Presented by
the Mesulam Center
for Cognitive Neurology
and Alzheimer's Disease

28TH ANNUAL ALZHEIMER DAY

THURSDAY, MAY 5, 2022 | 11:30-4 PM CDT

ABSTRACT BOOK

Northwestern Medicine®
Feinberg School of Medicine

Table of Contents

Welcome

Dear Friends and Colleagues:

Welcome to the 28th Alzheimer Day. From 1994 to 2019, our annual AD-Day events have attracted thousands of participants and have featured a procession of world-renowned keynote lecturers. COVID-19 interrupted the tradition. The 2020 and 2021 AD-Days were held remotely, also to sizable audiences, but without the excitement of face to face interactions. As I am writing this message, our plan is to hold the 2022 meeting in person. However, COVID-19 has taught us to be prepared for the unpredictable and we realize that we may need to modify plans, but I sincerely hope this will not be necessary.

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 P30 Center (ADRC), the SuperAging Program, the Primary Progressive Aphasia Program, the Glen and Wendy Miller Family Program, the Ken and Ruth Davee Laboratories, the Clinical Trials Program and the Neurobehavior Clinic are all thriving. The ADRC, which I founded in 1996 and led for 25 years, was awarded a sixth cycle of funding for years 25–30 under the new leadership of Drs. Vassar and Weintraub. The SuperAging Program, under the leadership of Drs. Rogalski and Geula, was awarded a huge $25M grant to establish a multi-center consortium that will greatly accelerate our knowledge of superior cognitive aging. The Primary Progressive Aphasia Research Program submitted a competitive renewal proposal to extend its activities into years 15-20 (Principal Investigators: Mesulam and Rogalski). The proposal was successful at the stage of peer review and received a priority score that placed it at the top 6% of all submissions nationally. We look forward to continuing this iconic research program of our Center into years 15-20. The Glen and Wendy Miller Family Programs continue to flourish and expand under the leadership of Dr. Morhardt and her team. As an expression of our gratitude for their enlightened support, we will be naming the world-renowned Buddy Program for Glen and Wendy Miller and their family. Another major milestone occurred in September with the opening of the brand new Mesulam Center Neurobehavior Clinic on Arkes 13. The new clinic doubles our space and will enable new and expanded clinical programs.

Recruitments and promotions are central to academic life. I am delighted to report that Emily Rogalski, Associate Director of the Mesulam Center and Professor of Psychiatry, has been named the inaugural Ann Adelmann Perkins and John S. Perkins Professor in Alzheimer's Disease Prevention. The professorial chair was established within the Mesulam Center through the generous gift of John S. Perkins, '68 in honor of his late wife Ann Adelmann Perkins, '68. In the area of recruitments, we have two members who are returning home. Adam Martersteck, who did his NUIN dissertation at our Center, returns as Assistant Professor of Radiology and Lauren Dowden, MSW returns as a member of the Quality of Life and Family Programs. Borna Bonakdarpour and Ian Grant have been appointed Associate Directors of the UCNS-accredited Behavioral Neurology and Neuropsychiatry Fellowship Program. Their mission will be to expand and strengthen this pivotal program that has launched the successful careers of many clinicians.

It is no secret that patient care and basic research on Alzheimer's disease are subject to major social and cultural influences. Health care disparities remain to be addressed more creatively and diversity in research remains a goal to be attained. I am delighted that this year's Mendelson Lecture will address these issues. It will be delivered by Professor Lisa L. Barnes, the Alla V. and Solomon Jesmer Professor of Gerontology and Geriatric Medicine at the Rush Alzheimer's Disease Center. Her lecture will be entitled "Social and Cultural Influences on Cognitive Aging: An Epidemiologic Perspective." This will be followed by a celebration of the Glen and Wendy Miller Family Buddy Program's 25-year history. The AD-Day events will start at 11:30 AM with a Poster Session where clinicians and basic scientists will showcase their latest work. Please plan to visit the posters and join us for lunch, which will be served starting at 11:30 AM.

I look forward to seeing you in person at the 28th Alzheimer Day festivities!

Marsel Mesulam, MD
Ruth Dunbar Davee Professor of Neuroscience and Neurology
Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Thank You

(Left to Right): Linda Mendelson, Robert 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, 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.

Glen and Wendy Miller, with their daughter Lauren (Left).

Schedule of Events

28th Annual Alzheimer Day | Thursday, May 5, 2022

Robert H. Lurie Medical Research Center
303 East Superior Street | First Floor

11:30 AM - 12:45 PM — Poster Session and Lunch

Potocsnak & Ryan Family Atriums

1:00 - 2:30 PM — Welcome and Center Update

Hughes Auditorium

M. Marsel Mesulam, MD
Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease; Ruth Dunbar Davee Professor of Neuroscience, Feinberg School of Medicine

Presentation of Marie and Carl Duncan Prize in Memory Research

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

Mendelson Lecture: "Social and Cultural Influences on Cognitive Aging: An Epidemiologic Perspective"

Lisa Barnes, PhD
Alla V. and Solomon Jesmer Professor of Gerontology and Geriatric Medicine, Department of Neurological Sciences, Rush Medical College; Neuropsychologist, Rush Alzheimer's Disease Center

2:30 - 2:45 PM — Break

2:45 - 4:00 PM — Quality of Life Symposium

Hughes Auditorium

A celebration of the Glen and Wendy Miller Family Buddy Program's 25-year history. Symposium sponsored by the Glen and Wendy Miller Family Foundation.

Thank You

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

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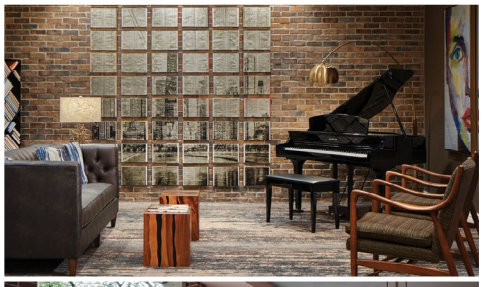
Thank you to all Mesulam Center staff and faculty who have made this day a success!
The Mesulam Center appreciates your dedication and commitment to making this day possible.



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Venue Map

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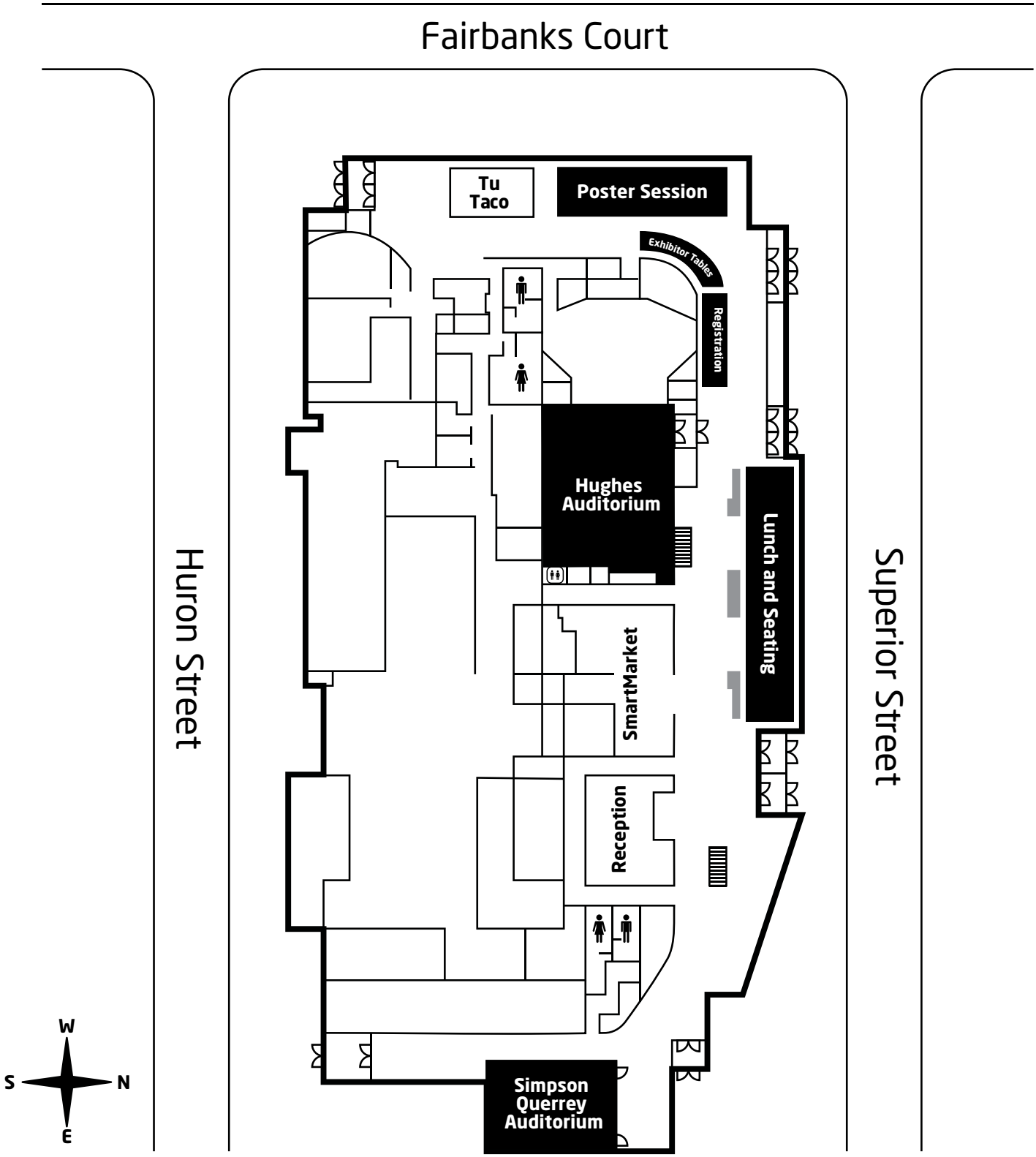

Welcome & Center Update

Marsel Mesulam, MD

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

Marsel Mesulam is the Ruth Dunbar Davee Professor of Neuroscience, founder and Director Emeritus of the National Institutes of Health Alzheimer's Disease P30 Center at Northwestern University (established in 1996), and current Director of the Mesulam Center for Cognitive Neurology and Alzheimer's Disease. He has served as president of the Organization for Human Brain Mapping, Vice President of the American Neurological Association, and Chair of the Medical Advisory Board of the Association for Frontotemporal Degeneration.

His research has addressed the connectivity of the cerebral cortex in the primate brain, anatomy of human cholinergic pathways, representation of cognitive functions by large-scale networks, and neurobiology of dementias. He received the Potamkin Prize from the American Academy of Neurology, the Javits Award from the United States National Institutes of Health, the McKnight Foundation Director's Award, and the Bengt Winblad Life Achievement Award from the Alzheimer's Association. He held the Robert Wartenberg and Houston Merritt lectureships of the American Academy of Neurology. He served on the editorial boards of Brain and Annals of Neurology.

His textbook, *Principles of Behavioral and Cognitive Neurology*, is used by multiple training programs. His current research focuses on the biology of neurocognitive networks and on the pathophysiology of focal dementias. His trainees in clinical, cognitive and basic neuroscience lead major research 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 in Physiology, 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 "suoer ager" 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. His laboratory is collaborating with Dr. Joel Voss' laboratory 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

"Social and Cultural Influences on Cognitive Aging: An Epidemiologic Perspective"

Lisa Barnes, PhD

Alla V. and Solomon Jesmer Professor of Gerontology and Geriatric Medicine, Department of Neurological Sciences, Rush Medical College; Neuropsychologist, Rush Alzheimer's Disease Center

Lisa L. Barnes, PhD is the Alla V. and Solomon Jesmer Professor of Gerontology and Geriatric Medicine, and a cognitive neuropsychologist within the Rush Alzheimer's Disease Center at Rush University Medical Center in Chicago, IL. USA. Dr. Barnes' research focus is on the epidemiology of cognitive aging with an emphasis on understanding mechanisms of cognitive health disparities of chronic diseases of aging among older African Americans. As the Principal Investigator of the Minority Aging Research Study, known as MARS, a longitudinal clinical-pathologic study of more than 800 African Americans without dementia who have been followed for over 15 years, and the Clinical Core Leader of the African American Core of the Rush Alzheimer's Disease Center, she is a leading expert on health disparities and minority aging.

Dr. Barnes completed her BA in psychology from Clark Atlanta University and her PhD in biopsychology from the University of Michigan in Ann Arbor. Next, she completed a post-doctoral fellowship at the University of California, Davis in the field of cognitive neuroscience. She joined the Rush Alzheimer's Disease Center as an assistant professor in July 1999.

Dr. Barnes has made significant contributions to our understanding of cognitive aging, cognitive decline, and Alzheimer's dementia in older African Americans. She has mentored numerous early career investigators, has published over 250 peer-reviewed manuscripts, and has received international recognition, awards, and honors from a number of universities and organizations for her work with communities under-represented in science.

Quality of Life Symposium

2:45 - 4:00 PM | Hughes Auditorium

Welcome and Introduction of the Buddy Program

Darby Morhardt, PhD , LCSW and M.-Marsel Mesulam, MD

Celebrating Current and Past Mentors and Students

Patricia Spear, PhD, Karin Larson-Pollock, MD, MBA, Jim and Lisa Butler

Students – Brooke Gleason, Raj Dalal, Sebastian Otto-Meyer

Honoring the Glen and Wendy Miller Family Foundation

Glen Miller, Wendy Miller, Lauren Izaks

Musical Performance: *Five pieces for two violins and piano (arranged for flute and oboe) by Dmitri Shostakovich*

I. Prelude II. Gavotte III. Elegy V. Waltz V. Polka

Joseph Pyle (Oboe), Melanie Zhang (Flute), Kimberly Pyle (Piano)

Darby Morhardt, PhD, LCSW

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

Darby Morhardt, PhD, LCSW is a Research Professor for the Mesulam Center for Cognitive Neurology and Alzheimer's Disease at the Northwestern University Feinberg School of Medicine. Dr. Morhardt directs the Center's Outreach, Recruitment and Engagement Core, Quality of Life and Family Programs in addition to the Glen and Wendy Miller Family Post Graduate Social Work Fellowship in Neurocognitive Disorders.

Dr. Morhardt's work has been in areas of clinical research, such as, the experience of families living with dementia, the development and evaluation of quality-of-life enrichment programs, support groups and other therapeutic interventions. These interventions include the award-winning Buddy Program, that pairs persons living with dementia as mentors to first year medical students. Dr. Morhardt is responsible for organizing the Mesulam Center's community engagement to increase dementia education, awareness, research participation and quality of life enhancing programs throughout Chicago, particularly in partnership with underrepresented and minoritized populations.

At the State level, she is a leader in the Illinois Cognitive Resources Network working with dementia friendly communities state-wide, a member of the Illinois Department of Public Health's Alzheimer's Disease Advisory Committee which writes the Illinois Alzheimer's State Plan and was recently appointed to the newly formed Supreme Court Commission on Elder Law.

Mesulam Center for Cognitive Neurology and Alzhemier's Disease Faculty Members

M. Marsel Mesulam, MD

Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Ruth Dunbar Davee Professor in Neuroscience and Neurology

Emily Rogalski, PhD

Associate Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Professor of Psychiatry and Behavioral Sciences

Borna Bonakdarpour, MD, FAAN

Assistant Professor of Neurology

Maureen Daly, PhD

Assistant Professor of Psychiatry and Behavioral Sciences

John Disterhoft, PhD

Professor of Physiology

Ernest J. and Hattie H. Magerstadt Memorial Research Professor of Physiology

Margaret Flanagan, MBBChBAO

Assistant Professor of Pathology

Tamar Gefen, PhD

Assistant Professor of Psychiatry and Behavioral Sciences

Changiz Geula, PhD

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

Ian Grant, MD

Assistant Professor of Neurology

Adam Martersteck, PhD

Assistant Professor of Radiology

Darby Morhardt, PhD, LCSW

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

Fred Osview, MD

Clinical Professor of Psychiatry and Behavioral Sciences

Alfred Rademaker, PhD

Professor Emeritus of Preventive Medicine

Deborah Reed, MD

Assistant Professor of Psychiatry and Behavioral Sciences

Robert Vassar, PhD

Professor of Neurology and Cell and Molecular Biology

Davee Professor of Alzheimer Research

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

M. Marsel Mesulam, MD
Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease
Ruth Dunbar Davee Professor in Neuroscience and Neurology

Emily Rogalski, PhD
Associate Director, Mesulam Center for Cognitive Neurology and Alzheimer's Disease
Professor of Psychiatry and Behavioral Sciences

Eskedar Yirga Alem, BS, MSC
Administrator, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

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

Darby Morhardt, PhD, LCSW
Research Professor, Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Robert Vassar, PhD
Professor of Neurology and Cell and Molecular Biology
Davee Professor of Alzheimer Research

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

Hui Zhang, PhD
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Ruth Davee
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Jerome Rosenstone
Kay 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: **www.brain.northwestern.edu/about/giving.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.

Past Winners

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

2020: **Chloe Parker**
The role of astrocytes in the propagation of $tau_{45\text{-}230}$-induced neuronal degeneration.

2020: **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

2019: **Timothy J Hark**
Decreased Resting Connectivity of Language Network with Extrasylvian Regi

2018: **Melvin Thompson and 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

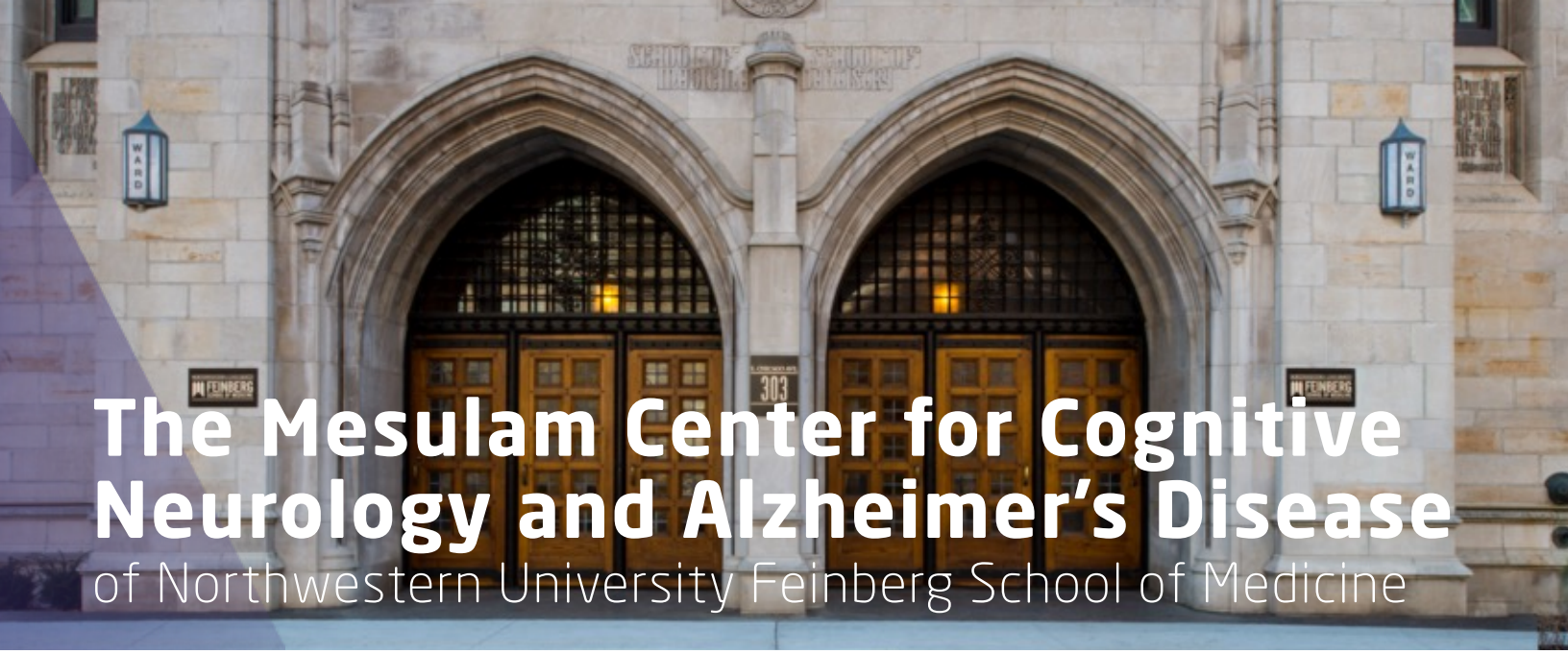
2012: **Tharinda Rajapaksha**
The Alzheimer's β-Secretase Enzyme BACE1 is Required for Accurate Olfactory Sensory Neuron Axon Guidance and Normal Glomerulus Formation in the Olfactory Bulb

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

of 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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Deborah Reed, MD

Neuropsychologists

Maureen Daly, PhD
Tamar Gefen, PhD
Jana Wingo, PhD
Sandra Weintraub, PhD, ABPP-CN

Social Workers

Lauren Dowden, MSW, LCSW
Debbie Dyslin-Kman, AM, LCSW
Kate Maley, AM, MSW
Darby Morhardt, PhD, LCSW

Clinic Manager

Kevin Reyes, BA

Former Clinic Manager

Caren Rodriguez, BSN

Resource Coordinator

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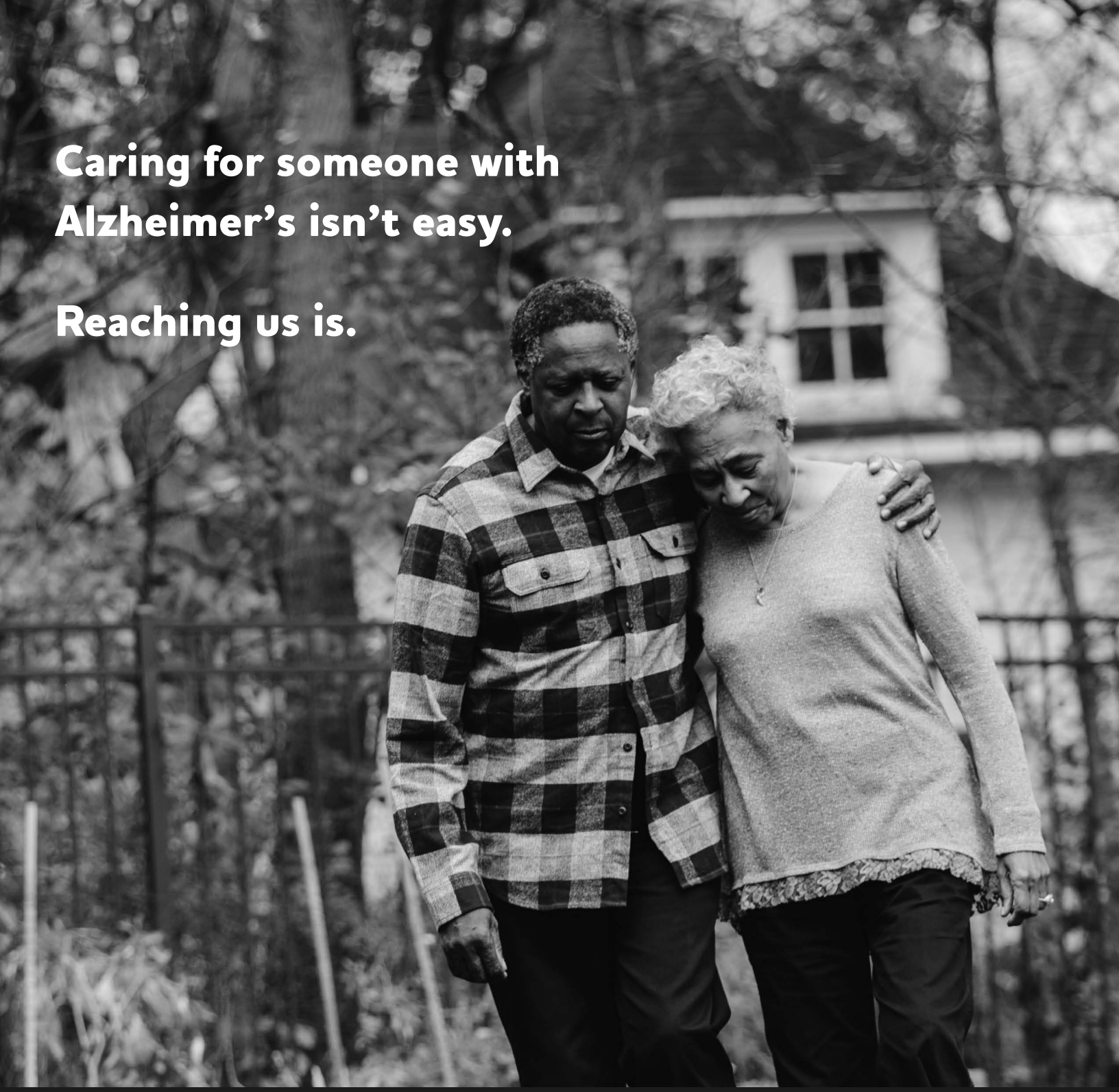
BEST OF HOME CARE EMPLOYER OF CHOICE 2022



The Alzheimer's Association® offers round-the-clock support and reliable information about memory loss, Alzheimer's disease and other dementias.

Free 24/7 Helpline: **800.272.3900**
Alzheimer's and Dementia Caregiver Center: **alz.org/care**

alzheimer's association®

16097625

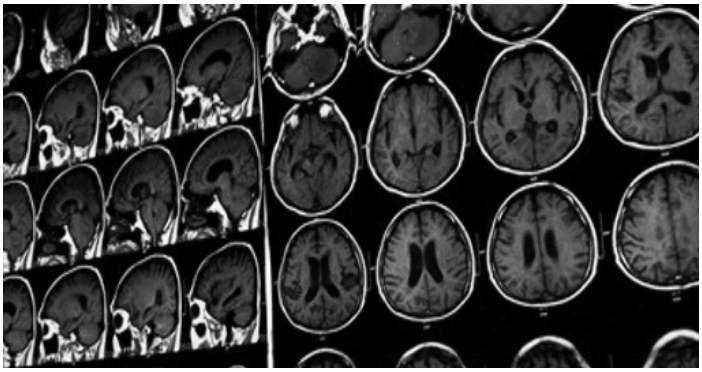
The Importance of Brain Donation

Help us combat dementia and better understand healthy aging.

To win the fight against Alzheimer's disease and other brain diseases that cause dementia we need more research. Brain donation at the time of death from individuals who have been well-studied during life is one of the most important and generous gifts a patient who has lived with dementia and their family can make. Brain donations from individuals who do not suffer from dementia are also critical for comparison and to learn why some people do not develop Alzheimer's and other dementias.

Brain donation is one of the most important contributions to research.

The study of brain tissue from individuals with and without disease who have been carefully studied during their lifetime allows scientists to understand the mechanisms of disease, and how those with and without disease differ in their genes and molecules. While 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. The family of the donor receives a full report detailing the neuropathologist's findings. At present, neurodegenerative diseases that cause dementia can only be diagnosed with 100% certainty through a brain autopsy, so families are provided with a definitive diagnosis. Such information is useful if other family members develop a 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.

Unfortunately, we cannot accept every brain donation.

If someone interested in brain donation was never seen as part of research, we will not be able to accept the brain donation. However, we can determine on a case-by-case basis if the individual should be enrolled in our research and thus donate their brain.

Brain donation is a decision that individuals and their families can make only after thoughtful consideration. The decision has important emotional and practical implications.

Members of the professional staff at the Mesulam Center for Cognitive Neurology and Alzheimer's Disease at Northwestern University are available to talk with you and answer your questions.

Phone: 312.908.9339

Email: adc@northwestern.edu

JOHNS HOPKINS MEDICINE

Approved October 5, 2021

ALLFTD
ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration

ALLFTD Longitudinal Study

ALLFTD is a multisite research project 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 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

Case Western Reserve University, Cleveland
Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas
Columbia University in the City of New York
Houston Methodist Hospital, Nantz National Alzheimer Center
Indiana University
Johns Hopkins University, Baltimore
Massachusetts General Hospital, Boston
Mayo Clinic, Jacksonville
Mayo Clinic, Rochester
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 Toronto
University of Washington, Seattle
Vanderbilt University
Washington University in St. Louis

Contact your site:

Find more information at www.allftd.org/sites.

Please note: Enrollment for this study is currently closed.

JOHNS HOPKINS MEDICINE

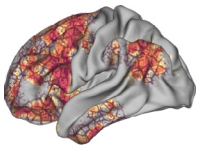
Approved October 5, 2021

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

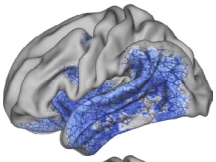
Behavioral Variant of Frontotemporal Dementia (bvFTD)



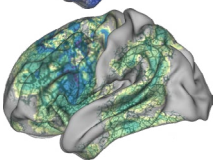
Behavioral Variant of Frontotemporal Dementia (bvFTD)

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)



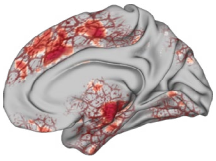
Non-Fluent Variant of Primary Progressive Aphasia (nfvPPA)



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.

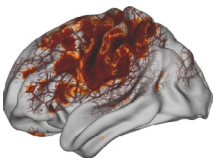
Progressive Supranuclear Palsy (PSP)



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.

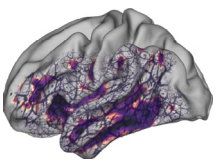
Corticobasal Syndrome (CBS)



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.

communication BRIDGE

Speech Therapy Study

Who?

Individuals with a diagnosis of Primary Progressive Aphasia and their Communication Partners

Why?

To help us better understand the effects of speech language therapy on communication abilities in individuals with PPA

Where?

All components of the study take place remotely via video-conferencing

How Long?

Over the course of one year, participants in our study will be involved in:

- 5 evaluations with a certified speech language therapist
- 15 therapy sessions with a certified speech language therapist
- Exercises through our web-application

There are no costs to participate in this study. Compensation will be provided.

If interested, contact us for more information

Phone: (312) 503-4012

Email: communicationbridge@northwestern.edu

Website: www.brain.northwestern.edu

Study funded by: National Institute on Aging, IRB#STU00206086, PI: Dr. Emily Rogalski

Study Title: Communication Bridge: Using Internet-Based Speech Therapy to Improve Quality of Life and Access to Care

Northwestern Medicine
Feinberg School of Medicine

Mesulam Center for Cognitive Neurology and Alzheimer's Disease

Help us understand
PRIMARY PROGRESSIVE APHASIA
Join our research study

What are our Goals?

The **Language in Primary Progressive Aphasia** research study uses the latest in imaging technology alongside neuropsychological testing to help better understand how and why this disease occurs.

We want to increase awareness of PPA, educate others about this unique disorder, and encourage more research to eventually develop a treatment.

I want to know more!

Please contact Christina Coventry at:
PPA.Research@northwestern.edu
312-908-9681 or,
fill out our online form at:
brain.northwestern.edu/join

Northwestern Medicine®

What is the Study Like?

You may be eligible for our study if you are:

- Diagnosed with PPA
- Right-handed
- Not claustrophobic
- Safe for an MRI scan

You and a study partner will be asked to come to our downtown Chicago campus for testing every other year. We will cover your travel, lodging, and meal expenses during your visit. Participants will be compensated.

Participation lasts up to four days, repeated every two years, and includes:

- An MRI scan of your brain
- Pen and paper tests that evaluate your language, memory, and other thinking abilities
- Tests on a computer

Funded by the National Institute of Deafness and Other Communication Disorders
Principal Investigator: Dr. M. Marsel Mesulam, STU00026372

Mesulam Center for Cognitive Neurology and Alzheimer's Disease
Northwestern University Feinberg School of Medicine

OVER 80 AND STILL GOING STRONG

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

Why are YOU important?

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

Who are we?

We are the Northwestern University SuperAging Team and we would love to hear from you!

What is involved?

- Visiting our Center every two years
- Pen & paper cognitive tests
- MRI/PET brain scans
- Surveys and questionnaires

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

If Interested Please Contact us for more Information
Phone: (312) 503-2716
Email: agingresearch@northwestern.edu
Website: brain.northwestern.edu

Mesulam Center for Cognitive Neurology and Alzheimer's Disease of Northwestern University

Study Funded by: National Institute on Aging and The Davee Foundation
Principal Investigator: Emily Rogalski, PhD
Grant #: 1R01AG067781-01/ 2R56AG045571-06, IRB# STU00027225
Study Title: Super Aging Study: Correlates of Active Engagement in Life in the Elderly

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."*
>
> **2021 Buddy Program Mentor**

Contact

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

Learn more at:
brain.northwestern.edu

Northwestern Medicine®
Feinberg School of Medicine

The Mesulam Center for Cognitive Neurology and Alzheimer's Disease

of 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. During the pandemic, 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.

For 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

For 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), and

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

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

For 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: Debbie Dyslin-Kman, LCSW, deborah.dyslin@northwestern.edu, 312.503.5559

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Feinberg School of Medicine

Learn more at:
brain.northwestern.edu

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.

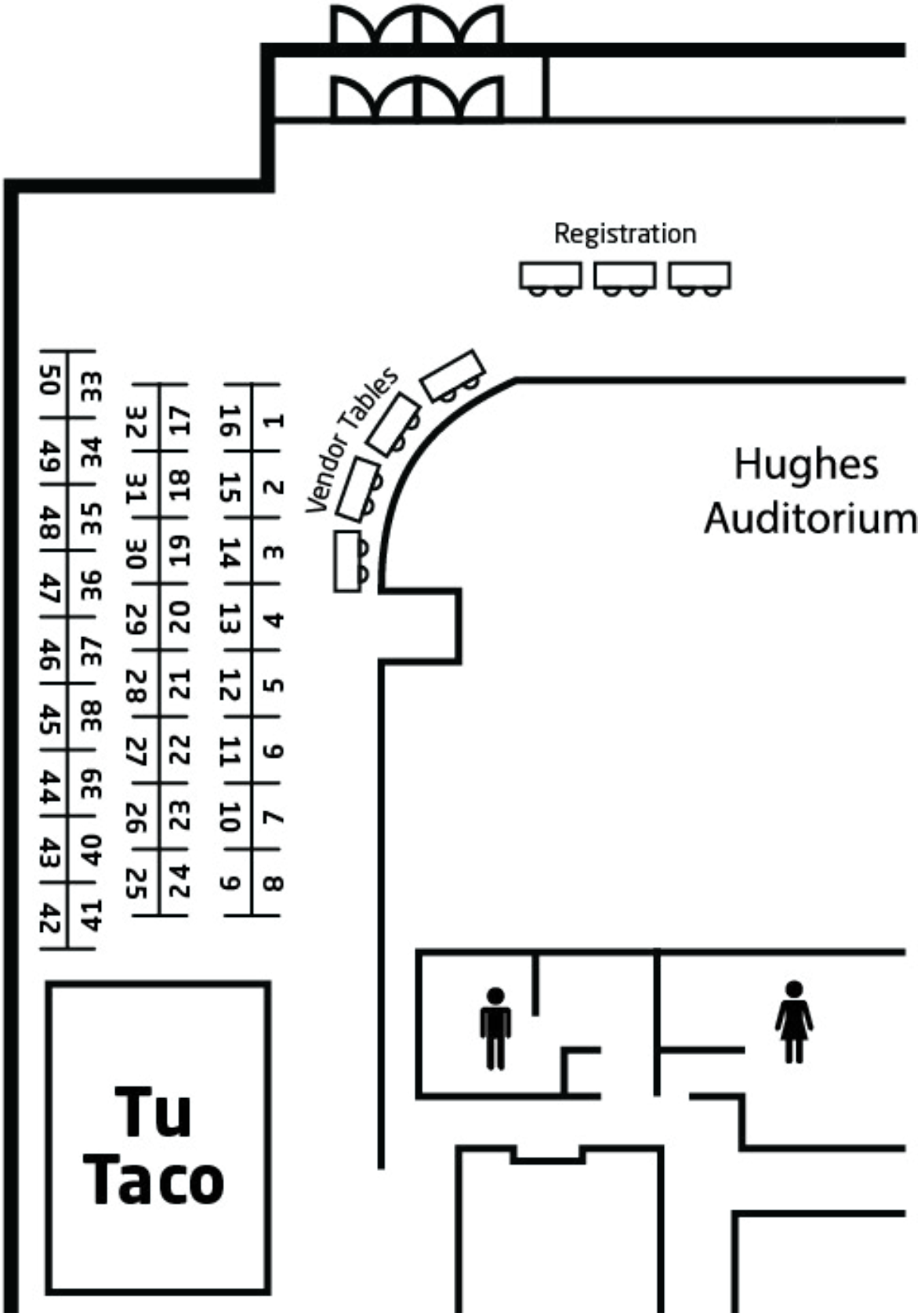
Become a Dementia Friend

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.

Poster Session Map



Poster Session

Cell & Molecular Biology

1. **A novel amyloid purification protocol for structural studies and quantitative proteomics**
   Arun Upadhyay, Robert Vassar, Jeffrey Savas

2. **Characterization of apathy-like behaviors and their relationship to Aβ pathology in5xFAD mice**
   Rachel Keszycki, Lupe Rodriguez, Andrea Locci, Hector D Orellana, Isabel Haupfear, Sky Dominguez, Daniel W Fisher, Hongxin Dong

3. **Genetic proxy of structural cortical asymmetry is potentially causal for agrammatic primary progressive aphasia: a mendelian randomization approach**
   Malik Nassan, MD

4. **Hippocampal Activity Regulates Bone Morphogenic Signaling in-vitro**
   Sara Rose Dunlop, Chian-yu Peng, John A. Kessler

5. **Investigating rare genetic variants in Angiotensin-1-Converting Enzyme and their role in Alzheimer's Disease pathogenesis**
   Miranda Salvo

6. **Pharmacological Studies of Behavioral Abnormalities in the 5XFAD Mouse Model of Alzheimer's Disease**
   Lakshmi Rajagopal, Sanaz Mahjour, Herbert Y Meltzer

Clinical Best Practices

7. **Suitability of Goal Attainment Scaling in Psychogeriatric Populations with Neurodegenerative Disease Experiencing Dementia or Cognitive Impairment: A Systematic Review**
   Ollie Fegter, Haylie Santos, Alfred Rademaker, Angela Roberts, Emily Rogalski

Clinicopathologic Studies

8. **Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3)**
   Brittanie Muse, MSPH, CCRC; Sydney Orr; Jelena Pejic; Shea Gold, MA; Joshua Cahan, MD; Allison Lapins, MD; Malik Nassan, MD; Sandra Weintraub, PhD; Ian Grant, MD; Darby Morhardt, PhD; Emily Rogalski, PhD; and for The Alzheimer's Disease Neuroimaging Initiative

9. **Concordance between Neocortical Distribution of Pick's Disease and the Salience of Distinct Dementia Phenotypes**
   Allegra Kawles, Rachel Keszycki, Grace Minogue, Antonia Zouridakis, Callen Spencer, Ivan Ayala, Robert Shepard, Nathan Gill, Jaclyn Lilek, Kaouther Ajroud, Christina Coventry, Emily Rogalski, Sandra Weintraub, Alex Feldman, Qinwen Mao, Margaret Flanagan, Hui Zhang, M-Marsel Mesulam, Changiz Geula, Tamar Gefen

Poster Session

10. Differential Vulnerability of the Dentate Gyrus to Tauopathies in Aphasic Dementia
Allegra Kawles, Grace Minogue, Antonia Zouridakis, Caren Nassif, Rachel Keszycki, Christina Coventry, Emily Rogalski, Margaret E. Flanagan, M-Marsel Mesulam, Changiz Geula, Tamar Gefen

11. Distinct Regional and Hemispheric Tau Distributions in Primary Progressive Aphasia with Neuropathologic Progressive Supranuclear Palsy: A Stereological Study
Antonia Zouridakis, Allegra Kawles, Grace Minogue, Rachel Keszycki, Christina Coventry, Sandra Weintraub, Emily Rogalski, Margaret E. Flanagan, Qinwen Mao, Eileen Bigio, M-Marsel Mesulam, Changiz Geula, and Tamar Gefen

12. Quantification of synaptic markers in Alzheimer disease
Kaouther Ajroud, Jaclyn Lilek, Callen Spencer, Arleen Matos, Shadi Ghourchian, Eva Bambakadis, Rachel Shapiro, Benjamin Danner, Alexander Feldman, Matthew McCord, Pouya Jamshidi, M. Marsel Mesulam, Tamar Gefen, Sandra Weintraub, Margaret E. Flanagan

13. Regional burden of pathology in hippocampal subregions can distinguish amnestic dementia with comorbid Alzheimer's and TDP-43 pathology from pure Alzheimer's and FTLD-TDP.
Grace Minogue, Allegra Kawles, Antonia Zouridakis, Rachel Keszycki, Nathan Gill, Makayla Kochheiser, Vivienne Lubbat, Kaouther Ajroud, Callen Spencer, Jaclyn Lilek, Qinwen Mao, Margaret E. Flanagan, Hui Zhang, M.-Marsel Mesulam, Changiz Geula, Tamar Gefen

14. TDP43 Associated Tri-Glial Dysfunction in Dementia
Jaclyn Lilek, Kaouther Ajroud, Callen Spencer, Arleen Matos, Xueyan Liu, Hui Zhang, Borna Bonakdarpour, M. Marsel Mesulam, Eva Bambakadis, Rachel Shapiro, Alexander Feldman, Rudolph J. Castellani, Matthew McCord, Pouya Jamshidi, Tamar Gefen, Sandra Weintraub, Margaret E. Flanagan

Health Services

15. Lorenzo's House
Diana Shulla Cose

Neuroscience

16. Alterations in Basal Ganglia Connectivity in Primary Progressive Aphasia Caused by Frontotemporal Degeneration and Alzheimer's Disease
Daniel Seog, Jordan Behn, Emily Rogalski, Christina Coventry, Sandra Weintraub, Marsel Mesulam, Borna Bonakdarpour

17. A transdiagnostic study of morphometric similarity networks in delusions in dementia
Lisanne M. Jenkins, Sonya Gupta, Maryam Kouchakidivkolaei, Sandra Weintraub, Howie Rosen, Lei Wang

18. Brain Hypometabolism and Behavior Correlation in Primary Progressive Aphasia
Jordan Q. Behn, Jackie Takarabe, Leigh Christopher, Christina Coventry, Sandra Weintraub, Emily Rogalski, Marsel Mesulam, Borna Bonakdarpour

Poster Session

19. Class 1 Histone Deacetylases Regulate Memory Function in Mouse Models of Aging and Alzheimer's Disease.
Bryan M. McClarty, Hongxin Dong

20. Differential glial protein expression in the setting of co-existing Alzheimer's disease neuropathologic change and pathologic TDP43
Shadi Ghourchian, Jaclyn Lilek, Kaouther Ajroud, Callen Spencer, Alexander Feldman, Matthew McCord, Pouya Jamshidi, Rudolph J. Castellani, Margaret E. Flanagan

21. Differential Phagocytosis of Fibrillar and Soluble Oligomeric Aβ by Primary Human Microglia in Culture
Atousa Bahrami, Cameron Swope, Erfan Taefi, Margaret E. Flanagan, Tamar Gefen, M.-Marsel Mesulam, Changiz Geula

22. Increased Accumulation of Synaptic Proteins in Microglia Suggests Enhanced Synaptic Pruning in Frontotemporal Lobar Degeneration with TDP-43 Proteinopathy
Ivan A. Ayala, Callen Spencer, Margaret E. Flanagan, Tamar Gefen, M.-Marsel Mesulam and Changiz Geula

23. Intra-network Functional Connectivity of the Default Mode Network in SuperAgers
Bram Diamond, Adam Martersteck, Jaiashre Sridhar, Jess Wood, Emily Rogalski

24. Nasal Exhaled Breath Proteome in Alzheimer's Disease
Spencer Lehmann, Gregory Lane, Julia Jamka, Katherina Hauner, Borna Bonakdarpour, Jeffrey Savas, Christina Zelano

25. Northwestern Alzheimer's Disease Research Center (NADRC) Clinical Core
Michaela Riley MPH, Miriam Chinkers BS, Janelli Rodriguez BS, Emma Pollner MA, Abbey Page MS, Allegra Kawles BS, Grace Minogue BA, Antonia Zouridakis BS, Brittanie Muse MSPH, Hui Zhang PhD, Ian Grant MD, Borna Bonakdarpour MD, Joshua Cahan MD, Changiz Geula, PhD, Darby Morhardt PhD, Emily Rogalski PhD, M-Marsel Mesulam MD, Robert Vassar PhD, Tamar Gefen PhD, Sandra Weintraub PhD

26. Primary Progressive Aphasia Research Program at the Mesulam Center for Cognitive Neurology and Alzheimer Disease
Hayley Olson, Shreya Kanchan, Rhiana Schafer, Christina Coventry, Henna McCoy, Sarah Simon, Jaiashre Sridhar, Fatima Eldes, Daniel Gustein, Eunbi Kwon, Libby Rogers, Marissa Esparza, Leela Rao, Erin Blaze, Zoe Sweeney, Aimee Mooney, Darby Morhardt, Angela Roberts, Cynthia Thompson, Sandra Weintraub, Emily Rogalski, M.-Marsel Mesulam

27. Synaptic Integrity in Cognitive SuperAgers
Regina Taefi, Kenton Haynes, Ivan Ayala, Erfan Taefi, Cameron B. Swope, Margaret E. Flanagan, Tamar Gefen, Emily Rogalski, M.-Marsel Mesulam, Changiz Geula

28. The effect of antibiotic-mediated gut microbiome alteration on astrocyte morphology in the APP/PS1 mouse model of Alzheimer's disease
Sidhanth Chandra, Antonio Di Meco, Jelena Popovic, Robert Vassar

Poster Session

29. Ubiquitin Immunoreactivity Identifies TDP-43 Inclusions and Marks Cortical Neurons Destined to Degenerate in a Mouse Model of Frontotemporal Lobar Degeneration
Amber Chiodini, Ivan A. Ayala, Katherine Sadleir, Robert Vassar, M.-Marsel Mesulam, Changiz Geula

30. Unique Combinations of Structural MRI-Derived Shape Morphometric Features Improves Discriminability of FTLD Phenotypes
Jane K. Stocks, Karteek Popuri, M. Faisal Beg, Yann Cobigo, Howie Rosen, Lei Wang

31. Elucidating the contribution of amyloidogenic APP processing to Alzheimer's disease related impaired synaptic proteostasis
Nalini R. Rao, Jeffery N. Savas

32. Northwestern Alzheimer's Disease Research Center Neuroimaging Biomarker Core
Daniel Gutstein, Jaiashre Sridhar, Abbey Page, Eunbi Kwon, Fatima Eldes, Sarah Simon, Ajay Kurani, Pierre Besson, Allison Lapins, Malik Nassan, Adam Martersteck, Robert Vassar, Sandra Weintraub, Ryan Avery, Todd Parrish, M-Marsel Mesulam, Emily Rogalski

33. Cognitive SuperAging: A model to explore resilience and resistance to aging and Alzheimer's disease
Janessa Engelmeyer, Stephanie Gutierrez, Erin Blaze, Fatima Eldes Allegra Kawles, Jaiashre Sridhar, Eunbi Kwon, Sarah Simon, Abbey Page, Daniel Gutstein, Bram Diamond, Nathan Gill, Hui Zhang, Amanda Cook-Maher, Matt Huentelman, Tamar Gefen, Sandra Weintraub, Changiz Geula, M-Marsel Mesulam, Emily Rogalski

Pharmacology

34. The AHEAD Study
Brittanie Muse, MSPH, CCRC; Jelena Pejic; Shea Gold, MA; Sydney Orr; Ian Grant, MD; Joshua Cahan, MD; Allison Lapins, MD; Malik Nassan, MD

35. The VIVA-MIND Study
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Poster 1

A novel amyloid purification protocol for structural studies and quantitative proteomics

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Purpose: In Alzheimer's disease, amyloid beta 42 (Aβ42) peptides, form supramolecular proteinaceous assemblies. Interest in these structures has grown in the past, as they could be the underlying causes of multiple neurodegenerative diseases. We have developed a robust biochemical method that help purify amyloid fibrils from human AD patients and mouse brain tissues.

Methodology: In our workflow, we have modified previously described sucrose density gradient ultracentrifugation protocol by adding ultrasonication and multiple SDS washing steps. These additional steps help get rid of many non-specifically bound proteins or cellular structures and yield highly pure and clean fibrils, as observed in negative staining transmission electron microscopy. We performed immunoblot assays, ELISA and quantitative proteomics to understand the composition of these fibrils and confirmed a very high (~200 fold) yield and (~10 fold) purity.

Findings: This robust biochemical method may provide a straightforward way to study the structural features of amyloid fibrils by performing solid-state NMR, cryoEM and detailed mass spectrometry based structural studies. Our analysis also help understand the composition of amyloid fibril core in a comprehensive manner and help us identify direct interaction partners of Aβ42 monomer, which might be playing important roles in the formation and stabilization of oligomer assemblies.

Lay Language: Alzheimer's disease is caused by loss of neurons due to the deposition of highly stable protein assemblies, called amyloids, in the extracellular space. The amyloids disrupt the cellular machinery in multiple ways, including causing inefficient protein degradation machinery, synaptic loss, evoking inflammatory responses, etc. A highly robust and reproducible method of purifying pathological deposits from the postmortem brain tissues is required to investigate the fibrillary structure and proteomic composition of amyloids. Here, we provide a novel method of isolating amyloid fibrils from the animal AD models and human brain tissues, which help us perform detailed studies to understand the composition of these fibrils. Understanding the composition may benefit us by giving us a better insight of how these structures are formed. We have successfully identified new candidate proteins, which may have possible roles in formation of the fibrils. This knowledge may help in designing new therapeutic strategies targeting novel molecular targets that can directly interfere with the amyloid formation and pathological changes in the AD brain.

Poster 2

Characterization of apathy-like behaviors and their relationship to Aβ pathology in5xFAD mice

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Background: Alzheimer's disease (AD) is a neurodegenerative disease that causes progressive cognitive decline and neuropsychiatric symptoms (NPS) with apathy being highly common. The neurobiological mechanisms of apathy in AD are unclear. This study characterized apathy-like behaviors in 5xFAD mice and their relationship to amyloid-beta (Aβ) pathology in the hippocampus and prefrontal cortex (PFC).

Methods: We examined apathy-like behavior in male and female 5xFAD mice and wildtype controls at 6, 12, and 16 months of age (n = 9-14 per group). Behavioral paradigms included nest building, marble burying, and food burrowing, and we calculated apathy composite scores for each mouse from the results of these three tests. Then, we measured soluble Aβ42 in the hippocampus and PFC of the male and female 5xFAD mice with the highest and lowest apathy composites within each age group by ELISA assay. Finally, we characterized Aβ plaque density and size in the hippocampal CA1 subregion and the PFC using thioflavin-S staining and ImageJ. We conducted linear regressions to determine the effects of age, gender, genotype, or apathy status on behavioral and biochemical outcomes.

Results: Apathy-like behaviors occurred in 5xFAD mice at all ages ($p < 0.001$ at 6, 12, and 16 months), were more prominent in females, and worsened with age. In the PFC, soluble Aβ42 was greater in high-apathy than in low-apathy 5xFAD mice ($p = 0.042$) and greater at 12 and 16 months than at 6 months of age ($p < 0.05$ and $p < 0.001$, respectively). Females had more plaques than males in the PFC overall ($p = 0.003$). Plaques were larger in high-apathy than in low-apathy 5xFAD mice ($p < 0.10$) and at 6 months compared to other ages (12 months $p = 0.034$, 16 months $p < 0.05$). In the hippocampus, soluble Aβ42 was greater at 16 months than at younger ages (both $p < 0.001$) and greater at 12 than at 6 months of age ($p = 0.006$). High apathy was associated with a greater density of hippocampal plaques than low apathy in certain groups (6-month males $p < 0.10$, 12-month females $p < 0.05$).

Conclusions: Findings suggest that apathy-like behaviors start at 6 months in 5xFAD mice, significantly worsen with age, and potentially differ between sexes. Additionally, our study demonstrates that apathy correlates positively with soluble and insoluble Aβ pathology with exact relationships varying by brain region.

Lay Language: Alzheimer's disease (AD) is characterized by pathology accumulating and spreading throughout the brain, leading to significant cognitive decline. Many AD patients also develop behavioral symptoms with apathy being the most common. Researchers often use mouse models of AD to study relationships between brain pathology and cognitive impairment in great detail; however, relatively fewer animal studies have focused on behavioral symptoms in AD. We investigated apathy in a mouse model of AD in this study and found that apathetic behaviors emerged at an early age, worsened with disease progression, and correlated with more severe brain pathology. Our results suggest that apathy may be an early indicator of underlying AD and likely worsens with the progression of pathology in the brain. Further, mouse models are useful for studying behavioral symptoms in AD, and future studies with this focus have the potential to identify early targets for intervention.

Poster 3

Genetic proxy of structural cortical asymmetry is potentially causal for agrammatic primary progressive aphasia: a mendelian randomization approach

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Introduction: Observational studies suggested an association between developmental dyslexia and an increased risk for primary progressive aphasia (PPA). On the other hand, the asymmetrical neurodegeneration seen in PPA (affecting mainly the left cerebral cortex) is of interest and might be relevant to handedness dexterity or mechanisms involved in cortical lateralization. We sought to assess if these relationships are causal through a mendelian randomization approach.

Methods: Genome wide significant variants associated with dyslexia and left-handedness identified in the most recent and largest genome wide association (GWAS) studies were used as genetic proxies for the exposures (42 SNPs for dyslexia, 48 SNPs for left-handedness; 18 of which with correlated asymmetries of the cerebral cortex). Summary GWAS statistics for all 3 types of PPA (logopenic/Alzheimer n=324, semantic/FTD n=308 and agrammatic/FTD n=269) were obtained. The whole cohort for AD (71,880 cases, 383,378 controls) and FTD (3526 cases, 9402 controls) were also included as outcomes. Inverse weighted median mendelian randomization was performed as the main analysis for testing the relationship between the exposures (dyslexia, left-handedness, and cortical asymmetry) and outcomes (3 type of PPA). Sensitivity analyses were completed to test the robustness of the results.

Results: Genetic proxy of cerebral cortex asymmetry was significantly associated with agrammatic PPA type (beta 4.3 P= 0.009) and with FTD whole sample (beta 1.67, P=0.03) [both of which are Tau diseases] but not with semantic PPA FTD type (beta 0.5, P= 0.7432883) [which is usually a TDP-43 disease]. None of the other exposures were significantly associated with any type of PPA or with AD or FTD whole samples (P>0.05). Sensitivity analyses were also consistent with the primary analysis.

Conclusion: Human genetic data provides - for the first time - evidence of a potential causal effect of cortical asymmetry on agrammatic PPA due to FTD disease. This effect was driven by cortical asymmetry rather than handedness or dyslexia. Of interest, the genes of the cortical asymmetry associated with agrammatic PPA are also implicated in microtubule-related proteins (TUBA1B, WASF3, TUBB, MAPT) which further support their role on Tau related neurodegeneration. Future studies should aim to investigate those genes in agrammatic PPA patients for better understanding of the pathology and potential therapeutic interventions. Furthermore, cortical asymmetry should be evaluated as possible predictor of disease development later in life or a region of selective vulnerability to neurodegeneration.

Lay Language: Primary progressive aphasia is a neurodegenerative disease in which patients slowly and gradually lose their language functions (like speaking, understanding and writing). The cause for primary progressive aphasia syndrome is not known yet. In this study we used genomic data to identify potential causes for this disease. We were able to find that genes implicated in brain asymmetry might be playing a role in the pathogenesis of this disease. Our finding will help understand the underpinning mechanisms of this disease and shed the light on genetic and molecular pathways that can be targeted to find treatments.

Poster 4

Hippocampal Activity Regulates Bone Morphogenic Signaling in-vitro

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Background: Aging exerts non-uniform changes on the brain affecting some neural networks and functions while leaving others spared. Hippocampal activity, neurogenesis, and signaling are affected by the aging process. We have previously reported a dramatic increase in bone morphogenic protein (BMP) signaling in aging, accompanied by a dramatic decline in the BMP inhibitor noggin. Exacerbated BMP signaling has also been reported in Alzheimer's disease. Further, we demonstrated that inhibiting BMP by genetic overexpression or intraventricular infusion of noggin was effective in increasing neurogenesis and improving cognitive performance in aged animals. Age associated changes in hippocampal network activity may contribute to age associated cognitive decline however the extent to which activity modulates hippocampal signaling cascades remains to be determined. Using an established in vitro model of hippocampal postnatal neuron cultures, we aimed to investigate the relationship between dentate gyrus activity, neurogenesis, and BMP signaling.

Method: Neurosphere cultures were generated from postnatal day 1 C57/B6 wildtype mice and IFT88 flx/flx (IFT88 KO). Neurospheres were dissociated into single cells and plated on Poly-Dlysine-laminin and allowed to differentiate for 32-35 days in media containing BDNF and NT3 before fixation. At 35 days in-vitro, cells were treated with vehicle, somatostatin, or sonic hedgehog (SHH) and collected at 24 hours of treatment. Cells were depolarized using 20mM KCl for 6 hours to model neuronal depolarization. Cells were collected for both immunocytochemistry and molecular analysis by western blot or RT-qPCR. Protein levels of noggin, pSMAD 1-5-8, and Gli-1 were evaluated by western blot in order to assess the effect of these different BMP signaling effectors independently and in combination with membrane depolarization with and without cilia ablation.

Results: In wildtype cells, 6 hours of KCl mediated depolarization caused a significant increase in noggin expression both at the mRNA and intracellular protein level. Somatostatin treatment reduced noggin levels by western blot. SHH treatment dramatically increased noggin. IFT88 KO neurons revealed lower levels of noggin at baseline and a further reduction in noggin with KCl depolarization.

Conclusions: BMP signaling appears to be regulated by neuronal activity in-vitro. Here we demonstrate that potassium mediated depolarization leads to an increase in noggin expression and intracellular protein levels. Further, treatment with somatostatin, associated with inhibitory interneurons, and SHH another positive regulator of neurogenesis increased noggin levels. IFT88 KO cultures showed reduced noggin levels. Together, these data suggest that modulating neuronal activity in the dentate gyrus may provide a potential mechanism in order to ameliorate age related increases in BMP signaling and declines in neurogenesis and that primary cilia are necessary for regulating BMP signaling within the neurogenic niche.

Lay Language: My work looks at how activity in the brain regulates one specific signaling pathway, BMP signaling, and how changes in this pathway relate to changes in memory performance. Our group has shown that BMP signaling increases as we age and the birth of new born neurons slows in the hippocampus as we get older. Previously, we found that animals with high levels of BMP signaling in their hippocampus have worse memory. We know that some elders experience memory loss but it is not yet known why others do not. Our work aims to understand whether BMP signaling might play a role in this difference and if so how we might be able to help elders experiencing memory loss.

Poster 5

Investigating rare genetic variants in Angiotensin-1-Converting Enzyme and their role in Alzheimer's Disease pathogenesis

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Recent genome- and proteome-wide association studies show that angiotensin-converting enzyme (ACE) is a risk locus for developing late-onset Alzheimer's disease (LOAD). Interestingly, whole genome sequencing of LOAD families revealed both AD-associated and AD-protective variants in ACE1. Though usually associated as the key enzyme in the renin-angiotensin system, this membrane bound metalloprotease is also present in the brain, and has other substrates, including Aβ. Our lab seeks to characterize these rare genetic variants in a cellular model system in order to understand the mechanisms by which they could alter ACE1 processing, expression, function, and its effect on cell viability. Preliminary data show that some mutations alter ACE1 substrate cleavage activity as well as its ability to be shed from the cellular membrane. Future directions involve further characterizing these mutations and testing their ability to cleave substrates that have been linked to AD pathology, such as Aβ and complement factor C3.

Lay Language: The Vassar Lab focuses on studying how one's genes can increase the risk for developing Alzheimer's disease (AD) by changing the way proteins act in the brain. My project specifically investigates how genetic alterations in the protein angiotensin-converting enzyme 1 (ACE1) can lead to AD. It is known that high blood pressure can increase the risk of developing AD and interestingly, ACE1 is most famous for its role in regulating blood pressure. However, ACE1 is involved in many other processes in the brain and has been genetically linked to AD. I study specific changes, or mutations, in ACE1 that are associated with AD and how those mutations could cause AD to develop. So far, my results show that mutations in ACE1 can change the way it acts in brain cells. There is potential to remedy these changes with common drugs normally used to regulate blood pressure, such as ACE inhibitors.

Poster 6

Pharmacological Studies of Behavioral Abnormalities in the 5XFAD Mouse Model of Alzheimer's Disease

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The 5xFAD mouse model, like other Alzheimer's disease [AD] mouse models, demonstrates a wide range of memory deficits, including, but not restricted to spatial and recognition memory. The 7-9-month-old 5xFAD mice showed significant novel object recognition [NOR] deficit, wherein they were unable to distinguish the novel from familiar object with 24 hours interval between the sample and test phase. This is represented by decrease in discrimination index to near zero using NOR assay. This deficit was rescued by the cholinesterase inhibitor, rivastigmine and the uncompetitive N-methyl-D-aspartate receptor [NMDAR] antagonist, memantine, both of which are widely used to treat early AD. We also found that dopamine [D] 1 partial agonist, SKF38393, an inhibitor of chloride transporter, bumetanide, and nutraceuticals, curcumin and quercetin also rescued NOR deficit in these mice. Literature review shows that serotonergic[5-HT] neurons are lost in advanced AD. So, we tested some serotonin subtypes. The 5-HT2A receptor[R] antagonist, pimavanserin was ineffective to rescue NOR, but showed efficacy to rescue obsessive compulsive behavior [OCD] using marble burying assay, indicating its potential as a treatment for OCD symptoms in AD. The 5-HT1AR partial agonist, tandospirone, showed efficacy to rescue object recognition memory and spatial egocentric memory using NOR and Y-maze tasks respectively. Hyperlocomotion, using locomotor activity [LMA] assay in the mouse is considered analogous to psychosis-like behavior, a frequent symptom of AD. The NMDAR antagonist, phencyclidine [PCP] and the D1R agonist, amphetamine [amph], induce increase in LMA, and are frequently used to model psychosis in schizophrenia [SCZ]. While PCP did not increase LMA in these mice, amphetamine induced significant increase in LMA. This amph-induced increase in LMA was blocked by the 5-HT2AR inverse agonist, pimavanserin. Taken together, these results suggest the significance of 5XFAD mouse model to test putative novel therapeutic agents to mitigate the behavioral disturbances in AD.

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Lay Language: Behavioral disturbances accompany memory loss in Alzheimer's disease. These behavioral disturbances add to the burden of the disease for patients and their caregivers. We have focused on treating these behavioral disturbances in an aggressive mouse model of AD, the 5XFAD mouse. We report here on a group of drugs, including two nutraceuticals [curcumin and quercetin], which were effective in minimizing memory loss, as well as obsessive-compulsive symptoms. Other therapeutic agents such as memantine, rivastigmine, bumetanide. pimavanserin and tandospirone were also effective in some of the behavioral disturbances in the 5XFAD mice. While memantine and rivastigmine have FDA approval for treating AD, rigorous testing is needed to determine if these translate to effective treatment in patients with AD or other dementias, e.g. frontal-temporal dementia.

Poster 7

Suitability of Goal Attainment Scaling in Psychogeriatric Populations with Neurodegenerative Disease Experiencing Dementia or Cognitive Impairment: A Systematic Review

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Goal Attainment Scaling (GAS) is an outcome measure used to formally specify goals and measure goal attainment in clinical settings, including in cognitive rehabilitation. GAS scores account for the importance and difficulty of attaining a specific goal, and therefore reflect changes in functional ability specific to the needs of patients and their caregivers. Evaluating the responsivity of GAS in specific populations is necessary to understand its clinical utility and ability to measure functional change. While the responsivity of GAS has been measured broadly across populations, no review has evaluated the suitability of GAS in older adult populations with neurodegenerative disease experiencing dementia or cognitive impairment. The purpose of this study is to conduct as systematic review to determine the suitability of Goal Attainment Scaling in older adults with neurodegenerative disease experiencing dementia or cognitive impairment, based on responsiveness. Eight databases and 4 grey literature sources were queried and 882 eligible articles were identified, 326 duplicate articles were removed, and 556 articles were then screened by title and abstract for eligibility. Articles were included if (i) the sample included adults with neurodegenerative disease experiencing dementia or cognitive impairment, (ii) GAS was used in the context of an intervention, and (iii) the report included pre- and post-intervention GAS scores. Additional inclusion criteria were specified after the initial screening (e.g., intervention and outcome measures focused on cognition, communication, activities of daily life, or quality of life) to exclude articles related to motor interventions. Twenty-three articles were then screened by full text for eligibility. Ten reports met inclusion criteria and will be included in the final analysis. Data extraction was performed using the Cochrane Data Extraction form, and Risk of Bias Assessments were done with the RoB 2.0 and the NIH Quality Assessment Tool. All eligibility screenings, data extraction, and risk of bias assessments were completed by two independent reviewers. Of the 10 reports to be included in the final analysis, 3 focus on dementia, 3 on Multiple Sclerosis, 1 on Parkinson's Disease, 1 on Mild Cognitive Impairment, 1 on Alzheimer's Disease, and 1 on Primary Progressive Aphasia. Three articles have a high risk of bias, 3 have a moderate risk of bias, and 4 have a low risk of bias. Responsiveness will be rated as positive in reports with significant differences between pre- and post-intervention GAS scores and rated as negative in reports where changes between pre- and post-intervention GAS scores are non-significant. A random-effects model will be used to calculate overall effect size. Preliminary results indicate that GAS has high responsivity in this population and likely has high clinical utility. Understanding the suitability of GAS in this population will allow for effective measurement of functional change in targeted interventions to improve cognition, communication skills, and quality of life in individuals experiencing dementia or cognitive impairment due to neurodegenerative disease.

Lay Language: My project looks at a measurement tool used in speech-language, occupational, and cognitive therapy called Goal Attainment Scaling (GAS). GAS allows people to set specific goals and then measures their progress towards those goals while they are receiving treatment. I am specifically looking at how well GAS measures change in people with neurodegenerative diseases who are experiencing dementia or cognitive difficulties. I searched 8 databases and found over 500 relevant articles. I searched these articles to make sure that they focus on people with dementia, include GAS scores, and include people receiving treatment focused on cognition, communication, or quality of life. After reviewing the articles, I have identified 10 articles that fit my criteria. My results so far suggest that GAS is an effective way to measure change, and may be useful in speech-language, occupational, and cognitive therapy.

Poster 8

Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3)

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The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a longstanding project to discover clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease. This work has been carried out in the ADNI1, ADNI-GO, and ADNI2 studies since 2004, and it continues with ADNI3. ADNI3 is a non-randomized, natural history, non-treatment study that lasts up to 5 years and enrolls participants across three cohorts: (1) individuals with Alzheimer's disease (AD), (2) individuals with Mild Cognitive Impairment (MCI), and (3) cognitively normal (CN) individuals. Overall 1,080 participants, age 55 to 90, have been enrolled at 59 sites in the Unites States and Canada. Participants undergo longitudinal clinical and cognitive assessments, computerized cognitive batteries, biomarker tests, brain imaging scans (including PET and MRI), and cerebral spinal fluid analysis. The data collected from the ADNI project has now contributed to more than 2,500 peer-reviewed publications, continuing to inform the field of Alzheimer's research. The ADNI project is very mindful of the need for diversity, equity, and inclusion in Alzheimer's research. In 2020, the ADNI Diversity Taskforce Initiative was launched to support the accelerated enrollment of individuals from underrepresented groups, including, but not limited to racial and ethnic minorities, Lesbian, Gay, Bisexual, Transgender or Queer (LGBTQ+) people, and individuals with lower socioeconomic standing. Across all sites, ADNI3 has reached 19% enrollment of individuals from these underrepresented groups. Our Northwestern site has 24 active ADNI participants, of which 42% are from underrepresented groups, and is currently recruiting.

Lay Language: The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a longstanding project to discover clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease.

Poster 9

Concordance between Neocortical Distribution of Pick's Disease and the Salience of Distinct Dementia Phenotypes

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Background: Frontotemporal lobar degeneration of the tau form (FTLD-tau) is a neurodegenerative disease that leads to different dementia syndromes. For example, primary progressive aphasia (PPA) is characterized by an isolated and progressive impairment of language, and focal atrophy of left-hemispheric regions. In contrast, behavioral variant of frontotemporal dementia (bvFTD) is characterized by progressive dysfunction in personality, and atrophy in bilateral frontal regions. Interestingly, both PPA and bvFTD can be caused by the common 3R FTLD-tauopathy of Pick's disease (PiD). This stereological study investigated the cortical distribution of Pick bodies in bvFTD and PPA to establish clinicopathologic concordance between Pick's disease and the salience of the aphasic versus behavioral phenotype.

Methods: 12 right-handed cases with PiD as the sole pathologic diagnosis were identified from the Northwestern University Alzheimer's Disease Center brain bank (bvFTD, N=6; PPA, N=6). Paraffin-embedded sections were stained immunohistochemically with AT-8 to visualize Pick bodies. Unbiased stereological analysis (MicroBrightField, MBF Bioscience) was performed on all 12 cases in 3 regions bilaterally [middle frontal gyrus (MFG), inferior parietal lobule (IPL), superior temporal gyrus (STG)] and unilaterally in occipital cortex (OCC). Bilateral anterior temporal lobe (ATL) was analyzed in PPA cases only. Paired t-tests and one-way nonparametric ANOVAs were used to compare regional and hemispheric distribution within and between groups.

Results: Highest densities of Pick bodies were found in ATL (M=31,634; SD=10,502) in PPA, whereas peak densities were evident in the MFG (M=26,036; SD=8,719) in bvFTD. In PPA cases, there was leftward asymmetry of Pick bodies in MFG, IPL, and STG, the latter of which reached statistical significance ($p<0.05$; L>R). Interestingly, the ATL showed slight rightward predominance. Cortical distributions of Pick bodies in bvFTD were generally symmetric. As expected, the occipital cortex showed extremely sparse to no pathology in both groups.

Conclusions: Stereological quantitation confirms that the distribution of Pick body pathology is concordant with salient clinical features unique to PPA vs bvFTD. In bvFTD, Pick bodies were symmetric and highest in MFG, a region implicated in behavior/comportment, while in PPA, Pick bodies showed leftward asymmetry consistent with the aphasic phenotype. The vulnerability of the ATL to Pick's disease is remarkable, raising future questions about its functional significance within the human language network and the relationship of tau pathology to neuronal degeneration.

Lay Language: Frontotemporal lobar degeneration caused by the protein tau (FTLD-tau) is a neurodegenerative disease found at autopsy that leads to different dementia syndromes. Types of FTLD-tau can cause primary progressive aphasia (PPA), characterized by progressive impairment of language and primary atrophy of left-brain regions. It can also cause behavioral variant of frontotemporal dementia (bvFTD), a dementia characterized by progressive dysfunction in personality, and atrophy in frontal regions. Interestingly, both PPA and bvFTD can be caused by a FTLD-tau subtype called Pick's disease (PiD). This study investigated the distribution of PiD pathology in various brain regions in bvFTD and PPA to establish important relationships between burden and location of the disease at death, and clinical symptoms demonstrated during life.

Poster 10

Differential Vulnerability of the Dentate Gyrus to Tauopathies in Aphasic Dementia

Allegra Kawles, Grace Minogue, Antonia Zouridakis, Caren Nassif, Rachel Keszycki, Christina Coventry, Emily Rogalski, Margaret E. Flanagan, M-Marsel Mesulam, Changiz Geula, Tamar Gefen
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Background: The dentate gyrus (DG) is a region of the hippocampal formation characterized by a single layer of densely packed granule cells, followed by an underlying polymorphic layer of the long-projecting hilus neurons. The granule cells receive input from the entorhinal cortex and send excitatory output to the hippocampal CA3 subfield via its mossy fibers. Prior work in Alzheimer's disease (AD) has shown that the dentate gyrus generally resists the development of tau tangles in the typical amnestic clinical syndrome. The susceptibility of the DG in non-AD tauopathies has not yet been investigated and can offer key insights into hippocampal function and selective vulnerability of the region to disease. Here, we report and compare stereologic densities of tau inclusions in the DG across four conformationally distinct tauopathies, namely the FTLD 3R-tauopathy of Pick's disease (PiD); the FTLD 4R-tauopathy of corticobasal degeneration (CBD); the FTLD 4R-tauopathy of progressive supranuclear palsy (PSP); and the 3/4R-tauopathy of Alzheimer's disease (AD), all of which manifested an aphasic dementia syndrome known as Primary Progressive Aphasia (PPA), in which language abilities are compromised and memory functions are spared.

Methods: Thirty-two right-handed cases with clinical diagnoses of PPA and autopsy-confirmed tauopathy diagnoses were obtained from the Northwestern Alzheimer Disease Research Center (PiD, N=8; CBD, N=8; PSP, N=8; AD, N=8). All specimens were stained immunohistochemically with AT-8 to visualize tau pathology of both the 3R and 4R type. Nissl staining was used to identify neurons. Unbiased stereological analysis (MicroBrightField Bioscience) was performed on the left dentate gyrus to quantitate densities of tau-positive inclusions and neurons. One-way parametric ANOVAs with Benjamini and Hochberg corrections were employed to compare tau pathologic burden and neuronal densities between tauopathies in granul and hilar populations.

Results: Highest densities of dentate gyrus tau pathology were found in PPA-PiD (~77,000 per mm3) by a wide margin, followed by PPA-CBD (~16,000 per mm3), PPA-AD (~6,000 per mm3), and then PPA-PSP (~1,000 per mm3). When comparing granule vs hilar densities, CBD and PiD cases had many more granule vs hilar inclusions, while PPA-AD showed the reverse pattern. PSP cases had little to no tau burden in both populations. PSP and AD cases showed greatest overall (granule plus hilar) neuronal densities. Interestingly, PiD had more preserved granule neuronal integrity compared to CBD despite very high inclusion counts in PiD.

Conclusion: The dentate gyrus of the hippocampal complex is differentially vulnerable to tauopathies, with high selectivity to certain FTLD species, particularly Pick's disease. These patterns of susceptibility in the non-amnestic, language-based clinical dementia syndrome known as PPA raise intriguing questions about the functional and structural integrity of hippocampal circuits in neurodegenerative dementias.

Lay Language: Frontotemporal lobar degeneration caused by the protein tau (FTLD-tau) is a neurodegenerative disease found at autopsy that leads to different dementia syndromes. Types of FTLD-tau can cause primary progressive aphasia (PPA), characterized by progressive impairment of language and primary atrophy of left-brain regions. It can also cause behavioral variant of frontotemporal dementia (bvFTD), a dementia characterized by progressive dysfunction in personality, and atrophy in frontal regions. Interestingly, both PPA and bvFTD can be caused by a FTLD-tau subtype called Pick's disease (PiD). This study investigated the distribution of PiD pathology in various brain regions in bvFTD and PPA to establish important relationships between burden and location of the disease at death, and clinical symptoms demonstrated during life.

Poster 11

Distinct Regional and Hemispheric Tau Distributions in Primary Progressive Aphasia with Neuropathologic Progressive Supranuclear Palsy: A Stereological Study

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Introduction: Primary Progressive Aphasia (PPA) is a dementia syndrome characterized by isolated and progressive impairment of language and focal atrophy of left-hemispheric cortical regions. PPA presents with various underlying FTLD-tauopathies such as Pick's disease (PiD), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP). This study investigated clinicopathologic concordance between the aphasic phenotype of PPA and regional distributions of PSP markers quantified in language-related cortical areas and the dentate gyrus (DG) of the hippocampus—an area of interest due to intact memory exhibited in PPA. Another goal was to compare regional distributions of tau-positive markers in PSP compared to CBD and PiD to identify differential susceptibility patterns across FTLD-tauopathies.

Methods: Paraffin-embedded sections were stained immunohistochemically with AT-8 to visualize neuronal tau inclusions and astrocytes containing phosphorylated tau in 8 right-handed cases with PPA and autopsy-confirmed PSP. Modified unbiased stereology was performed in bilateral middle frontal gyrus (MFG) and inferior parietal lobule (IPL), and left DG. A secondary analysis compared distributions of tau markers in cases with PiD (N=6; tau-positive inclusions) and CBD (N=4; tau-positive inclusions + astrocytic plaques). One-way ANOVAs and students' t-tests were used to analyze distributions.

Results: Within the PSP group, there was significant left-sided asymmetric predominance of tau-positive neuronal inclusions and astrocytic tau in cortical areas; left MFG showed over double the total marker density vs right (3,490 vs 1,549 counts/mm3, respectively; $p<0.05$). In PSP, there was significantly less tau-positive inclusions and astrocytes in the DG relative to cortical regions, where the ratio of left-sided dentate-to-cortical inclusions was ~1:2. This was remarkably lower than dentate-to-cortical ratios of ~2:1 in CBD and ~3:1 in PiD ($p<0.01$). Finally, PSP cases showed significantly greater astrocytic tau in cortical regions compared to CBD, by ~100 fold in the left hemisphere ($p<0.01$).

Conclusions: Findings from this stereological study of PPA with FTLD-PSP show leftward cortical predominance of pathology concordant with the salience of the aphasic phenotype. Dentate predominance of pathology in PPA due to FTLD-tau remains a mystery. The relative distribution of dentate-to-cortical tau pathology is different across FTLD-tau species, offering insights into the selective vulnerability of distinct neuronal populations in neurodegenerative dementias.

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. Interestingly, 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 my project, we analyzed the brains of people with Primary Progressive Aphasia (PPA), a language-based dementia, that also showed a disease known as Progressive Supranuclear Palsy (PSP), which is characterized by abnormalities in the protein "tau." We examined the distribution of PSP disease markers in several brain regions to distinguish PSP from other diseases that can also present with PPA and found several features unique to those with PPA due to PSP. Further study of this clinicopathologic relationship will lead to earlier and more accurate diagnoses as well as better treatment outcomes.

Poster 12

Quantification of synaptic markers in Alzheimer disease.

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Introduction: Alzheimer's Disease (AD), a common cause of dementia, is a progressive neurodegenerative disease neuropathologically characterized by amyloid-beta plaques and Tau neurofibrillary tangles. Emerging evidence points to reduced synaptic function in AD that contributes to the development of memory impairment. There have been conflicting reports in mouse models of AD vs, human brain autopsy samples regarding synaptic dysfunction. This highlights the need for further investigation in this area.

Materials and methods: Clinically and neuropathologically characterized human brain autopsy samples from two separate brain regions (hippocampus and middle frontal gyrus) across brain autopsy cases (n=30) encompassing the entire spectrum of AD neuropathologic change (ADNC-Not, Low, Intermediate & High), were immunohistochemically stained to assess the distribution of four synaptic markers (AMPA, PSD95, synaptophysin and spinophilin) reported to be altered in the progression of AD. Indica Labs Halo software was used to perform quantitative analyses on whole slide images. Using One-way ANOVAs and students' t-tests as well as SPSS Kruskal-Wallis we compared the distribution of various synaptic markers and expression among the four ADNC groups (Not, Low, Intermediate, & High).

Results: By assessing regions involved by Tau tangles in early (hippocampus) and late (middle frontal gyrus) stages in AD pathogenesis, we found significant differential staining in total AMPA receptors ($p=0.03$) and PSD95 ($p=0.04$) in the hippocampus. When comparing individuals with Not and low vs. intermediate AD neuropathologic change, we also observed a decrease in hippocampal PSD95 ($p=0.02$).

Conclusion: Quantitative hippocampal AMPA receptor and PS95 differences across AD neuropathologic change groups highlight early disruptions in synaptic function in AD neuropathologic progression. Early disruption of synaptic function may occur in individuals with pre-clinical AD prior to the development of memory impairment. However, future studies are needed to clarify the role of these proteins in the development of early AD neuropathologic change related synaptic dysfunction.

Lay Language: Alzheimer's Disease (AD), a common cause of dementia, is a progressive neurodegenerative disease. Neuropathologically AD is characterized by protein deposits in and around the neurons, the brain cells. Emerging evidence points to reduced synaptic function in AD that contributes to the development of memory impairment. Synapses are forms of communication neurons relay on to optimally function.

We compared the distribution of various proteins expressed in the synapses (AMPA, PSD95, Synaptophysin and Spinophilin) among four AD neuropathologic change (ADNC-Not, Low, Intermediate & High) human brain autopsy samples from two separate brain regions (hippocampus and middle frontal gyrus).

We found significant differential staining in total AMPA receptors and PSD95 in the hippocampus, a region involved early in AD which highlight early disruptions in synaptic function. This early event may occur in individuals with pre-clinical AD prior to the development of memory impairment. However, future studies are needed to clarify the role of these proteins in the development of early AD neuropathologic change related synaptic dysfunction.

Poster 13

Regional burden of pathology in hippocampal subregions can distinguish amnestic dementia with comorbid Alzheimer's and TDP-43 pathology from pure Alzheimer's and FTLD-TDP.

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Introduction: Dementia syndromes are often not related to a single pathophysiologic process, leading to multiple neuropathologies found at autopsy. For example, an amnestic dementia syndrome can be associated with comorbid phosphorylated transactive response DNA-binding protein 43 (TDP-43) and Alzheimer's disease. These pathologies are typically observed in hippocampal regions- including the CA1 sector, CA3 sector, and dentate gyrus. Here, we investigated neuronal integrity and pathologic burden of TDP-43 and tau in the dentate gyrus, CA1 sector, and CA3 sector of the hippocampus, in amnestic dementia due to Alzheimer's disease and TDP-43 (AD/TDP), due to Alzheimer's disease alone (AD), and non-amnestic dementia due to TDP-43 associated with frontotemporal lobar degeneration (FTLD-TDP).

Participants and Methods: Seventeen individuals with AD/TDP [mean age at death=80 (SD=8.84)], 14 individuals with AD [mean age at death=81 (SD=10.94)], and 19 individuals with FTLD-TDP [mean age at death=69 (SD=9.12)] were identified from the Northwestern AD Research Center brain bank. AD/TDP and AD cases carried an antemortem diagnosis of amnestic dementia and met criteria for high AD neuropathologic change. AD/TDP and FTLD-TDP cases were positive for at least medial temporal TDP-43. FTLD-TDP cases carried a clinical diagnosis of primary progressive aphasia (language-based dementia) or behavioral variant frontotemporal dementia (personality-based dementia). Left hippocampi were stained immunohistochemically with phosphorylated TDP-43 and AT-8 antibodies to visualize TDP-43 and tau-positive immunoreactivity, respectively. HALO software (Indica Labs) was used to generate % area occupied by immunopositivity in each hippocampal subregion. Student t-tests and one-way ANOVAs were used to determine group differences.

Results: AT-8 immunopositivity was significantly greater in DG ($p<0.002$) and CA3 ($p<0.05$) in AD/TDP compared to pure AD; there was no significant difference in CA1. TDP-43 immunoreactivity was generally low and of equal distribution across DG, CA1, and CA3 in AD/TDP. TDP-43 immunopositivity was significantly greater in FTLD-TDP cases compared to AD/TDP across CA1 ($p<0.05$), CA3 ($p<0.01$), and DG ($p<0.001$). When pathologic burden was totaled (AT8 + TDP-43 immunoreactivity), the AD/TDP group showed significantly greater pathology in DG and CA3 compared to the pure AD ($p<0.01$, $p<0.05$) and FTLD-TDP ($p<0.0001$, $p<0.001$); as expected, AD and AD/TDP groups had significantly higher total pathology in the CA1 compared to the FTLD-TDP cases ($p<0.0001$, $p<0.0001$), driven by the predominance of tangle pathology in that region. The CA1 had higher AT-8 immunopositivity compared to CA3 and DG in both AD ($p<0.0001$), $p<0.0001$) and AD/TDP ($p<0.05$, $p<0.05$). In FTLD-TDP, however, the DG had significantly higher TDP-43 immunoreactivity compared to CA3 and CA1($p<0.01$, $p<0.05$).

Poster 13 cont.

Conclusions: AD/TDP can be distinguished from AD and FTLD-TDP based on differential regional distribution of tau and TDP-43 pathology in the hippocampus. The contribution of TDP-43 immunoreactivity in AD/TDP is minimal but appears to be additive, particularly in the CA3 and DG. These results may indicate that the amnestic phenotype caused by AD/TDP has a distinct pathophysiologic process from that caused by AD. Future studies will address questions of clinicopathologic concordance between markers of neurodegeneration and cognition during life.

Lay Language: Recently, it has been discovered that memory-related (amnestic) dementia is often caused by more than one disease in the postmortem brain. This study aimed to investigate two proteins that appear together in almost 80% of individuals with amnestic dementia: 1) Alzheimer's disease characterized by amyloid plaques and tau-tangles and 2) abnormal inclusions in brain cells known as TAR DNA-binding protein 43 (TDP-43). The goal was to distinguish the role each disease plays in amnestic dementia. We focused our analysis on 3 regions of the memory-center of the brain, the hippocampus. We found important and significant differences between the amount and location of tau vs TDP-43 in regions of the hippocampus, which helps us to distinguish and better understand these two diseases as separate entities.

Poster 14

TDP43 Associated Tri-Glial Dysfunction in Dementia

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Background: Alzheimer's disease (AD) is a substantial cause of death and disability. In addition to the plaques and tangles that are classically observed in AD, other co-existing brain lesions also contribute to the development of cognitive impairment, such as pathologic trans-active response DNA-binding protein 43 (pTDP43). TDP43 is ubiquitously expressed in the brain and mechanistic studies suggest potential roles for TDP43 in maintaining normal physiologic conditions in glia (astrocytes, microglia, oligodendrocytes)1,2. Effective glial functioning and signaling are crucial to maintaining functional connectivity. pTDP43 is strongly associated with lower cognitive test scores3–5. However, pTDP43's role in tri-glial dysfunction remains unclear. We hypothesize that nuclear astrocytic TDP43 loss alters astrocyte-to-microglial signaling, and results in tri-glial dysfunction. Here we examine glial pTDP43 subtypes in amnestic and non-amnestic clinical dementia syndromes with matched AD pathology.

Method: Paraffin embedded autopsy samples (hippocampus and middle frontal cortex) were stained using multiplexed immunofluorescence (Pu.1: microglia, GLUL: astrocytes, total TDP43), and imaged. Indica Labs Halo software was used to perform quantitative analyses on whole slide images. Cases were matched for AD pathology (low and high)6,7. Clinical phenotypes (AD dementia vs. behavioral variant frontotemporal dementia (bvFTD)) and pTDP43 status were compared (n=50). One-way ANOVAs and students' t-tests were performed to compare cell-type counts across groups. Spatial localization plots, NSInC colocalization indices, and Box plot comparisons were used to assess the impact of glial pTDP43 on the microenvironment.

Result: Hippocampal astrocyte counts are lowest in the setting of AD dementia with the highest AD pathology burden, and presence of co-existing pTDP43. Cases with high AD pathology had lower astrocyte counts when co-existing pTDP43 was present when comparing both AD dementia with pTDP43 vs. AD dementia without pTDP43 ($p=0.03$), and AD dementia with pTDP43 vs. bvFTD without pTDP43 ($p=0.05$).

Conclusion: Results support the role of astroglial heterogeneity contributing to white matter dysfunction via the selective vulnerability of specific brain regions to pTDP43 in astrocytes. Although contradictory to studies showing increased GFAP in mutant TDP43 mice8, lowest astrocyte counts were seen in individuals with AD dementia, highest burden of AD pathology, and presence of pTDP43. There are many potential explanations, including astrocyte heterogeneity.

Lay Language: Alzheimer's disease (AD) is a substantial cause of death and disability. In addition to the plaques and tangles that are classically observed in AD, other co-existing brain lesions also contribute to the development of cognitive impairment, such as pathologic trans-active response DNA-binding protein 43 (pTDP43). TDP43 plays a role in maintaining normal conditions in glial cells. In this project we looked at the expression of various glial cells in brains with and without AD as well as pTDP43. The results so far suggest that brains with both AD and pTDP43 pathology are most susceptible to glial cell loss.

Poster 15

Lorenzo's House

Diana Shulla Cose
Lorenzo's House

Background: More than 5 million people across America currently live with an Alzheimer's diagnosis. The Blue Cross Blue Shield Association Shield noted a 200% increase in younger-onset diagnoses from 2013 to 2017, indicating that younger-onset Alzheimer's is rapidly challenging society's typical narrative about who is impacted by conditions that primarily touch the lives of older adults. There is a serious lack of tailored younger-onset resources, leading to overwhelming isolation and burnout for carepartners, emotional trauma for (oftentimes still-school-age) children who have a parent with the diagnosis, and missed opportunities for connection, support, and increased quality of life for the person at the center of the diagnosis. The inconsistent availability of tailored programming compounds the physical and emotional toll of younger-onset Alzheimer's with each passing year. Many times, people with younger-onset may not be age-eligible for typical memory care spaces until they have been living with the diagnosis for several years.

Methods: Lorenzo's House is a startup in its second year of operation and aims to be a safe haven for younger onset families. Lorenzo's House was founded by Diana Shulla Cose after her husband was diagnosed with younger-onset Alzheimer's. Virtual and in-person services to families impacted by younger-onset Alzheimer's are offered with an innovative, holistic, comprehensive approach. The model includes four cores - Carepartner Companions, Youth Initiatives, Memory Academy and Respite & Healing Spaces.

Results: Lorenzo's House hosted and will host again this summer a Youth Summit with participants across 17 states, and in partnership with UChicago Medicine, Rush University Without Warning, Hilarity for Charity HFC, and Yale University Art Gallery. Bimonthly youth caregiver support groups are held specifically designed for young people ages 10-30 with a parent living with younger-onset Alzheimer's or other dementias. An infrastructure is being developed for Carepartner Companions, a peer-to-peer matching program. mirroring a proven model and in formal partnership with Imerman Angels to guide this work. In addition, a virtual Healing & Respite Series is taking shape with experiences such as a virtual social brunch on Saturdays for carepartner spouses, in addition to art, yoga and music. Finally, the discovery phase of a Memory Academy, an innovative day lab for individuals with memory loss, was recently launched. In just over a year of operation, there has been an astonishing demand for services and Lorenzo's House has become a force for inspiration, innovation, and hope.

Conclusion: Inspired by the remarkable enthusiasm from experts in the field, and inquiries from families diagnosed with younger-onset dementia, Lorenzo's House will continue the mission to bring light to one of aging's most devastating, isolating conditions. We expect this work will not only improve the outcomes for people with this diagnosis as they age, it will make a long-term impact on the memory care space by revolutionizing mindsets about how we support people and families living with dementia.

Lay Language: Youth are often affected by a parent's diagnosis at a neurobiologically vulnerable time in their lives. Youth whose parents have younger-onset Alzheimer's frequently don't know how to explain their experience as a care partner with their peers, leaving them isolated and managing the ongoing change by themselves. By creating spaces specifically catered towards these young care partners, we have radically shifted the journey of what younger-onset Alzheimer's looks like for children and young adults.

Poster 16

Alterations in Basal Ganglia Connectivity in Primary Progressive Aphasia Caused by Frontotemporal Degeneration and Alzheimer's Disease

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Background: Primary progressive aphasia (PPA) is a syndrome of progressive language impairment caused by neurodegenerative disease (Mesulam, 1982). There has not been many studies investigating the role of basal ganglia in PPA although they have been shown to be affected by the underlying causes of PPA: Alzheimer disease (AD) and frontotemporal degeneration (FTLD). Based on neuropathologic studies, the pattern of basal ganglia involvement is different in AD vs. FTLD with more basal ganglia inclusions seen in the latter (Novacs, 2015). In this study we investigated whether connectivity between basal ganglia (specifically caudate nucleus) and the language network is decreased in PPA, and if so, whether the impairment is more in agrammatic PPA (PPA-G; more commonly due to FTLD), versus logopenic PPA (PPA-L; more commonly due to AD).

Methods: This study consisted of 27 right-handed individuals with PPA-G, 16 right-handed participants with PPA-L, and 30 controls. Diagnosis of PPA subtype was made by clinical consensus using established criteria (Gorno-Tempini et al, 2011). Functional MRI were conducted for each participant and each scan was preprocessed via DPARSF-A v4.3, 2014 in the Statistical Parametric Mapping (SPM) based platform (Yan C and Zang Y, 2010). Two-sample t-tests, thresholded at FDR = 0.05, comparing voxel-wise whole brain connectivity of the caudate nucleus (CN) across PPA-G and PPA-L subtypes to controls. Caudate connectivity was investigated within both left and right hemispheres.

Results: In PPA-G patients, as compared to controls, connectivity between CN and the perisylvian region was decreased with more significantly decreased clusters within the left IFG and the left frontal lobe. Abnormal CN-perisylvian connectivity was worse in the left hemisphere when compared to the right. Subjects with PPA-L also showed decreased connectivity between CN and the perisylvian region compared to controls, however, there were more significantly decreased clusters in the temporoparietal junction (TPJ). Like PPA-G, abnormal perisylvian connectivity was worse on the left side. Comparisons between PPA-G and PPA-L showed no difference in connectivity between the two subtypes.

Discussion: Based on our results, in both PPA-G and PPA-L subtypes there is decreased n connectivity between the left CN and the perisylvian language region. However, the pattern of decreased connectivity in PPA-G and PPA-L were different. Decreased CN-perisylvian connectivity was localized more anteriorly (frontal) in PPA-G and more posteriorly (temporoparietal) in PPA-L. Contrary to our original hypothesis which stated that PPA-G would display more significant decreased CN-perisylvian connectivity, the analyses showed no significant difference between PPA-G and PPA-L. Abnormal connectivity between CN and the language network could be due to presence of pathology to either of the two regions. To determine whether our findings are due abnormal physiologic function within CN or the perisylvian region we plan to compare regional brain metabolism in each subtype, using FDG-PET imaging. Such multimodal analysis will help us better understand the underlying pathophysiology of PPA.

Lay Language: Primary progressive aphasia (PPA) is a syndrome of progressive language impairment caused by neurodegenerative disease. There has not been many studies investigating the role of deeper brain structures known as basal ganglia in PPA. In this study we investigate whether connection between basal ganglia and brain language region are increased and whether this pattern is different in different causes of PPA.

Poster 17

A transdiagnostic study of morphometric similarity networks in delusions in dementia

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Background: Delusions in dementia of the Alzheimer's type (DAT) and behavioral variant frontotemporal dementia (bvFTD) are distressing and lead to psychiatric misdiagnoses, and antipsychotic use has been found to predict mortality in dementia. We identified structural brain networks associated with delusions across bvFTD and DAT.

Methods: 534 individuals with T1w MRI from the Alzheimer's Disease Neuroimaging Initiative and Frontotemporal Lobar Degeneration Neuroimaging Initiative included 93 with clinical diagnosis of DAT, 62 bvFTD, 209 mild cognitive impairment (MCI) and 170 cognitively normal (CN). The Neuropsychiatric Inventory Questionnaire identified 31 individuals with delusions (1 CN, 6 MCI, 11 DAT, 13 bvFTD). Freesurfer calculated 7 statistics (e.g. cortical thickness) per 360 parcels. We created within-subject morphometric similarity networks for cognitive control (CCN), salience (SN) and default mode (DMN) subnetworks. We calculated Transitivity reflecting network segregation, and Global efficiency for network integration. The Network Based Statistics (NBS) toolbox identified nodes with reduced similarity in delusions using FDR correction.

Results: NBS identified a pattern of decreased nodal similarity across the whole brain in individuals with delusions, covarying demographics and dementia severity. 2 (delusions vs no delusions) x 2 (diagnosis) ANCOVAs found main effects of delusions on CCN transitivity ($p=.008$) and CCN global efficiency ($p=.019$), with both lower in individuals with delusions than without, regardless of diagnosis. There were no effects for the SN or DMN, and no main effect or interactions with diagnosis.

Conclusions: Delusions were associated with alterations to the cognitive control network, independent of diagnosis. This finding has implications for treatments focused on modifications of brain networks.

Lay Language: Delusions in dementia are distressing to patients and their caregivers, and treatments with antipsychotics can have harmful effects. We found that individuals with delusions have structural changes in a brain network that is important for higher-level thinking, regardless of the type of disease that caused the dementia. This finding could help to develop new treatments for delusions in individuals with dementia.

Poster 18

Brain Hypometabolism and Behavior Correlation in Primary Progressive Aphasia

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Background: Primary progressive aphasia (PPA) is a syndrome of progressive language impairment caused by neurodegenerative disease (Mesulam, 1982). PPA can present in at least three different subtypes (logopenic, PPA-L; agrammatic, PPA-G; and semantic, PPA-S). Using fluorodeoxy-glucose positron emission tomography (FDG-PET), research groups have previously shown distinct regional hypometabolism in PPA subtypes in three left-hemisphere language network regions (inferior frontal gyrus=IFG, temporoparietal junction=TPJ, and anterior temporal lobe=ATL) (Rabinovici et al., 2008, 2014). Though FDG-PET provides some insight into the underlying neurological drivers of language impairment present in PPA, less has been studied about the quantitative relationship between cortical metabolism and aphasic symptoms. The goal of this study was to examine severity of decrease in brain regional metabolic activity as it correlates with severity of language symptoms in PPA.

Methods: Thirty-three right-handed individuals with PPA (15 PPA-G, 5 PPA-L, 8 PPA-S, 5 PPA-Mixed) and 11 healthy controls participated in this study. Diagnosis of PPA subtype was made by clinical consensus using established criteria (Mesulam et l., 2009; Gorno-Tempini et al, 2011). PPA individuals also underwent a language assessment for naming (Boston Naming Test= BNT), grammar (Northwestern Anagram Test and Northwestern Assessment of Verbs and Sentences= NAT-NAVS), repetition (Western Aphasia Battery Repetition subtest= WAB-Rep), and word comprehension (Peabody Picture Vocabulary Test= PPVT). FDG-PET scans were performed for each participant, where fluorescently dyed glucose uptake was detected using PET. Images were preprocessed using Statistical Parametric Mapping 12 (SPM12) software, which generated a standardized uptake value ratio (SUVR) whole-brain map for each participant. Brain metabolic activity for each PPA individual was tested against the control group using a t-test. Voxel-wise correlation values between SUVR and language scores for language tests were calculated and then corrected for family wise error at $p<0.05$.

Results: In PPA-G individuals, FDG-PET maps showed a pattern of hypometabolism in left IFG. Decreased metabolic activity in PPA-L was mostly located within the left TPJ. In PPA-S group hypometabolism was localized mostly to the left ATL. Across PPA subtypes, decreased metabolism in left ATL correlated with lower scores on naming (BNT) and word comprehension (PPVT), while decreased metabolism in the temporoparietal junction correlated with lower repetition scores (WAB-Rep).

Discussion: All subtypes showed hypometabolism patterns consistent with what has been previously reported in literature. In addition to what had previously shown in the literature, we provided evidence that decreased metabolism in three major regions (IFG, TPJ, and ATL) correlate with measures of grammar, repetition, and naming/word comprehension. These findings are in line with previous research showing thinning of brain cortex (atrophy) within the same regions underly disorders of grammar, repetition, naming and word comprehension (Rogalski et al. 2011) strengthening our understanding the importance of these regions in supporting grammar, lexical/semantic and repetition processing. The next step is to compare patterns of hypometabolism with patterns of atrophy and abnormal resting connectivity to gain better understanding of pathophysiology of primary progressive aphasia. Better understanding of abnormal physiology will reveal more possibilities regarding therapeutic interventions for PPA.

Poster 18 cont.

Lay Language: Primary progressive aphasia is a syndrome of language impairment caused by diseases of brain degeneration, such as Alzheimer's disease. Though many different language issues fall under the umbrella of "aphasia", the difficulties an individual patient is dealing with are varied. In our study, these differences were quantified by looking at differences in scores on various language evaluations. We compared these behavioral scores to how much activity is present in different brain areas. This comparison gives us insight into the underlying relationship between what's going on in the brain and an individual's specific behavior profile. Put simply, a patient's scores on specific language tests can to some degree predict the location of decreased activity in that patient's brain. Specifically, we found evidence that decreased brain activity in three important brain language regions correlate with measures of grammar, word repetition, and word comprehension. This builds on current knowledge by growing our understanding of these regions and their role in language. As this understanding continues to grow, we hope it will ultimately offer more possibilities for therapeutic intervention.

Poster 19

Class 1 Histone Deacetylases Regulate Memory Function in Mouse Models of Aging and Alzheimer's Disease.

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Background: Studies have demonstrated that epigenetics plays a vital role in both aging and Alzheimer's disease (AD) pathogenesis, however, whether epigenetic dysregulation during aging can initiate AD development and/or exacerbate AD progression remains unclear. Given aging is the major risk factor of AD, it is critical to determine the epigenetic alterations occurring during aging and how these changes influence AD pathogenesis.

Methods: In this study, young (3 months old), middle-aged (12 months old) and aged (18 months old) APP/PS1 mice (APPswePsen1de9; B6.Cg-Tg(APPswe,PSEN1dE9)85Dbo/Mmjax transgenic strain, Jackson Laboratory), and WT littermates including males and females were used. Different aged group animals underwent a series of behavioral tests to evaluate different memory domains including recognition memory (Novel Objective Recognition test), short-term working memory (Y-maze test), and long-term reference memory (Morris water maze test). After behavioral testing, the prefrontal cortex (PFC) and hippocampus were collected for biochemical assessment to determine the dynamic changes of class 1 histone deacetylases (HDACs) and histone acetylation marks on specific gene promoters in these areas during aging and AD progression using RT-PCR and ChIP assays.

Results: Our behavioral results demonstrated a decline in recognition and short-term working memory WT mice at 18 months of age. A significant decline in all memory domains was found in both 12- and 18-month APP/PS1 mice compared to WT controls, however, 18 months of age APP/PS1 mice showed exacerbated recognition and short-term working memory deficits. For the biochemical assays, in the hippocampus, WT mice showed an increase of HDAC 2 levels, along with increased abundance of HDAC 2 at synaptic gene promoters (NR2A, GluR1, GluR2, PSD95) only at 18 months of age. However, APP/PS1 mice showed significant increase of HDAC 2 levels and abundance at synaptic gene promoters at both 12- and 18-month of age compared to WT controls and aging further exacerbated this effect as 18-month APP/PS1 mice display the highest levels. There were no changes in global expression or abundance of HDAC 1 and 3 between genotype and age in this area. In the PFC, there was no significant changes in global HDAC1, 2, and 3 mRNA expression levels, but an increased abundance of HDAC 3 was seen at synaptic gene promoters in 12- and 18-month APP/PS1 mice compared to controls, with the highest levels in 18-month APP/PS1 mice in this area. Given HDAC's regulate histone acetylation, we measured histone acetylation mark H3K9ac, a common histone modification involved in transcriptional processes, at synaptic gene promoters, and found a decrease of H3K9ac in the WT mice at 18 months of age, but this decrease was more significant in both 12- and 18-month APP/PS1 mice compared to WT controls and aging further exacerbated this effect as 18-month APP/PS1 displayed the lowest levels of H3K9ac.

Conclusion: Although this project is ongoing, our current findings suggest a differential HDAC regulation of memory function between normal aging and AD. Ongoing studies are using a pharmacological approach via histone deacetylase inhibitors to further confirm such mechanism that HDACs, especially HDAC 2 and 3, regulate histone acetylation and synaptic gene expression related to memory in aging and AD. Future studies will also investigate differential HDACs impact on the neuropathology in AD.

Lay Language: Alzheimer's disease (AD) is an aging-dependent disorder, but the relationship between aging and AD remains unclear. This study addresses the relationship of aging and AD at an epigenetic level. Epigenetics is a process that influences gene expression but not structure. Current results indicate that the changes in the epigenetic landscape are differentially regulated in brain regions associated with memory function in a mouse model of AD. In addition, we found various forms of memory deficits in our mouse model of AD, which aging further worsened such deficits. These results suggest that aging may worsen various forms of memory in our mouse model of AD. Our ongoing studies involve the investigation of epigenetic mechanisms surrounding memory and other AD-related processes.

Poster 20

Differential glial protein expression in the setting of co-existing Alzheimer's disease neuropathologic change and pathologic TDP43

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Background: Under normal conditions, trans-active response DNA-binding protein 43 (TDP43) is predominantly confined to the nucleus. It has been proposed that pathologic cytoplasmic accumulation of TDP43 within astrocytes and microglia leads to proinflammatory activation and neuronal dysfunction, contributing to cognitive impairment in neurodegenerative conditions, such as Alzheimer's disease. Objective: To systematically compare 73 proteins in astrocytes and microglia from hippocampal autopsy samples in four groups: Aβ+/Tau-/TDP-, Aβ+/Tau-/TDP+, Aβ-/Tau+/TDP-, Aβ-/Tau+/TDP+.

Methods: Study groups included individuals with matched levels of either Tau tangles or Aβ plaques, but with differing TDP43 status (TDP+ vs. TDP-). Nanostring's GeoMx™ Digital Spatial Profiling platform was used to quantify proteins in hippocampal samples. Cell-type specific antibody "masks" were applied with ionized calcium binding adaptor molecule 1 (Iba1) used for the detection of microglia, and glial fibrillary acidic protein (GFAP) used for the detection of astrocytes. SPSS v28, Mann-Whitney U tests were used for group comparisons (significance<0.05).

Results: Comparisons of Iba1+ microglia (n=1478) in Aβ+/Tau- samples revealed increased microglial C4B, CD68, HLA-DR, and P2RX7 in the Aβ+/Tau-/TDP+ group when compared to the Aβ+/Tau-/TDP- group. Notably, C4B is a complement protein involved in phagocytic microglial pruning. GFAP+ astrocytes (n=1780) showed decreased ApoE in the Aβ+/Tau-/TDP43+ group when compared to the Aβ+/Tau-/TDP- group. Comparisons of Iba1+ microglia (n=1226) in Aβ-/Tau+ samples revealed decreased Cathepsin-D in the Aβ-/Tau+/TDP+ group when compared to the Aβ-/Tau+/TDP- group.

Conclusion: Using a spatial proteomic technique, we highlight increased pro-inflammatory microglial proteins (e.g. C4B, CD68, HLA-DR, P2RX7) and decreased astrocytic ApoE in the presence of pathologic TDP43 and co-existing Aβ plaques. Alternatively, decreased microglial Cathepsin-D in the presence of pathologic TDP43 and co-existing Tau tangles is suggestive of impaired microglial autophagy. In summary, we have identified numerous changes in protein expression profiles that offer insight into the mechanistic contributions of TDP43 in the development of dementia.

Key words: TDP43, Neurodegeneration, Tau, Amyloid Beta, Inflammatory Protein

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Lay Language: Under normal conditions, transactive response DNA-binding protein 43 (TDP43) is predominantly confined to the nucleus. It has been proposed that abnormal accumulation of TDP43 within cytoplasm of brain cells leads to inflammation , contributing to cognitive impairment in neurodegenerative conditions, such as Alzheimer's disease. Our study showed that the level of inflammatory proteins increased in the presence of pathologic TDP43 in brain cells and these changes increase the risk of dementia.

Poster 21

Differential Phagocytosis of Fibrillar and Soluble Oligomeric Aβ by Primary Human Microglia in Culture

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The amyloid-β (Aβ) peptide accumulates in plaques in the brains of patients with Alzheimer's disease (AD) and contributes to disease pathogenesis. Aβ forms aggregates that assume various conformations based on size and arrangement of oligomers. Large aggregates of Aβ can form fibrils, with abnormal β-pleated sheet conformation, that deposit in compact, neuritic plaques, and have been shown to exert toxic effects on neurons. Smaller soluble Aβ oligomers disperse across various brain compartments and are proposed to cause synaptotoxicity. One mechanism of Aβ clearance from the brain involves phagocytosis and degradation by microglia, the resident macrophages of the central nervous system. While it is known that microglia phagocytose Aβ, it is not known whether they phagocytose fibrillar and soluble oligomeric Aβ with the same level of efficiency. Furthermore, the ability of cultured primary human microglia to phagocytose each Aβ conformation has not be investigated. In this study we investigated phagocytosis of fibrillar and soluble oligomeric Aβ by cultured primary human microglia. Microglia were isolated and cultured from postmortem human brains using protocols in routine use at our laboratory. Cells were seeded in multi-chamber slides and treated with 0, 2.5, 5 and 10 μg/ml of fibrillar or soluble oligomeric Aβ conjugated to the 5-FAM fluorescent tag suspended in sterile BSA. The optical density of 5-FAM fluorescence in individual microglia was determined in triplicate experiments as a measure of Aβ phagocytosis. Both fibrillar and soluble oligomeric Aβ were phagocytosed by microglia in a dose-dependent manner. However, soluble Aβ oligomers were phagocytosed more efficiently that fibrillar Aβ. At every dose, optical density of 5-FAM soluble oligomeric Aβ was significantly greater than the control condition ($p<0.001$), while this difference reached significance only at the highest dose of fibrillar Aβ ($p<0.001$). Furthermore, at 5 and 10 μg/ml concentrations, optical density of 5-FAM soluble Aβ oligomers was significantly greater than fibrillar Aβ. 5-FAM fibrillar Aβ was often observed in clumps extracellularly, and apposed to microglia membranes. These findings indicate that human microglia phagocytose soluble Aβ oligomers much more readily when compared with fibrillar Aβ. Continuous interaction of extracellularly accumulating fibrillar Aβ with receptors on microglia membranes is likely to contribute to the inflammatory activation of microglia observed in AD.

Lay Language: The amyloid- β peptide (Aβ), which is deposited as plaques in the brains of patients who suffer from Alzheimer's disease, can aggregate and form different structures, including small soluble oligomers and large fibrils. One mechanism of Aβ clearance (method of clearing Aβ) from the brain involves microglia, which are the immune cells of the brain. In this study we investigated phagocytosis of Aβ by microglia, a process involving engulfment and digestion of invading elements, abnormal proteins, and cell fragments. (Could this be re-phrased as: In this study, we investigated a process called phagocytosis, which involves microglia engulfing and digesting invading elements, abnormal proteins, and cell fragments?) We found that human microglia are more efficient in clearing (small) soluble Aβ when compared with large Aβ fibrils. These results indicate that microglia inability to properly remove large Aβ fibrils is one cause of this protein depositing in the brain (Amyloid plaques in the brain?). Enhancing uptake of small (soluble) Aβ oligomers from the brain may be of therapeutic value in (may help prevent/treat) Alzheimer's disease.

Poster 22

Increased Accumulation of Synaptic Proteins in Microglia Suggests Enhanced Synaptic Pruning in Frontotemporal Lobar Degeneration with TDP-43 Proteinopathy

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Frontotemporal lobar degeneration (FTLD) is characterized by degeneration of the frontal and temporal lobes and abnormalities in behavior and/or language. Synaptic loss is among the first changes that is associated with cognitive decline in aging and in the dementia of Alzheimer's disease (AD). It has been suggested that aberrant synaptic pruning by microglia may contribute to the loss of synapses in AD. We have observed decreased cortical levels of synaptic proteins in FTLD with TDP-43 pathology (FTLD-TDP). In this study we investigated accumulation of synaptic proteins in microglia as a surrogate marker for potential increased synaptic pruning in behavioral variant FTD with TDP-43 pathology. Fixed tissue from middle frontal gyrus of seven participants was used in this study (Control, n=3, mean age=84; FTLD-TDP, n=4, mean age=68). Paraffin-embedded sections underwent double immunofluorescent processing to concurrently visualize microglia and synaptic proteins in the same section. Specific antibodies to the presynaptic protein synaptophysin, the postsynaptic protein PSD-95, and the dendritic spine protein spinophilin were used to visualize immunoreactivity for each synaptic protein. Antibodies to Iba1 or HLA-DR were used to visualize microglia. Reagents were chosen to fulfill the requirement of double immunofluorescent staining that the two antibodies are raised in different species. Modified unbiased stereological methods were used for quantitative analysis using the StereoInvestigator software. Counts were obtained from three types of synaptic staining in microglia: 1) microglia with no synaptic protein immunoreactivity, 2) microglia with punctate synaptic protein immunoreactivity, and 3) microglia with large aggregates of synaptic proteins. The three patters of synaptic proteins in microglia were observed in all cases and for all synaptic proteins. Significantly larger numbers of microglia displayed aggregates of PSD-95 than punctate staining in FTLD-TDP participants ($p<0.05$), whereas there were no significant differences between the two patterns in control participants ($p>0.05$). Furthermore, the percentage of total microglia that contained aggregates of synaptophysin was significantly larger in FTLD-TDP participants when compared with control participants ($p<0.03$). The number of microglia containing aggregates of spinophilin was significantly higher than microglia containing punctate spinophilin staining in both FTLD-TDP and control participants ($p<0.02$). These results point to accumulation of synaptic proteins in microglia, with larger aggregates predominating for some synaptic proteins in FTLD-TDP. One potential interpretation of these results is increased synaptic pruning. Mechanistic studies in animal models are required to determine whether aberrant synaptic pruning is indeed a feature of TDP-43 proteinopathies.

Lay Language: Microglia are immune cells of the brain that internalize and digest invaders, abnormal proteins, and cell fragments. Under normal conditions, they are known to engulf and digest synapses, the points of contact between nerve cells that are involved in neural communication. Some scientists think that microglia display excessive engulfment of synapses in dementia, causing synaptic loss and resulting in cognitive abnormalities. To test this possibility, we investigated the presence of synaptic proteins in microglia in frontotemporal lobar degeneration with TDP-43 pathology. We found significantly greater proportion of microglia with clumps of synaptic proteins when compared with microglia containing small specks of synaptic proteins in frontotemporal dementia when compared with normal individuals. These findings suggest that overactive microglia's removal of synapses may participate in synaptic loss and cognitive abnormalities in frontotemporal dementia with TDP-43 pathology.

Poster 23

Intra-network Functional Connectivity of the Default Mode Network in SuperAgers

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Objective: Memory decline in late life is a hallmark of aging, yet there are older individuals that have maintained youthful memory abilities. SuperAgers are 80+ year-olds with episodic memory performances at least as good as cognitively average 50- to 60-year-olds. The current study explored whether resistance to age-related shifts in resting state networks (RSNs) may contribute to the superior memory performance of SuperAgers.

Methods: Intra-network functional connectivity of the default mode network (DMN) was compared between 25 SuperAgers and 16 cognitively average elderly controls using resting state functional MRI (rs-fMRI) scans. Classification of SuperAgers or cognitively average elderly controls (Controls) was determined based on measures of episodic memory, executive functioning, verbal fluency, and picture naming (for details see Harrison et al., 2012). In addition, inclusion criteria for this study required stable cognitive status across two visits (on average 1.76 years apart). T1-weighted structural and rs-fMRI (Siemens Trio 3T) scans from a single visit were used in our analysis. Region-to-region FC was calculated for five DMN atlas-based regions: the inferior parietal lobe (IPL), posterior cingulate cortex (pCC), medial prefrontal cortex (mPFC), parahippocampal gyrus (PHC), and middle temporal gyrus (MTG). Functional connectivity was compared across groups using two-sample independent t-tests.

Results: Group differences in FCs between the 5 DMN regions of interest (ROIs) were nonsignificant. However, FC (reported as r-z values) between medial ROIs (pCC-mPFC & mPFC-PHC) trended greater in SuperAgers than Controls (group-Δ=0.07 [$t(40)=-1.62$, $p=0.11$] & group-Δ=0.09 [$t(40)=-1.72$, $p=0.09$], respectively).

Conclusion: Although intra-network FC differences within the DMN of SAs and Controls did not reach significance, medial hubs may have subtle strengths in functional connectivity favoring SuperAgers. Age-related weakening of the pCC and mPFC functional connectivity is well documented and relates to performance decline on episodic memory tasks in elderly adults. The trends found in our study appear to agree with rs-fMRI aging literature. Our results will inform future analyses into the functional connectivity patterns underlying SuperAgers' superior memory performance.

Summary: Complaints of memory decline in late life are common but not universal. SuperAgers are adults 80-years or older with better-than-expected memory abilities. In fact, SuperAgers have memory performance at least as good as adults in their 50's and 60's. The Northwestern SuperAging Study is exploring what factors contribute to SuperAgers' superior memory performance. Brain networks are regions of the brain that tend to talk with one another. The strength of their communication fades with age and has been related to decline in memory performance. In our study, we investigated whether SuperAgers were able to maintain connections between brain regions better than normal agers (controls). We used a special type of brain scan called functional magnetic resonance imaging (fMRI) to measure the integrity of a brain network called the default mode network (DMN). In a comparison between SuperAgers and controls, we were unable to find any significant differences in DMN integrity. However, we did notice that regions of the DMN near the midline

Poster 23 cont.

of the brain tended to show stronger connections in SuperAgers than controls. Our findings suggest that SuperAgers may have subtle preservation of brain networks, but more analyses are required to be certain.

Lay Language: Complaints of memory decline in late life are common but not universal. SuperAgers are adults 80-years or older with better-than-expected memory abilities. In fact, SuperAgers have memory performance at least as good as adults in their 50's and 60's. The Northwestern SuperAging Study is exploring what factors contribute to SuperAgers' superior memory performance. Brain networks are regions of the brain that tend to talk with one another. The strength of their communication fades with age and has been related to decline in memory performance. In our study, we investigated whether SuperAgers were able to maintain connections between brain regions better than normal agers (controls). We used a special type of brain scan called functional magnetic resonance imaging (fMRI) to measure the integrity of a brain network called the default mode network (DMN). In a comparison between SuperAgers and controls, we were unable to find any significant differences in DMN integrity. However, we did notice that regions of the DMN near the midline of the brain tended to show stronger connections in SuperAgers than controls. Our findings suggest that SuperAgers may have subtle preservation of brain networks, but more analyses are required to be certain.

Poster 24

Nasal Exhaled Breath Proteome in Alzheimer's Disease

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Olfactory sensory neurons are unique in that their peripheral ends touch air in the nose, and their central ends touch the brain. When air moves through the nasal cavities during natural breathing, it comes into contact with olfactory sensory neurons. We hypothesized that during exhalation, turbulent air flowing past the olfactory neurons could volatilize proteins from the surface of the olfactory epithelium into the exhaled breath, which could then be captured and analyzed. Using a new nasal breath collection technique, we are analyzing nasal and oral breath samples collected from healthy young controls, healthy age-matched controls, and Alzheimer's disease patients. Preliminary results suggest differences in several proteins associated with mitochondrial function in Alzheimer's Disease patients compared to age-matched controls. Furthermore, we found differences in proteins associated with normal aging. These preliminary results will guide further analyses into specific proteins that change on breath in Alzheimer's Disease.

Lay Language: Here, we used a non-invasive biological sampling method—exhaled breath condensate collection—to study proteins in breath across healthy and diseased populations. We are looking for differences in the presence and levels of proteins across three sets of participants: healthy young participants, healthy aged participants, and patients with Alzheimer's Disease. The goal is to identify differences in protein composition on breath that could lead to novel biomarkers that are early predictors of Alzheimer's disease. In the long term, results could also help us understand mechanisms of the disease. Preliminary results show differences between Alzheimer's and the other groups, as well as differences between aged and young participants.

Poster 25

Northwestern Alzheimer's Disease Research Center (NADRC) Clinical Core

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Introduction: The Northwestern Alzheimer's Disease Research Center (NADRC) is entering its 27th year of funding from the National Institute on Aging (NIA). The NADRC is one of 38 sites in 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 specturm to support clinical and basic research on memory and aging. The Clinical Core follows research participants annually and collects, stores, and disseminates clinical data, brain imaging scans, and biological samples. The data collected by each ADRC (the Unifrom Data Set, UDS) are contributed to the National Alzheimer Coordinating Center to all large-scale, multicenter research collaborations. Over the past year, the Clinical Core has worked closely with the 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.

Methods: The Clinical Core recruits individuals with different forms of cognitive impairment and dementia (e.g. memory dementia, primary progessive aphasia, behavioral variant frontotemporal dementia, due to Alzheimer's disease, Pick's disease, Lewy body disease and other neurodegenerative diseases). Participants and designated study partners complete annual assessments using the methods of the UDS (demographic information, health and family history, and neuropsychological tests. If eligible, participants also undergo MRI, amyloid (Florbetaben-PET), and tau (Flortaucipir-PET) scans so researchers can investigate brain structure, connectivity, and amyloid and tau proteins. Blood is collected to supportstudies 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.

Results: Since 1996, the Clinical Core has enrolled more than 2,300 participants; 467 are active with 11% followed for 10 or more years. Since the onset of the COVID-19 pandemic, the Clinical Core has completed over 622 remote research visits. Approximately 243 research participants and their care partners were surveyed about the impact of COVID-19, as well as their technology accessibility. Additionally, we were able to accept brain donations from 38 research participants in 2021.

Conclusions: The Clinical Core is a valuable resource for researchers on Alzheimer's disease, frontemporal dementia, primary progressive aphasia and age-related cognitive change. For many, participation is a lifelong, meaningful commitment and promotes national and international research efforts.

Lay Language: The Clinical Core is a longitudinal study that collects information on research participants yearly, following their neuropsychological testing scores throughout their participation. Our data includes participants across the cognitive aging spectrum to study memory and aging. Information collected from this study is shared across different collaborators associated with the National Alzheimer Coordinating Center. Participants are also able to donate their brain for research as the culminating aspect of their dedication to Clinical Core.

Poster 26

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

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Mesulam Center for Cognitive Neurology & Alzheimer's Disease, Northwestern University, Chicago, IL, USA

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 Diseas 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 37 US states, Canada, Singapore, and Spain have enrolled in PPA studies at the Mesulam Center. Participants visit Chicago every 1-2 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. 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 web-based speech-language therapy and educational research programs, which are tailored to the needs of people living with PPA. These life-enrichment interventions use innovative technology to improve access to specialized care.

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

Funding from the National Institutes of Health, Illinois Department of Public Health, Run4Papa campaign, Association for Frontotemporal Degeneration, and generous personal donations have 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 that is identifiable by the progressive loss of language. Our research program brings participants with PPA to Chicago for neuropsychological testing, MRI scans and PET scans every 1-2 years. Some Mesulam Center research participants also take part in web-based speech-language therapy and educational research programs. The Mesulam Center works to advance PPA research through a collaborative program aimed at studying, educating, and improving treatment for individuals living with PPA and their families.

Poster 27

Synaptic Integrity in Cognitive SuperAgers

Regina Taefi, Kenton Haynes, Ivan Ayala, Erfan Taefi, Cameron B. Swope, Margaret E. Flanagan, Tamar Gefen, Emily Rogalski, M.-Marsel Mesulam, Changiz Geula

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Decline in memory is a normal characteristic of aging. However, there is an alternative trajectory that resists the cognitive changes of normal aging. Our center has been engaged in investigations of a subset of individuals over the age of 80 with performance on tests of episodic memory equal to or better than individuals 20-30 years their junior. We have used the term "SuperAger" to refer to such individuals. SuperAgers show larger cortical volumes, less ApoE4, more von Economo neurons, and fewer instances of Alzheimer's disease (AD) pathology than their cognitively average peers. Synaptic loss is one of the strongest correlates of cognitive decline in the normal elderly and in AD. The purpose of this study was to investigate whether greater synaptic integrity is a characteristic of SuperAger brains. The status of synaptic proteins in individuals with a range of cognitive performance was studied. We examined the levels of the presynaptic protein synaptophysin and the postsynaptic density protein 95 (PSD-95) in fresh frozen tissue homogenates of the middle frontal gyrus (MFG) and the superior temporal gyrus (STG) of SuperAgers, cognitively average elderly, and AD patients (N ≥ 3 per group) using Western blot analysis and specific antibodies. Optical densities of bands were determined using the Image J software, and synaptic protein levels were expressed as percentage of the housekeeping protein GAPDH. As expected, levels of synaptic proteins were decreased in AD brains when compared with controls (0-31%). Interestingly, results indicated higher levels of synaptophysin in MFG (21%), and of PSD-95 in STG (51%) in SuperAgers when compared with cognitively average elderly. While preliminary, these findings suggest that enhanced integrity of cortical synapses, assessed through levels of synaptic proteins, may contribute to the SuperAging phenotype.

Lay Language: Synapses are points of contact between nerve cells that allow neural communication. The goal of this experiment was to determine whether there are differences in the levels of synaptic proteins in cognitive SuperAgers when compared with cognitively normal elderly. Research had already shown that synaptic proteins decrease in those with Alzheimer's Disease. The initial results suggest that SuperAgers may have higher levels of synaptic protein than their cognitively average peers. These findings suggest that integrity of synapses is an important factor in preservation of cognitive abilities in old age.

Poster 28

The effect of antibiotic-mediated gut microbiome alteration on astrocyte morphology in the APP/PS1 mouse model of Alzheimer's disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the most common cause of dementia in the elderly for which there are no disease-modifying therapies. AD is characterized pathologically by the presence of amyloid beta (Aβ) plaques and neurofibrillary tau tangles in the brain. Additionally, neuroinflammation in the form of microgliosis and astrogliosis is a crucial hallmark of AD. Recent genome-wide association studies have identified numerous AD genetic risk factors that are associated with innate immunity. However, the mechanisms governing glial activation in the context of AD pathogenesis are still unclear. Greater understanding of these mechanisms could lead to the development of novel disease modifying therapies.

Astrocytes are key players in the neuroinflammation of many neurodegenerative diseases. Activated microglia release interleukin 1α, TNFα, and complement factor C1q, which convert homeostatic astrocytes into neurotoxic reactive astrocytes. These neurotoxic astrocytes, which are defined by unique morphology and gene expression profile, can kill neurons and modulate Aβ deposition in AD models.

The gut microbiome (GMB), comprised of trillions of bacteria that inhabit the human intestine, has been implicated in numerous disease etiologies. In AD, it has been shown that perturbation of the GMB via an antibiotic (abx) cocktail causes a reduction in Aβ plaque deposition in the brains of APPPS1-21 (Appps1) male mice a well-studied animal model of AD. Additionally, abx causes a shift in microglial reactivity from disease associated microglial (DAM) phenotype to a homeostatic phenotype. Ab deposition and DAM phenotype were restored to control levels when abx-treated mice received fecal matter transplants (FMT) from mice with an unperturbed GMB. These results suggest that abx-induced reduction of Ab pathology is mediated by the GMB. Furthermore, these results suggest that the GMB can influence microglia, which can in turn influence Aβ deposition. Although the role of the GMB on microglial response in AD has been explored, the role of the GMB in modulating astrocyte phenotype and astrocyte-mediated Aβ deposition has not been investigated.

Herein, we have investigated the effect of abx-mediated GMB manipulation on astrocyte morphology in Appps1 mice. To investigate astrocyte morphology, we performed immunofluorescence staining on tissue sections containing cortex for Aβ, GFAP to mark astrocytes, and complement component C3 to mark reactive astrocytes. Then, we captured confocal z-stacks of periplaque astrocytes in abx and vehicle control treated mouse cortex. IMARIS software was used to make 3D reconstructions of the periplaque astrocytes and quantify morphological parameters. We report that abx treatment in Appps1 male mice results in a smaller astrocyte cell body, an increase in astrocyte processes, increase in process length, increase in terminal and branching points, reduced complement component C3 positive area, and reduced Aβ load compared to vehicle control treated Appps1 male mice. However, there is no difference in morphological phenotypes in abx-treated female Appps1 mice compared to vehicle control treated female mice. Our results indicate that GMB manipulation alters astrocyte morphology from a reactive, activated phenotype to a homeostatic phenotype. This suggests that the GMB might have a role in activating astrocyte-mediated neuroinflammation in AD.

Poster 28 cont.

Lay Language: My project is to understand how the gut microbiome (GMB), which consists of trillions o microorganisms that live in the human digestive tract, regulates the structure and functionality of a cell type in the brain called astrocytes. Astrocytes are crucial for normal brain function. However, in Alzheimer's disease (AD) and other neurodegenerative disorders, astrocytes change their functionality to become inflammatory and release substances that kill other brain cells and lead to the progression of AD . Another cell type in the brain called microglia sends signals to astrocytes which leads to their inflammatory transition in Alzheimer's disease. Recent studies from our collaborators at UChicago suggest that the GMB controls microglia functionality in AD mouse models. Therefore, we predict that the gut microbiome will regulate astrocytes through microglia in AD models. Our results do in fact suggest that altering the gut microbiome does change astrocyte activity in AD. Our next steps will be to determine whether the GMB alters astrocytes directly or through microglia. If the GMB is altering astrocyte functionality which can lead to the progression of AD then the GMB or astrocytes may be viable therapeutic targets for AD.

Poster 29

Ubiquitin Immunoreactivity Identifies TDP-43 Inclusions and Marks Cortical Neurons Destined to Degenerate in a Mouse Model of Frontotemporal Lobar Degeneration

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Accumulation of TDP-43 inclusions is one of the pathological hallmarks of frontotemporal lobar degeneration (FTLD). Mouse models have shown that overexpression of wild-type or mutant human TDP-43 (hTDP-43) can result in the formation of inclusions and neuronal loss. In the human brain, TDP-43 inclusions are strongly ubiquitinated. The purpose of this study was to investigate ubiquitination within cortical neurons in a conditional transgenic mouse model expressing wild-type hTDP-43 under the control of tetracycline operator sequences (tTA). tTA and hTDP-43 transgenic mice were bred on 129SVE and FVB backgrounds respectively. Double transgenic pups were weaned at 21 days of age, at which time expression of TDP-43 was initiated. Brains were examined after 14 days, 8 weeks and 24 weeks of TDP-43 expression. Consistent with our previous findings, small round intraneuronal inclusions containing phosphorylated TDP-43 were observed in many cortical areas after 14 days of TDP-43 expression. After 8 weeks, the number of these inclusions was significantly reduced, and by 24 weeks, no inclusions were observed. This course of events matches the progression of cortical atrophy and decreased density of neurons we observed in these animals at 8 and 24 weeks of expression. After 14 days of expression, ubiquitin immunoreactivity visualized small round cytoplasmic inclusions identical to those observed with phosphorylated TDP-43 staining. In addition, intense ubiquitin immunoreactivity was observed in a subset of cortical neurons. At 8 weeks of TDP-43 expression, ubiquitin-stained inclusions and neurons with intense ubiquitin staining displayed a substantial decrease, and by 24 weeks none could be identified. Thus, as is the case in FTLD, TDP-43 inclusions in transgenic mice are highly ubiquitinated. Furthermore, prominent cytoplasmic ubiquitin immunoreactivity is present in neurons that contain inclusions. Ubiquitin immunoreactivity appears to mark neurons that are destined to degenerate, resulting in disappearance of inclusions with dying neurons and cortical atrophy.

Lay Language: TDP-43 is a protein that accumulates in abnormal clusters within the brains of some individuals who suffer from frontotemporal dementia (FTD). In such patients, a protein called ubiquitin, which is involved in the process of degradation of abnormal proteins, binds to TDP-43. The goal of this experiment was to investigate whether ubiquitin is present in nerve cells that accumulate abnormal clusters in a mouse model with an overabundance of TDP-43. Consistent with the findings in the human brain, these mice showed intense ubiquitin accumulation in some of the nerve cells and as clusters within them. Of interest, these darkly stained neurons that were filled with high amounts of TDP-43 and ubiquitin disappeared as the nerve cells containing them degenerated. These findings indicate that ubiquitin is a marker of neurons that degenerate in FTD with TDP-43 pathology.

Poster 30

Unique Combinations of Structural MRI-Derived Shape Morphometric Features Improves Discriminability of FTLD Phenotypes

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Objective: Frontotemporal lobar degeneration (FTLD) is associated with diverse clinical phenotypes underlain by multiple disease pathologies and genetic mutations. However, traditional structural MRI analyses lack sensitivity and specificity for discriminating FTLD syndromes early in disease. Here, we use data-driven methods to extract a concise set of MRI-derived shape morphometric features and examine the discriminatory capability of their unique combinations in four FTLD clinical phenotypes.

Participants & Methods: 190 patients with sporadic or familial FTLD spectrum disorders (i.e., behavioral variant (bvFTD, n = 107), non-fluent variant primary progressive aphasia (nfvPPA, n = 27), semantic variant primary progressive aphasia (svPPA, n = 12) and progressive supranuclear palsy (PSP, n = 44)) and 27 controls without pathogenic mutations from the ALLFTD cohort were evaluated. MRI data were preprocessed with FreeSurfer software and four cortical measures were extracted and indexed to a normalized surface atlas: cortical thickness (CT), surface area (SA), surface curvature (SC) and jacobian white matter surface metric distortion (JW). For all phenotypes, each shape morphometric feature was contrasted with controls using linear models adjusted for age and gender. Principal component analysis (PCA) was then applied and the discriminatory power based on individual and combined measures was assessed using logistic regression and 10-fold cross-validation.

Results: Figure 1 displays FDR-corrected T-scores of differences from controls in each morphometric feature in bvFTD. Results reveal complementary patterns of CT, SA, SC and JW for each phenotype, with greatest differences observed in CT across groups. In Figure 2, we display the features derived from the PCA, weighted by eigenvector coefficients, in bvFTD. In Figures 3-6, receiver operating characteristic curves for individual and combined measures alongside areas under the curve (AUCs) are shown for each phenotype. In bvFTD, nfvPPA and PSP, the superior model included CT and SC at AUCs of 88.3, 87, and 78.6, respectively. For svPPA, the superior model included CT, SC and JW at an AUC of 85.6.

Conclusions: Integrating additional MRI-derived surface morphometric features improved classification performance in all FTLD phenotypes. The principal component analysis-based approach indicated distinctive brain regions contribute to discrimination for each shape feature, suggesting they may reflect unique aspects of neurodegeneration across groups. This method could prove invaluable in future studies for early detection of FTLD phenotypes

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Lay Language: There are many types of frontotemporal dementia (e.g., behavioral variant, non-fluent variant primary progressive aphasia, semantic variant primary progressive aphasia, progressive supranuclear palsy). However, early in the disease, researchers aren't yet able to tell which dementia someone has based on traditional MRI techniques. We wanted to improve discriminability between dementias by extracting unique features of brain shape that aren't typically analyzed in an MRI. We found that brain thickness, brain curvature, and brain white matter changes vastly improve discrimination between frontotemporal dementias. This study is important because it could be used to improve early detection of frontotemporal dementia.

Poster 31

Elucidating the contribution of amyloidogenic APP processing to Alzheimer's disease related impaired synaptic proteostasis

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Alzheimer's disease (AD) is a debilitating neurodegenerative disease and the most prevalent form of dementia. AD is a proteinoapthy best characterized by two misfolded and aggregated proteins: amyloid-beta peptides ($A\beta_{42}$) and hyperphosphorylated tau. Although $A\beta_{42}$ accumulation, produced by amyloidogenic processing of the amyloid precursor protein (App), is one of the earliest pathological events, the initial trigger in this proteostasis imbalance remains unknown. To investigate proteostasis impairments in AD, our research utilizes metabolic pulse-chase (pc) labeling with stable isotopes in combination with quantitative mass spectrometry (MS) based proteomic analysis. Using this strategy with the recently developed APP knock-in (*App* KI) mouse models of amyloid pathology, we discovered that axon terminals are selective sites of impaired protein degradation, specifically synaptic vesicle (SV) and their associated proteins. This alteration occurred before elevated $A\beta_{42}$ levels. This is important as it suggests we have identified the earliest synaptic impairment in protein turnover that occurs before amyloid pathology. Additionally, we recently discovered that targeting SVs with small molecule antiepileptic drug levetiracetam in *App* KI mice mitigated AD pathology by decreasing $A\beta_{42}$ accumulation via alteration of amyloidogenic processing of App. Therefore, we aimed to uncover the mechanism for impaired synaptic proteostasis in models of preclinical amyloid pathology that may underlie the initial trigger in the cascade of pathologies seen in AD. One mechanism for protein turnover at the presynapse is thought to rely on the ubiquitin-proteasome system (UPS) marking proteins for transport out of the axon terminal to the soma for degradation. The central hypothesis of this study is that amyloidogenic processing of App leads to a deficit to this key process resulting in an impairment to axon terminal proteostasis. To address if disrupting this process impairs axon terminal protein turnover, I first investigated in vivo if the UPS is disrupted in *App* KI brains using previously pc-ed tissue and advanced MS techniques for isolation and quantification of ubiquitinated proteins. Next, I determined that blocking retrograde transport pharmacologically disrupts axon terminal protein degradation. Additionally, using lentiviral overexpression *in vitro*, I found that amyloidogenic App processing leads to impaired axon terminal proteostasis. Finally, I determined that disruptions in SV transport result from amyloidogenic processing of App *in vitro*. Taken all together, these findings are significant as it contributes to the understanding of the initial mechanisms of AD-relevant protein degradation impairments, crucial to determining the cause of protein accumulation in AD which currently remains unknown.

Lay Language: Alzheimer's disease (AD) is the most prevalent form of dementia and is characterized by the accumulation of two proteins; primarily amyloid beta (Aβ) in plaques and then eventual tau in tangles. It has been well studied how the Aβ protein is toxic and build up creates havoc in neurons in the brain leading to AD pathology. However, the initial reason that Aβ peptides are not degraded and therefore accumulate is not known. We previously identified a select impairment in the degradation of specific proteins in an AD mouse model. This work aims to unravel the mechanism of identified early dysfunction in protein degradation. As we currently do not know what triggers initial protein accumulation in AD, developing a profound understanding of mechanisms of protein degradation impairments could help to bolster therapeutics and further our ability to target early AD.

Poster 32

Northwestern Alzheimer's Disease Research Center Neuroimaging Biomarker Core

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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. Neuroimaging is focused on the spectrum of extraordinary cognitive aging to dementia, including the frontotemporal lobar degeneration-spectrum of disorders. The Imaging Core contains multimodal data from MR and PET scans that provide optimal quantitative information on brain structure (MPRAGE), white matter properties (FLAIR), axonal pathways (diffusion MR), resting state hemodynamic fluctuations for establishing functional connectivity (rsfMRI), cerebral blood flow (PASL), amyloid (Florbetaben PET), tau (Flortaucipir PET) binding and glucose (18F-FDG – PET) uptake. Neuroimaging data are available to enhance diagnostic characterization of the participants and to enrich projects of our collaborators.

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. Neuroimaging is focused on the spectrum of cognitive aging from extraordinary to dementia. The Imaging Core contains multimodal data from scans that provide optimal quantitative information on a variety of brain properties such as structure, regional connectivity, and abnormal protein buildup.

Poster 33

Cognitive SuperAging: A model to explore resilience and resistance to aging and Alzheimer's disease

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Many individuals have come to expect that memory and thinking abilities will begin to deteriorate with advancing age. Though such decline is common, the SuperAging Project at the Northwestern University Mesulam Center for Cognitive Neurology and Alzheimer's Disease has found that some individuals are able to maintain high levels of cognitive function despite older age. The Northwestern SuperAging Project has identified a group of individuals over the age of 80 with exceptional episodic memory ability that is at least as good as that of individuals 20-30 years their junior. The study seeks to identify factors that help individuals avoid age-related cognitive decline and memory loss.

To qualify as a SuperAger, individuals must 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.

Participants visit our Center every two years for a comprehensive cognitive evaluation, structural and functional MRI scans, and blood collection. SuperAgers also complete questionnaires investigating personality, family history, and daily health habits. 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.

Since its inception, the SuperAging Project has used a multidisciplinary approach to study successful cognitive aging. Findings suggest that SuperAgers resist the cortical brain atrophy that is typically associated with normal aging. They show significantly lower density of brain pathology associated with Alzheimer's disease in the entorhinal and anterior cingulate cortices, and display a higher density of von Economo neurons, a specialized neuronal population implicated in social intelligence, in the anterior cingulate. The study has wide ranging implications and may ultimately provide clues on how to slow or avoid age-related cognitive decline. This year we have been working to expand SuperAging research by launching four additional SuperAging research enrollment sites across North America under a recently awarded U19 grant from the NIA/NIH.

Lay Language: Many individuals have come to expect that memory and thinking abilities will begin to deteriorate with advancing age. Though such decline is common, the SuperAging Project at the Northwestern University Mesulam Center for Cognitive Neurology and Alzheimer's Disease has found that some individuals are able to maintain high levels of cognitive function despite older age. The study has wide ranging implications and may ultimately provide clues on how to slow or avoid age-related cognitive decline.

Poster 34

The AHEAD Study

Brittanie Muse, MSPH, CCRC; Jelena Pejic; Shea Gold, MA; Sydney Orr; Ian Grant, MD; Joshua Cahan, MD; Allison Lapins, MD; Malik Nassan, MD

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The AHEAD 3-45 Study is a Phase III multi-center, placebo-controlled study that will evaluate whether an investigational drug can slow or stop brain changes due to Alzheimer's disease. The investigational drug, BAN2401 (lecanemab), is a new treatment that may reduce amyloid plaque in the brain. This study will enroll approximately 1,400 participants at 100 global research sites across two cohorts: (1) individuals with intermediate amyloid and (2) individuals with elevated amyloid. Participation lasts for 4 years and involves biweekly or monthly infusions, clinical and cognitive assessments, biomarker and genetic tests, brain imaging scans (including PET and MRI), and cerebrospinal fluid (CSF) analysis. Enrollment for this trial is open and we continue to screen and enroll additional participants age 55 to 80.

Lay Language: The AHEAD 3-45 Study is a Phase III multi-center, placebo-controlled study that will evaluate whether an investigational drug can slow or stop brain changes due to Alzheimer's disease.

Poster 35

The VIVA-MIND Study

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The VIVA-MIND Study is a Phase II multi-center, placebo-controlled study that will evaluate whether an investigational drug can slow or stop brain changes due to Alzheimer's disease. The investigational drug, varoglutamstat, is a new oral treatment that may reduce amyloid plaque in the brain. VIVA-MIND is specifically designed for Early Alzheimer's disease (Early AD) targeting individuals with Mild Cognitive Impairment (MCI) or mild Alzheimer's disease (AD) at ages 50 to 89. This study will enroll approximately 180 participants at 30 research sites. Participation lasts for at least 8 months and involves clinical and cognitive assessments, biomarker tests, MRI brain scans, and cerebrospinal fluid (CSF) analysis. Enrollment for this trial is open and we continue to screen and enroll additional participants.

Lay Language: The VIVA-MIND Study is a Phase II multi-center, placebo-controlled study that will evaluate whether an investigational drug can slow or stop brain changes due to Alzheimer's disease.

Poster 36

Feasibility of comprehensive heart-brain MRI for investigating aging

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Introduction: Increased aortic pulse wave velocity (PWV) has been linked with dementia risk in aging adults. However, mechanisms underlying heart-brain hemodynamic coupling and effects on the brain remain unclear due to non-trivial challenges of measuring both heart and brain in a single MRI exam. 4D flow MRI is uniquely poised to systematically evaluate complex hemodynamics along the heart-brain pathway, including aortic PWV and intracranial pulsatility. Owing to advancements in imaging acceleration, 4D flow MRI can be acquired in approximately 7 minutes (heart) and 10 minutes (brain) supporting feasibility of comprehensive heart-brain MRI evaluation in a 1-hour exam.

Methods: Heart-brain MRI was acquired in 12 healthy participants (3 young adults <45 years, 5 midlife 45-65 years, 4 later life >65 years) at 3T (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany). Exam included prototype free-breathing whole heart 4D flow MRI (venc=120-150 cm/s, compressed sensing R=10.2), intracranial dual-venc 4D flow MRI (venc=50-60 cm/s and 100-120 cm/s, k-t GRAPPA R=5) and structural neuroimaging (T1-MPRAGE, T2W, high resolution hippocampal T2W, T2-FLAIR, TOF MRA). Participants were screened for history of cardio- and cerebrovascular problems that may influence blood flow. Whole heart 4D flow MRI data was used to evaluate aortic PWV. Intracranial 4D flow MRI data was used to evaluate pulsatility index (PI) for intracranial vessels of interest including the internal carotid arteries (ICAs). Structural neuroimaging data was reviewed by an expert neuroradiologist for brain atrophy, hippocampal atrophy, white matter lesions and narrowed arteries.

Results: Aortic PWV was significantly increased with age ($R^2=0.36$, $p=0.038$) (n=12). For ICA PI, a significant relationship with age was observed only for the midlife and later life participants ($R^2=0.73$, $p<0.01$) (n=9). There were no neuroradiological findings of brain atrophy in gray matter or white matter overall or in hippocampus; ventricular dilation, where present, was considered acceptable for participant age. There were no neuroradiological findings for narrowed arteries. White matter hyperintensities were rated clinically mild in 5 of the 12 participants (1 young, 2 midlife and 2 later life participants); all were subclinical mild punctate foci (<2 mm diameter) with no confluence.

Conclusion: This study demonstrates heart-brain MRI as a promising tool for comprehensive evaluation of hemodynamic coupling along the entire heart-brain pathway. This approach provides new capabilities for capturing advanced hemodynamic measures of aortic PWV and cerebrovascular pulsatility together with a neuroradiological evaluation in a 1-hour MRI exam. This approach may yield new insights concerning mechanisms of hemodynamic coupling in aging.

Lay Language: Studies have linked cardiovascular risk factors and dementia, including that caused by Alzheimer's disease. However, the underlying details of how this can occur remain unclear. Imaging tools can be very helpful in improving our understanding of these mechanisms. Advanced technologies, such as 4D flow MRI, can be used to analyze blood flow in the heart and large vessels of the body, including the brain. However, the heart and brain are usually evaluated separately on scanners dedicated to either heart or brain imaging. This preliminary study describes a novel combination of blood flow imaging of the heart and brain, together in one imaging session ("heart-brain MRI"), in order to better characterize relationships with age. Our findings demonstrate heart-brain MRI as a promising tool for evaluation of blood flow from the heart to the brain.

Poster 37

A randomized controlled trial of a positive affect skills intervention to reduce stress in family caregivers of individuals with Alzheimer's disease: Protocol and design for the LEAF 2.0 study

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Caring for a loved one with Alzheimer's Disease can be stressful. Family caregivers of individuals with dementia face detriments to both emotional and mental health due to the daily stressors they face. Studies are increasingly demonstrating the unique importance of positive emotions in coping with stress and depression (Folkman, 1997). However, few have examined the benefits of interventions that target positive emotions for caregivers of individuals with a chronic and debilitating disease such as Alzheimer's. This poster presents the design and methods of LEAF 2.0 (Life Enhancing Activities for Family caregivers), a randomized controlled trial (RCT) of a positive affect skills intervention for family caregivers of individuals with Alzheimer's disease. LEAF 2.0 builds on previous randomized trial findings from LEAF 1.0 that demonstrated that facilitated web delivery of the LEAF positive affect skills decreased depression in dementia caregivers. However, facilitated delivery of interventions is resource intensive and may limit dissemination and scalability. Thus, in the present study, we will compare the effects of two different delivery methods of the skills-based intervention on AD caregiver well-being: (1) by trained facilitators via six one-on-one Zoom video sessions, similar to LEAF 1.0, or (2) via an online, self-guided version on the study website, which aims to make the program more widely accessible in the future if its effects are comparable to the facilitated version. The control group is an emotion reporting/waitlist that receives the intervention after 7 months in one of the two ways listed above. Follow-up assessments are conducted post-intervention and at about every two months during the fourteen-month study involvement. Outcomes include caregiving burden, positive emotion, perceived stress, depression, and anxiety), caregiving self-efficacy, positive aspects of caregiving, quality of care, and AD patient quality of life. We hypothesize that LEAF will positively influence these caregiving outcomes and that the effects will be mediated through increased caregiver positive emotion.

Lay Language: Life Enhancing Activities for Family caregivers (LEAF) is a positive emotion skills program that teaches coping skills to family caregivers of individuals with Alzheimer's disease. We know that caregiving for a family member can be extremely stressful, and the LEAF program offers an online, accessible format that aims to lower caregiver stress and increase positive mood by teaching skills such as personal strengths, mindfulness, and positive reappraisal. We want to show caregivers that positive emotion can co-exist in the midst of stressful, difficult times. This study is ongoing, and we do not have results yet.

Poster 38

Caffeine consumption, dementia and age-related neuropathology

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Background: Acute studies of caffeine intake support a cognitive benefit but whether habitual intakes protect against dementia onset and cognitive decline is inconclusive. We examined the association between caffeine intake and cognitive impairment. Caffeine-neuropathology correlations and interactions with lifestyle and genetic factors impacting caffeine metabolism and response were also tested.

Methods: We included 888 participants aged 59+ from the Rush Memory and Aging Project (MAP) and 303,887 participants aged 55+ from UK Biobank (UKB). MAP participants took part in annual cognitive testing. Diagnosis of dementia was based on clinical neurological examination and standardized criteria. A subset provided postmortem tissue for neuropathologic evaluation for common age-related diseases (e.g. Alzheimer's disease, Lewy bodies, vascular). For UKB, dementia was determined by linked hospital and death records. Self-reported caffeine intake was estimated using food-frequency questionnaires in both cohorts. Cox proportional hazard ratio (HR), regression and mixed models were used to examine associations of caffeine intake with incident dementia, cognitive decline, and neuropathology.

Results: In MAP, compared to £100mg/d, caffeine intake >100mg/d was associated with a significantly higher HR (95%CI) of all-cause [1.35(1.03, 1.76)] and Alzheimer's [1.41(1.07,1.85)] dementia. Caffeine intake was not associated with cognitive decline. In UKB, compared to £100mg/d, the HRs (95%CI) of all-cause dementia for consuming 100£200, 200£300, 300£400 and >400mg/d were 0.83 (0.72, 0.94), 0.74 (0.64, 0.85), 0.74 (0.64,0.85) and 0.92 (0.79,1.08), respectively. Similar results were observed for Alzheimer's dementia. In MAP, caffeine intake was inversely associated with postmortem Lewy bodies but no other age-related pathologies. Caffeine intake >100mg/d was associated with lower neocortical type Lewy bodies [Odds ratio (95%CI): 0.40 (0.21, 0.75)].

Conclusions: Caffeine intake was inconsistently associated with clinical dementia; potentially explained by cohort differences in underlying dementia etiology. Lewy bodies may link caffeine to lower risk in some persons.

Lay Language: Caffeine intake was inconsistently associated with clinical dementia in a US community and UK Biobank; potentially explained by study differences in underlying dementia etiology. Lewy bodies may link caffeine to lower risk in some persons

Poster 39

Characterization of Distinct Neuropsychiatric Trajectories in FTLD-tauopathies

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Introduction: Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disease commonly caused by 3R (Pick's disease, "PiD") or 4R tauopathies (corticobasal degeneration, "CBD" and progressive supranuclear palsy, "PSP"). FTLD-tauopathies can lead to language decline in primary progressive aphasia (PPA) or personality/comportmental changes in behavioral variant frontotemporal dementia (bvFTD). Patients diagnosed with these distinct dementias often develop debilitating neuropsychiatric symptoms (NPS) over time. This study examined NPS in PiD, PSP, and CBD early and late in the disease course, as well as their change over time, in participants with PPA or bvFTD.

Methods: Participants (N=44) with clinical diagnoses of PPA (N=23) or bvFTD (N=21) and autopsy-confirmed PiD (N=16), PSP (N=11), or CBD (N=17) were identified from the Mesula Center for Cognitive Neurology and Alzheimer's Disease research programs. NPS (total=12) were examined at initial and final visit (M=0.76 years before death; SD=72) with the Neuropsychiatric Inventory–Questionnaire (NPI-Q) and placed into 3 domains based on co-occurrence: 1) Behavioral/Comportmental (apathy, disinhibition, motor disturbance, and appetite changes), 2 Affective (depression, anxiety, elation, and irritability), and 3) Disruptive/Psychotic (delusion hallucinations, agitation, and nighttime behaviors). Linear and logistic regressions controlling for disease duration and dementia severity (CDR global score) compared group differences in average percentage of total and domain-specific symptoms endorsed at initial and final evaluation between PiD, PSP, and CBD with PPA or bvFTD.

Results: Across all participants with FTLD-tau, the most common symptom at initial presentation was irritability (50%) whereas apathy (68%) predominantly emerged at final evaluation. Psychosis (e.g., hallucinations) was nearly absent at both timepoints, ranging from 0-5%. Total NPS increased in CBD and PiD over time (by ~11%) and was driven by high endorsement of Behavioral/Comportmental symptoms; compared to CBD and PiD, total symptom endorsement in PSP remained relatively stable ($p<0.01$). Regardless of pathology, Behavioral/Comportmental symptoms increased in both bvFTD and PPA over time, but the magnitude of this was significantly higher in PPA (by ~25%; $p<0.05$).

Conclusions: FTLD-tauopathies can present with distinct neuropsychiatric phenotypes. PPA and bvFTD, though clinically distinct at onset, appear to converge in their neuropsychiatric presentations close to death. Findings highlight the prognostic value of identifying and monitoring NPS in non-amnestic neurodegenerative dementias.

Lay Language: Primary progressive aphasia (PPA) is a language-based dementia, whereas behavioral variant frontotemporal dementia (bvFTD) is characterized by personality changes. PPA and bvFTD can be caused by different brain pathologies that are discovered at autopsy. For a substantial proportion of patients with PPA and bvFTD, symptom arise when abnormal clumps of a protein known as tau accumulate and spread in the brain. This study examined psychiatric symptoms in participants diagnosed with PPA or bvFTD due to different tau pathologies. Psychosis (e.g., hallucinations) was relatively uncommon overall. Initially, symptoms like apathy and disinhibition were more common in bvFTD than in PPA, but these groups became more similar as their diseases progressed. Psychiatric symptoms at early and late stages of disease also varied between participants with different tau pathologies. Findings suggest that characterizing psychiatric symptoms in PPA and bvFTD at different stages may help us predict underlying brain pathology and optimize treatment strategies.

Poster 40

Communication Bridge: A person-centered Internet-based intervention for individuals with Primary Progressive Aphasia

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The diagnosis of primary progressive aphasia (PPA) is made when a relatively isolated progressive impairment of language occurs as a result of neurodegenerative disease. Although there are no pharmacological treatments for PPA, speech-language therapy (SLT) is an intervention that can offer individuals with PPA a means to compensate for their communication difficulties. Unfortunately, individuals with PPA are under-referred for SLT treatment. Other barriers individuals with PPA may face in receiving care include limited availability of speech-language pathologists (SLPs) who specialize in PPA, and limited insurance coverage of SLT. In hopes of circumventing these barriers, the Communication Bridge study provides web-based SLT to individuals with PPA and their care partners residing both nationally and internationally. The study aims to understand SLT effects on communication abilities in people living with PPA and to determine optimal intervention strategies for this population.

Results from a pilot study (CB1) of 57 participants with PPA demonstrated that functional gains and increased confidence in communication after eight weeks of SLT were maintained for the following four months. The next phase of Communication Bridge (CB2) is currently underway in a randomized controlled trial that delivers web-based SLT to individuals with PPA and their communication partners. Participants will be in the study for approximately one year and take part in 15 SLT sessions, five SLP evaluations, and a web-based activity regimen to support communication through a custom web-application on a computer provided for the length of the study.

Enrollment of 95 individuals with mild PPA and their communication partners for CB2 occurred from May 2018 through March 2022. Participants are from 25 U.S. states, one U.S. territory, three Canadian provinces, England, and New Zealand. Study retention has been high. To enroll in the study, participants had to be English speaking, be in the mild stages of PPA, have adequate experience with computers, and have a communication partner who was willing to participate.

Pilot testing for the next phase of Communication Bridge (CB3 Pilot) was started in July 2021 to identify the feasibility of using an iPad for intervention and incorporating social work sessions into the program. There are currently three dyads enrolled in the study, all of which completed the randomized controlled trial (CB2). Participants receive ten speech therapy sessions, four social work sessions, five speech therapy evaluations, and five social work evaluations over the course of approximately 13 months. All participants use a study-provided iPad to connect to sessions and complete an app-based language program.

Lay Language: The Communication Bridge program connects individuals with mild primary progressive aphasia (PPA) and their communication partners to speech-language pathologists as part of a year-long research study. Participants complete 15 speech therapy sessions, five evaluations, and a weekly web exercise regimen during the course of the study. The next phase of Communication Bridge is currently being piloted to understand the feasibility of adding social work sessions to the program and transitioning the study to an iPad tablet. The Communication Bridge program connects individuals with mild primary progressive aphasia (PPA) and their communication partners to speech-language pathologists as part of a year-long research study. Participants complete 15 speech therapy sessions, five evaluations, and a weekly web exercise regimen during the course of the study. The next phase of Communication Bridge is currently being piloted to understand the feasibility of adding social work sessions to the program and transitioning the study to an iPad tablet.

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Lexical and semantic fluency in pathologically confirmed early Alzheimer's disease

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Background: The typical clinical presentation of Alzheimer's disease (AD) involves initial decline in memory related to neurodegenerative changes in the mesial temporal lobes, with eventual development of multi-domain impairment as the disease spreads to frontal and language networks. Verbal fluency (i.e., the ability to rapidly generate words) involves both language and frontal executive abilities and is often affected relatively early in the disease process. The timing of decline in different aspects of verbal fluency may inform our understanding of the course of progression of underlying brain changes. Previous studies have found that semantic fluency (i.e., the ability to generate words within a category) tends to be more impaired than lexical fluency (i.e., the ability to generate words that start with a specific letter) in patients clinically diagnosed with AD (e.g., Henry, Crawford, & Phillips, 2004). However, differential decline in semantic versus lexical fluency has not been studied in pathologically confirmed AD. In this study we sought to evaluate lexical and semantic fluency performance in patients with pathologically confirmed AD.

Method: This study included 26 patients (Mage = 68.33, SDage = 7.90; 27% female; MEducation = 17 years) seen at the Mesulam Center Neurobehavior and Memory clinic with primary memory deficits and pathologically confirmed Alzheimer's disease (i.e., CSF [n=21], amyloid PET [n = 1], autopsy [n = 4]). Only patients with mild impairment (CDR < 1.5) were included. All patients were administered semantic and lexical fluency at either a neurology visit or as part of a neuropsychological evaluation. Age- and education-adjusted z-scores for semantic and lexical fluency were derived (Tombaugh, Kozak, & Rees, 1999).

Results: Age, years of education, and CDR score were not significantly associated with either semantic or lexical fluency scores (ps > .05). Raw lexical fluency scores (M = 14.69, SD = 5.03) were significantly lower than semantic fluency scores (M = 11.04, SD = 4.73), consistent with patterns of performance in the general population. Semantic and lexical fluency scores were moderately correlated (r = .50, p = .009). Average standardized scores for both semantic and lexical fluency scores fell within the low average range; there was not a significant difference between standardized scores for semantic and lexical fluency, p > .05. A higher percentage of scores on semantic fluency fell in the impaired range (i.e., z < -1.4) compared to lexical fluency scores (semantic: 34.6%; lexical: 23.1%). Interestingly, a smaller percentage of scores on lexical fluency than semantic fluency was in the average range or above; the mode for lexical fluency was in the low average range and the mode for semantic fluency was in the average range.

Discussion: Consistent with prior findings in clinically diagnosed AD, the current study found that more patients had impaired semantic fluency scores than impaired lexical fluency scores. However, standardized scores for lexical and semantic fluency were not significantly different. Additionally, there were subtle indications that fewer patients had lexical fluency scores that were average or above average than semantic fluency scores. These results indicate that there may be a different pattern of impairment in verbal fluency in pathologically confirmed compared to clinically diagnosed AD samples. Longitudinal studies may allow for a better understanding of the timing of decline in lexical and semantic fluency in AD and identify underlying neural substrates.

Lay Language: This project looks at a specific type of language ability—verbal fluency, or the ability to rapidly come up with words—in early Alzheimer's disease. Different types of verbal fluency are linked to different brain networks. Understanding the pattern of change in verbal fluency may help us better understand how Alzheimer's disease progresses through different parts of the brain. Our findings suggest that people with early Alzheimer's disease have more difficulty coming up with words in a certain category than words starting with a certain letter, but further research is needed to understand the timing of decline in these abilities.

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Neural Changes and Neuropsychiatric Symptoms in Amnestic Mild Cognitive Impairment

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Objective: Depressive symptoms and apathy are common in amnestic mild cognitive impairment (aMCI) and are associated with increased risk of conversion to Alzheimer's disease (AD). The shared neuropathological model of neuropsychiatric symptoms (NPS) in AD suggests that symptoms of depression and apathy represent noncognitive manifestations of neuropathological changes. Neurodegeneration in aMCI occurs in areas of the brain that support emotion regulation, including the limbic system and prefrontal control regions. Depression and apathy in aMCI have been linked to atrophy in the limbic system and prefrontal cortex and reduced connectivity in resting-state networks. However, it is not yet established whether neural changes in emotion centers in the brain predict symptoms of depression and apathy in persons with aMCI, or whether neural changes in the limbic system and prefrontal cortex are associated with higher risk of conversion from aMCI to AD. The current study utilized longitudinal clinical and neuroimaging data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to determine whether change in neural structure and function in emotion centers predicted symptoms of depression and apathy in aMCI and conversion to AD.

Participants and Methods: Participants were 563 subjects from the ADNI database that were diagnosed with normal cognition (CN) or mild cognitive impairment (MCI) at enrollment (n = 224 CN; n = 339 MCI), and who had at least two study timepoints with imaging data (median visits = 5). Participants enrolled in ADNI undergo an initial screening assessment, during which demographic, clinical, medical, and neuropsychological information is collected. Participants also undergo a baseline 3T fMRI within two weeks of the initial screening visit. Subsequent study visits are conducted at every six months from baseline. Depressive symptoms were assessed with the Geriatric Depression Scale (GDS) and apathy was assessed with the Neuropsychiatric Inventory Questionnaire (NPI-Q). Structural and functional MRI data used in the current study were derived from standardized imaging datasets.

Results: Multilevel longitudinal structural equation models determined associations between neural changes, neuropsychiatric symptoms, and progression of disease. Cortical volume in emotion centers in the brain decreased over time, with faster atrophy in the MCI group compared to the CN group. The slope of change in neural markers was not associated with the slope of change in depressive symptoms or with the presence versus absence of apathy. There was partial evidence for neural markers predicting later symptoms of depression and apathy. Apathy, slope of change in depressive symptoms, and speed of atrophy in the amygdala and cingulate cortex predicted progression of disease.

Conclusion: Results provide preliminary support for the shared neuropathological model of NPS in aMCI, although certain findings may suggest a more complex relationship between neural changes and depressive symptoms. Early neuropathological changes in emotion circuitry may serve as prognostic markers for persons with aMCI.

Lay Language: Neuropsychiatric symptoms, or symptoms that involve emotional and behavioral changes, are common in Alzheimer's disease even very early in the disease process. However, the cause of these types of symptoms is poorly understood and treatments are not very effective. Some previous research has suggested that emotional/behavioral symptoms may be caused by underlying brain changes in parts of the brain that contribute to emotional and psychological well-being. This project looks at the relationship between two specific types of emotional symptoms-apathy and depression-and changes in the emotion centers of the brain. Results of this study provide some support for the idea that emotional/behavioral changes in very early Alzheimer's disease are linked to changes in emotion centers in the brain.

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NIH Toolbox Episodic Memory Measure Differentiates Older Adults with Exceptional Memory Capacity from those with Average Memory

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Background: "SuperAgers" are older adults over the age of 80 with exceptional memory abilities, at least as good as cognitively average individuals in their 50s and 60s. The purpose of this study was to compare SuperAgers with their cognitively normal-for-age peers on subtests of the NIH Toolbox Cognition Battery (NIHTB-CB), including a test of nonverbal picture sequence memory.

Methods: Participants categorized as SuperAgers (n=46) or as cognitively average-for-age (n=31) completed standard neuropsychological tests of attention, executive functions, language, and episodic memory. SuperAgers are classified by a delayed recall score on the Rey Auditory Verbal Learning Test that falls at or above the average score of 50 to 65-year-old norms, while scores in non-memory domains must be at least in the average range for age. Multivariable linear regression models were used to examine differences across subtests between the groups.

Results: After controlling for IQ, gender, age, and education, Picture Sequence Memory Scores were higher in Super Agers than in the cognitively normal-for-age group ($p = 0.007$). However, the groups did not differ in their scores on all other Cognition measures.

Conclusions: Findings from this study demonstrated that SuperAgers scored higher on a test of nonverbal memory in the NIHTB-CB compared to cognitively average-for-age peers, while groups scored similarly on non-memory domains. These findings demonstrate that memory abilities in SuperAgers are strong not only on tests of verbal memory, but on nonverbal measures, as well. These findings extend the potential to identify SuperAgers with more efficient assessment methods.

Lay Language: Older adults with exceptional memory abilities, termed "SuperAgers" have been characterized by an established test of memory that relies heavily on verbal abilities. Our project examined their performance compared with cognitively average older adults on the NIH Toolbox, which is a computerized set of tests that includes a test of nonverbal memory. We found that SuperAgers had stronger performance on this test compared to cognitively average older adults, showing that Super Agers have superior memory in not only verbal but also nonverbal memory abilities. This study also adds to the utility of using the NIH Toolbox to measure cognitive functioning in the oldest of old age groups.

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PPA Tele-Savvy: Piloting an Online Intervention with Care Partners of Persons Living with Primary Progressive Aphasia

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Background: Primary Progressive Aphasia (PPA) brings unique challenges for caregiving families. Most evidence-based interventions available to dementia caregivers do not match their needs for tailored psychosocial support.

Method: This pilot study funded by the Emory University Roybal Center is an adaptation of the evidence-based online psychoeducation program (Tele-Savvy) to address the unique challenges facing informal caregivers of those living with PPA and to help these caregivers achieve competence in their role. Using focus group data from PPA caregivers previously enrolled in Tele-Savvy, the program curriculum was adapted to address caring for persons living with PPA and offered online for seven 90-minute weekly videoconference sessions with weekly homework, coaching, and debriefing sessions. Nine spousal caregivers were recruited to pilot the revised curriculum. We engaged in a process of Formative Evaluation throughout the delivery of the PPA Tele-Savvy program to assess and integrate feedback throughout the intervention. We will look pre/post at the effects of the intervention on PPA knowledge, mood, caregiver burden, perceived stress, competence, quality of life and relationship, and host a focus group discussion 4 weeks post-intervention.

Result: The 7-week course was partially completed at the time of abstract submission. Interim results show caregiver appreciation of and desire for increased opportunities to engage with course material and other participants. These preliminary findings indicate participants are finding value in the PPA Tele-Savvy program's PPA-specific psychoeducational and relational components.

Conclusion: We aim to demonstrate the feasibility of offering an online PPA caregiver intervention tailored to meet their specific needs.

Lay Language: Tele-Savvy is an online program that provides education and support to care partners of people living with dementia. We updated the Tele-Savvy program to address the unique needs of care partners of people living with Primary Progressive Aphasia (PPA), a type of dementia that begins with challenges with language and the ability to communicate. We launched our seven-week 'PPA Tele-Savvy' program with nine care partners of people with PPA, hosting weekly 90-minute videoconference sessions and weekly homework assignments. We asked for feedback and updated our approach throughout the program to make sure it was as useful as possible. We will analyze pre- and post-tests to measure how the program changed PPA knowledge, mood, caregiver burden, perceived stress, caregiving skills, and quality of life and relationships. We will also hold a focus group with participants to get more feedback. The PPA Tele-Savvy was not finished when we submitted this abstract, but responses so far show that PPA care partners are finding benefits in participating in this program tailored to meet their specific needs.

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Psychosocial Pathway

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Background: Longitudinal research on trajectories of cognitive aging depends on retaining participants, which can be quite challenging. Research participants with and without cognitive impairment and their support networks may experience psychosocial barriers to ongoing research participation over an extended period of time. Since the Center's inception (1996) and as part of enrollment into Clinical Core, Mesulam Center social workers, in the model of the "therapeutic encounter," have conducted a psychosocial assessment of persons living with dementia (PLWD) and their support networks at no cost. This is done with the goal of ascertaining how the PLWD and their support networks are coping, determining needed resources, and providing education, counseling and assistance in developing a long-term plan tailored to their needs. The social work team is trained and equipped to assess, educate and counsel individuals presenting with Alzheimer's dementia, younger and middle onset dementias and those presenting with language (PPA), visuospatial (PCA), or behavioral (bvFTD) presentations. These research participants and families have access to this psychosocial support throughout their research participation. Since 2019, we have worked to standardize this Psychosocial Pathway approach and test it as a method for research retention.

Method: Mesulam Center social work staff developed a training program to educate research staff to identify psychosocial factors that have the potential to influence participant retention and well-being. When a psychosocial concern is identified by research staff, they refer the patient and family to the social work team who reviews and responds to the referral. A social worker then contacts the research participant and/or family for psychosocial assessment, planning and resource linkage so they can find appropriate help for the purposes of facilitating participant retention. A tracking mechanism for referrals and outcomes has been developed.

Results: Since the development of the Psychosocial Pathway in 2019, Mesulam Center social workers have responded to 67 referrals. For each accepted referral, ORE Core social workers provided therapeutic and logistical support, resulting in the retention of all participants. Common concerns directly related to research activities include decline in cognitive scores, barriers to brain donation, and potential discontinuation due to incomplete or missed study activities (e.g., study partner unreliable, missing visits). Other concerns include anxiety, depression, caregiver burden, family conflict, abuse, neglect, suicidal ideation, homicidal ideation, and difficulty accessing community resources. In each referral involving brain donation, ORE Core social workers assessed barriers to brain donation and coordinated with Clinical Core to provide additional information and/or support. In both referrals involving a decline in cognitive scores, Mesulam Center social workers coordinated with Clinical Core to provide connection to clinical care.

Conclusion: The Psychosocial Pathway successfully facilitates retention of research participants through psychosocial assessment, planning, and resource linkage.

Lay Language: Research participants with and without cognitive impairment may experience psychosocial barriers to ongoing research participation, particularly over the course of longitudinal research studies. Mesulam Center research staff are trained to identify psychosocial factors that affect participant retention and well-being. For each accepted referral, a social worker contacts the research participant and/or family for psychosocial assessment, planning and resource linkage so they can find appropriate help and this, in turn, facilitates participant retention. The *Psychosocial Pathway* successfully facilitates retention of research participants by providing psychosocial support, in the model of the "therapeutic encounter."

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Northwestern Alzheimer's Disease Center Outreach, Recruitment and Engagement Core (ORE CORE) 2021–22

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Introduction: The Northwestern Alzheimer's Disease Research Center's Outreach, Recruitment and Engagement Core goals are to 1) provide targeted community engagement and recruitment to meet the needs of Center priorities; 2) optimize the retention of research participants through novel psychosocial interventions; and 3) initiate and coordinate public education programs in conjunction with city, state and national entities.

Methods: We achieve these goals through the establishment of collaborative local community partnerships, particularly with underrepresented groups (URGs), recognition and support for the psychosocial needs of research participants, and the design and evaluation of innovative programs that support patients' and families' strength and resilience.

Results: Highlights of the past year include:

Community Engagement

- Our outreach/educational activities reached over 1000 community members
  - South Loop Village: Memory Cafes and Brain Health Strategies Webinar
  - Carter G Woodson Library: Town Hall Meeting and Holiday Sing-a-long
  - Arts for Brain Health Coalition: Holiday Sing-a-long, Facebook Posada Decembrina, Theater Care Package, Recipe and Coloring Book and Libations Coloring Book
  - Francis J Atlas Center: Brain Health Strategies Webinar
  - Healthy Washington Heights Webinar
  - Far South Side Coalition Facebook Live Event for Caregivers
- Mesulam Center monthly E-news Connections and annual print newsletter

Quality of Life Enhancement

- Offer 3 monthly care partner support groups: 1) Primary Progressive Aphasia, 2) Frontotemporal Dementia, 3) Younger Onset Dementia
- The Buddy Program is celebrating its 25th year. This academic year we paired 20 first-year medical students and their mentors for a total of 314 since the program's inception.
- Developed a Psychosocial Pathway for all research participants of the Northwestern Alzheimer's Disease Research Center (see separate abstract)
- Developed *PPA TeleSavvy*, an online intervention with care partners of persons living with Primary Progressive Aphasia (see separate abstract)

Education

- Hosted our 27th Annual Alzheimer Day May 2021
- Mesulam Center Seminar Series showcased the work of local, national, and international speakers

Conclusion: The ORE Core engages with communities for the purposes of raising public awareness of brain health and dementia, treatment and care, in addition to recruiting and retaining participants in center research. We are committed to training scientists and clinicians, and providing targeted psychoeducational programs and support services for persons living with dementia and their families.

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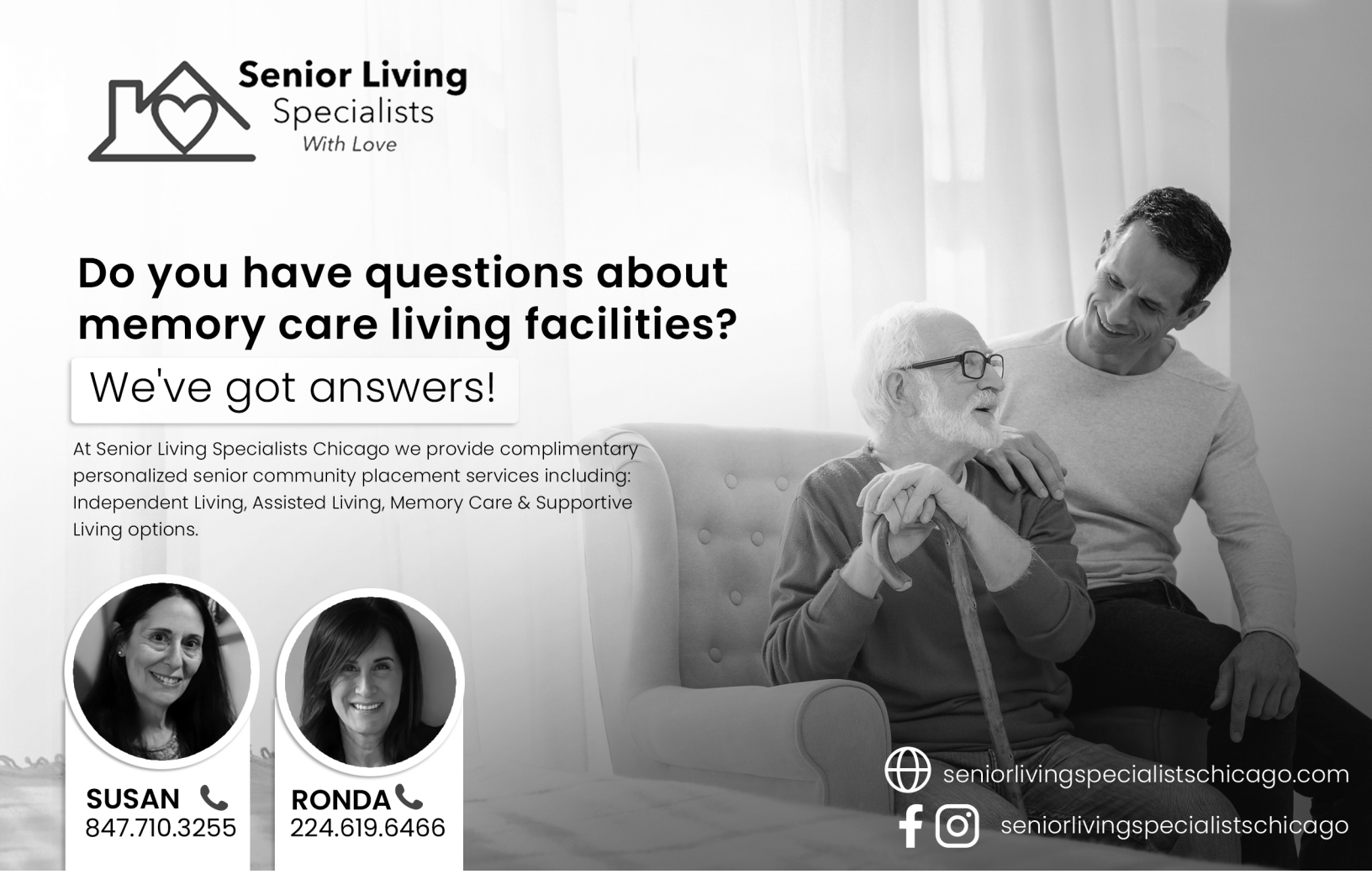

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