New Investigators in Alzheimer's Disease Grantee Meeting

The Small Research Grant Program for the Next Generation of AD/ADRC Research

Tuesday, April 9 – Thursday, April 11, 2024

Bethesda Marriott Pooks Hill, Bethesda, Maryland

Program Book – Table of Contents

Meeting Objectives:

- Provide an introduction to the grantees funded by The Rosalinde and Arthur Gilbert Foundation and the National Institute on Aging
- Gain a better understanding of how this support influences the career development and research progress of these investigators
- Provide an opportunity for the grantees to share and disseminate their research and experiences as new investigators
- Discuss opportunities for linking Alzheimer's disease research with treatment, clinical management, prevention, and policy change
- Build a learning community to facilitate sharing of research and professional networking.

Thank you to the Sponsors:

This meeting is supported by The Rosalinde and Arthur Gilbert Foundation and the National Institute on Aging through an administrative supplement to the Nathan Shock Centers Coordinating Center (3U24AG056053-07S1).

Thank you to the Planning Committee:

Moshahid Khan, University of Tennessee Health Science Center
Brittney Lange-Maia, Rush University
Luci Roberts, NIA
Lisa Robison, Nova Southeastern University
Nina Silverberg, NIA
Beth Stutzmann, Rosalind Franklin University
Mo-Kyung Sin, Seattle University College of Nursing
Zheng Sun, Baylor College of Medicine

New Investigators in Alzheimer's Disease Grantee Meeting
The Small Research Grant Program for the Next Generation of AD/ADRC Research

Tuesday, April 9 – Thursday, April 11, 2024

Bethesda Marriott Pooks Hill, Bethesda, Maryland

Tuesday, April 9

3:00 – 3:30 p.m.
Congressional Ballroom Salon 1 and 2

Registration

3:30 – 4:00 p.m.

Welcome and Opening Remarks

Liz Schwarte, MPH
Ad Lucem Consulting
On Behalf of The Rosalinde and Arthur Gilbert Foundation

Nina Silverberg, PhD
Director, Alzheimer's Disease Centers Program
Division of Neuroscience
National Institute on Aging, NIH

4:00 – 5:30 p.m.

Datablitz! Session

Academic equivalent of speed dating – a fast-track vehicle to understand research and has led to collaborations and other networking opportunities with others. Each session involves a research theme and 6-7 presenters. This is a chance to share a snapshot of your research with an audience of peers and learn about what others are working on. There will be time for questions after each presentation.

Tuesday, April 9 (continued)

Those not presenting or moderating a Datablitz! should choose a group to join. Group listings are in the program booklet.

Group 1 – Hart
Group 2 – Russell
Group 3 – Chesapeake
Group 4 – Annapolis

5:30 – 7:30 p.m.
Congressional Ballroom - Salon 3

Networking Dinner

Wednesday, April 10

7:30 – 8:45 a.m.
Congressional Ballroom Salon 3

Breakfast

8:45 – 9:15 a.m.
Congressional Ballroom

Datablitz wrap-up
Presented by alumni moderators, highlighting new and promising research

9:15 – 10:45 a.m.

NIA Funding Initiatives in AD and round-table discussion with a Program Officer
Introduction: Luci Roberts, PhD

Introduction and NIH Funding Overview
Ken Santora, PhD
Director, Division of Extramural Activities
National Institute on Aging, NIH

NIA Grants
Luci Roberts, PhD
Program Director, Division of Neuroscience
National Institute on Aging, NIH

Overview of Career Development (K) Funding at NIA
Jamie Lahvic, PhD
Training Officer, Office of Strategic Extramural Programs
National Institute on Aging, NIH

The presentations will be followed by breakouts with NIA Program Officers.

Wednesday, April 10 (continued)

10:45 – 11:15 a.m. **Break**

11:15 a.m. –12:00 p.m. ***Keynote*: The Etiology of Tau Pathology in Alzheimer's Disease: Insights from the Aging Macaque Cortex**

Amy Arnsten, PhD
Albert E. Kent Professor of Neuroscience and Professor of Psychology; Member, Kavli Institute of Neuroscience
Yale University

12:00 – 1:30 p.m. **Networking Lunch**
Congressional Ballroom Salon 3

1:30 – 3:00 p.m. ***Career development breakouts*: consultancies or aims page workshops – *group assignments are attached.***

Consultancies:
We will be using a popular and effective group problem-solving activity known as a "consultancy." This is structured to enable a set of people with a variety of knowledge and expertise to provide support, new perspectives, and ideas to one another, particularly around an important or difficult challenge. We will focus on a limited set of career-related topics. Each participant will get approximately 10 minutes. You will have 2-3 minutes or so to present what you view as the major career development challenge you are facing (or will soon face). Following your presentation, the group will ask clarifying questions for the next 1-2 minutes. For the remainder of the time, you will receive feedback and advice from the group. In the last minute or so, you will then have a chance to respond to the ideas presented. We will follow a strict timetable, so that each person will have the same opportunity for constructive feedback.

Aims Page Workshops:
All participants will receive Aims Pages for those who will be in their group. Participants who are in the process of preparing grants can present their "Aims Page" to a small to get feedback and suggestions. You must have a fairly well-developed draft of your aims since we want you to walk away with something tangible. You'll receive feedback from your peers and from others attending the meeting. In order to participate, it is expected that you also read and give feedback on the other participants' Aims pages and that you keep the materials and discussions confidential.

Wednesday, April 10 (continued)

Aims Page Workshop, Group 1 – Hart
Aims Page Workshop, Group 2 – Dirksen
Aims Page Workshop, Group 3 – Russell
Consultancy Session, Group 1 – Chesapeake
Consultancy Session, Group 2 – Annapolis

3:00 – 5:00 p.m. **Free time/one-on-one mentoring, sign up in advance, *see program booklet for assignments*.** Mentors and mentees should meet outside of the Congression Ballrooms (main meeting room).

5:00 – 7:00 p.m. ***Poster Session and reception with heavy hors d'oeuvres***
Congressional Ballroom *Kindly remove your poster at the conclusion of the session.*

5:00 – 5:30 pm – General Viewing
5:30 – 6:15 pm – Odd numbers attend poster.
6:15 – 7:00 pm – Even numbers attend poster.

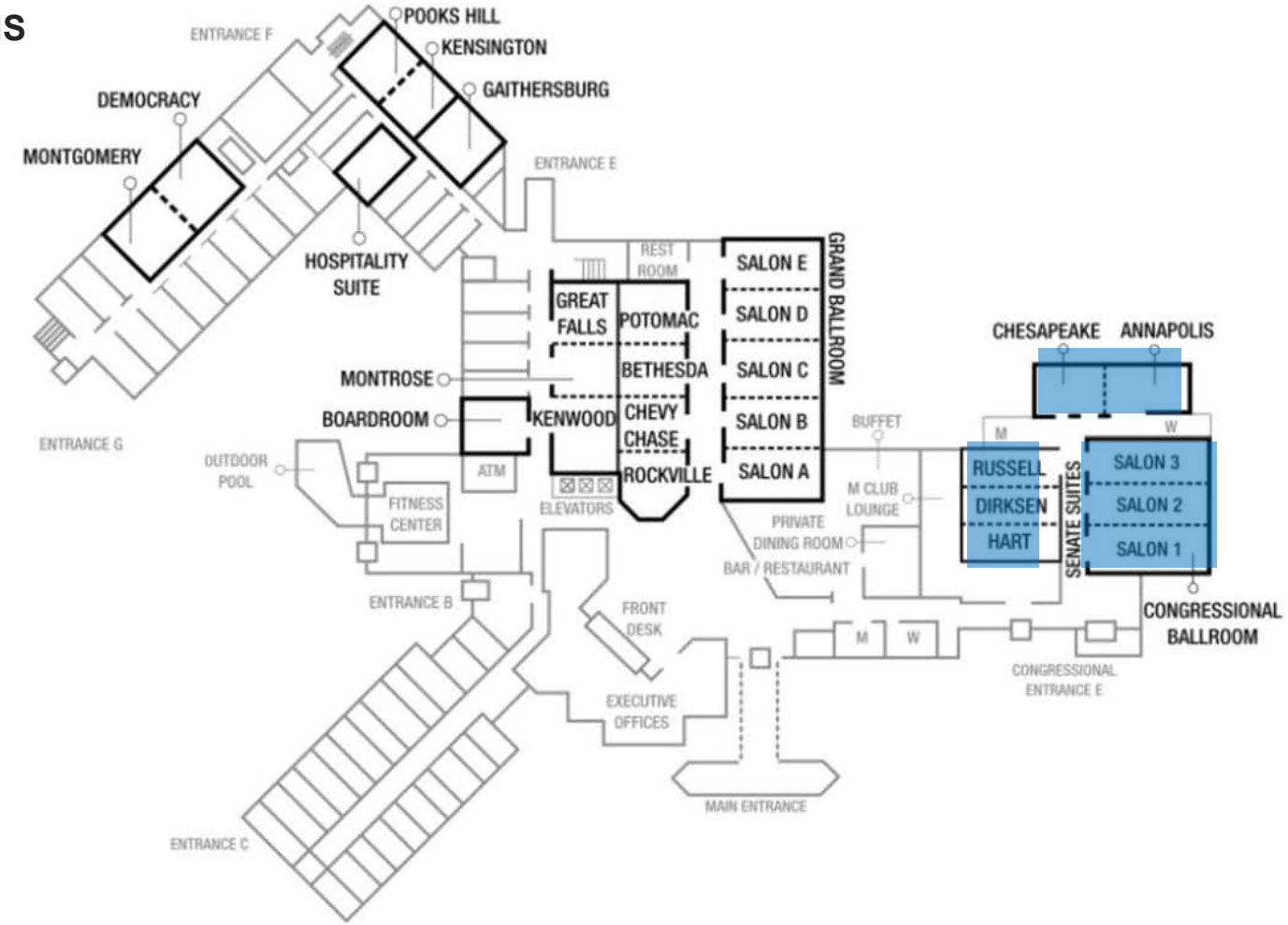
Thursday, April 11

7:00 – 8:30 a.m. ***Breakfast***
Congressional Ballroom Salon 3

Adjourn

SPACE DIAGRAM

MEETING ROOMS



Meeting

MARRIOTT BETHESDA

New Investigators in AD Meeting
Datablitz Assignments

FIRST:	LAST:	INSTITUTION:	research insterest key words	group
Michael	Bancks	Wake Forest University School of Medicine	epidemiology; aging; diabetes; cardiovascular; health disparities	4
Michael	Breen	Mount Sinai School of Medicine	Investigating A-to-I editing in brain aging and Alzheimer's disease	1
Aaron	Burberry	Case Western Reserve University	Neuroinflammation, Microbiome, Dementia, ALS	3
Julia	Burgdorf	Visiting Nurse Service of New York	Home health care, Home-based care, Family caregiving, Medicare	4
Weikang	Cai	New York Institute of Technology	Astrocytes, Purinergic signaling, Amyloid-beta pathology.	1
Arun Richard	Chandrasekaran	University at Albany State University of New York	Nucleic acid nanotechnology, siRNA, Alzheimer's disease, nucleic acid therapeutics, DNA nanostructures	1
Casey	Crump	The University of Texas HSC at Houston	Mental health and chronic disease outcomes of Alzheimer's disease; Epidemiology; Cohort studies; Population health	4
Weiwei	Dang	Baylor College of Medicine	Tau, tau toxicity, tau aggregation, yeast genetics, genetic screening	3
Michael	Dent (with Lauer)	University of Buffalo	hearing loss, auditory phenotyping, animal model, otopathology	4
Madalina	Fiterau	University of Massachusetts Amherst	Alzhimer's forecasting; machine learning; multimodal learning; deep learning; feature extraction; brain MRI processing;	1
Jody	Greaney (with Mogle)	University of Delaware	vascular biology, sympathetic function, daily stress, depression	2
Xiufang	Guo	University of Central Florida	neurodegenerative disease, AD, ALS, iPSC, in vitro, modeling	1
Erin	Harrington	University of Wyoming	Subjective Cognition; Prospective Memory; Gender; Inflammation; Neurodegeneration; Biomarkers	3
Tiffany	Kindratt	University of Texas at Arlington	Middle Eastern and North African, ADRD, diagnosis, risk factors, National Health Interview Survey, Medical Expenditure Panel Survey	4
Brittney	Lange-Maia	Rush University Medical Center	social determinants of health, health disparities, mobility, cognition	4
Amanda	Lauer (with Dent)	Johns Hopkins School of Medicine	hearing loss, auditory phenotyping, animal model, otopathology	4
Xiang	Li	Massachusetts General Research Institue, Harvard	Medical Foundation Model, Multi-modal Fusion, Causal Inference	3
Mike	Malek-Ahmadi	Banner Alzheimer's Institute	amyloid-PET, tau-PET, APOE, VEGF, MTHFR, CRP, KIF6	1
Brice	McConnell	University of Colorado Alzheimer's and Cognition Center	Sleep, EEG, Digital Biomarker	2

New Investigators in AD Meeting
Datablitz Assignments

Jacqueline	Mogle (with Greaney)	Clemson University	daily reports of memory lapses, affective responsivity to memory, daily performance-based cognitive assessment	2
Vasileios	Petrou	Rutgers New Jersey Medical School	APP, APLPs, structural biology, membrane protein purification, cryo-EM	1
Sathyanarayanan	Puthanveettil	University of Florida	Axonal transport, learning and memory	3
Senthil	Radhakrishnan	Virginia Commonwealth University	Transcription factor Nrf1/NFE2L1, proteasome genes, autophagy lysosomal genes, tau aggregates, proteotoxic stress, proteostasis	2
Maryam	Raeeszadeh-Sarmazdeh	University of Nevada, Reno	Protein engineering and design, Blood-brain barrier, metalloproteinase inhibition, MMP, TIMP, tight junction.	2
Yoni	Savir	Technion	AI for diagnostics of neurodegenerative diseases | Aging and the Immune System | Aging and proteotoxicity	1
Mo-Kyung	Sin	Seattle University College of Nursing	Cerebral amyloid angiopathy, cerebral vasculopathies, dementia, hypertension, Amyloid-related imaging abnormalities	1
Zheng	Sun	Baylor College of Medicine	hormone, hypothalamus, neuroendocrinology, circadian clock	2
Stefano	Tarantini	University of Oklahoma Health Sciences Center	aging, cerebrovascular, mitochondria, lifestyle interventions, geroscienc	3
Yong-Xiao	Wang	Albany Medical College	Diabetes, Vascular Dementia, Vasoconstriction, Type-2 Ryanodine Receptor/Calcium Release Channel, Reactive Oxygen Species Signaling	2
Jun	Wang	Mount Sinai School of Medicine	aging, Alzheimer's disease, brain infiltration, cognition, low grade inflammation, periphery immunity,	3
Guoyan	Zhao	Washington University School of Medicine	Neurodegenerative disease, Bioinformatics, Transcriptional regulation, Genomics	2

DataBlitz! - Group 1
Tuesday, April 9, 4:00 - 5:30 pm
Moderator: Ehud Cohen
AFAR Staff: Hattie Herman
Room: Hart

FIRST:	LAST:	INSTITUTION:	Research Insterests
Michael	Breen	Mount Sinai School of Medicine	Investigating A-to-I editing in brain aging and Alzheimer's disease
Weikang	Cai	New York Institute of Technology	Astrocytes, Purinergic signaling, Amyloid-beta pathology.
Arun Richard	Chandrasekaran	University at Albany State University of New York	Nucleic acid nanotechnology, siRNA, Alzheimer's disease, nucleic acid therapeutics, DNA nanostructures
Madalina	Fiterau	University of Massachusetts Amherst	Alzhimer's forecasting; machine learning; multimodal learning; deep learning; feature extraction; brain MRI processing;
Xiufang	Guo	University of Central Florida	neurodegenerative disease, AD, ALS, iPSC, in vitro, modeling
Mike	Malek-Ahmadi	Banner Alzheimer's Institute	amyloid-PET, tau-PET, APOE, VEGF, MTHFR, CRP, KIF6
Vasileios	Petrou	Rutgers New Jersey Medical School	APP, APLPs, structural biology, membrane protein purification, cryo-EM
Yoni	Savir	Technion	AI for diagnostics of neurodegenerative diseases | Aging and the Immune System | Aging and proteotoxicity
Mo-Kyung	Sin	Seattle University College of Nursing	Cerebral amyloid angiopathy, cerebral vasculopathies, dementia, hypertension, Amyloid-related imaging abnormalities

DataBlitz! - Group 2
Tuesday, April 9, 4:00 - 5:30 pm
Moderator: Ling Qi
AFAR Staff: Andrea Sherman
Room: Russell

FIRS:	LAST:	INSTITUTION:	Research Interests
Jody	Greaney	University of Delaware	vascular biology, sympathetic function, daily stress, depression
Brice	McConnell	University of Colorado Alzheimer's and Cognition Center	Sleep, EEG, Digital Biomarker
Jacqueline	Mogle	Clemson University	daily reports of memory lapses, affective responsivity to memory, daily performance-based cognitive assessment
Senthil	Radhakrishnan	Virginia Commonwealth University	Transcription factor Nrf1/NFE2L1, proteasome genes, autophagy lysosomal genes, tau aggregates, proteotoxic stress, proteostasis
Maryam	Raeeszadeh-Sarmazdeh	University of Nevada, Reno	Protein engineering and design, Blood-brain barrier, metalloproteinase inhibition, MMP, TIMP, tight junction.
Zheng	Sun		hormone, hypothalamus, neuroendocrinology, circadian clock
Yong-Xiao	Wang	Albany Medical College	Diabetes, Vascular Dementia, Vasoconstriction, Type-2 Ryanodine Receptor/Calcium Release Channel, Reactive Oxygen Species Signaling
Guoyan	Zhao	Washington University School of Medi	Neurodegenerative disease, Bioinformatics, Transcriptional regulation, Genomics

DataBlitz! - Group 3
Tuesday, April 9, 4:00 - 5:30 pm
Moderator: Vivek Swarup
AFAR Staff: Sabrina Isaacs
Room: Chesapeake

FIRST:	LAST:	INSTITUTION:	Research Interests
Aaron	Burberry	Case Western Reserve University	Neuroinflammation, Microbiome, Dementia, ALS
Weiwei	Dang	Baylor College of Medicine	Tau, tau toxicity, tau aggregation, yeast genetics, genetic screening
Erin	Harrington	University of Wyoming	Subjective Cognition; Prospective Memory; Gender; Inflammation; Neurodegeneration; Biomarkers
Xiang	Li	Massachusetts General Research Institue, Harvard	Medical Foundation Model, Multi-modal Fusion, Causal Inference
Sathyanarayanan	Puthanveettil	University of Florida	Axonal transport, learning and memory
Stefano	Tarantini	University of Oklahoma Health Sciences Center	aging, cerebrovascular, mitochondria, lifestyle interventions, geroscienc
Jun	Wang	Mount Sinai School of Medicine	aging, Alzheimer's disease, brain infiltration, cognition, low grade inflammation, periphery immunity,

DataBlitz! - Group 4
Tuesday, April 9, 4:00 - 5:30 pm
Moderator: Daniel Kaganovitch
Co-moderator: Casey Crump
Room: Annapolis

FIRST:	LAST:	INSTITUTION:	Research Interests
Michael	Bancks	Wake Forest University School of Medicine	epidemiology; aging; diabetes; cardiovascular; health disparities
Julia	Burgdorf	Visiting Nurse Service of New York	Home health care, Home-based care, Family caregiving, Medicare
Casey	Crump	The University of Texas HSC at Houston	Mental health and chronic disease outcomes of Alzheimer's disease; Epidemiology; Cohort studies; Population health
Michael	Dent	University of Buffalo	hearing loss, auditory phenotyping, animal model, otopathology
Tiffany	Kindratt	University of Texas at Arlington	Middle Eastern and North African, ADRD, diagnosis, risk factors, National Health Interview Survey, Medical Expenditure Panel Survey
Brittney	Lange-Maia	Rush University Medical Center	social determinants of health, health disparities, mobility, cognition
Amanda	Lauer	Johns Hopkins School of Medicine	hearing loss, auditory phenotyping, animal model, otopathology

Consultancies

Wednesday, Apil 10, 1:30 - 3:00 pm

Group 1
Room: Chesapeake

Co-moderator:	Subhojit Roy	Univ. of California, San Diego
Co-moderator:	Micheal Dent	University of Buffalo
Michael	Bancks	Wake Forest Univ School of Medicine
Julia	Burgdorf	Visiting Nurse Service of New York
Weiwei	Dang	Baylor College of Medicine
Erin	Harrington	University of Wyoming
Brice	McConnell	Univ of Colorado Alz and Cognition Cntr
Sathyanarayanan	Puthanveettil	University of Florida

Other Participants

Madalina	Fiterau	University of Massachusetts Amherst

Group 2
Room: Annapolis

Co-moderator:	Ling Qi	University of Virginia Medical School
Co-moderator	Jacqueline Mogle	Clemson University
Weikang	Cai	New York Institute of Technology
Mike	Malek-Ahmadi	Banner Alzheimer's Institute
Vasileios	Petrou	Rutgers New Jersey Medical School
Tristan	Shuman	Icahn School of Medicine at Mount Sinai
Yong-Xiao	Wang	Albany Medical College

Other Participants

Senthil	Radhakrishnan	Virginia Commonwealth University
Amanda	Lauer	Johns Hopkins School of Medicine

How a Consultancy Session works:
This is a popular and effective group problem-solving activity known as a "consultancy." This is structured to enable a set of people with a variety of knowledge and expertise to provide support, new perspectives, and ideas to one another, particularly around an important or difficult challenge.

Each participant will get approximately 10 minutes, 2-3 minutes or so to present what he/she views as **the major career challenge he/she are facing (or will soon face)**. This may include, but is certainly not limited to:

- Time Management
- Balancing Career and Family
- Strategies for promotion
- Balancing research, clinical, teaching and administrative responsibilities
- Issues related to your lab/team members (supervision, quality control, hiring, firing, disciplinary action, etc.)
- Transitioning relationship with your mentor(s).
- Finding/solidifying your niche, area of expertise

Following each participant's presentation, the group will ask clarifying questions for the next one-two minutes. For the bulk of the remainder of the time, the participant will receive feedback and advice from the group. In the last minute or so, the participant will then have a chance to respond to the ideas presented.

We will follow a strict timetable, so that each person will have the same opportunity for constructive feedback.

Wednesday, Apil 10, 1:30 - 3:00 pm

Aims Page Workshop

Room: Hart

Group 1

Michael	Breen	Icahn School of Medicine at Mount Sinai
Heather	Ferris	University of Virginia
Xiang	Li	Massachusetts General Research Institue, Harvard
Stefano	Tarantini	University of Oklahoma Health Sciences Center

Moderators

Delany	Torres	National Institute on Aging
Guoyan	Zhao	Washington University School of Medicine

Wednesday, Apil 10, 1:30 - 3:00 pm

Aims Page Workshop

Room: Dirksen

Group 2

Aaron	Burberry	Case Western Reserve University
Arun Richard	Chandrasekaran	University at Albany State University of New York
Tiffany	Kindratt	University of Texas at Arlington
Mo-Kyung	Sin	Seattle University College of Nursing
Jun	Wang	Mount Sinai School of Medicine

Moderators

Paul	Barrett	National Institute on Aging
Xiufang (Nadine)	Guo	University of Central Florida

Wednesday, Apil 10, 1:30 - 3:00 pm

Aims Page Workshop

Room: Russell

Group 3

Jody	Greaney	University of Delaware
Brittney	Lange-Maia	Rush University Medical Center
Maryam	Raeeszadeh-Sarmazdeh	University of Nevada, Reno
Zheng	Sun	Baylor College of Medicine

Moderators

Jamie	Lahvic	National Institute on Aging
Yoni	Savir	Technion

One-on-One Mentoring					
Wednesday, April 10, 3:15 - 4:00 pm					
Meet outside of the Congressional Ballroom (main meeting room)					
Mentor			**Mentee**		
Ehud	Cohen	The Hebrew University of Jerusalem	Julia	Burgdorf	Visiting Nurse Service of New York
Casey	Crump	The University of Texas HSC at Houston	Erin	Harrington	University of Wyoming
Michael	Dent	University of Buffalo	Madalina	Fiterau	University of Massachusetts Amherst
Xiufang (Nadine)	Guo	University of Central Florida	Weikang	Cai	New York Institute of Technology
Subhojit	Roy	University of California, San Diego	Brittney	Lange-Maia	Rush University Medical Center
Sathyanarayanan	Puthanveettil	University of Florida	Mike	Malek-Ahmadi	Banner Alzheimer's Institute
Senthil	Radhakrishnan	Virginia Commonwealth University	Michael	Bancks	Wake Forest University School of Medicine
Yonatan	Savir	Technion	Maryam	Raeeszadeh-Sarmazdeh	University of Nevada, Reno
Ophir	Shalem	Children's Hospital of Philadelphia	Stefano	Tarantini	University of Oklahoma Health Sciences Center
Vivek	Swarup	University of California, Irvine	Yong-Xiao	Wang	Albany Medical College
Guoyan	Zhao	Washington University School of Medicine	Jun	Wang	Mount Sinai School of Medicine

Research Abstracts
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Abstract: Epidemiology of potentially inappropriate medication use and risk for mild cognitive impairment and dementia among ARIC, Look AHEAD, and MESA.

Mike Bancks, Andrea Anderson, Chris Gillette, Courtney Perry, Dave Reboussin, Lynne Wagenknecht. Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC, 27157.

Key words: Beers Criteria; pharmacoepidemiology; potentially inappropriate medications; mild cognitive impairment; dementia

Introduction: In the United States, the American Geriatrics Society (AGS) Beers Criteria establishes potentially inappropriate medications (PIMs) to be avoided or dosed differently in older adults to prevent adverse events. Classes of PIMs (e.g., anticholinergics) are associated with risk for Alzheimer's disease and other related dementias (AD/RD). The goals of this R03 proposal are to characterize the epidemiology of use of PIMs that meet AGS Beers Criteria in older adults and assess whether the use of such medications is associated with mild cognitive impairment (MCI)/dementia and AD/RD brain pathology.

Methods: We are applying the AGS Beers Criteria to self-reported and medications inventory data from three racially diverse epidemiological and clinical study populations The Multi-Ethnic Study of Atherosclerosis (MESA, n=6814), Action for Health in Diabetes (Look AHEAD, n=5145) Study, and Atherosclerosis Risk in Communities Study (ARIC, n=15,792). We will assess multiple aspects of PIM exposure for each individual age ≥65 years: any PIM use (yes/no), total number of PIMs, and PIM drug class. Each cohort has adjudicated cognitive status: mild cognitive impairment (MCI) or dementia using data from multiple sources (e.g., study exams, hospital and death records, proxy interviews), not solely based on cognitive test scores. Each cohort offers unique brain imaging measures for assessment of pathology.

Results: In ARIC, the prevalence of PIM use increased with time (table). Proton pump inhibitors and non-aspirin pain medications were the two most used PIM categories (excluding multivitamins, MVM, and aspirin). Only one category in the top five used PIMs was a prescription medication (cardiovascular agents).

	ARIC Study Visit (Year)			
	V4 (1996-1999)	V5 (2011-2013)	V6 (2016-2017)	V7 (2018-2019)
Participants, n	4,015	6,537	4,003	3,587
PIM use, n (%) excluding MVM/aspirin	368 (9%)	3155 (48%)	2524 (63%)	2214 (62%)
Median number PIMs used, overall (IQR)	0 (0,0)	0 (0,1)	1 (0,2)	1 (0,2)
Median number PIMs used, PIM users (IQR)	1 (1,1)	1 (1,2)	2 (1,2)	2 (1,2)
Medication Category				
Proton Pump Inhibitors, n (%)	0 (0.0%)	0 (0.0%)	1029 (26%)	867 (24%)
Non-aspirin pain, n (%)	42 (1%)	971 (15%)	855 (21%)	708 (20%)
Ibuprofen	0 (0.0%)	120 (1.8%)	304 (7.6%)	266 (7.4%)
Naproxen	0 (0.0%)	654 (10.0%)	309 (7.7%)	217 (6.1%)
Other	42 (1.1%)	239 (3.7%)	306 (7.6%)	278 (7.8%)
Cardiovascular agents, n (%)	78 (2%)	548 (8%)	427 (11%)	381 (11%)
Cold / Allergy / Sleep, n (%)	123 (3%)	623 (10%)	399 (10%)	379 (11%)
Laxatives, n (%)	0 (0.0%)	486 (7.4%)	279 (7.0%)	292 (8.1%)

Conclusion: Potentially inappropriate medication use is highly prevalent among a cohort of older Black and White US adults, particularly use of non-prescription medications. We will assess and present whether these results are observed in other racially diverse cohorts and whether these PIMs are associated with incident MCI/dementia.

Title: A-to-I editing in brain aging and Alzheimer’s disease.

Presenting author: Michael S. Breen, PhD[1]
Co-authors: Andy Yang[1], Laura Sloofman[1]

Affiliations: [1]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

Abstract: Adenosine to inosine (A-to-I) editing, a common post-transcriptional RNA modification, is fundamental for brain aging and implicated in neurodegeneration, including Alzheimer's disease (AD). Despite recognition of its significance, the nuanced role of A-to-I editing remains understudied in AD neuropathology. Our research aims to bridge this gap by systemically profiling A-to-I editing across major cell populations and anatomical regions in the human brain, assessing its genetic regulation, and determining its contribution to AD severity. Employing large-scale data and advanced computational techniques, our work sheds light on A-to-I editing dysregulation and its contribution to AD molecular pathology, identifying functional A-to-I modifications. Our findings have the potential to redefine our understanding of AD etiology and open new avenues for intervention through ADAR-mediated RNA editing modulation.

Keywords: Adenosine deaminase acting on RNA (ADAR), A-to-I editing, normal aging, Alzheimer's disease

Poster Abstract

C9orf72 in myeloid cells prevents an inflammatory response to microbial glycogen

Aaron Burberry[1,]*, Blake McCourt[1], Vaidhvi Singh[2], Katelyn Lemr[3], Shinjon Chakrabarti[1], Elizabeth Woidke[1], Naseer Sangwan[4], Fabio Cominelli[2], Alex Rodriguez-Palacios[2]

[1]Department of Pathology, Case Western Reserve University, Cleveland, OH, USA. [2]Division of Gastroenterology and Liver Disease, Case Western Reserve, Cleveland, OH 44106, USA. [3]Department of Molecular Biology and Microbiology, Case Western Reserve University, Cleveland, OH, 44106, USA. [4]Department of Cardiovascular & Metabolic Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, 44106, USA. *Presenting author, address correspondence to aaron.burberry@case.edu.

Key words: Gut-brain-axis, neuroinflammation, gene-by-environment, Amyotrophic lateral sclerosis

Dysbiosis of the gut and neural inflammation occur in Amyotrophic lateral sclerosis (ALS) patients without overt loss of gut barrier integrity or inflammation of the bowel. An obstacle to translating this knowledge into new therapies is our incomplete understanding of how complex microbial communities interact with common ALS genotypes to impart risk of neural inflammation. We hypothesized that commensal bacteria, which are normally tolerated by the immune system, become neurotoxic when sensed by macrophages that experience a reduction of *C9ORF72*—a gene whose mutation is the most common cause of ALS. Here we report the identification of ten bacterial species that enhance murine macrophage cytokine release in a *C9orf72*-dependent fashion. Supplementation of one such bacteria—*Parabacteroides merdae*—into germ-free *C9orf72* loss of function mice enhances blood brain barrier breakdown, monocyte infiltration and Pro-IL-1β production in the central nervous system. Meta-transcriptomics and machine learning identify glycogen biosynthesis as a pathway that distinguishes commensal bacteria with divergent inflammatory properties. Accordingly, we show that enzymatic degradation of microbial glycogen reduces macrophage cytokine production, mitigates systemic inflammation, and improves survival of *C9orf72* loss of function mice. Our work provides insight into the physiologic signals that govern immunologic tolerance to gut microbes and establish a pre-clinical platform to evaluate the neural inflammatory potential of each patient's gut microbiome.

Title: Home Health Care for Persons with Dementia: Understanding Unique Needs, Recognizing Caregivers' Roles, and Identifying Opportunities for Improvement

Presenting author: Julia G Burgdorf, PhD

Co-authors: Jennifer L. Wolff, Margaret McDonald, Yolanda Barron-Vaya, Kathryn H. Bowles

Institution: Center for Home Care Policy & Research at VNS Health

Key words: Home health, home care, Medicare, caregiving, care partner

Abstract: Most (70%) of the 5.4 million persons with dementia in the US live in the community (as opposed to congregate living or skilled nursing facilities) and this figure is projected to increase. These individuals have unique and significant care needs, but community-based supports are difficult to access, siloed, and expensive. As a result, over 90% of community-living older adults with dementia experience unmet care needs, increasing their risk for institutionalization and hospitalization. Medicare home health care (HH) delivers skilled nursing and therapy services, along with ancillary supports including social work and personal care, through visits to the patient's home. Due to their significant care needs, older adults with ADRD are more likely to access HH than those without dementia and 31% of the 3.4 million Medicare beneficiaries who receive HH each year have dementia.

Through a portfolio of complementary projects, my research is aimed at characterizing current patterns of home health access, utilization, and outcomes for those with dementia and uncovering opportunities to improve care efficiency and quality in this setting, with a particular focus on the role of family and unpaid caregivers. I pursue these research objectives using a range of health services research methods, including secondary analysis of national-level linked Medicare claims, assessment, and administrative data, as well as nationally representative survey data, and primary data collection and analysis of qualitative data through key informant interviews and focus groups with dementia caregivers and home health frontline staff.

My recent work has found that older adults with dementia have higher rates of HH utilization, compared to those without dementia, and are more likely to enter HH through a community referral, to receive a greater number of nursing visits, and to remain in HH for a longer period of time (as measured by both number of days under care and number of certified HH episodes). Additionally, HH agencies incur higher costs when caring for patients with diagnosed dementia. Among HH patients *without* a dementia diagnosis, we identified select items on the current standardized assessment that were highly predictive of incident diagnosis within a year of the HH episode. Through a series of key informant interview projects, both HH staff and dementia caregivers identified poor communication of caregiver needs as a major barrier to connecting caregivers with necessary supports during the episode. Specifically, HH care team members reported having no standardized means to gather and track information regarding caregiver capacity and needs and relying on subjective impressions formed during a hectic initial visit.

My ongoing projects are aimed at: (1) Understanding the types of agencies and visit patterns that are associated with higher quality outcomes for HH patients with dementia, with a particular focus on social work visits during HH. (2) Characterizing the role of family and unpaid caregivers in HH care delivery for those with dementia, including the types of tasks caregivers take on and their needs for support. (3) Working with a major HH agency, creating an intervention to better assess and address the needs of dementia caregivers during the HH episode, leveraging consumer-facing Health Information Technology to maximize impact and uptake.

Exocytosis of ATP in astrocytes regulates amyloid-beta pathology

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Alzheimer's disease (AD) is a devastating neurodegenerative disease with no cure. It is characterized by β-amyloid (Aβ)-containing senile plaques and tau-containing neurofibrillary tangles in the brain. Excessive deposition of toxic Aβ peptides in the brain is believed one of the key mechanisms contributing to AD. A growing body of evidence has demonstrated that dysregulation of astrocyte functions and astrocytic gliotransmitter release is involved in Aβ pathology. Here, we aim to investigate the potential role of astrocyte-derived purinergic signaling in the progression of AD. Aβ42 induced adenosine triphosphate (ATP) release in primary cultured astrocytes. Further, 2-Me-SATP (an ATP analog) triggered a largely overlapping transcriptional response in astrocytes comparable to those treated with Aβ42, exemplified by the induction of inflammation, suppression of pathways involved in extracellular matrix, and regulation on phagocytosis. These data strongly suggest that in response to Aβ42 exposure, astrocytes may release ATP to trigger functional alterations in astrocytes, related to inflammatory response, extracellular protein production and phagocytosis. To further test this hypothesis, we developed a unique transgenic mouse model to specifically target ATP exocytosis in astrocytes. Thus, we crossed astrocyte-specific *Aldh1l1*-CreERT2 mice with transgenic mice carrying floxed cassette flanking the exon 1 of *Slc17a9 (Vnut)* gene, which encodes the vesicular nucleotide transporter essential for loading cytosolic ATP into the secretory vesicles. Loss of Vnut in astrocytes effectively reduced vesicular ATP loading and release by ~50% without any major alterations in total intracellular ATP content, nor major SNARE complex proteins responsible for cellular exocytosis. Notably, loss of Vnut significantly increased the uptake of HiLyte647-conjugated Aβ42 by primary astrocytes likely due to the increased activity of receptor-independent endocytosis/phagocytosis. In agreement with the KO cell model, overexpression of Vnut inhibits Aβ42 uptake by astrocytes. To further examine the role of astrocytic Vnut in AD pathology in vivo, we crossed the Vnut^{Aldh1l1}KO mice with the 5xFAD mice. Consistent with our data showing increased Aβ42 uptake in VnutKO astrocytes, loss of Vnut in astrocytes of the female 5xFAD mice dramatically reduced Aβ plaques by ~50% at 6 months of age. These alterations were most prominent in selective brain regions, including the prefrontal and motor cortex, lateral septum, and subiculum of the hippocampal formation. The induction of Gfap expression was greatly blunted in Vnut^{Aldh1l1}KO/5xFAD mice, accompanied by a normalized expression of key cytokines implicated in neuroinflammatory conditions in the brain. More importantly, loss of astrocytic Vnut greatly improved cognitive deficit in the female mice with 5xFAD background. Together, our results suggest that Vnut-mediated vesicle storage and release of ATP is an important mechanism in astrocytes to regulate astrogliosis, neuroinflammation, and Aβ pathology. Inhibiting astrocytic Vnut and astrocytic-derived purinergic signaling could represent a unique and novel glial-based therapeutic strategy for AD.

Key words: Astrocytes, Amyloid-beta, ATP, and exocytosis.

Design and construction of DNA nanostructures for siRNA delivery

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Targeted delivery is a major challenge in the use of therapeutic oligonucleotide drugs such as antisense oligonucleotides (ASOs) and small interfering RNAs (siRNA). DNA nanostructures have the potential to be used as multifunctional drug delivery carriers with enhanced biostability, controllable drug-loading, site-specific targeting and tunable drug release. In this work, we designed synthetic DNA tetrahedra as drug carriers for siRNA cargos. We characterized assembly of DNA tetrahedra, purified intact structures, and programmed the design of the DNA tetrahedra to load different number of siRNA cargos using DNA mimics.

Risk of Depression in Persons With Alzheimer's Disease: A National Cohort Study

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Background: Depression is a reported risk factor and possible prodromal symptom of Alzheimer's disease (AD); however, little is known about subsequent risk of developing depression in persons diagnosed with AD. A better understanding of such risk is needed to guide interventions that may improve quality of life and health outcomes in persons with AD. We sought to determine risks of major depression following diagnosis with AD or all-cause dementia in a large population-based cohort.

Methods: A national cohort study was conducted of all 129,410 persons diagnosed with AD and 390,088 persons diagnosed with all-cause dementia during 1998-2017 in Sweden, and 3,900,880 age- and sex-matched population-based control persons without dementia, who had no prior diagnosis of depression. AD and all-cause dementia were identified from nationwide outpatient and inpatient diagnoses. Cox regression was used to compute hazard ratios (HRs) for major depression, identified from nationwide outpatient and inpatient diagnoses through 2018, while adjusting for sociodemographic factors and comorbidities.

Results: In 10 million person-years of follow-up, the cumulative incidence of major depression was 13% in persons with AD and 11% in those with all-cause dementia, compared with 3% in control persons without dementia. After adjusting for sociodemographic factors and comorbidities, the relative rate of major depression was >2-fold higher in persons with AD (adjusted HR, 2.38; 95% CI, 2.29-2.47) or all-cause dementia (2.30; 2.25-2.35), compared with controls. These risks were elevated among both women (AD: adjusted HR, 2.21; 95% CI, 2.11-2.32; all-cause dementia: 2.15; 2.08-2.21) and men (AD: 2.68; 2.52-2.85; all-cause dementia: 2.52; 2.43-2.62). Risks were highest in the first year (>3-fold), then subsequently declined but remained significantly elevated (1.1- to 1.3-fold) ≥3 years after dementia diagnosis. Risks were elevated regardless of age but were highest in persons aged ≥85 years at dementia diagnosis.

Conclusions: In this large national cohort, women and men with AD or all-cause dementia had >2-fold increased risks of major depression, which remained elevated for ≥3 years and were highest in those aged ≥85 years. Persons diagnosed with AD or related dementias need close clinical monitoring, particularly in the first year, for timely detection and treatment of depression.

Key words: Alzheimer disease; cohort studies; dementia; depression; mental health

Poster number 8

Developing and Validating a Novel Tau Toxicity Model in the Budding Yeast

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Neurofibrillary tangles composed of hyperphosphorylated and aggregated Tau protein are a major pathological hallmark of Alzheimer's disease. Despite the strong clinical association, how wildtype human Tau proteins become hyperphosphorylated and cytotoxic remains poorly understood. Budding yeast models expressing human neurodegenerative disease proteins have been used to study the cellular and molecular basis of disease pathogenesis and cytotoxicity of these misfolded disease proteins. Interestingly, expressing human tau, including pathogenic mutant forms, produced no apparent phenotype. This observation led to the hypothesis that a strong protective mechanism may be present in the yeast cells to neutralize the toxicity of tau aggregation. An unbiased screen using the yeast gene knockout library identified an mRNA export complex, TREX2, is critical for yeast cells to survive tau aggregation. This project aims to further characterize the roles of TREX2 in detoxification of tau aggregates and establish a novel tau toxicity model in this simple model organism, which will serve as a platform for future unbiased genetic suppressor screen for tau toxicity.

Behavioral and physiological measurements of hearing in mouse models of Alzheimer's Disease

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Key words: hearing, aging, hearing loss, mice, behavior, physiology, psychoacoustics

There is a critical need to understand the role of hearing loss in AD since they are so closely linked in epidemiological studies. Unfortunately, we do not know much about the functional consequences for acoustic communication related to specific neuropathologies associated with Alzheimer's Disease (AD). Similarly, it is not clear how peripheral (or central) auditory pathologies contribute to hearing dysfunction in AD. Using mouse models of AD to screen for hearing deficits allows us to control many of the variables we cannot control in humans, including experiences like noise exposure histories and other aspects of the exposome, throughout the natural aging process. Studies have been emerging reporting both positive or null links between hearing dysfunction and brain pathologies in animal models of AD; however, these hearing assessments are limited to far-field evoked potentials recorded in anesthetized mice, and results from these studies are quite variable. Further, the passive listening situation may not recapitulate hearing abilities measured in humans in clinical and epidemiological studies because the animals are not attending to a sound, limited stimulus parameters can be used to elicit responses, and anesthesia may suppress important active listening mechanisms such as olivocochlear-mediated selective attention and anti-masking. Additionally, though auditory evoked potentials can reflect gain compensation in the presence of peripheral input, central compensation may improve behavioral thresholds beyond what is detectible in typical auditory brainstem response threshold measurements. Thus, it is critical to understand the relationship between behavioral and non-behavioral measures of hearing loss to validate animal models and increase their relevance to humans with AD.

We have been measuring hearing in two mouse models of AD (APP/PS1 and 5xFAD) using trained operant behavioral methods and auditory brainstem response (ABR) methods. Behavioral results reveal significant differences between the two models, where APP/PS1 mice show progressive age-related hearing loss across the lifespan and sex differences, while 5xFAD mice show significant variability between subjects, making results difficult to interpret. ABRs from the same mice show similar hearing phenotypes but higher thresholds than those measured behaviorally. Surprisingly, ABR profiles varied across cohorts of young and old adult 5xFAD mice, indicating possible background gene interactions from the mixed C57 and SJL strain.

These experiments will strengthen the ability to use these AD models to better understand the underlying pathologies of the relationship between AD and hearing loss and present an opportunity for exploring factors contributing to heterogeneous phenotypes in AD mouse models.

Daily Memory Lapses and Markers of Cardiovascular Health (R03 AG083323)

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Keywords: daily memory lapses, cardiovascular risk, blood pressure

INTRODUCTION: Daily memory lapses—defined as instances of forgetfulness during routine everyday life (e.g., forgetting someone's name, misplacing car keys)—occur on nearly 20% of days, even in healthy young-to-midlife adults without objective cognitive deficits. Further, daily memory lapses are associated with affective responsivity (e.g., higher negative affect) implicating lapses as a source of fluctuations in daily mood consistent with other daily stressors. Importantly, daily reports of memory concerns may be the earliest pre-clinical symptomatic stage in the development of more substantial cognitive decline, including dementia. Blood pressure (BP) variability (BPV; i.e., the fluctuation in BP over a period of monitoring time) may also particularly contribute to declines in cognitive function and eventual dementia regardless of BP level. Augmented resting beat-to-beat BPV may predict cardiovascular risk and target organ damage better than traditional 24 h ambulatory or home-based BP monitoring. Together, daily memory lapses and BPV may enhance risk for development of cognitive decline as well as serve as early warning signs for primary prevention efforts to ward off cognitive decline.

PURPOSE: This project examined the relationships among frequency of daily memory lapses and cardiovascular health including resting beat-to-beat BPV in depressed young adults. Depressed young adults are at a greater risk for development of dementia and we hypothesized that daily memory lapse occurrence (frequency) will be associated with markers of poorer cardiovascular health in this high risk subgroup.

METHODS: Daily memory lapses were assessed for 8 consecutive days using a web-based survey in 39 young adults (18-30 yrs) who met criteria for major depression. Each evening, participants reported whether they had forgotten anything from a list of retrospective (names, words, past events or information, where something was placed) and prospective lapses (appointments, chores, medications, finishing a task, why you entered a room). Beat-to-beat BP was continuously measured via finger photoplethysmography (Finometer) during 20 min of supine rest on Day 8 of the daily surveys. We calculated two memory lapse occurrence indicators: frequency (i.e., percentage of interview days with at least one memory lapse) and total (i.e., total number of memory lapses reported across all interview days). Resting BP was calculated as mean values over the duration of the entire 20 min period. Mean arterial pressure (MAP) was calculated as an average of automated sphygmomanometer BP values obtained during the resting period, and BP waveforms were calibrated once to the average of these systolic BP, diastolic BP, and MAP measurements.

RESULTS: Participants reported retrospective memory lapses on 13% of days and prospective memory lapses on 23% of days. The most common lapses were where something was placed and why you entered a room, respectively. Higher systolic BP and higher MAP were associated with greater frequency of retrospective lapses (r_s=.41, p=.01) but not prospective lapses (ps>.12).

CONCLUSION: The results of this ongoing data analysis suggest that among younger adults with depression memory lapses are associated with higher cardiac system load significantly increasing risk for future cognitive decline. Future work will continue to explore the relationships among indicators of real-world cognitive functioning and intensive assessments of cardiovascular functioning among young adults at higher risk for dementia.

Title: Everyday Prospective Memory Performance as an Early indicator for Cognitive Decline

Authors: Erin E. Harrington, Jennifer E. Graham-Engeland, Christopher G. Engeland, Martin J. Sliwinski

Prospective memory (PM) refers to our memory for future events, like remembering to take medication on time or to turn the oven off after cooking. PM is a vital component of daily life and can have serious implications for maintaining independence in older adulthood. Furthermore, recent research suggests that PM may help distinguish between cognitively health older adults and those experiencing pathological memory aging. Yet, few examinations of cognitive decline, mild cognitive impairment (MCI), or Alzheimer's disease and related dementias (ADRD) include measures of PM within their cognitive test batteries. Even fewer of these studies address PM performance outside of laboratory or diagnostic settings. This research seeks to examine PM within daily life contexts and determine whether daily self-reported PM lapses are predictive of future cognitive decline and impairment. Moreover, this project examines PM in association with other known biological correlates of cognitive decline (i.e., blood-based inflammatory and neurodegenerative biomarkers) to better assess possible biological underpinnings of this vital daily cognitive ability that may contribute to further decline. Finally, this research examines gender differences in the links between self-reported PM lapses and inflammatory and neurodegenerative biomarkers to possibly indicate who is at greater risk for pathological memory decline. This research contributes to a growing body of work on daily cognitive experiences and ADRD risk. The present work may also shed light on intervention strategies to help individuals maintain PM into late life and possibly avoid more serious impairment. Ultimately, this project is expected to contribute to 1) early detection efforts for MCI and AD; 2) identification of individual variations in risk for MCI and AD; and 3) future intervention strategies to prevent, reduce, or delay cognitive decline.

Key Words: Prospective Memory, Inflammation, Neurodegenerative Biomarkers, Gender Differences

Presenter's (First Author's) affiliation: Erin E. Harrington, University of Wyoming, Laramie, WY.

2024 New Investigator in AD Meeting Abstract

Title: Evaluating ADRD underdiagnosis and risk factors among Middle Eastern and North African older adults in the United States using national health surveys

Author: Tiffany B. Kindratt, PhD, MPH, University of Texas at Arlington

Introduction: Formed in the 2019, the Health Survey Research Lab at the University of Texas at Arlington conducts research on the epidemiologic factors that contribute to health outcomes across the life course using data from national health surveys. One research arm focuses on racial/ethnic disparities, particularly among Middle Eastern and North African (MENA) Americans on various health topics from low birth weight in infancy to cognitive impairments and Alzheimer's disease and related dementias (ADRD) in later life. According to federal Office of Management and Budget guidelines, MENA Americans are defined as part of the White race. Yet, research shows their health and lived experiences differ from Whites. By defining MENA as White, it limits their ability to receive resources and hides true disparities that exist between other groups and Whites. On January 27, 2023, the Chief Statistician of the US opened a comment period for a proposal that includes a separate check box for MENA individuals on the 2030 US Census and other federal forms. The decision whether to include a separate checkbox should be made in Summer 2024. This presentation provides an overview of Dr. Kindratt's NIA-funded research projects on ADRD underdiagnosis and risk factors among MENA adults.
Methods: Few national health surveys can be used to examine ADRD health-related outcomes among MENA Americans. The National Health Interview Survey (NHIS) includes questions on a wide range of health topics that can be used to evaluate potentially modifiable risk factors for ADRD. The health of foreign-born MENA adults can be examined using a country and region of birth question measured from 2000-2018. US-born MENA adults cannot be identified. The Medical Expenditure Panel Survey (MEPS) is administered to a subsample of participants who completed the previous years' NHIS to examine a broader range of health care utilization, diagnostic billing codes, and patient experience data. Suspected undiagnosed ADRD can be measured using ICD-9/ICD-10 codes. Similar to the NHIS, the health of only foreign-born MENA adults can be examined. The American Community Survey (ACS) includes questions on disability, specifically one question on cognitive difficulty. US- and foreign-born MENA individuals can be identified. The other health-related content in the ACS is limited to questions on health care access and health insurance.
Results: Using linked 2000-2017 NHIS and 2001-2018 MEPS data, the prevalence of suspected undiagnosed ADRD was highest among foreign-born MENA older adults (15.8%) compared to US- (8.1%) and foreign-born (11.8%) non-Hispanic Whites. The age-adjusted and sex-stratified prevalence of suspected undiagnosed ADRD was highest among MENA women (22.5%) and lowest among US-born White men (7.6%). Foreign-born MENA adults (ages 18+ years) had higher odds of reporting less than ninth grade education (OR=1.93; 95%CI=1.17-3.21) and depressive symptoms (OR=1.28; 95%CI=1.06-1.56) compared to US-born Whites. Foreign-born MENA adults had lower odds of reporting hearing loss (OR=0.42; 95%CI=0.28-0.64), hypertension (95%CI=0.67; 95%CI=0.56-0.81), obesity (OR=0.79; 95%CI=0.63-0.98), current smoking (OR=0.60; 95%CI=0.46-0.77), and alcohol use (OR=0.42; 95%CI=0.31-0.56) than US-born Whites.
Discussion: The findings provide the first comprehensive look at ADRD underdiagnosis and potentially modifiable risk factors among foreign-born MENA adults. This research is timely, significant, and contributes to the dialogue advocating for a separate racial/ethnic category for MENA Americans to uncover ADRD prevention, morbidity, and mortality.

Keywords: Middle Eastern and North African, ADRD, dementia, risk factors, National Health Interview Survey, Medical Expenditure Panel Survey

A Latent Class Analysis of Community-Level Characteristics and the Association with Cognitive and Physical Function Decline in Older African Americans

Presenter: Brittney S. Lange-Maia, PhD, MPH
Coauthors: Melissa Lamar, PhD; Tianhao Wang, PhD; Lisa Barnes, PhD
Institution: Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL

ABSTRACT

Background: Maintaining good cognitive and physical function are among the highest priorities for older adults. However, older African Americans are disproportionately impacted by age-related dementia and physical impairments. Community-level sociodemographic characteristics have been previously studied in relation to age-related functional declines, though few studies have used comprehensive approaches to assess the impact of multiple community-factors on cognitive and physical function, particularly among older African Americans.

Methods: Participants were older African Americans from the Minority Aging Research Study who reside in Cook County, IL. Participants completed annual assessments on cognitive function (composite of 19 cognitive tests) and physical function (composite of 10 motor tests) as well as measurements of health, social, and socioeconomic factors. Participant addresses were geocoded and community-level data from external sources were merged with cohort data. Community-level data included neighborhood disadvantage (Area Deprivation Index) Black-White racial segregation (Index of Concentration at the Extremes), access to parks and greenspace, walkability, access to public transit, and access to health promoting resources of grocery stores, supermarkets, and fitness facilities. We used latent class modeling to determine unobserved subgroups of community-level characteristics, and then used linear mixed models to test whether these groupings were associated with level and change in cognitive and physical function. Models were adjusted for age, sex, education, physical activity participation and vascular risk factors (hypertension, diabetes, and smoking history).

Results: Participants (N=530) had a mean age of 72.6 (standard deviation [SD]: 5.6) years, completed a mean of 14.9 (SD: 3.3) years of education, and 78% were female. Four latent classes of community characteristics were evident: 1) racially and ethnically diverse, lowest walkability and transit access (12% of participants), 2) low income, highly walkable and good transit access (13.8%), 3) highly segregated, moderate walkability, access to small stores but not supermarkets (58.9%), 4) greatest access to health promoting resources (15.3%). Cognitive function did not vary between the different community characteristics subgroups. However, compared to class 3, participants in class 1 had lower initial physical function (β=-0.072, standard error [SE]=0.021, p=0.001) but no difference in longitudinal change in physical function.

Conclusions: Participants lived in communities that vary on a wide range of characteristics, though participants living in the least walkable communities appeared to have worse initial physical function.

Keywords: Health disparities, minority aging, latent class analysis, social determinants of health.

Poster number 14

Counterfactual Causal Discovery from Neuroimaging

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Keywords: Generative Modeling; Counterfactual Causal Discovery; Neuroimaging

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive decline in cognitive function, with amyloid-β accumulation being a key pathological hallmark. Positron emission tomography (PET) imaging has been widely used to measure amyloid-β accumulation in the brain and aid in early AD diagnosis. While there have been abundant studies on PET-aided diagnosis and treatment planning for AD, the causal relationship between amyloid-β accumulation and AD pathophysiology remains unclear. To address this issue, we propose a novel graph-based varying coefficient neural network (GVCNet) for estimating the individual treatment effect of amyloid-β accumulation on AD progression using counterfactual inference.

The key technical components of the proposed model include 1) Graph-based modeling of the PET signals to leverage the inherent complexity and interconnectedness of brain regions. Specifically, the model incorporates the brain's structural topology as a graph to capture spatial relationships and dependencies among different regions, providing a comprehensive representation of the possible underlying proteinopathic dynamics. 2) A targeted regularization approach to mitigate model complexity and ensure robustness, effectively handling the inherent noise and variability in PET imaging data. 3) A varying coefficient modeling for the treatment effect allows for the capture of the relationship between continuous PET signal value and patient outcomes rather than the discretization of the images.

We evaluate the performance of GVCNet using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The dataset consists of subjects categorized into three groups: AD, normal control (NC), and mild cognitive impairment (MCI). GVCNet achieves an accuracy of 88.72% in AD classification, demonstrating the effectiveness of incorporating graph structure and regularization techniques in the model. More importantly, we can identify the regions with different types of treatment response functions between the amyloid-β level and outcome. To gain insights into the regional causal associations between amyloid-β accumulation and AD progression, we employ a K-means clustering approach on the average dose-response function (ADRF) curves generated by GVCNet for each of the 62 brain regions defined by the Harvard-Oxford Atlas (HOA). The analysis reveals that the precentral/postcentral gyrus and left/right pallidum are key regions where amyloid-β accumulation exhibits a strong causal effect on AD progression. Interestingly, both the cortical (precentral gyrus) and subcortical (pallidum) regions responsible for voluntary motor movements are found to be highly responsive to AD, suggesting a potential link between the behavioral and pathological aspects of the disease.

The proposed GVCNet model has significant potential for understanding the mechanisms of AD and performing early AD diagnosis for personalized disease management. By measuring regional causal associations between amyloid-β accumulation and AD pathophysiology, GVCNet can enable personalized projections of disease trajectories and treatment effect predictions. Such personalized predictions can guide clinicians and patients in making informed decisions about treatment strategies and long-term care plans, especially with the recent advancement in amyloid-targeting medications for AD, ultimately leading to improved patient outcomes and more efficient resource allocation. The integration of imaging-guided diagnosis, prognosis, and mechanistic insights provided by GVCNet will shape the future of AD research and pave the way for improved patient care and therapeutic strategy development.

Interactions of VEGF 1154A and 2578C with APOE ε4 on Amyloid Load in Cognitively Unimpaired Older Adults.

Michael Malek-Ahmadi, Ignazio Piras, Qi Wang, Kewei Chen, Vivek Devadas, Ji Luo, Yi Su

Background

Previous studies have shown that carriage of the VEGF 1154A (rs1570360) and the VEGF 2578C (rs699947) alleles may confer a protective effect on the development of Alzheimer's disease (AD). However, it is unknown if these associations are APOE-dependent and whether they can be observed in asymptomatic individuals with varying levels of amyloid pathology. The aim of this study is to determine whether interactions between the APOE ε4 allele, VEGF 1154A, and VEGF 2578C are associated with amyloid load in cognitively unimpaired (CU) older adults.

Methods

Data from 341 CU ADNI subjects (57% female) with a mean age of 74.35±6.94 years and a mean education level of 16.63±2.44 years were included in the analysis. Thirty-two percent (n=109) were APOE ε4 carriers with the following distributions for each VEGF allele: 1154A – GG=165, AG=147, AA=29; 2578C – AA=88, AC=166, CC=87. AV-45 mean cortical standard uptake value ratio (MCSUVR) was used to determine amyloid load. Generalized linear models were used to quantify the main effects of the VEGF alleles and their interactions with APOE ε4 on demographically-adjusted MCSUVR values. Cohen's d effect size was used for groupwise comparisons.

Results

The interaction between VEGF 1154A and APOE was statistically significant (β = -0.02, 95% CI (-0.04, -0.008), p = 0.002). Further analysis among those with two A alleles of VEGF 1154 found that APOE ε4 carriers had substantially lower amyloid load relative to ε4 non-carriers (p = 0.01, d = 1.04). Within APOE ε4 carriers, there were no significant differences among the GG, AG, and AA genotypes. The interaction for VEGF 2578C and APOE approached statistical significance for amyloid load (β = 0.01, 95% CI (-0.001, 0.03), p = 0.06).

Conclusion

Homozygosity for the AA genotype of VEGF 1154 is associated with reduced amyloid load in APOE ε4 carriers and warrants further investigation as a potential protective factor for AD.

Keywords

VEGF, APOE, amyloid, cognitively unimpaired, preclinical Alzheimer's disease

Title: Decoding Sleep EEG for Alzheimer's Risk: A Machine Learning Approach to “Wearable” Brain Health Monitoring

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Key Words: Digital Biomarkers, Wearables, Electroencephalography, EEG, Sleep, Brain Health, Aging, Alzheimer’s Disease

Background: Single-channel sleep electroencephalography (EEG) is a promising technology for creating cost-effective and widely accessible digital biomarkers for monitoring brain health and detection of early Alzheimer’s disease (AD). Sleep, notable for its numerous connections to brain health, is of particular interest in this context. Indeed, several of the best studied and widely recognized risk factors for neurodegenerative disease are also connected to aspects of sleep physiology, including biological sex, hypertension, diabetes, obesity/metabolic dysregulation, and immune system dysfunction. In this study, we utilized the unique signal characteristics of slow wave sleep (SWS) oscillatory events as features in machine learning models to predict underlying biological processes that are highly relevant to brain health and risk of AD. We further assessed these oscillatory events as machine learning features to predict cognitive performance and molecular AD pathology among aging adults as an exploratory analysis. Our objective is to establish a foundation for algorithms capable of effectively monitoring physiological processes in sleep that directly and indirectly inform brain health using single-channel sleep EEG as a functional metric of brain activity.

Methods: Utilizing data from the Cleveland Family Study, we analyzed 726 overnight polysomnography recordings to extract features from slow waves and adjacent oscillatory events. Advanced signal processing and machine learning techniques, including random forest models, were employed to engineer features and predict health-related outcomes such as age, cerebrovascular risk factors, endocrine functions, immune system activity, and sleep apnea. Additional at-home sleep EEG recordings from 205 participants within the Knight Alzheimer Disease Research Center were also used in an exploratory machine learning analysis to predict cognition and molecular AD pathology.

Results: Our models demonstrated significant predictive capability for several outcomes, including age ($R^2 = 0.643$, $p < 0.001$), and sex classification (area under the receiver operator characteristic (AUROC) curve = 0.808), diabetes and hypertension diagnosis (AUROC = 0.832 and 0.755, respectively). Significant predictions were also modeled for metabolic/endocrine functions (including blood concentrations of IGF-1, leptin, ghrelin, adiponectin, and glucose), immune markers (including IL-6, TNF-alpha, and CRP), and both body mass index (BMI) and sleep apnea. Exploratory analyses also demonstrate successful prediction of cognitive abilities and molecular AD pathology.

Discussion: This study demonstrates the potential of using features from oscillatory events in single-channel sleep EEG as digital biomarkers. These biomarkers can identify key health and demographic factors that both affect brain health and are indicative of core brain functions. By capturing the complex interactions of neural, metabolic, endocrine, and immune systems during sleep, our findings support the development of single-channel EEG as a practical tool for monitoring complex biological processes through metrics that originate in brain physiology. In addition, successful prediction of cognitive scores and AD pathology suggests that EEG-derived digital biomarkers may be used to detect preclinical and early-stage AD. Future research should aim to refine these digital biomarkers for broader home-based applications that may utilize inexpensive “wearable” devices to provide a scalable and accessible tool for tracking brain health and predicting early stages of AD.

Investigating the structural organization of APP family members using cryo-electron microscopy

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Keywords: APP, APP-like, protein purification, cryo-EM, structural biology, structure-function

The amyloid precursor protein (APP) is a type I transmembrane glycoprotein widely known for its involvement in the physiopathology of Alzheimer's disease (AD) as the precursor of the beta amyloid peptide (Aβ). The identification of Aβ as the main protein component of amyloid plaques, and APP mutations associated with increased Aβ accumulation in early-onset familial Alzheimer's disease (FAD) cases, has led to the establishment of the amyloid cascade hypothesis. This hypothesis alleges that Aβ is the primary pathological element of AD dementia. Yet, it is increasingly appreciated that, apart from being the precursor of Aβ peptide, APP is involved in a wide range of biological activities; deregulation of which can lead to synaptic dysfunction and neuronal death, also key hallmarks of AD. Thus, understanding the full contribution of APP to the onset and progression of AD requires a deeper understanding of the physiological functions of APP, which is currently very limited and further hindered by the lack of structural information available for the full-length protein.

In addition, APP is part of a gene family, which carries two more members, the Amyloid Precursor Like Protein 1 (APLP1) and the Amyloid Precursor Like Protein 2 (APLP2). Both APLPs are highly homologous to APP and are proteolytically processed in a similar way by α -, β -, and γ -secretases, except for the lack of release of Aß peptide as they both lack the Aβ region. APP and APLP2 are expressed ubiquitously in largely overlapping patterns, whereas APLP1 is found primarily in neurons. Single and combined knockouts have indicated functional complementation within the APP gene family. In the adult nervous system all three mammalian APP family members (APP, APLP1, and APLP2) are involved in synaptogenesis, maintenance of spine density and synaptic plasticity.

Structural biology studies of isolated domains of APP/APLPs and various functional peptides, have produced detailed information regarding the structure of these fragments, domains or subdomains. Yet, this torrent of information has not so far translated into a significant advancement of our understanding of the physiological functions of APP family proteins and how their overall architecture enables their diverse functions in the nervous system and beyond.

The goal of our AD-related research program is to develop experimental resources (methods, procedures and constructs) for characterizing the structure of APP family members in full-length. We are planning to use the tools of structural genomics, fluorescent size-exclusion chromatography, inducible stable cell lines constructed via lentiviral transduction, and single-particle cryo-electron microscopy (cryo-EM) to achieve this goal. Our early preliminary results with human APP and APP-like proteins after transient transfection indicate that APLP1 may be a particularly good target for structure determination based on expression and stability in detergent. A high-resolution reconstruction of a full-length APP family protein will enable us to better understand the structural basis of the physiological functions of APP and APP-like proteins and inform our understanding of how these functions are deregulated in AD.

Axonal Transport and Pathogenesis of Alzheimer’s disease

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Alzheimer's Disease (AD) is characterized by the presence of distinct lesions, marked by the formation of filamentous deposits of abnormal brain proteins within neurons. These deposits consist of tau, a critical intracellular protein responsible for microtubule stabilization, and fibrillar amyloid beta plaques resulting from the aggregation of amyloid precursor protein (APP). Research indicates that both tau and APP play pivotal roles in facilitating fast axonal transport within neurons. While the causal relationship between axonal transport and AD remains unclear, studies have consistently shown deficits in axonal transport in models featuring mutations in tau and APP associated with AD pathology. Drawing from our investigations into the manipulation of kinesins—where RNAi-mediated loss of function led to memory loss and overexpression resulted in memory enhancement—we are now exploring the effects of kinesin manipulations in the APP-NL-G-F knock in mouse model of AD. Specifically, our goal is to evaluate the impact of overexpression on mitigating plaque formation, microgliosis, synaptic proteins, and memory deficits. Building upon our findings demonstrating memory enhancement through kinesin overexpression, we anticipate observing improvements in cytopathology and memory deficits in APP NL-G-F knock in mice. Extending these studies to human iPSC neurons, we find that AD mutations results in the impairments in the expression of kinesins and transport of mitochondria.

A role for transcription factor Nrf1/NFE2L1 in the clearance of tau aggregates in Alzheimer's Disease

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Keywords: Transcription factor Nrf1/NFE2L1, proteasome genes, autophagy lysosomal genes, tau aggregates, proteotoxic stress, proteostasis

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is characterized by cognitive decline and memory loss. One of the defining pathological hallmarks of AD at the molecular level is the presence of neurofibrillary tangles (NFTs) composed of aggregates of hyperphosphorylated tau in the neurons. These aggregates impose a severe burden on the neuronal protein quality control pathways resulting in severe proteotoxic stress in these cells. Sustained proteotoxic stress typically results in neuronal cell death culminating in brain atrophy, a prominent pathological feature of AD. Given that tau can be degraded by the proteasome as well as the autophagy-lysosomal network, possible defects in one or both of these catabolic pathways could explain its accumulation in the diseased neurons. Consistent with this notion, accumulating evidence points to a progressive decline in the function of both the proteasome and the autophagy-lysosomal network during the aging process. Therefore, it is important to understand how these protein clearance systems operate in cells of neuronal origin and elucidate how these cells handle proteotoxic stress. This could lead to the development of novel strategies aimed at enhancing these protein degradation pathways resulting in the clearance of tau and alleviation of proteotoxic stress in the neurons.

Our previous work has firmly established the transcription factor Nuclear factor erythroid derived 2-related factor 1 (Nrf1; also called NFE2L1) as a central player in responding to cellular proteotoxic stress. Nrf1, by its ability to induce *de novo* synthesis of proteasome subunit genes in response to proteasome inhibition, promotes the recovery of proteasome activity, thus mitigating proteotoxic stress and enhancing cellular survival. Furthermore, our recent work indicates that under similar circumstances, Nrf1 can also transcriptionally upregulate multiple components of the autophagy pathway, and so could offer the cells an additional route to cope with proteasome insufficiency. Thus, Nrf1 appears to be a master transcription factor that shapes the cellular response to proteotoxic stress. However, whether or not the Nrf1 pathway is active in AD neurons experiencing proteotoxic stress is currently unclear. Here, we show that Nrf1-knockout ($Nrf1^{KO}$) HT22 mouse hippocampal cells accumulate more tau P301L/S320F (aggregate-prone mutant) in insoluble fraction when compared to control cells. Also, overexpression of active Nrf1 p110 seemed to clear these aggregates. Further experiments are underway to define the mechanism behind these effects.

Engineering Metalloproteinase Inhibitors for Developing Neurodegenerative Disease Therapeutics

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Metalloproteinases (MPs) play a multifaceted role in \neurological disorders, and neurodegenerative diseases, based on their critical role in remodeling the extracellular matrix. Protein-based MP inhibitors offer higher stability and selectivity which is critical for developing efficient therapeutics with low off-target effects. Tissue inhibitors of metalloproteinase (TIMPs), natural inhibitors of matrix metalloproteinases (MMPs), and monoclonal antibodies (mAbs), provide excellent protein scaffolds for engineering selective or dual MP inhibitors. Our research group has engineered and designed MP inhibitors based on TIMPs and single chain fragment (scFv) antibody by combination of directed evolution, computational modeling, and machine learning approaches.

TIMPs have a high level of sequence and structure homology, with a broad range of inhibition selectivity and binding affinity to the family of MMPs. We used DNA shuffling between the human TIMP family to generate a minimal TIMP hybrid library to identify the dominant minimal MMP inhibitory regions with higher flexibility and higher tissue penetration features. Interestingly, several minimal TIMP variants selected after screening toward MMP-3cd or MMP-9cd, with lengths as short as 20 amino acids, maintained or improved binding to MMP-3cd and MMP-9cd. The TIMP-MMP binding dissociation constant (K_D), in the nM range, and MMP inhibition constants (Ki), in the pM range, of these minimal TIMP variants were similar to the N-terminal domain of TIMP-1 on the yeast surface and in solution indicating the potency of these minimal variants as MMP inhibitors. We further used molecular modeling simulation, and molecular protein docking of the minimal TIMP variants in complex with MMP-3cd to understand the binding and inhibition mechanism of these variants.

Further, we evaluated the therapeutic potential of these minimal TIMP variants using *in vitro* models of the blood-brain barrier (BBB). MMP-3 and MMP-9 were shown to disturb the BBB measured by permeability assays using FITC conjugated dextran (10kDa) across the rat brain endothelial cells (RBMECs) in a Transwell setting. TIMP minimal variants restored the permeability of BBB and increased transendothelial electrical resistance (TEER) comparable to wild-type TIMP-1 and TIMP-3 recombinant proteins. This research will shed light on the engineering and design of the next generation of enzyme inhibitors as potential protein therapeutics.

Title: Harnessing AI to Rank the Importance of Spatiotemporal Windows of EEG Signals for a Better Alzheimer's Disease Prediction

Author: Yonatan Savir, PhD

Abstract: The integration of Electroencephalogram (EEG) measurements with machine learning holds the promise of enhancing diagnostic accuracy and providing personalized insights into the progression of neurodegenerative diseases (NDs) and Alzheimer's disease (AD) in particular. The complex nature of EEG signals, influenced by individual variability and noise, poses difficulties in interpreting the rich and dynamic embedded information, thus requiring algorithms capable of discerning meaningful patterns. In this work, we develop a novel approach for ranking the importance of spatiotemporal EEG information based on the Smart Aggregation Framework (SAF) framework in which each spatiotemporal window is weighted non-linearly using the Boltzmann distribution with a hyperparameter, analogous to temperature. We validate our model on a dataset that includes EEG recordings of 65 healthy and AD subjects. We rank the significant spatiotemporal windows for each subject and show that the features of the top-ranked windows provide significant separability between the AD and healthy subjects. We determine the most significant electrode and show that taking only the top two electrodes provides a better classification of the AD patients compared with taking all the electrodes or a random pair. Besides providing cutting-edge accuracy in classifying AD, our work provides an interpretability framework for ranking spatiotemporal information in EEG signals that can be harnessed to enhance the diagnostics of other neurodegenerative conditions.

The Associations of Late-life Blood Pressure with CERAD and Braak Stages: Findings from the National Alzheimer's Coordinating Center Dataset

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Abstract

Background: CERAD and Braak staging are two major scoring systems for quantifying neuropathological features of Alzheimer's disease (AD). Midlife hypertension is a risk factor for AD, but less is known about the relationships between late-life systolic blood pressure (SBP) with CERAD and Braak staging, the examination of which was the objective of the current study.

Methods: This study analyzed data from 5,160 participants in the National Alzheimer's Coordinating Center dataset which had data on 4 longitudinal SBP measurements before death and on CERAD (n=2,600) and Braak (n=2,560) autopsy data. CERAD score was dichotomized into moderate/severe versus none/sparse; Braak stage was dichotomized into groups: III-VI vs 0-II. Logistic regression models were used to examine odds of higher CERAD or Braak staging associated with SBP ≥130mmHg (mean of 4 late-life measures).

Results: In a model that controlled for age at death, last BP to death (in years), and sex, a late-life mean SBP ≥130mmHg compared to SBP < 130mmHg was associated with an estimated odds ratio for a more severe CERAD score of 1.13 (95% CI: 1.00, 1.26). In a model that also controlled for antihypertensive medications and APOE ε4 status, SBP ≥130mmHg was associated with a slightly increased estimated odd for a more severe CERAD score of 1.15 (95% CI: 1.02, 1.30).

Conclusion: We found a direct association between late-life mean SBP with CERAD score, but not with Braak stage. This analysis supports the importance of maintaining control of BP into late life as a strategy to slow the rate of progression of AD pathology.

Key words: Alzheimer's dementia, Braak, CERAD, late-life blood pressure

Single-nucleus multi-omics delineate exercise effects in neurocognition through growth factors

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ABSTRACT

Physical exercise is a first-line prevention against aging-related cognitive decline and neurodegenerative diseases such as Alzheimer's disease (AD). To dissect unbiasedly the underlying mechanism, we performed single-nucleus transcriptomic and chromatin accessibility analyses (snRNA-seq and ATAC-seq) in the hippocampus of mice carrying AD-associated NL-G-F mutations in the amyloid precursor protein (APP) gene after chronic wheel-running exercise. We find that exercise counteracts amyloid-induced transcriptomic and chromatin accessibility changes by cell type-specific transcription regulatory networks that converge on activation of growth factor signaling pathways, notably the epidermal growth factor receptor (EGFR) and insulin signaling, which is associated with increased immature dentate granule cell proportion and oligodendrocytes. The favorable cognitive effect of exercise can be blocked by pharmacological inhibition of EGFR and PI3K. Exercise elevates heparin-binding EGF (HB-EGF) levels in the blood, and intranasal administration of HB-EGF robustly improves memory functions in sedentary mice carrying APP NL-G-F mutations. These findings provide a panoramic delineation of cell type-specific hippocampal transcriptional networks activated by exercise and suggest anabolic stimulation is a major druggable contributor to exercise-induced memory benefits, with therapeutic implications for AD-related cognitive decline.

Key words: exercise, Alzheimer's disease, growth factor, snATAC-seq

Time-Restricted Feeding Targets Vascular Mechanisms to Mitigate Age-Related Cognitive Decline

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The risk for vascular cognitive impairment and dementia (VCID) increases with age and can be signified by structural and functional changes in cerebrovasculature. Age-related changes in endothelial mitochondrial health may play a role in cerebrovascular function during aging. The brain endothelium plays a crucial role in maintaining homeostasis, not only by preserving cerebral blood flow (CBF), but also by ensuring an intact barrier function. This is achieved by properly directing blood flow to the most active brain regions, a process known as neurovascular coupling (NVC). Moreover, an intact blood-brain barrier (BBB) is essential to prevent the extravasation of immunogenic substrates and to ward off neuroinflammation. Time-restricted feeding (TRF) is a dietary intervention that may protect the aging cerebromicrovasculature and reduce risk for VCID. The objective of this study is to identify the effects of TRF on age-related cognitive decline through investigating cerebromicrovascular and endothelial mitochondrial health. We hypothesized that TRF would improve age-related cognitive decline by protecting endothelial mitochondrial function in aging. Adult C57BL/6 mice underwent TRF regimen, including six hours of ad libitum feeding daily. Young and age-matched control mice were fed ad libitum. Spatial learning and memory of all groups were tested using radial arm water maze. CBF responses were measured by laser speckle contrast imaging (LSCI) to assess NVC, and BBB integrity was measured by two-photon imaging after 6 months of TRF. After 12 months of TRF, wire myography was performed on aorta to measure endothelial function. Dihydroethidium staining and fluorespirometry evaluated ROS generation and mitochondrial respiration in vascular tissue. TRF significantly improved spatial learning and memory compared to aged mice. TRF improved impairments in NVC responses and endothelial function and ameliorated weakened BBB integrity that occurred with age. Age-related changes in vascular mitochondrial health were alleviated by TRF. This highlights endothelial mitochondrial function as a potential mechanism for the benefits of TRF in preserving cerebromicrovascular health and preventing age-related cognitive decline. The knowledge gained from this study may be relevant to the development of novel therapeutic strategies for VCID in the future.

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Keywords: Dietary Interventions in Aging, Cerebral Blood Flow Regulation, Mitochondrial Respiration in Vascular Health, Oxidative Stress and Aging, Neuroinflammation Prevention

Contribution of peripheral immune dysregulation to Alzheimer's disease

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Background: For many years, AD is viewed as a disorder restricted to the brain. The brain is traditionally considered an immune privileged organ and its immunity is mediated by innate immune cells localized in the brain under homeostasis condition. The brain is protected by the blood brain barrier (BBB) and communicates with the outside through the choroid plexus, meningeal linings and perivascular spaces. There is increasing evidence that systemic immune responses may play a role in AD pathogenesis. Over the years, in search for blood biomarkers for AD, numerous studies found elevated inflammation in the periphery and is associated with increased risks for AD. For example, proteomic assessment of human plasma revealed significant alterations of multiple immunological pathways in AD subjects. More recent report revealed the presence of elevated number of CD8+ T effector memory cells in the circulating blood of AD subjects and its number is negatively associated with cognitive function. These CD8+ T cells are also found in the AD brain and are primarily localized in the perivascular space of $A\beta^{+}$ blood vessels or adjacent to Aβ plaques, implicating specific infiltration of peripheral immune cells into the brain and direct crosstalks between peripheral and brain immunity. Moreover, in AD and other neurodegenerative conditions, the BBB integrity is compromised which may further facilitate the migration of peripheral cells and exchange of immune mediators to the affected brain region. Despite the evidences of a continuous crosstalk between the CNS and peripheral immune system, how peripheral immune responses may influence the onset and progression of AD remains to be elucidated.

Methods: We induced peripheral immune dysregulation by bone marrow (BM) transplant using BM derived from donor mice (C57BL/6-CD45.1) either healthy or with dysregulated peripheral immunity, to the recipient ARTE10 (APP-PS1) AD mice (C57BL/6-CD45.2). Specifically, AD mice were lethally irradiated at 10 weeks of age, prior to the development of Aβ neuropathology, with lead shielding to protect the CNS from radiation. BM isolated from **a)** healthy control mice (10 weeks) **b)** aged mice (14 months old) and **c)** mice with increased basal inflammation were transferred to the AD mice by retro-orbital injection. AD mice without BM transplant were used as control for BM transplant procedure on AD pathology.

Results: AD mice transplanted with BM from old or increased basal inflammation performed significantly worse in spatial memory test compared to the AD mice transplanted with control BM at 6 months of age. At 12 months of age, male AD mice transplanted with BM from mice with increased basal inflammation had reduced peripheral T cells. Female mice transplanted with BM from mice with increased basal inflammation had reduced peripheral T cells and increased the number of neutrophils. We are currently evaluate whether the peripheral cells infiltrate into the perivascular space or the brain parenchyma.

Cerebral Vascular Calcium Signaling in Diabetic Vascular Dementia

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Vascular dementia is a neurodegenerative disease. This disease is also known as vascular contributions to cognitive impairment and dementia (VCID). As well documented, VCID has high morbidity and mortality, and diabetes is a leading factor in the development of VCID. However, the cellular and molecular mechanisms underlying the development of diabetes-induced vascular disease remain to be largely unknown. Moreover, the current treatments for VCID are neither very specific nor effective. It has been generally believed that dysfunctions of cerebral arteries (CAs) to cause blood hypoperfusion to the brain makes an important contribution in the initiation and progress of VCID. Perfusion of CAs is predominantly generated and controlled by contraction and relaxation of smooth muscle cells (SMCs). These two cellular processes are fundamentally produced and regulated by cell calcium signaling. The cell calcium signaling is primarily determined by ion channels on the plasma membrane and sarcoplasmic reticulum (SR) membrane. Therefore, we have started to explore whether and which ion channels might be essential for diabetes-evoked VCID. Consistent with previous reports by us and other investigators, we have found that intraperitoneal injection of streptozotocin caused a large increase in blood glucose, leading to diabetes in mice. A series of our studies have also discovered that the diabetic mice had declined cognition, impaired memory, and increased anxiety, thereby exhibiting significant VCID. This diabetic vascular dementia might occur due to cerebral vasoconstriction and subsequent blood hypoperfusion, as revealed by Laser Speckle Imaging System. Diabetic cerebral vasoconstriction could result from increased intracellular calcium concentration ($[Ca^{2+}]_i$) in CASMCs. Increased $[Ca^{2+}]_i$ was attributed to the augmented Ca^{2+} release from the SR, the major intracellular Ca^{2+} store, which followed the hyperfunctional activity of type-2 ryanodine receptor (RyR2), the calcium release channel on the SR in CASMCs. Biochemical and genetic experiments indicated that the hyperfunction of RyR2 channel was a result of dissociation of FK506 binding protein 12.6 (FKBP12.6), an endogenous channel stabilizer (or inhibitor). In conclusion, our findings provide the first evidence that RyR2/FKBP12.6 dissociation exerts a crucial role in the development of diabetes-caused VCID; presumably, specific pharmacological and genetic inhibition of RyR2 and/or FKBP12.6 stabler in vascular SMCs may become specific and effective treatment options for diabetic VCID and vascular complications.

Key Words: Vascular Dementia, Diabetes, Cerebral Artery, Blood Hypoperfusion, Type-2 Ryanodine Receptor/Calcium Release Channel; FK506 Binding Protein 12.6

Human striatal glia differentially contribute to AD and PD-specific neurodegeneration

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Abstract
The commonalities and differences in cell-type specific pathways that lead to Alzheimer disease (AD) and Parkinson disease (PD) remain unknown. Here, we performed a single-nucleus transcriptome comparison of control, AD, and PD striata. We describe three astrocyte subpopulations shared across different brain regions and evolutionarily conserved between humans and mice. We reveal common features between AD and PD astrocytes and regional differences that contribute toward amyloid pathology and neurodegeneration. In contrast, we found that transcriptomic changes in microglia are largely unique to each disorder. Our analysis identified a population of activated microglia that shared molecular signatures with murine disease-associated microglia (DAM) as well as disease- and regional-differences in microglia transcriptomic changes linking microglia to disease-specific amyloid pathology, tauopathy, and neuronal death. Finally, we delineate undescribed subpopulations of medium spiny neurons (MSN) in the striatum and provide neuronal transcriptomic profiles suggesting disease-specific changes and selective neuronal vulnerability.

Forecasting Alzheimer's Disease Two Years Before Onset from Longitudinal Multimodal Data

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Alzheimer's disease (AD) is the most common form of dementia, causing progressive cognitive impairment, disorientation, and memory loss. Despite years of clinical trials, there is currently no cure for AD and, by the time of diagnosis, as much as 60% of brain matter is already lost. Thus, forecasting Alzheimer's disease years ahead of onset is critical for attempts at early treatment, the selection of subjects for clinical trials, and to facilitate neurologists' study of the disease.
Past research on machine learning for Alzheimer's disease prediction was limited to using cognitive test scores and highly engineered volumetric features, while failing to leverage the potential information found in brain MRIs. Attempts to train 3D and 2D CNNs on the MRIs have been unsuccessful thus far, due to the insufficient amount of data samples available for the massive number of parameters that need to be learned. Moreover, forecasting AD using standard statistical models, simple MLPs and sequential models is typically limited to 6-12 months windows, model stability and performance dropping significantly for longer time windows.

To introduce more complex longitudinal data and detect future disease stages, we propose a sequential deep learning approach that is expressive enough to handle multimodal longitudinal data, with an added unsupervised mutual information CNN encoder to process the 3D MRI scans, while still maintaining stable forecasting performance over forecasting windows of two years or more. We integrate certain domain knowledge via selective features of the disease-relative areas' volumetric data, cognitive test scores and demographic information. The model is designed to get latent features from the multimodal data during the training process that are informative to the forecasting task. To achieve this, we propose a hybrid model of RNN and CNN. On the RNN side, we study a RNN-like structure introducing latent anticipated features to enhance the forecasting performance. On the CNN side, we train a mutual information based unsupervised encoder and extract latent features from the 3D MRIs as supportive side information. The model we are developing will be capable of performing forecasting tasks 2-year ahead of time, while the instability issue brought by long-term forecasting is addressed by our new mechanism of training different parts of the model separately in different stages. One of the future directions of the project lies in forecasting the disease on a longer time gap without loss of accuracy and robustness.

While models trained and evaluated on ADNI data go some way to address the need to predict the incidence of AD years ahead of symptomatic onset, there are still several impediments in the application of the models toward the study of preemptive or palliative treatments. First, the specialized features in ADNI might not match what might be encountered in the real world. Cognitive tests might be different that the ones performed as part of ADNI, while the features engineered from brain MRIs in ADNI may not be practically obtainable for hospital-collected MRIs, placing barriers in the deployment of the models. Second, the distribution from the perspective of health status is different in the general population than in carefully controlled studies with AD-specific cohorts. Further, real-world data is more likely to be cross-sectional as opposed to longitudinal, with the predictive problem closer to survival analysis than a classification problem as it is often set up in studies using ADNI. Finally, the modalities exhibit various levels of predictive capacity over different time windows. We present techniques that address these challenges to make models trained on ADNI applicable to cross-sectional data from the UK biobank, as a proxy for data collected 'in the wild'. We aim to understand the model performance and limitations, and the relative merits of the different modalities, in forecasting long term outcomes of ADRD.

New Investigators in AD Meeting
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New Investigators in AD Meeting
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