living with PPA are often younger onset at the time of diagnosis which can lead to complicated psychosocial issues that are compounded by complex terminology and uncertainty regarding progression and pathology. Most interventions available to dementia caregivers do not match PPA caregiving families' needs for tailored psychosocial support.

Methodology: PPA Tele-Savvy is an adaptation of the evidence-based online psychoeducation caregiver program, Tele-Savvy. Aligning with this program, PPA Tele-Savvy targets caregivers' coping by strengthening their knowledge of the effects of PPA, skills in supporting those living with PPA and the caregiver's sense of their own abilities to deal with current and future care challenges The goals of the adapted PPA Tele-Savvy were to: (1) address communication and other cognitive and behavioral challenges facing informal caregivers of those living with PPA throughout disease progression, and (2) help caregivers achieve competence in their role. 15 spousal caregivers (n=9, n=6) participated in 2 sessions (an initial pilot and an informed pilot mixed methods study), which included seven 90-minute weekly videoconference sessions, mindfulness exercises, readings from an adapted PPA-specific manual, and homework assignments. Pre-post effects were assessed on PPA knowledge, mood, caregiver burden, perceived stress, competence, quality of life and dyadic relationship. A focus group was held post-intervention for both pilots. A thematic analysis was performed using recorded videos and transcribed weekly sessions.

Results: Combined quantitative results were aligned with Tele-Savvy results, demonstrating trends of caregiver decreased depression, increased competency. In addition, there was decreased burden and increased PPA knowledge. Results were significant for increased positive dyadic interaction (from the perspective of the caregiver). Qualitative analysis of both pilots revealed five themes: 1) Increasing knowledge of PPA and wanting this sooner in the disease course, 2) Learning new ways of approaching communication and connection, 3) Adjusting expectations of the person with PPA, 4) Initiating care planning, and 5) Assessing self-care needs.

Conclusion: The adaptation, PPA Tele-Savvy has demonstrated not only the feasibility of offering a tailored PPA caregiver intervention; it demonstrates positive results for improving caregiver well-being, competence, increased knowledge and most significantly positive impact on the dyadic relationship. Further testing of this project in a larger trial is warranted.

Lay Language: Primary Progressive Aphasia (PPA) is a rare dementia syndrome characterized by early symptoms of language impairment followed by progressive impairment to other cognitive domains. By tailoring the evidence-based caregiver intervention, Tele-Savvy, to the unique experience of care partners for persons living with PPA, we were able to demonstrate improvement in caregiver well-being, competence, increased knowledge as well as impact on the relationship between the care partner and the person for whom they care.

Protocol & Preliminary Results for a Multi-Domain Scoping Review to Identify Measures of Decision-Making Ability

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Background: Neurodegenerative diseases that arise in aging - collectively referred to as Alzheimer's Disease and related Dementias (ADRD) - are marked by a decline in cognitive domains such as memory, language, and decision-making (DM), among others. With respect to DM ability, specifically, there is ample evidence that deficits in this domain can lead to adverse outcomes in areas like financial management, medical compliance, and other instrumental activities of daily living. However, routine cognitive screening typically does not include systematic and comprehensive assessment of DM ability. As such, the Advancing Reliable Measurement in Cognitive Aging and Decision-making Ability (ARMCADA) research initiative seeks to address these issues to enhance the quality of life for older adults, especially those with other markers of ADRD. The current scoping review protocol described here details the examination of published literature on existing measures designed to assess DM ability in an aging population as our first step towards revolutionizing early detection, intervention, and outcomes for older adults with and without ADRD.

Methods: Guided by Arksey and O'Malley's (2005) scoping review methodology framework, we systematically searched Embase (Elsevier), MEDLINE (Ovid), PsycINFO (EbscoHost), Cochrane Library (Wiley), Web of Science (Clarivate), and Scopus (Elsevier) to identify studies published between January 2018 and November 2023 that met our eligibility criteria. Following best practice recommendations, we applied a two-stage study selection process: First, titles and abstracts were independently reviewed by two reviewers based on our eligibility criteria; second, full texts were screened, and data were extracted from the articles that were included after the full text review. Results will be reported in adherence to PRISMA-ScR guidelines.

Preliminary Results: The scoping review search criteria initially identified 32,235 articles related to DM in adults aged 45 and older. Endnote and Covidence were used to remove 15,957 duplicate articles. The research team then screened the remaining 16278 articles, first by title and abstract (14622 excluded at this point) and then with full-text screening (868 excluded during this stage). The remaining 786 articles were then moved to the extraction phase, completed using Qualtrics. The final extraction data included 708 articles after the further exclusion of an additional 78 articles, which failed to meet eligibility criteria. Extraction data includes information about article sample characteristics and measures used, administration method (e.g., remote vs. In-person), reliability/validity metrics, and DM domain area assessed. Analysis of extracted data is still ongoing.

Conclusion: The goal of the current scoping review is to provide a more complete understanding of existing measures of DM, which can then aid in the creation and validation of a suite of measures to assess decision-making in aging individuals at risk for AD/ADRD. The better we can understand and systematically measure DM ability, the more we stand to improve the quality of life for older adults in this country.

Lay Language: Deficits in decision-making (DM) can lead to adverse outcomes across multiple domains such as financial management and medical care. By hindering such DM abilities, cognitive impairment (CI) often affects quality of life. Routine screening for CI, however, does not currently include systematic and comprehensive assessment of DM ability. While there are many individual measures of DM ability used in clinics and research studies alike, there is considerable variation in what constructs are measured by those tests and the populations in which they have been validated. The current scoping review protocol details the proposed comprehensive examination of published literature on existing measures designed to assess DM ability in an aging population.

Anti-Amyloid Treatments for Alzheimer's Disease: Patients' and Families' Perception and Experience with Drug Consultation

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Background: Anti-amyloid therapies are becoming available for persons with Alzheimer's Disease that aim to slow the progression of the disease. Patients who are potentially eligible for anti-amyloid therapies must be in the early stages of the disease and have biomarker evidence of Alzheimer's Disease pathology. Drug consultations for these therapies are currently taking place at the Northwestern Neurobehavior and Memory Clinic with potentially eligible patients and their families. Study aims are to: 1) measure patient and family perception, barriers and concerns of the drug treatment following a formal consultation or informal discussion with a neurologist, and 2) gather data on the patient and family experience with the drug consultation as a method for making an informed decision.

Methods: After drug consultation with their behavioral neurologist individuals are invited to participate in the study survey. Interested participants complete consent and survey activities over the phone with a study team member. The survey asks questions aimed to measure interest in starting this treatment (retrospectively before and after consultation), concerns and barriers surrounding the treatment, as well as overall experience with the drug consultation.

Result: To date, 10 participants have completed the survey following consultation with a neurologist. 1 care partner and 9 persons living with Alzheimer's Disease (PLWAD) were interviewed. The average age for the PLWAD was 69.4 years old. The sample includes 4 females and 6 males. All participants identified as white, and 1 participant identified as Hispanic or Latino. Preliminary results found the highest reported concerns with starting anti-amyloid therapies to be medical complications [larger brain bleeds, brain swelling, micro-hemorrhages] and financial burden. The majority of participants' interest levels remained the same or were increased following the consultation. Those who reported a decrease in interest level were concerned that the therapy would not be impactful on their daily life.

Conclusion: After consultation, PLWAD and their families identified their biggest concerns about anti-amyloid treatments as medical side effects and financial burden. Participants overall reported a positive experience with the drug consultation and felt more informed about the treatment than they did prior. Patients and families will continue to be surveyed following consultation with a neurologist with additional results reported in the coming months.

Lay Language: With new drug therapies available aimed to slow the progression of Alzheimer's Disease, this study aims to gain insight into the perceptions, concerns and perceived barriers from patients and families who are impacted by the disease as well as the best ways to talk with families about their treatment options.

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20 Years of Friendship and Understanding the Buddy Program's Legacy: Introducing Medical Students to the Lived Experience of Cognitive Impairment and Dementia.

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Background: The Buddy Program is a longitudinal study that provides opportunities for first year medical students and persons living with early dementia to participate in an experiential learning program. The Buddy Program is designed to educate students about dementia, provide an opportunity to see firsthand how persons living with dementia respond to their changing abilities and heighten an awareness of remaining strengths. To ascertain the impact this experience had on medical students' professional development, a survey was sent to students who participated in the Buddy Program between 1997-2017.

Methodology: A 47-question survey was distributed in 2022 via email by the Feinberg School of Medicine alumni office to 218 medical students who participated in The Buddy Program between 1997-2017. Survey questions included demographics, year of participation, and both Likert scale and open-ended questions about impact and influence the Buddy Program had on their professional development.

Results: Respondents included 27 physicians with 3 incompletes. 55% agreed the Buddy Program influenced their choice in medical specialization. All who completed the full survey agreed or strongly agreed the Buddy Program helped their ability to assess patients who present with cognitive impairment or dementia. 92% agreed or strongly agreed the time spent with their Buddy mentors helped with their professional development in the following ways: communicating with and recognizing strengths of those with a cognitive impairment or dementia and witnessing how those living with cognitive impairment or dementia respond to their changing environment.

Conclusion: The Buddy Program offers the opportunity for a personal connection between a person living with cognitive impairment and a first-year medical student. Survey respondents provide insight on the program's impact to their careers, including increased understanding of how to assess and communicate with those living with cognitive impairment or dementia.

Lay Language: The Buddy Program offers the opportunity for a personal connection between a person living with cognitive impairment and a Northwestern University Feinberg School of Medicine first-year medical student. This sample of respondents provide insight on the program's impact to their careers. Respondents shared this program helped them learn effective assessment and communication strategies, the role of care-partner support, and how to recognize the skills and strengths that remain in people living with cognitive impairment and dementia.

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Mediterranean Eating Patterns Amongst Cognitive SuperAgers

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Although decline in memory is consistently observed within the aging process, there is a subset of the population who maintain superior memory into old age. These unique individuals are identified as "SuperAgers" (SA) by the Northwestern University SuperAging Program (NUSAP) and are 80 years or older and demonstrate episodic memory at the level of individuals 20-30 years their junior. We have shown previously that SuperAgers show less inflammation in white matter and harbor less Alzheimer's Disease (AD) pathology in the entorhinal cortex, a brain area responsible for memory, compared to their cognitively-average peers. Currently, there is no cure and very few treatments for AD. There is, however, a growing body of evidence that shows certain diets have protective effects against cognitive decline. One such diet is the Mediterranean Diet (MedDiet). This style of eating includes high consumption of a variety of fruits and vegetables, nuts, seeds, whole grains, legumes, and extra virgin olive oil (EVOO). Dairy is moderately consumed, poultry is less often consumed, and red meat is rarely consumed. This type of diet has also been associated with lower risk of heart disease, cancer, abnormal glucose metabolism and overall mortality. The diet itself is rich in polyphenols which are powerful antioxidants found in plants. Since aging and cognitive decline are associated with higher levels of reactive oxygen species (ROS) and inflammation, the purpose of this study was to determine whether there is a connection between higher adherence to a Mediterranean eating pattern and the SuperAging phenotype. The Mediterranean Eating Pattern for Americans (MEPA)-III food frequency questionnaire (FFQ) was administered to approximately 30 adults over the age of 80 in the Northwestern University Alzheimer's Disease Research Center (ADRC) who were designated as either cognitively healthy controls or SuperAgers based on the Northwestern SuperAging designation criteria. The FFQ assesses overall adherence to the MedDiet, as well as fruit, vegetable, nut, bean, and other types of food intake. The data were analyzed using t-tests to determine differences between the SA and normal control groups. Preliminary results (n=19) show that there were no significant differences between total MEPA-III score between the SuperAgers (N = 13; M=10.4; SD=3.2) compared to their same aged cognitively-average peers (N = 6; M=10.7; SD=2.2). Future analyses will determine differences between groups in larger cohorts and across individual MEPA-III questionnaire items. The underlying factors that affect the SA phenotype are still largely unknown. Future studies aimed at understanding the effect of dietary patterns on the aging brain will allow for a more in-depth study into the nutritional conditions that promote longevity and protect against cognitive decline.

Lay Language: SuperAgers have been identified as individuals over age 80 with superior memory. Although we are beginning to identify certain distinct features of a SuperAger, researchers are still trying to figure out why there are these differences in aging brains. There are various diets that researchers have found to have positive effects on the brain. The Mediterranean Diet (MedDiet) includes many brain healthy foods that are high in antioxidants, healthy fats, and vitamins and minerals, while remaining lower in unhealthy fats, processed foods, and added sugar. We began a pilot study to see if SuperAgers have a higher adherence to a MedDiet compared to others their age. Although our initial findings did not find a difference in overall adherence, we will next analyze any differences in specific food groups. Understanding the diet patterns for healthy aged older adults will help to identify the conditions that can promote longevity and protect against cognitive decline.

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Relatedness effects in Primary Progressive Aphasia

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Introduction: Primary progressive aphasia (PPA) is a progressive language disorder that can be caused by various neurodegenerative diseases including Alzheimer's disease (AD) and frontotemporal lobar degeneration with TDP-43 proteinopathy (FTLD-TDP-C). The distinctive feature of FTLD-TDP-C is a progressive dissolution ("blurring") of the distinction in meaning between members of the same category. In this study, we investigated the sensitivity of an experimental paradigm in detecting this phenomenon in the early stages of PPA.

Methods: Twenty-four individuals with autopsy-confirmed AD (n=18) or FTLD-TDP-C (n=6) diagnosis underwent a word-to-picture matching task (Picture Pairs test) that is part of the Northwestern Multi-Modal Naming Assessment, or NOMINA battery. Only individuals with PPA who scored within the mild to normal range on the Western Aphasia Battery – Revised (WAB-R, Aphasia Quotient range: 71.7-97) were included in the study. Participants heard single words depicting objects and were instructed to point to the corresponding object from a selection of two, presented one on the left and one on the right side of the screen. Objects either belonged to the same sematic category (e.g., "corn" and "pumpkin", hereafter "related") or to different semantic categories (e.g., "corn" and "elephant", hereafter "unrelated"). Both accuracy and reaction times were measured. Using the average and standard deviation obtained from a group (n = 34) of healthy participants, Z-scores were computed for accuracy (acc) and reaction time (RT), separately for related and unrelated trials.

Results: Results showed accuracy levels that were within normal limits for both AD and TDP-C groups (AD: Related=-0.144; Unrelated=-0.259; TDP-C: Related= -1.335; Unrelated=-0.320), although TDP-C scores for related trials were low average. Reaction times were abnormal for both related and unrelated trials in the AD group (Related=1.764; Unrelated=1.601) but only for related trials in the TDP-C group (Related=1.804; Unrelated=1.025).

Discussion: Individuals with PPA due to FTLD-TDP-C show reduced accuracy and significantly increased reaction times to a word-to-picture matching task when required to choose between members of the same semantic category, but not when items belonged to different semantic categories. Conversely, PPA due to AD showed similar responses to the items regardless of their semantic relationship. Therefore, this task is highly sensitive to semantic deficits in PPA and can detect such deficits even in the early stages of the disease.

Lay Language: This study investigated Primary Progressive Aphasia, a progressive language disorder that affects speech, comprehension, grammar, and word recall. This dementia syndrome can be caused by different neurodegenerative diseases; specifically, we examined groups with a confirmed diagnosis of Alzheimer's disease (AD) or frontotemporal lobar degeneration (FTLD-TDP-C). Our findings revealed that those with FTLD-TDP-C had greater difficulty understanding words that were related to each other, whereas those with AD showed similar responses regardless of their semantic relationship.

The Northwestern Anagram Test for Primary Progressive Aphasia: Computer Module (NAT-C)

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Background: The Northwestern Anagram Test (NAT) assesses grammar in the nonfluent agrammatic variant of primary progressive aphasia (PPA-G) without the need for speech production. The NAT requires sequencing individual word cards to create canonical (i.e., sentences that follow the preferred word order of a language, which in English is subject-verb-object) and noncanonical sentences describing pictured actors and actions. The NAT is sensitive to agrammatism and differentiates patients with PPA-G from those with other variants. The current method is cumbersome and to facilitate administration and automate scoring a tablet-administered format, NAT-Computerized (NAT-C), was created.

Methodology: Twelve Participants (mean age: 66.7 ± 8.4, range: 54 -81; 5 female) in the Northwestern Longitudinal PPA Program were administered the standard (paper) and computerized versions of a 30-item version of the previously published NAT, which has also been translated to German (NAT-G) and Italian (NAT-I). Order of administration of the two formats was counterbalanced across participants. Test scores from each format were analyzed in two ways: 1) using correlations, to evaluate how similar performance was across formats, and 2) using linear regressions, to determine whether the order of administration of the two formats affected performance on the task.

Results: Participants scored in the mild to normal range on the Western Aphasia Battery – Revised (WAB-R, Aphasia Quotient(100): 86.5 ± 6.6, range: 78.4 – 97.5), and showed various levels of impairment on the Boston Naming Test (BNT(60): 36.3 ± 20.3, range: 8-58). On the NAT, scores on the paper and computerized format were highly correlated (total score: r = 0.76; canonical score: r = 0.72; noncanonical score: r = 0.75). Regression analyses confirmed that performance on the paper and computerized format of the NAT was not statistically different and revealed no order effect of the two formats for any of the selected measures (total, canonical, noncanonical, all ps >.1).

Conclusion: The NAT-C offers a convenient, alternative format to the original paper version for testing grammatical production in individuals with PPA. Not requiring speech production to create sentences eliminates the potential for motor speech deficits to interfere with normal grammatical production.

Lay Language: The Northwestern Anagram Test (NAT) evaluates the ability to build sentences of various complexity without requiring participants to speak. This test is used in the diagnosis of Primary Progressive Aphasia (PPA), a dementia syndrome in which language skills become progressively impaired over time. This study introduces a convenient computerized version of the NAT and shows that this version is equally sensitive to grammatical deficits in PPA as the traditional (paper-and-pencil) version of the test.

Personalized Intervention Enhancing Communication, Education, and Support: Putting the PIECES together after a PPA diagnosis

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Background: PIECES is a newly designed intervention for persons living with primary progressive aphasia (PPA) and their care partners, delivered entirely online. Inspired by a program formerly run at the Mesulam Center (Support and Education for Early Dementia), PIECES focuses on persons with early-stage PPA and their care partners integrating psychoeducation, support groups, and both impairment-based and life-participation speech-language therapy interventions. The aim of PIECES is to improve quality of life, provide education and tools to support life after diagnosis, and implement strategies/interventions for better communication.

M**ethodology:** PIECES will be implemented in two phases. Three to five dyads will be enrolled. Phase one is an eight-week, two-hour psychoeducational and support program for persons with PPA and their care partners. The first hour will focus on informative/educational lectures and in the second hour the dyads will break into support groups facilitated by a social worker (and speech-language pathologist, SLP, for the individuals with PPA group). We will cover topics including PPA disease education, relationships and disclosure, communication strategies, legal and financial considerations, and community resources. Phase two is also eight weeks with twice-weekly speech-language therapy sessions. The first session will be a 1:1 impairment-based language intervention targeting salient vocabulary with the PPA participant and the SLP. The second session will employ a life participation approach with the PPA participants and their care partners, focusing on training functional and individualized communication strategies that aim to increase the ability to participate in meaningful conversations with their care partners. Participants' quality of life, impact of diagnosis individually and as a dyad, knowledge of PPA, ability to practice and retain conversational language, ability to connect with others navigating this disease, and awareness of available resources will be evaluated before phase one, between phases one and two, and at the program's conclusion.

Results: Although the study is in the final planning stages and no results are available, we anticipate that both phases (psychoeducational and speech-language intervention) will have a positive impact on the quality of life of persons living with PPA and their care partners and that the program will result in 1) improved knowledge of the disease and its progression, 2) increased awareness of the available resources, and 3) acquisition of communication strategies that will facilitate conversation with care partners.

Conclusion: The PIECES program, which is delivered entirely remotely, proposes to address the dearth of interventions designed specifically for PPA and the difficulties persons with PPA and their care partners encounter in finding similar services in their local communities. With this multi-disciplinary program, we hope to positively impact the lives of persons with PPA and their care partners and to provide them with tools to help them navigate ongoing care needs and changes brought by the disease.

Lay Language: PIECES is a new intervention, delivered online, designed to address both psychoeducational/support and speech-language therapy needs of persons living with PPA and their care partners by providing them with tools that will increase their ability to navigate ongoing care needs and changes brought on by the disease.

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Primary Progressive Aphasia Asymmetry as a Predictor of Neuropathological Diagnosis

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Background: Primary progressive aphasia (PPA) is a neurodegenerative dementia syndrome involving a progressive loss of language function. It is commonly accepted that language is predominantly processed in the left hemisphere of the brain. Work at the Mesulam Center has shown in the past that greater atrophy occurs in the left rather than right hemisphere in participants with language deficits such as PPA. However, previous work has suggested that atrophy patterns may differ depending on the underlying pathology causing PPA. This study aims to further elucidate quantitative neurophysiological change that occurs in PPA groups defined by underlying pathologies.

Methods: The cortical thickness values of the right and left hemisphere of the initial visit (A visit) for 59 PPA participants – of which 30 had been diagnosed with Alzheimer's Disease (AD), 15 had been diagnosed with either Progressive Supranuclear Palsy (Tau-PSP) or Corticobasal Degeneration (Tau-CBD) both 4R-Tau, and 14 with Frontotemporal Lobar Degeneration (FTLD) TDP-C – were generated with FreeSurfer version 7 and summarized into 35 regions per hemisphere using the Desikan-Killiany cortical parcellation. Correlation values comparing the left hemispheric atrophy and the right hemispheric atrophy were then calculated using R.

Results: The results of our analysis indicate a generalized degree of hemispheric asymmetry in the PPA group, as well as varying degrees of hemispheric asymmetry between PPA disease subtypes. Analysis of the correlation revealed significant differences in hemispheric asymmetry in each of the AD, Tau, and FTLD TDP-C groups, as compared to the relevant group of age-matched healthy participants. Furthermore, the Tau-PSP and Tau-CBD group was the most symmetrical and the FTLD TDP-C group the least. Both the 4R-Tau and AD groups' cortical thickness were significantly more symmetrical between hemispheres than the FTLD TDP-C group. However, there was no significant difference between the correlation values of the AD and 4R-Tau groups.

Conclusion: It appears that in early stages of PPA, the underlying neuropathology influences the laterality of atrophy. While any of the neuropathologies can also lead to rightward asymmetrical atrophy, the leftward asymmetry in our cohort is a reflection of our focus on language, the primary domain of impairment in PPA and a behavior that is lateralized to the left hemisphere for almost all right handed individuals. To further investigate these differences, we will be creating brain maps illustrating the symmetry of atrophy in the brain as well as calculating laterality indices.

Lay Language: While PPA has been associated with a larger degree of atrophy in the left hemisphere, it appears that the degree to which that asymmetrical atrophy occurs is dependent on the disease underlying the PPA syndrome.

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Primary Progressive Aphasia Research Program at the Mesulam Center for Cognitive Neurology and Alzheimer Disease

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Primary progressive aphasia (PPA) is a neurodegenerative dementia syndrome characterized by a progressive loss of language function. PPA has a low prevalence in clinical practice compared to Alzheimer's dementia. The Mesulam Center 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 38 US states, Canada, Singapore, and Spain have enrolled in PPA studies at the Mesulam Center. 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 Center 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 Center's support groups, 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 quality of specialized care.

Collectively, these studies allow us to improve the diagnosis, prognosis, and quality of life for individuals living with PPA and their care partners, 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 provided the opportunity for the Mesulam Center to research novel diagnostic and therapeutic initiatives in PPA. Through its multidisciplinary approach to both research and patient care, Northwestern University's Mesulam Center remains one of the top referral centers in the world for PPA. We are grateful for the time and dedication of our research participants.

Lay Language: Primary progressive aphasia (PPA) is a neurodegenerative dementia syndrome characterized by a progressive loss of language function. PPA has a low prevalence in clinical practice compared to Alzheimer's dementia. The Mesulam Center 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.

Alzheimer's Association

UPCOMING EDUCATIONAL CONFERENCES

SATURDAY
APRIL 27
10AM - 2PM

Release the Silence: RACE
(Research, Awareness, Community Resources, Education)
into Action

bit.ly/ReleaseTheSilence

SATURDAY
MAY 4
9AM - 2PM

Springfield African American Conference: Release the Silence

bit.ly/ReleaseTheSilence-SF

WEDNESDAY
JUNE 5
8:30AM - 3:30PM

Navigating Alzheimer's & Dementia: A Conference for First Responders

tinyurl.com/AlzFirstResponderConf

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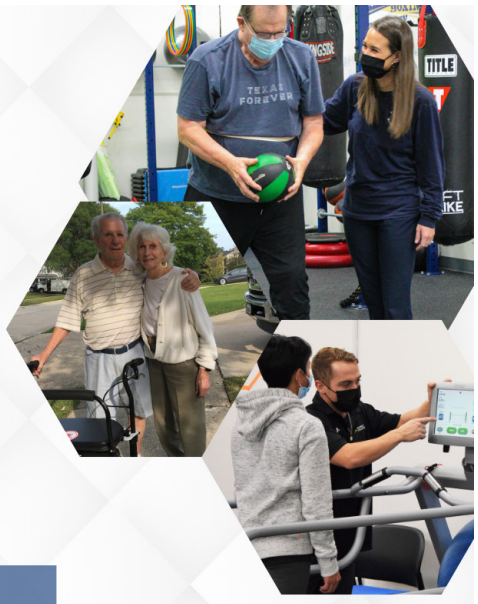

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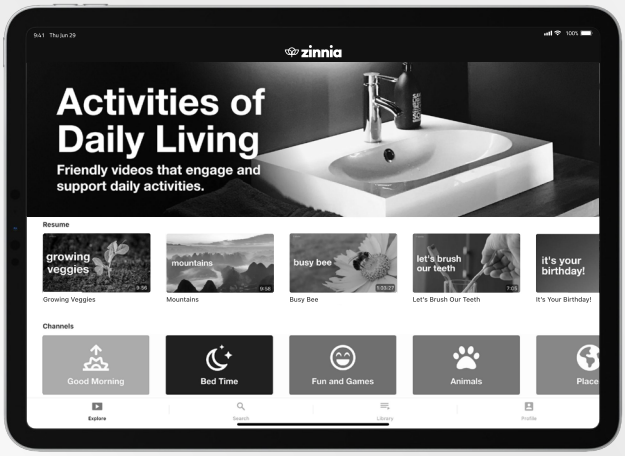

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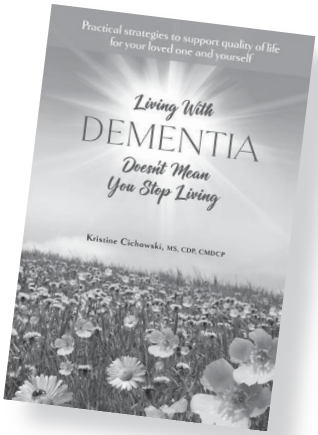

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