Welcome

Welcome to the USC Alzheimer's Disease

Research Center

and

Leonard Davis School of Gerontology

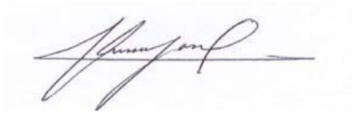
1st ANNUAL FINCH AD

SYMPOSIUM

2017

We are pleased that you could join us today for this event. The goal of this meeting is to honor Dr. Finch for his life-long contributions to Alzheimer's disease (AD) research at USC, to provide a platform for students and post doctoral fellows to present their research, and to bring the USC AD community together.

I hope you enjoy this meeting



Hussein Yassine

University of Southern California

Caleb Finch, Ph. D.

Caleb Finch is an ARCO Professor of Gerontology and Biological Sciences at the University of Southern California, with adjunct appointments in the Dept. of Anthropology, Molecular Biology, Neurobiology, Psychology, Physiology, and Neurology. His major research interests are the neurobiology of aging and human evolution.

Finch received his undergraduate degree from Yale in 1961 (Biophysics) and Ph.D. from Rockefeller University in 1969 (Biology). His life's work is the fundamental biology of human aging, started in grad school and continued on since 1972 at USC. His discoveries include a new form of neurotoxicity of amyloid peptides relevant to Alzheimer disease and the role of shared inflammatory pathways in normal and pathological aging process.

Fifteen of his mentored students hold senior positions in universities or pharmaceutical corporations. Finch has received most of the major awards in biomedical gerontology, including the Robert W. Kleemeier Award (1985), the Sandoz Premier Prize (1995), and the Irving Wright Award (1999). He was the founding Director of the NIA-funded USC Alzheimer Disease Research Center (1984), and continues as co-Director and co-PI. He also co-founded Acumen Pharmaceuticals, which develops therapeutics for Alzheimer disease.

Environmental Determinants of Neuroanatomic Risk for Alzheimer's Disease in Older Women: Role of Fine Particulate Matter

Diana Younan*, Department of Preventive Medicine, University of Southern California, Los Angeles, CA; Xinhui Wang, Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA; Andrew J Petkus, Department of Neurology, University of southern California, Los Angeles, CA; Ramon Casanova, Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC; Ryan Barnard, Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC; Sarah Gaussoin, Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC; Santiago Saldana, Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC; Margaret Gatz, Center for Economic and Social Research, University of Southern California, Los Angeles, CA; Helena C Chui, Department of Neurology, University of Southern California, Los Angeles, CA; Mark A Espeland, Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC; Jiu-Chiuan Chen, Department of Preventive Medicine, University of Southern California, Los Angeles, CA

Background: Emerging epidemiologic and neurotoxicological data suggest ambient particulate matter (PM) as a novel environmental determinant of brain aging. However, whether air pollution exposure is associated with neuropathological changes in preclinical Alzheimer's disease (AD) is unclear.
Methods: We used the AD pattern similarity (AD-PS) score (range: 0-1) as a neuroanatomical brain MRI biomarker for increased risk of AD. The AD-PS algorithm, developed by supervised machine learning and validated with MRI data from Alzheimer's Disease Neuroimaging Initiative, was applied to women aged 71-89 years in the Women's Health Initiative Memory Study (WHIMS) with two 1.5-T scans (2005-6; 2010-11) over an average of 4.7 years. Changes in AD-PS scores were calculated and standardized (as the 5-year difference) to summarize the underlying progression of neuroanatomical (amygdala; hippocampus; parahippocampal gyrus; thalamus; bilateral inferior temporal lobe; midbrain) changes associated with AD. Individual-level daily exposure to $PM_{2.5}$ (PM with aerodynamic diameters <2.5μm), based on residential histories and the Bayesian Maximum Entropy spatiotemporal modelling approach, was estimated and aggregated to 3-year averages preceding the first MRI. Generalized linear models were used to assess the adverse effect of $PM_{2.5}$ on standardized AD-PS change scores.
Results: For 649 women aged 69.2±3.5 years in 2005-6 who remained cognitively normal in 2010-11, each interquartile (2.82 $\mu g/m^3$) increment of 3-year average $PM_{2.5}$ exposure was associated with a 6% ($p<0.01$) increase in AD probability over 10 years. The adverse $PM_{2.5}$-effects remained after adjustment for socio-demographic factors (age; geographic region; race/ethnicity; education; income; employment status), lifestyle (smoking; alcohol use; physical activity), and clinical characteristics (history of depression; body mass index; diabetes; high cholesterol; hypertension; cardiovascular diseases; hormone replacement therapy).
Conclusions: These results provide evidence suggesting that long-term $PM_{2.5}$ exposure contributes to the progression in neuroanatomical risk of AD in preclinical stage. These findings further strengthen the evidence for neurodegenerative effects of exposures to airborne particles.

Boston Naming Test as a Predictor in Cerebral Spinal Fluid Pathology Associated with Alzheimer's Disease in Cognitively Healthy Adults

Authors:

Charleen Wilder, MA, Fuller Theological Seminary
Kristina Moncrieffe, MA, Fuller Theological Seminary

Co-authors:
David Buennagel, BA, Clinical Research Coordinator, Huntington Medical Research Institutes

Dr. Michael Harrington, MD, Molecular Neurology Director, Huntington Medical Research Institutes

Background: Identifying early predictors of Alzheimer's disease is crucial in order to provide early treatment and minimize the negative impact of the disease. The current study is a longitudinal neuropsychological examination of cognitively healthy pre-symptomatic elderly participants with cerebral spinal fluid (CSF) amyloid and tau measurements. CSF amyloid and tau levels are established biomarkers of Alzheimer's disease. Based on their amyloid and tau measurements, participants were classified as having normal amyloid/tau levels (NAT) or pathological amyloid/tau levels (PAT). Examining then neuropsychological differences between cognitively healthy individuals with normal biochemistry, NATs, and those who convert over time to abnormal biochemistry, PATs, can identify predictive behavioral markers. The hypothesis is that the differences in neuropsychological data will predict the change in biochemistry in participants who convert from NATs to PATs.

Methods and Findings: A total of 63 elderly participants were classified by clinical consensus as cognitively healthy (CH). They were tested at two time points: first at an average age of 80 years, then again 40 months later. At each visit, participants underwent a series of biochemical and neuropsychological assessments. Out of the 23 NATs, 14 remained NATs (NAT-NAT) and 9 converted to PATs (NAT-PAT) at the second time point. A logistic regression was used to classify participants based on their amyloid and tau measurements. T-test analyses of neuropsychological data indicated that there was a significant difference between NAT-N and NAT-P on the Boston Naming Test (BNT) at the first time point. Small population size is a limitation of this study.

Conclusions: Our neuropsychological data suggests that CH individuals who will convert to abnormal CSF biochemistry perform lower on the BNT than CH individuals who will maintain normal biochemistry. We propose that performance on the BNT may predict changes in amyloid and tau biochemistry in CH individuals.

PROGRAM

8:30 **INTRODUCTION AND WELCOME**

Pinchas Cohen, Helena Chui and Hussein Yassine

9:00 **Plenary Talk:** Caleb Finch

Past, Present and Future of USC AD research

9:40 **AD biomarkers:**

Introduction: *Meredith Braskie,*

Oral Abstracts

10:30 **AD genetics and Therapy**

Introduction: Jean C. Shih,

Oral Abstracts

11:30 **Lunch Break and Poster Sessions**

1:30 **Introduction:** Kelvin Davis

1:45 **Guest Speaker***:* Bruce McEwen

The Resilient Brain: Epigenetics, Stress and the Lifecourse

2:30 **Clinical studies in AD**

Introduction: *Helena Chui,*

Oral Abstracts

3:00 **Basic AD Mechanisms**

Introduction: *Berislav Zlokovic,*

Oral Abstracts

4:05 **Conclusion and abstract winners**

Bruce S. McEwen, Ph.D.

Dr. McEwen is the Alfred E. Mirsky Professor and Head of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at The Rockefeller University. He is a member of the US National Academy of Sciences, the Institute of Medicine, the American Academy of Arts and Sciences and a Fellow of the New York Academy of Sciences. He served as Dean of Graduate Studies from 1991-93 and as President of the Society for Neuroscience in 1997-98.

As a neuroscientist and neuroendocrinologist, McEwen studies environmentally-regulated, variable gene expression in brain mediated by circulating steroid hormones and endogenous neurotransmitters in relation to brain sexual differentiation and the effects of sex, stress and thyroid hormones on the adult brain. His laboratory discovered adrenal steroid receptors in the hippocampus in 1968.

His laboratory combines molecular, anatomical, pharmacological, physiological and behavioral methodologies and relates their findings to human clinical information. His current research focuses on the effects of stress on amygdala, prefrontal cortex as well as Hippocampus. His laboratory also investigates sex hormone effects and sex differences in these brain regions. In addition, he served on the MacArthur Foundation Research Network on Socioeconomic Status and Health, in which he helped to reformulate concepts and measurements related to stress and stress hormones in the context of human societies. This led to the concept of "allostatic load" that describes the wear and tear on the body and brain from chronic stress and related life style behaviors that lead to dysregulation of physiological stress pathways that are normally protective.

He is also a member of the National Council on the Developing Child which focuses on healthy brain development as a key to physical and mental health. He is the co-author of a book with science writer Elizabeth Lasley, for a lay audience, called "The End of Stress as We Know It", published in 2002 by the Joseph Henry Press and the Dana Press and another book with science writer Harold M. Schmeck, Jr. called "The Hostage Brain", published in 1994 by The Rockefeller University Press.

VEGF's Relationship to Brain Aging Biomarkers

Meral Tubi, Franklin Feingold, Fabian Corlier, Nicki Mostowfi, Paul Thompson, Meredith Braskie

Introduction: Vascular endothelial growth factor (VEGF) is the primary regulator of angiogenesis and has associated neuroprotective properties.[1] VEGF levels may decline with age and Alzheimer's disease (AD) progression.[2,3] However, it remains unclear whether VEGF levels in aging adults relate to brain aging biomarkers.[4,5] VEGF levels may be dependent on the presence of AD-relevant biological stressors, such as amyloid-beta (Ab).[6,7] We hypothesized that in amyloid positive, but not amyloid negative, participants, higher cerebral spinal fluid (CSF) VEGF levels would be associated with greater cortical thickness in regions susceptible to AD-related cortical thinning.[8]

Methods: We evaluated 241 non-demented participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We calculated MRI-derived surface area and cortical thickness (FreeSurfer 5.3) in the entorhinal cortex, posterior cingulate, mean temporal cortex (superior, middle, and inferior temporal and fusiform gyri), and mean parietal cortex (superior and inferior parietal gyri and precuneus), grouping by their shared variance. We related these cortical thickness regions to baseline CSF VEGF levels according to amyloid status (CSF Ab ≤ 192 pg/ml; Ab+). We performed multiple linear regression controlling for age, sex, education, *APOE*4 status, and CSF T-tau and used false discovery rate (FDR) to correct for multiple comparisons.

Results: In Ab+ participants, higher CSF VEGF levels were significantly associated with greater temporal cortex thickness (FDR adjusted VEGF partial p=0.027, t= 2.752, omnibus p<0.001). VEGF was not significantly associated with cortical thickness in the Ab- participants.

Conclusion: Higher CSF VEGF levels were positively associated with higher mean temporal cortical thickness measurements in Ab+, but not Ab-, participants. These results may indicate that the upregulation of VEGF levels early in AD pathogenesis serves a compensatory neuroprotective role in response to Ab deposition. This study provides insight into how VEGF, a modifiable factor, relates to brain aging biomarkers, providing focus to future AD research and intervention efforts.

Hypoxia-induced vascular responses in the adult mouse brain

Melanie D. Sweeney[1], Axel Montagne[1], Robert D. Bell[2], Kassandra Kisler[1], Andrew J. Brumm[3], and Berislav V. Zlokovic[1]

[1]Department of Physiology and Biophysics, Zilkha Neurogenetic Institute, Keck School of Medicine, University of Southern California (USC), Los Angeles, CA, USA
[2]Pfizer Inc. New York, NY, USA
[3]Nikon Instruments, Inc. Melville, NY, USA

Mild continuous hypoxia is a phenomenon observed in several central nervous system (CNS) conditions including diabetic retinopathy, chronic hypoperfusion, and Alzheimer's disease (AD). Pericytes, mural cells that cover capillaries, become dysfunctional and degenerate in ischemic stroke, diabetic retinopathy and AD. Pericytes are vital orchestrators of key neurovascular functions including blood-brain barrier (BBB) integrity, cerebral blood flow (CBF), and angiogenesis. Increased CBF and angiogenesis are physiological responses in brain elicited by a mild hypoxic state. The transcriptional regulation of these structural/functional hypoxic responses has never before been investigated in the adult brain, nor has its corresponding impact on brain microvascular health. Adult wild-type mice exposed to mild continuous hypoxia up to 21 days show a 60% increase in capillary diameter at day 3 and 53% increase in red blood cell velocity by day 7 in the somatosensory cortex using longitudinal multiphoton imaging. Immunohistochemistry reveals an increased regional rate of microvascular density, suggesting that some brain regions are more susceptible to mild hypoxia. Additionally, RNA-sequencing analysis of differentially expressed genes from brain microvascular cells after mild continuous hypoxia reveals significantly upregulated expression of the Gene Ontology categories including cytoskeleton reorganization, cellular response to stress, and cell division. Furthermore, since pericyte-deficient mice are reported to have disrupted oxygen availability and BBB dysfunction, pericyte deficiency is hypothesized to impair the normal physiologic response to mild continuous hypoxia in adult brains. Altogether, elucidating the transcriptional, structural and functional responses to mild continuous hypoxia in the adult brain is vital to inform therapeutic efforts to combat hypoxic insults and/or microvascular dysfunction in numerous CNS disorders such as diabetic retinopathy, chronic hypoperfusion, and AD.

FACULTY SPEAKERS

Helena Chui, M.D.

Dr. Chui is internationally recognized for her research in Alzheimer disease and vascular cognitive impairment. She is the principal investigator for the NIA-funded Alzheimer Disease Research Center, as well as a multi-institutional program project on vascular dementia. Dr. Chui is the author of over 120 publications and has served on the editorial board for Stroke, Alzheimer Disease and Associated Disorders, and Archives of Neurology. She holds the Raymond and Betty McCarron endowed Chair at the Keck School of Medicine and serves as the Chair of the Department of Neurology.

Hussein Yassine, MD.

The Yassine Lab seeks to address the contributions of lipid metabolism to Alzheimer's disease (AD) pathology. Specifically, his laboratory's work has focused on understanding how APOE4 lipid metabolism contributes to AD. The lab utilizes a combination of cellular, animal, imaging and clinical studies to understand changes to the ApoE HDL in the brain and its effects on omega-3 fatty acid brain transport. The lab investigates whether activating the ABCA-1 transporter to form ApoE HDL can offset AD risk in APOE4 carriers.

Meredith Braskie, Ph.D.

Dr. Braskie is an Assistant Professor of Research at the University of Southern California. She received a PhD in Neuroscience from the University of California in Los Angeles. Her research focuses on neuroimaging Alzheimer's disease (AD) risk and cognitive aging, with an emphasis on preclinical AD and early mild cognitive impairment. In particular, her lab seeks to better understand how genetic and environmental risk factors for AD - and their underlying biological mechanisms - relate to brain structure, function, and connectivity. To do this, they use relevant blood and cerebrospinal fluid measures and multimodal imaging (structural and functional MRI, diffusion tensor imaging, FLAIR imaging, and PET).

Jean C. Shih, Ph.D.

Dr. Shih is a University Professor, and the Boyd & Elsie Welin Professor of Pharmacology and Pharmaceutical Sciences at USC's School of Pharmacy. She has defined two types of monoamine oxidase (MAO) and has won international acclaim for her study establishing the link between gene and behavior by showing that mice lacking MAO A gene display aggression. Her important contributions have formed the present knowledge of MAOs in brain development and peripheral functions ; and provided new strategy for the treatment of autism spectrum disorders (ASD), anxiety and other mental disorders. She has discovered and developed MAO A inhibitors as novel diagnostic and therapeutic agents for brain and prostate cancers for which she holds two patents. Among numerous awards she received are NIH MERIT Awards, twice; USC Associates Award for Creativity in Research and Scholarship; Volwiler Research Achievement Award from American Association of College of Pharmacy; Lifetime Achievement Award, SCBA; Fellow AAAS; Honorary Professor, Taipei Medical University, China Jiaotong University, Member of Academia Sinica, Taiwan.

Gastrointestinal vagal afferent signaling promotes hippocampal-dependent memory function in rats

Andrea N Suarez[1], Ted M Hsu[1], Guillaume De Lartigue[2], Scott E Kanoski[1]

[1]University of Southern California, Los Angeles, CA, United States

[2]John B. Pierce Laboratory, Yale University, New Haven, CT, United States

The vagus nerve is the primary conduit of communication between gastrointestinal (GI) signals and the brain. Electrical stimulation of the vagus nerve increases synaptic plasticity in the hippocampus (HPC) in rodents and may have potential efficacy in the treatment of Alzheimer's disease. However, the physiological relevance of GI-derived vagal signaling to HPC-dependent memory function is unknown, as are the neurobiological pathways linking the vagus nerve to the HPC. Here we explored whether chronic disruption of gut-to-brain vagal tone via subdiaphragmatic vagotomy (SDV) negatively impacts HPC-dependent memory function in rats. Results reveal that SDV impaired spatial working memory (Barnes maze) and contextual episodic memory (novel object in context; NOIC), two HPC-dependent tasks that involve mnemonic processing of visuospatial stimuli. Next, to determine whether GI vagal sensory/afferent vs. motor/efferent signaling regulates HPC-dependent memory function, we employed a novel approach in which a saporin conjugated to cholecystokinin (CCK-SAP) or an unconjugated control saporin is injected into the nodose ganglia, a strategy that preserves 100% of vagal efferent signaling while eliminating ~80% of GI-derived vagal afferent signaling. Similar to SDV rats, CCK-SAP rats were impaired in both the Barne's maze task and NOIC learning relative to controls. Consistent with the memory deficits, immunoblot protein analyses in dorsal HPC lysates revealed reduced neurotophic (brain-derived neurotrophic factor [BDNF]), and neurogenesis (doublecortin [DCX]) markers in both SDV and CCK-SAP rats relative to controls. Lastly, our viral-based neuroanatomical tracing methods revealed a multisynaptic pathway connecting the medial nucleus tractus solitarius in the caudal brainstem, the first brain region to receive vagal afferent signaling, to the dorsal HPC via medial septum input to HPC glutamatergic neurons. These findings reveal that endogenous GI-derived vagal afferent signaling is critical in regulating HPC-dependent memory function, and that vagally-mediated signals are communicated to the HPC via a rainstem-septal multisynaptic pathway.

Dance Experience and Associations with Cortical Gray Matter Thickness in the Aging Population

Porat Shai.[a, b] · Goukasian N.[a, b] · Hwang K.S.[a,b,e] · Zanto T.[c] · Do T.[a, b] · Pierce J.[a, b] · Joshi S.[a] · Woo E.[a, b] · Apostolova L.G.[a,b,d]

Author affiliations

[a]Department of Neurology, David Geffen School of Medicine at UCLA, and [b]Mary S. Easton Center for Alzheimer's Disease Research, Los Angeles, Calif., [c]Department of Neurology, UCSF, San Francisco, Calif., [d]Department of Neurology, Indiana University, Indianapolis, Ind., and [e]Oakland University William Beaumont School of Medicine, Rochester, Mich., USA

Introduction: We investigated the effect dance experience may have on cortical gray matter thickness and cognitive performance in elderly participants with and without mild cognitive impairment (MCI).

Methods: 39 cognitively normal and 48 MCI elderly participants completed a questionnaire regarding their lifetime experience with music, dance, and song. Participants identified themselves as either dancers or nondancers. All participants received structural 1.5-tesla MRI scans and detailed clinical and neuropsychological evaluations. An advanced 3D cortical mapping technique was then applied to calculate cortical thickness.

Results: Despite having a trend-level significantly thinner cortex, dancers performed better in cognitive tasks involving learning and memory, such as the California Verbal Learning Test-II (CVLT-II) short delay free recall ($p = 0.004$), the CVLT-II long delay free recall ($p = 0.003$), and the CVLT-II learning over trials 1-5 ($p = 0.001$).

Discussion: Together, these results suggest that dance may result in an enhancement of cognitive reserve in aging, which may help avert or delay MCI.

Kelvin Davies, Ph.D., D.Sc.

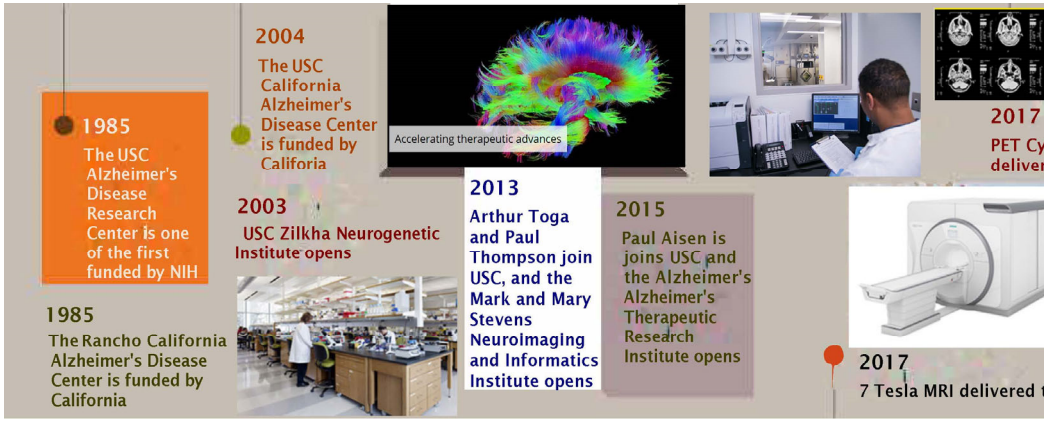
Dr. Davies is the James E. Birren Chair of Gerontology. Professor Davies was born and raised in London, England. Deeply involved in research into oxidative stress and free radicals, Professor Davies is the (founding) Editor-in-Chief of the premier scientific journal in the field, Free Radical Biology & Medicine. Professor Davies is a Fellow of the Oxygen Society; a Fellow of the Society for Free Radical Biology & Medicine; a Fellow of the Gerontological Society of America; a Fellow of the American Association for the Advancement of Science; a Fellow of the Royal Institution (London); winner of the Harwood S. Belding award of the American Physiological Society; and holder of various medals, honorary degrees, and fellowships from several universities and scientific societies.

Berislav V. Zlokovic, MD., Ph.D.

Dr. Zlokovic is the director of the Zilkha Neurogenetic Institute, Professor and Chair of the Department of Physiology & Biophysics at the Keck School of Medicine of USC, and a Professor of Biological Sciences at the Dornsife College of Letters, Arts and Sciences. Zlokovic has a life-long career in studying the role of cerebral blood vessels in the pathogenesis and treatment of neurological disorders such as Alzheimer's disease and related disorders. He is the recipient of many awards, including the MetLife Award, the Potamkin Prize, the Javits Award and the MERIT Award. He is a fellow of the American Association for Advancement of Science (AAAS) and a member of The Dana Alliance for Brain Initiative, the Serbian Academy of Sciences and Arts and The European Academy of Sciences (Academia Europeae).

Timeline of Alzheimer's

USC TIMELINE



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Assessing test-retest reliability of phase contrast MRI for measuring cerebrospinal fluid flow dynamics in Alzheimer's disease

Ashwin Sakhare, A. Lisette Isenberg, & Judy Pa
Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA

Department of Biomedical Engineering, University of Southern California, Los Angeles, CA

OBJECTIVE
To establish test-retest reliability of cerebrospinal fluid flow (CSF) in cognitively normal (CN) adults to investigate CSF flow dynamics in Alzheimer's disease (AD).

BACKGROUND
The pathogenesis of AD is characterized by the accumulation of amyloid plaques in the brain. Evidence from animal studies suggests an association between AD and CSF flow, as increased CSF flow in perivascular pathways caused greater amyloid plaque clearance. However, few studies have examined CSF flow dynamics and AD in humans. The goal of this study was to test the reliability of CSF flow parameters in humans to be used as a biomarker of CSF flow.

DESIGN/METHODS
Flow data was acquired on 22 CN young adults (ages 20-35), on a 3T Siemens Prisma MRI using a 2D cine-PC pulse sequence with retrospective gating: 32 frames/CC; 140x140mm^2 FOV; 20° flip-angle; venc-10cm/s (CA), 5cm/s (SS); 60% phase oversampling; 336x336 matrix with interpolation; 5mm slice thickness. Three consecutive flow measurements were obtained at the cerebral aqueduct (CA) and C2-C3 subarachnoid space (SS). Coefficient of variance (CV) and intra-class correlation coefficient (ICC) analysis was used to assess reliability.

RESULTS
Stroke volume (SV), considered to be the strongest indicator of CSF flow dynamics, showed excellent reliability at the aqueduct (CV<15%, ICC=.97), as well as the C2-C3 SS (CV<10%, ICC=.98). Six of eight additional exploratory CSF flow parameters also showed excellent reliability (CV<=10%, ICC>.80). Preliminary results from a sub-study of 7 older adults show that aqueductal SV is strongly associated with time spent daily in moderate-vigorous physical activity ($p<.05$).

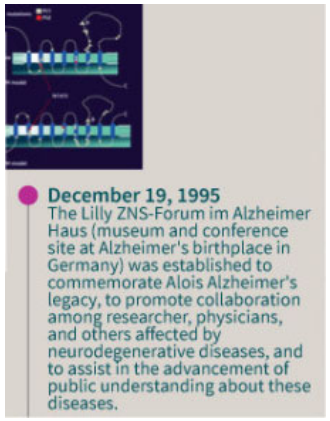
CONCLUSIONS
CSF flow can reliably be measured in humans using PC-MRI. Additional studies are currently looking at the association between CSF flow dynamics, amyloid burden, and physical activity levels in a cohort of older adults with MCI. Results from this study could provide evidence for exercise as a disease-modifying intervention for AD.

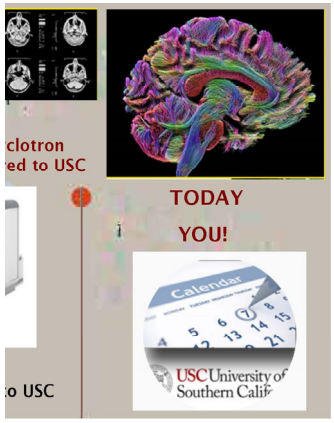
The genetic heritability component of optimal brain aging

Brandalyn C. Riedel, Faisal Rashid, Sophia Thomopoulos, Marc Harrison, Lauren Salminen, Neda Jahanshad, Sarah Medland, Paul M. Thompson

Studying aging of the human brain allows for understanding of how healthy an individual's brain appears for their age, while also allowing insights into deviations from this normal trajectory. For instance, debate exists as to whether neurodegenerative diseases follow this trajectory at an accelerated rate, or whether conditions like Alzheimer's indicate an altered aging trajectory altogether. Understanding heritability, or the proportion of phenotypic variance that is due to genetic factors, provides further insights into whether or not optimal brain aging is itself genetically determined, or whether ancillary genetically linked conditions, such as cardiovascular disease are the primary drivers in deviations from this normal trajectory. To better answer these questions requires large-scale studies across the aging spectrum. Here, we studied an optimal aging neurologically healthy cohort from the UK Biobank, a long-term study in the United Kingdom, to predict and subsequently better understand aging in a cohort across a wide-range of diseases (N > 5,000). We use differences between actual and predicted structural brain measurements to then investigate the broad-sense heritability of these differences using genome-wide variations through a kinship matrix. We investigated individuals age 45-64 and 65-77, both separately and jointly, to better understand differences across age, and also looked within sex to determine sex-specific characteristics. While preliminary, these results show that the heritable component to deviations from an optimal trajectory interacts with disease, age, and sex, and that certain regions show greater impact to both.

Disease 1985 — Today





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2017 Observational Studies at USC

- Healthier Vessels, Healthier Brain Study (HVHB)
- Vascular & Genetic Contributions to Alzheimer's Disease
- Structural & Functional Connectome in Familial & Sporadic Alzheimer's Disease
- ADNI 3 Imaging Study

2017 Clinical Trials at USC

- LEARNit (Lifestyle Enriching Activities for Research in Neuroscience, intervention trial)
- A4 Study for Healthy Older Adults
- The EMERGE Study of Aducanumab for Early Alzheimer Disease
- The CREAD Study of Crenezumab for Early Alzheimer Disease

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Detailed Schedule of Symposium

Time	Events	Speakers/Title
8:30-8:45	Introduction	Pinchas Cohen
8:45-9:00	USC ADRC	Helena Chui and Hussein Yassine
9:00-9:40	Plenary Talk	Past, Present and Future of USC AD research (Tuck Finch)
9:40-9:50	AD biomarkers	Meredith Braskie
9:50-10:00	Oral Abstract	Assessing test-retest reliability of phase contrast MRI for measuring cerebrospinal fluid flow dynamics in Alzheimer's disease (Sakhare)
10:00-10:10	Oral Abstract	VEGF's Relationship to Brain Aging Biomarkers (Tubi)
10:10-10:20	Oral Abstract	Predicting Alzheimer's disease markers and clinical diagnosis (Iddi)
10:20-10:30	Oral Abstract	Environmental Determinants of Neuroanatomic Risk for Alzheimer's Disease in Older Women: Role of Fine Particulate Matter (Younan)
10:30-10:40	AD Genetics and Therapy	Jean Shih
10:40-10:50	Oral Abstract	Neuronal-specific PICALM deficiency causes cognitive impairment and brain atrophy (Lazic)
10:50-11:00	Oral Abstract	Effects of APOE genotype and Western diet on metabolic and Alzheimer-related outcomes in female mice (Christensen)
11:00-11:10	Oral Abstract	An FDA-approved drug as a therapeutic agent to upregulate PICALM (Kisler)
11:10-11:20	Oral Abstract	In vitro, In vivo and cerebrospinal fluid studies implicate decreased ABCA-1 activity with APOE4 (Rawat)
11:20:1130	Oral Abstract	Intersection of TREM2-C1q in Alzheimer's disease (Leung)
11:30-1:30	Lunch and Poster Sessions	Poster session

In vitro, In vivo and cerebrospinal fluid studies implicate decreased ABCA-1 activity with APOE4

V. RAWAT[1], A. BOEHM-CAGAN[2], , J. JOHANSSON[4],, H. C. CHUI, , M. G. HARRINGTON[3]; D. M. MICHAELSON[6], H. N. YASSINE[1]

[1]USC, Los Angeles, CA; [2]Tel Aviv Univ., Herzilya, Israel; [3]Huntington Med. Res. Inst., Pasadena, CA; [4]Artery Therapeut., San Ramon, CA; [5]UC Berkeley, Berkeley, CA; [6]Tel-Aviv Univ., Tel-Aviv, Israel

Background: We previously reported decreased ABCA-1 activity in cerebrospinal fluid of participants with cognitive impairment and Alzheimer's disease (AD). Our aim is to study the interaction of APOE4 with ABCA-1 activity and expression in astrocytes, in APOE4 mice, and in cerebrospinal fluid form participants grouped by APOE genotype.

Methods: ABCA-1 expression was assessed in astrocytes that express human APOE isoforns and in APOE mice. The ability of cerebrospinal fluid (CSF) to activate ABCA-1 was examined in cells. Samples from 59 older individuals with and without cognitive impairment were analyzed for ApoE particle size as a proxy for lipidation using native PAGE, and ABCA-1 cholesterol efflux activity.

Results: ApoE4 astrocytes had decreased ABCA-1 expression (71.51 % less than ApoE3 astrocytes, n=3, $p<0.001$) that was associated with hypolipidated APOE4. These findings were also observed in human apoE4 targeted replacement mice (17.14 % less than apoE3 mice n=3, $p<0.05$). In humans, CSF ApoE is resolved in four distinct bands by electrophoresis α_0 (>669 KDa), α_1 (600 KDa), α_2 (440 KDa) and α_3 (232-140 KDa). Amount of total ApoE present in α_0 size was reduced in ε4/ε4 vs ε3/ε3 individuals (3.208 (0.6156) % N=3 vs 8.904 (4.019) % N=29, $p<0.05$), whereas total ApoE in α_2 size was increased in ε4/ε4 vs ε3/ε3 individuals (60.68 (8.207) % N=3 vs 37.34 (16.80) % N=31, $p<0.05$). ABCA-1 mediated cholesterol efflux capacity of CSF was assessed in by cell culture assays. CSF from ε4/ε4 individuals (N=3) has reduced capacity to induce cholesterol efflux compared to CSF from non ε4 individuals (N=9) (adjusted efflux 1.29 vs 1.59, $p<0.05$).

Conclusions: APOE4 was associated with reduced ABCA-1 activity and hypolipidated APOE4 both in vivo and in vitro. Compared with ε3/ε3, CSF samples from individuals with ε4/ε4 demonstrated significantly lower

Evaluation of potential MR contrast agent brain accumulation using high resolution T1-weighted MRI analysis in cognitively impaired participants: A longitudinal study

Gautham Rajagopal[1], Axel Montagne[1], Meng Law[2], Arthur W. Toga[3], Berislav V. Zlokovic[1]

[1]Zilkha Neurogenetic Institute and Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA
[2]Department of Radiology, Neuroradiology Division, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA
[3]Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA

Gadolinium chelates are widely used as contrast media for magnetic resonance (MR) imaging in both clinical diagnostic and pre-clinical studies. Recent reports have shown that repeated administrations of Gadolinium-based contrast agents (GBCAs) may cause Gadolinium retention in the brain parenchyma. Indeed, research studies have indicated that an increase in T1-weighted magnetic resonance imaging (MRI) signal intensity in specific deep cerebellar brain regions (*i.e.*, globus pallidus and dentate nucleus) have been observed in participants having received multiple administrations of linear chelates (*i.e.*, a mean of 4-6 injections within a 36-45-month period which corresponds to one injection every 4-8 months in average), but not or significantly less with cyclic chelates. These data were also confirmed using post-mortem electron microscopy and inductively coupled plasma mass spectrometry techniques. While all studies retrospectively focused on primary brain tumors, brain metastasis, multiple sclerosis and stroke, we aimed at identifying MR signal change differences in several grey and white matter areas between gadobenate dimeglumine (linear) and gadoterate meglumine (cyclic) in individuals with no cognitive impairment (NCI) and mild cognitive impairment (MCI). We re-invited 20 participants for an additional MR scan session without contrast, several months after their intravenous GBCA injection. Ten received a dose of linear contrast (age range 67-91y; 78% females; 6 NCI vs 4 MCI; average interval between first injection and re-invitation: 21 months) and the other ten a dose of cyclic contrast (age range 65-86; 50% female; 8 NCI vs 2 MCI; average interval between first injection and re-invitation: 11 months). T1-weighted signal intensities between pre- and post-GBCA data were investigated and compared within different brain regions including the hippocampus and its subfields since it has been recently reported that BBB breakdown during normal aging begins in the hippocampus and may contribute to cognitive impairment. After the use of a modified pre-processingautomated skull stripping and brain segmentation software, no difference in MR signal intensities between linear and cyclic groups were observed in all grey and white matter regions-of-interest including the hippocampus as well as globus pallidus and dentate nucleus. No significant difference either in NCI versus MCI brains. Our study concludes that there is no Gadolinium brain accumulation detected in cognitively normal and impaired individuals who received one administration of either linear of cyclic chelates after a 10-20-month period.

1:30-1:45	Introduction	Kelvin Davies
1:45-2:35	Plenary Speaker	The Resilient Brain: Epigenetics, Stress and the Lifecourse (Bruce McEwen)
2:35-2:45	Clinical AD	Helena Chui
2:45-2:55	Oral Abstract	Changes in Depression Severity Correlate with Quality of Life in Alzheimer Disease: a Longitudinal Study (Joe)
2:55-3:05	Oral Abstract	Changes In T-cell Mitochondrial Metabolism In Pre-Dementia Stages of Alzheimer's Disease. (Hubbard)
3:05-3:15	AD Mechanisms	Betza Zlokovic
3:15-3:25	Oral Abstract	T cell TGF-beta signaling control of the immune response to cerebral Aβ (Im)
3:25-3:35	Oral Abstract	Gastrointestinal vagal afferent signaling promotes hippocampal-dependent memory function in rats (Suarez)
3:35-3:45	Oral Abstract	Hypoxia-induced vascular responses in the adult mouse brain (Sweeney)
3:45-3:55	Oral Abstract	Cranial pericytes derived from neural crest cells reveal a pericyte-specific functional defect in Alzheimer's Disease (Griffin)
3:55-4:05	Oral Abstract	Traffic-Derived Nanoparticles ('Vehicular Smog') Attenuate Adaptive Homeostasis and Promote Protein Dysregulation in an Age-Dependent Manner: An Accelerator of Alzheimer's Disease? (Pomatto)
4:05-4:15	Concluding remarks and abstract winner announcement	Helena Chui and Hussein Yassine

Peripheral blood markers of cell cycle dysregulation are associated with Alzheimer's disease biomarkers

Jocelyn Argueta & Judy Pa

Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA

OBJECTIVE
This study aims to identify peripheral blood markers implied in cell cycle dysregulation that can be used as biomarkers of neurodegeneration and pathology specific to Alzheimer's disease.

BACKGROUND
Neurons are fully differentiated cells that do not divide and remain in an arrested, G0, stage of the cell cycle. Analysis of postmortem brain tissue from patients with Alzheimer's disease (AD), however, shows expression of key cell cycle proteins suggesting that neurons have erroneously re-entered the cell cycle. Coupled with other early markers of AD, such as oxidative stress and inflammation, cell cycle dysregulation could be used to understand etiology of AD and indicate early neurodegeneration.
DESIGN/METHODS
Using gene expression data derived from blood samples from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we compared expression of different cell cycle markers to changes in brain volume, clinical diagnosis, and changes in Aβ, total tau, and phosphorylated tau CSF levels.
RESULTS
The study included 94 subjects (mean age 79.6 ± 6.9 years, 39 female, 55 male) with clinical diagnosis of cognitively normal, mild cognitive impairment, or AD. We found an inverse relationship between blood concentrations of MDM4 and hippocampal volume, across all subjects. Additionally, we found a direct correlation between blood concentrations of MDM4 and ATR with CSF levels of total tau and phosphorylated tau (all p's < 0.05)

CONCLUSIONS
MDM4 is an upstream regulator of cell division. Our results indicate that high levels of MDM4 are associated with overproduction of tau and neurodegeneration in the hippocampus. ATR is also involved with the regulation of DNA damage leading to prolonged cell cycle arrest or apoptosis. Together our results suggest that MDM4 and ATR can be used as potential biomarkers for aberrant cell cycle re-entry that fails to complete division and instead results in cell death.

A Statistical Model for Automatic Staging and Prediction of Alzheimer's Disease

Arya A. Pourzanjani[1]
Benjamin B. Bales[1]
Michael Harrington[2]
Linda R. Petzold[1]

[1] Department of Computer Science, University of California, Santa Barbara, CA
[2] Huntington Medical Research Institute, Padadena, CA

The continual progression of Alzheimer's Disease (AD) is characterized by marked changes in various biomarkers, imaging diagnostics, and psychological evaluations. In practice, panels of clinicians assess these actors, as well as patient history, to determine whether a patient has, or is at risk of developing AD and/or other types of dementias. The heterogeneity in patients, types of dementias, and specific progression paths makes this a painstaking task whereby experts in neurology, cardiology, radiology, and psychology must meticulously analyze this data to come to a consensus diagnosis. Building off of previous works, we introduce a new statistical model for tracking the progression of AD using a patient's longitudinal clinical data. The model uses available clinical data to categorize patients with AD and identify what stage of the disease they are in by assigning them a continuous disease progression score ranging from 0 to 100 with confidence bounds. The model can be extended to identify the relevant clinical values that determine why a patient's score was within a certain range. This approach in combination with the score itself, can be used to aid clinicians in their diagnoses, quickly point them to relevant diagnostic values, and ultimately free up time to assess more patients. Furthermore, the model provides forecasts and confidence intervals of how a patient's disease progression score and biomarkers will evolve, which can be useful in assigning and testing the efficacy of interventions. Lastly, the model is not limited by the modality of data it requires; it can produce estimates and predictions using any available data even when a patient has for example, CSF data, but not imaging data. Less data or missing modalities will be reflected in wider confidence intervals, but the model can also be used to determine which tests will narrow these confidence intervals the most, and thus provide the most information relevant information regarding a patient's state. This latter feature is particularly useful in determining which diagnostics will be most useful in cost constrained settings.

Traffic-Derived Nanoparticles ('Vehicular Smog') Attenuate Adaptive Homeostasis and Promote Protein Dysregulation in an Age-Dependent Manner: An Accelerator of Alzheimer's Disease?

Laura C.D. Pomatto[1], Mayme Cline[1], Nicholas Woodward[1], Todd E. Morgan[1], Caleb E. Finch[1,2], Henry Jay Forman[1], and Kelvin J. A. Davies[1,2*]

Environmental toxicants, such as vehicular-derived particulate matter, can act as accelerators of protein damage and accumulation of protein aggregates in various age-related diseases such as Alzheimer's disease (AD). Indeed, long-term exposure to vehicular derived nanoparticles accelerated all-cause dementia and caused significant declines in cognitive function (Cacciottola et al., 2017 Translational Psychiatry). Organisms rely on proteolytic enzymes, and their induction by adaptive homeostasis, to minimize accumulation of damaged proteins. The leading transcriptional activator associated with adaptation to oxidative stress is Nrf2, which regulates a plethora of stress responsive proteins, including the 20S proteasome. To better understand the impact of environmental toxicants on adaptive homeostasis, young (6 month) and middle-aged (21 month) mice were exposed to either filtered air or reaerosolized vehicular-derived nanoparticulate (nPM) matter. In young mice, nPM exposure caused an adaptive increase in expression of Nrf2 target genes such as Proteasome and Immunoproteasome, with concomitant increases in cellular capacity to degrade oxidatively damaged proteins. These protective effects were lost, however, in middle age where an increase in the Nrf2 transcriptional inhibitors, Bach1 and c-Myc, appeared to block Nrf2 adaptive responses. Thus, both age and nPM exposure negatively impact Nrf2 inducible adaptive responses that are crucial for the clearance of damaged proteins. Our results demonstrate a conserved trend of age-dependent loss of adaptive homeostasis, first demonstrated by us in worms and fruit flies. Dysregulation of protein clearance systems may accelerate age-associated diseases, including AD, and loss of Proteasome activity is a feature of Alzheimer's pathology. Both amyloid accumulation and Tau hyper-phosphorylation appear to negatively impact Proteasome, which normally degrades both Tau and amyloid. Greater mechanistic understanding of the mechanism(s) behind Proteasome dysfunction with age and exposure to environmental pollution will be critical in unraveling Alzheimer's disease initiation and development, and in the targeted exploration of disease prevention or effective therapies.

A multi-modal, multi-atlas based approach for Alzheimer detection via machine learning

[a]Yousra Asim, [b]Saima Rathore, [c]Lal Hussain, [a]Mohammad Aksam Iftikhar
[a] Department of Computer Science, Comsats Institute of Information Technology, Pakistan.
[b] Center for Biomedical Image Computing and Analytics, Perelman School of Medicine, University of Pennsylvania, U.S.A.
[c]Department of Computer Science and Information Sciences, University of Azad Jammu and Kashmir, Pakistan.

Brain parcellation-based computer-aided methods, which segregate the brain in different anatomical regions and use features of these regions, for detecting Alzheimer's disease (AD) and mild cognitive impairment (MCI) have gained increasing attention in the last decade. Brain parcellation generally is carried out based on existing anatomical atlas templates, which vary in size and number of delineated anatomical regions and hence capture the brain atrophy from different angles. We hypothesized that if we were to divide the brain based on different atlases and combine the features extracted from the resultant parcellations, the AD/MCI classification accuracy may increase. We collected 300 subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database and divided brains based on two well-known atlases: LONI Probabilistic Brain Atlas (LPBA40) and Automated Anatomical Labeling (AAL). We used baselines images of structural magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), and calculated average gray-matter density and average relative-cerebral-metabolic-rate-of-glucose in each region. Later we classified AD, MCI and cognitively normal (CN) subjects using single- (LPBA40, AAL) and multi-atlas (LPBA40+AAL) features. We reduced the dimensionality of single- and multi-atlas features using the principal component analysis, and employed 10-fold cross-validation through Gaussian kernel of support vector machines. The most important region involved in classification was left hippocampus for AAL atlas (p-value<0.0001) and left inferior occipital gyrus for LPBA40 atlas (p-value<0.0001). Multi-atlas features showed considerably improved classification accuracy (ADvsCN=94.0, ADvsMCI=75.5, ADvsMCI=76.5) compared to best single-atlas accuracy (ADvsCN=88.5, ADvsMCI=68.5, ADvsMCI=71.5). The results indicate that features of LBPA40 atlas yield better classification success rate compared to AAL in all the cases (P<0.0001). Results revealed that advanced quantitative image analysis and multi-atlas features can reveal AD predictive patterns, which would otherwise not be appreciated by visual examination or use of individual features. These multi-atlas predictive patterns can significantly augment diagnostic process of AD.

THE ROLE OF CSF REGULATION AND PARAVASCULAR SPACES IN THE PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE AT 7T

Giuseppe Barisano[1], Samantha J. Ma[2], Danny J. Wang[2], Yonggang Shi[2], Arthur Toga[2], Meng Law[1,2].

1 USC Department of Radiology, Los Angeles, CA, USA

2 USC Stevens Institute of Neuroimaging and Informatics, Los Angeles, CA, USA

PURPOSE: Alzheimer's disease (AD) is the most common cause of dementia and significantly affects morbidity and mortality in the aging population. Despite the huge effort made by the scientific community, the pathogenesis of AD is still unclear. In recent years, the mechanisms for clearance of waste products such as amyloid-beta (Aβ) and tau have been proposed to occur via cerebral lymphatic drainage pathways, including the glymphatic system and its network of paravascular spaces (PVS). Our purpose is to report what is currently known about the glymphatic system and its potential role in the pathophysiology of AD. Moreover, we aim to accurately characterize and quantify the PVS at 7T MRI and determine their role as a potential biomarker of vascular cognitive impairment and dementia (VCID) and AD.

APPROACH: In this educational exhibit, we review the scientific literature and analyze the morphologic characteristics of the brain's PVS at ultrahigh field 7T MRI compared to 3T MRI. The glymphatic system is a major component for the clearance of Aβ, and an underlying cerebrovascular disease may influence its normal functioning; therefore, the scanned subjects included participants with vascular risk factors. Young and old healthy subjects were used as controls.

FINDINGS: Our preliminary study confirmed that PVS are enlarged on MRI scans in subjects with vascular risk factors. 7T MRI provides improved visualization of perforating vessels and PVS, and quantitative analysis is currently in progress to characterize their structural differences.

CONCLUSION: The glymphatic system is fundamental for a healthy brain, and its impairment leads to accumulation of toxins, including Aβ and tau. Subsequently, neuroinflammation and astrogliosis develop, resulting in an additional progressive deterioration of the lymphatics' function. Enlarged

LDL particle species and cerebral amyloidosis.

Trusha Parekh[1], Sarah M. King[2], Bruce Reed[3], Helena C. Chui[1], Ronald M. Krauss[2], and Hussein N. Yassine[1]

University of Southern California
Children's Hospital Oakland Research Institute and University of California San Francisco
National Institutes of Health

Cerebral amyloidosis is a condition in which β-Amyloid (Aβ) proteins are deposited in the cerebral cortex and is a predictor of Alzheimer's disease (AD). In the Aging Brain Study, we reported an association between LDL cholesterol and cerebral amyloidosis assessed using PET PiB imaging. LDL comprises multiple species of varying size, density and protein composition, including very large LDL-I which is enriched in ApoE and can bind to ApoE receptors. In this study, LDL particle fractions were measured in plasma samples of 58 participants (40 women and 18 men) of the Aging Brain study. Cerebral amyloidosis was assessed using Pittsburgh Compound B index-Positron Emission Tomography (PiB-PET) imaging. LDL subfractions were analyzed by the method of ion mobility. The subjects were divided into three groups based on PiB tertiles. Compared to the first tertile, total plasma cholesterol as well as LDL cholesterol were greater in patients in the second and third PiB index tertiles (p values = 0.05 and 0.03 respectively). Amongst the LDL subfractions, levels of LDL-I as well as very small LDL-IVa particles were significantly greater in the second and third PiB index tertiles and independent of LDL cholesterol levels (p values = 0.03 and 0.04 respectively). A significant inverse association was also observed between LDL-I and hippocampal volumes (r=-0.33, p=0.02). We suggest that LDL-I level may be a mechanistic biomarker for extent of cerebral amyloidosis. Lipoprotein receptors, particularly LRP-1, participate in Aβ clearance from the brain and its hepatic degradation. One potential mechanism for our findings is competition between plasma-derived LDL-I and brain Aβ that may retard Aβ clearance and degradation.

Intersection of TREM2-C1q in Alzheimer's disease

Authors: **Leung, B. P.*[1]**, Doty, K. R*[1]., Miller, C. J.[1], Uchoa, M.F.[1], Weitz, T. M.[1], Vesling A. R.[1], Im, K. W.[1], Guillot-Sestier, M.V.[1,2], Quihuis, A. M.1, Razi, R. S.[1], Gate. D.[1,3], Rodriguez, J. Jr.[1], Chang, K. T.[1], Tenner A. J.[4], Colonna M.[5], Town., T[1].

** Both authors contributed equally to this work*

Affiliations:

University of Southern California, Department of Biophysics and Physiology, Zilkha Neurogenetics Institute, Los Angeles, CA 90033.
Trinity College, Department of Physiology, Institute of Neuroscience, Dublin, Ireland.
Stanford University, Department of Neurology and Neurological Sciences, MSLS Building, Stanford, CA 94305.
Yale University
University of California Irvine, Department of Neurobiology and Behavior, McGough Hall, Irvine, CA 92697.
Washington University of Medicine in St. Louis, Department of Pathology and Immunology, BJC-IH Building, St. Louis, MO

Alzheimer's disease (AD), the most common form of dementia, is a debilitating neurotoxic cascade of events driven by the aggregation of Amyloid β (Aβ) peptides, ultimately robbing patients of their memories. Late onset AD (LOAD) is thought to be a complex interplay of both environmental exposures and genetic variants of key risk factors. Recent gene-wide association studies and gene-network analyses indicate that two distinct innate immune pathways are strongly associated with LOAD: Triggering Receptor Expressed on Myeloid cells 2 (TREM2) and the complement system. While classically regarded as regulators of distinct immunological responses, limited data has suggested roles of TREM2 or the C1 complex in the AD inflammatory environment. In this study, we biochemically demonstrate that TREM2, C1q, and Aβ physically interact in a heteromeric complex. We further show that soluble Aβ preferentially binds to TREM2, while C1q more avidly associates with Aβ aggregates. In AD mouse models, compound genetic loss of TREM2 and C1q abrogates ERK signaling. Peripheral monocyte experiments demonstrate that C1q opsonized Aβ phagocytosis is not only Trem2 dependent but also pERK1/2 dependent. These results indicate an unexpected physical and signaling intersection between TREM2 and C1q in AD pathogenesis, with important implications for myeloid Aβ phagocytosis, clearance, and immunoproteostasis.

TRAP-nPM induced pro-amyloidogenic, pro-inflammatory and neurotoxic effects in rodent model exposure.

M. CACCIOTTOLO[1], T. E. MORGAN[1], N. C. WOODWARD[1], C. D'AGOSTINO[1], A. SAFFARI[2], F. SHIRMOHAMMADI[2], C. SIOUTAS[2], C. E. FINCH[1]

1. USC Leonard Davis School of Gerontology, Los Angeles, CA

2. USC Viterbi School of Engineering, Los Angeles, CA

In the search for environmental neurotoxic factors in AD and related disorders (ADRD), traffic-related air pollution (TRAP) is getting increasing consideration. Many groups, including ours, have reported that exposure to air pollutant particulate matter (PM) from different sources (diesel, urban traffic, nickel) has a toxic impact on the brain.

Using a laboratory-based exposure model, in collaboration with the USC Viterbi School of Engineering, we are examining the role of PM exposure on amyloidogenesis, behavioral and inflammatory outcomes. We used TRAP-nPM (<200nm) collected adjacent to the CA-110 freeway in downtown Los Angeles. TRAP-nPM retains similar composition compared to the ambient TRAP (Morgan et al 2011). In the laboratory, rodents are exposed to TRAP-nPM for 5 hours/day, 3 days/week, for a total of 10-15 weeks, mimicking a chronic long term exposure. Three mouse models - C57BL/6 (wild-type), J20 (ADtg, expressing human mutated APP) and EFAD (ADtg, expressing both human mutated APP and APOE alleles) - were used to address the neurotoxicity of TRAP-nPM.

In C57BL/6 mice, TRAP-nPM exposure increased sAPPβ:sAPPα ratios and Aβ-40 and -42 peptides suggesting a pro-amyloidogenic effect. We observed increased inflammation, as shown by the increase of both Iba1 and TNFα after TRAP-nPM exposure. Moreover, a selective decrease of glutamatergic receptors (GluR1) by western blot analysis and neurite density (CA1>DG) as analyzed by silver staining was detected in TRAP-nPM exposed mice. These changes parallel the deficit in hippocampus-mediated contextual memory, measured by the novel object in context test. Pro-amylodogenic effect of TRAP-nPM exposure was confirmed in two ADtg mouse models (J20, EFAD), for which an increased accumulation of Aβ plaque load and Aβ fragments was observed. The use of EFAD model also identified ApoE4 as the first genetic risk factor associated with air pollution.

Our studies support a strong role for TRAP exposure in Alzheimers Disease which warrants further investigations.

Correlation of cerebrospinal fluid with urine fatty acids in pursuit of non-invasive biomarkers of Alzheimer's disease

Hannah Chew[1], Michael Kwong[2], Katherine Castor[2], Matthew Cipolla[2], Michael Harrington[2], Alfred N. Fonteh[2]

[1]University of California, Los Angeles, Los Angeles, CA

[2]Neurosciences, Huntington Medical Research Institute, Pasadena, CA

There is growing evidence that a disturbance in lipid metabolism is linked to Alzheimer's disease (AD) pathophysiology. We hypothesize that dysregulation of fatty acid (FA) metabolism can be detected in cerebrospinal fluid (CSF) and urine from subjects with AD compared with cognitively healthy (CH) subjects.

CH (n=63) and AD (n=25) subjects were classified based on neuropsychological assessment. CSF was collected and fractionated into supernatant fluid (SF), nanoparticulate (NP) fraction, and unesterified fatty acids (UFA). Fatty acids in CSF fractions, total fatty acid (TFA), and UFA in urine were determined using gas chromatography - mass spectrometry. Fatty acid data are expressed as a percentage in CSF fractions or urine, and the ratio of fatty acids in CSF versus urine. Correlation of CSF with urine fatty acids was determined using Spearman's ranked analyses.

The CSF to urine ratios of unesterified C16:0, C16:1, C22:1, and TFA C18:0 were significantly higher in the AD group than in the CH group. Contrastingly, unesterified C10:0 and TFA C20:1 ratios were significantly lower in AD than CH subjects. C20:4n-6 and C18:3n-3 in urine positively correlated with the proportion in CSF while the proportion of C18:3n-6 in urine negatively correlated with the proportion in CSF in CH but not in AD. Conversely, there was a positive correlation between the proportions of C20:3n-3 in urine and CSF in AD but not in CH. UFA exhibited a positive correlation in CH participants for C22:4n-6 but not for AD subjects. In contrast, proportions of unesterified C22:1 correlated in AD but not CH.

CSF to urine ratios of five fatty acids differentiate CH from AD and CSF levels of six other fatty acids correlate with their urine levels. Therefore, urine fatty acid levels can be non-invasive surrogate biomarkers that will be useful in population screening, and monitoring new AD therapies.

Neuronal-specific PICALM deficiency causes cognitive impairment and brain atrophy

Divna Lazic[1,2], Axel Montagne[1], Zhen Zhao[1], Takahiro Maeda[3], Berislav V. Zlokovic[1]

[1]Physiol. and Biophysics, USC, Los Angeles, CA; [2]Neurobio., Inst. for Biol. Research, Univ. of Belgrade, Belgrade, Serbia; [3]Medicine, Harvard Medical School, Boston, MA

PICALM, a gene encoding phosphatidylinositol-binding clathrin assembly protein, is a highly-validated genetic risk factor for Alzheimer's disease (AD). Besides its well-known role in regulating the intracellular trafficking of endocytic vesicles, studies in *Picalm+/-* mice revealed that PICALM is involved in the transcytotic clearance of amyloid-β across the blood-brain barrier. On the other hand, genetic analyses and magnetic resonance imaging (MRI) in humans suggested the positive correlation between protective *Picalm* allele and higher hippocampal volume as well as increased entorhinal cortical thickness. Furthermore, studies had shown that in developing neurons PICALM assists fusion of synaptic vesicles with presynaptic membranes and regulates the size and density of synaptic vesicles, suggesting its role in synaptic transmission. Because PICALM plays essential roles in regulating axonal growth and turnover of synaptic vesicles and receptors, a complete deletion of PICALM from neurons can be detrimental to neuronal homeostasis. In order to examine the role of PICALM in neuronal health and cognitive performances in adult mice, we generated tamoxifen-inducible neuron-specific PICALM knockout line (*Picalm$^{lox/lox}$; Camk2a-CreER*). Four weeks after tamoxifen administration, *Picalm$^{lox/lox}$; Camk2a-CreER* mice showed cognitive impairment as demonstrated with novel object location/recognition and fear conditioning behavioral paradigms. Volumetric studies using 11.7T MRI scanner and immunohistochemistry on neuronal markers revealed that *Picalm$^{lox/lox}$; Camk2a-CreER* mice exhibit brain atrophy, most prominent in the hippocampus. After bilateral intrahippocampal injections of amyloid-β oligomers, we found more susceptibility to neuronal death compared to vehicle injected *Picalm$^{lox/lox}$; Camk2a-CreER* mice. Studies in primary neuronal culture using *Picalm$^{-/-}$* pups confirmed *in vivo* findings on increased susceptibility of PICALM-lacking neurons to insults such as amyloid-β. Altogether, our data suggest that neuronal PICALM plays an important role in cognition and neuronal health.

Identification of Alzheimer's disease biomarkers by analyzing fatty acids in cerebrospinal fluid and urine

Michael Kwong[1], Hannah Chew[2], Katherine Castor[1], Matthew Cipolla[1], Michael Harrington[1], Alfred N. Fonteh[1]

[1]Neurosciences, Huntington Medical Research Institute, Pasadena, CA

[2]University of California, Los Angeles, Los Angeles, CA

Although fatty acid oxidation is associated with Alzheimer's disease (AD) pathology, no links have been established between brain lipids and excreted oxidized products. We hypothesize that oxidation of brain polyunsaturated fatty acids (PUFA) can generate dicarboxylic acids (DCA) excreted in urine by AD subjects at different rates compared with cognitively healthy (CH) subjects.

Subjects > 70 years were classified as CH (n=64) or AD (n=26) after neuropsychological assessment. Cerebrospinal fluid (CSF) was fractionated and PUFA levels quantified in supernatant fluid (SF), nanoparticles (NP), and unesterified fatty acid (UFA). DCA was derivatized to pentafluorobenzyl ester, and quantified using gas chromatography and isotope dilution negative ion chemical ionization mass spectrometry. PUFA data are expressed as percentages of fatty acids detected in CSF fractions while DCA is calculated as a percentage of 7 DCAs (C4-C10) in urine. Spearman's ranked correlation was calculated for urinary DCAs and CSF PUFAs.

C10 DCA negatively correlated with 6 of 8 PUFAs in SF from CH. In contrast, C9 DCA negatively correlated with 7 of 8 PUFAs in SF from AD. C6 and C8 DCAs positively correlated with SF C18:3n-3 and C20:3n-3 in AD, respectively, but not in CH. In the NP fraction of CH, C4 DCA positively correlated with C20:2n-6, C20:3n-3, C20:5n-3, and C22:5n-3 PUFAs while C8 DCA negatively correlated with C20:5n-3. Only C9 DCA positively correlated with C20:4n-6 in AD NP fractions. For UFA of CH, C6 DCA negatively correlated with C20:2n-6, C20:3n-3, and C22:6n-3, while C5 and C7 DCAs positively correlated with homo-g-C20:3n-6 and C18:2n-6, respectively. C8 DCA positively correlated with unesterified C22:6n-3 while C9 DCA negatively correlated with unesterified C20:5n-3 in AD subjects.

Differential correlation of urinary DCAs with CSF PUFAs in clinical groups suggests a link with AD pathology. PUFAs and DCAs that segregate CH from AD subjects are potential disease biomarkers.

Effects of *APOE* genotype and Western diet on metabolic and Alzheimer-related outcomes in female mice

Amy Christensen and Christian J. Pike

Alzheimer's disease (AD) risk is significantly influenced by several genetic and environmental factors. The greatest genetic risk factor for late-onset AD is apolipoprotein E (*APOE*) genotype, with carriers of the *APOE* e4 allele (*APOE4*) being at a greater risk than carriers of the more prevalent *APOE* e3 allele (*APOE3*). This increased AD risk in *APOE4* carriers is exacerbated in women. Further, AD risk in both men and women is significantly increased by obesity. The potential gene-environment interactions between *APOE* and obesity in regulation of AD pathogenesis are not well understood. To investigate this issue, we used the EFAD mouse model, which has knock-in of human *APOE3* (E3FAD) or *APOE4* (E4FAD) in the presence of AD-related transgenes. Young adult female EFAD mice were maintained on either Western diet (WD; 45% fat, 21% sugar) or a control diet (10% fat, 7% sugar) for 12 weeks. E3FAD mice showed significant metabolic dysfunction and cognitive impairment in response to WD. E4FAD mice showed greater metabolic and cognitive impairment overall, but no significant worsening with WD. Amyloid accumulation, a primary neuropathological hallmark of AD, showed a similar pattern with WD associated with higher beta-amyloid deposition in E3FAD females. Amyloid load was relatively higher in E4FAD versus E3FAD mice, but was not significantly increased by WD. To begin identifying factors that underlie the observed interactions between *APOE* and obesity, we performed hippocampal gene microarrays in transgenic *APOE3* and *APOE4* mice that lack AD transgenes but were maintained on the same diet interventions. The microarray data indicate numerous changes in expression of inflammation- and metabolism-related genes across diet and *APOE* groups that are consistent with roles in regulation of pathology. Overall, these findings demonstrate significant gene-environment interactions between *APOE* genotype and obesity in female mice. Continued investigation of how AD is affected by the interactive effects of risk factors such as obesity and *APOE* is essential to the identification of at-risk populations and the development of preventive strategies.

Using the Human Connectome Project pipeline to investigate alterations in brain structure and function within an AD risk cohort

Joey A Contreras, Arthur W Toga & Judy Pa

Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA

Studies have shown that the brain can be modeled as a large-scale complex network. Using concepts from graph theory, we have learned to study this organizational structure and the dysfunction that can arise in pathological brain states. In some cases, organizational breakdown within certain brain areas has been shown to precede cognitive dysfunction. In the case of Alzheimer's disease (AD), abnormal functional connectivity between brain regions has shown to be correlated with some of the earliest symptoms of AD. We are developing a multi-modal approach to visualize and study how dysfunction between well-known functional networks affects structural connections within the brain.

A major challenge in neuroimaging visualization is how to integrate structural and functional connectivity data to form a comprehensive visual context for data exploration, quality control, and hypothesis discovery. Therefore, we will utilize the human connectome project (HCP) processing guidelines to better acquire, align, and analyze local data. HCP pipelines were charged with bringing data from major imaging modalities: structural, functional, and diffusion into a cohesive framework. This allows for direct cross-subject comparisons and multi-modal analysis which has been shown to provide a more comprehensive picture of brain architecture and function.

Our study includes 25 older adults at risk for AD who received structural MRI, resting-state fMRI, and diffusion MRI (11M, 14F; mean age=71.44, SD=7.52; mean education=16.06, SD=3.28). Subjects are classified as APOE4 carriers or non-carriers. Imaging data are prepared and processed using guidelines laid forth by HCP minimal preprocessing structural, functional and diffusion pipelines. Final analysis will use Connectome Workbench to compare functional connectivity maps (produced as part of the functional HCP pipeline) between APOE4 carriers and non-carriers, and those with normal cognition or mild cognitive impairment. Additionally, we will examine the functional and structural connectivity of the posterior cingulate, medial prefrontal cortex, and angular gyrus (areas known to be part of the default mode network) and all other cortical brain areas.

An FDA-approved drug as a therapeutic agent to upregulate PICALM

Kassandra Kisler, Sam Bazzi, Amy R. Nelson, Abhay P. Sagare, Erica Lawson, Zhen Zhao, Berislav V Zlokovic

Department of Physiology and Biophysics and the Zilkha Neurogenetic Institute, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

Picalm, phosphatidylinositol binding clathrin assembly protein, is a known genetic risk factor in Alzheimer's disease (AD). In healthy mice and humans, Picalm is highly expressed in brain endothelial cells, is involved in clathrin-mediated endocytosis and trafficking, and clearance of amyloid from the brain across the blood-brain barrier. However, in AD Picalm brain endothelial levels are reduced. Using a Picalm deficient mouse model, we have previously shown that Picalm reduction leads to reduced amyloid clearance from brain and exacerbation of amyloid pathology, which could be reversed by increasing Picalm endothelial expression. Thus,
therapeutic strategies that upregulate Picalm expression in the vasculature could lead to novel advancements in AD treatment. Currently, no therapeutic treatment targeting Picalm regulation in AD exists, and existing treatments to ameliorate or slow the progression of AD have met with little or no success. To identify a possible Picalm therapeutic treatment, we developed a luciferase reporter assay and screened a library of 2000 FDA-approved drugs. Secondary screening of the identified hits yielded a compound capable of elevating Picalm mRNA and protein levels *in vitro* by 1.5-3 fold in a human endothelial cell line. Similarly, the compound
increased Picalm protein levels *in vivo* in the brain endothelium of a Picalm-deficient mouse model compared to vehicle treated littermates. In addition to Picalm upregulation, we found this compound also upregulates low density lipoprotein receptor related protein 1 (LRP1), a key protein involved in clearance of amyloid from brain, but does not affect key elements of the clathrin-mediated endocytosis machinery. Together this data indicates that Picalm upregulation could be a promising new therapeutic technique for AD.

Changes in Depression Severity Correlate with Quality of Life in Alzheimer Disease: a Longitudinal Study

Elizabeth Joe, MD[1]; John Ringman, MD, MS[1]; CADC Investigators

[1]Keck School of Medicine, University of Southern California, Los Angeles CA

Background: Depression has been consistently associated with both self- and caregiver-rated quality of life (QoL) in Alzheimer disease (AD) in cross-sectional studies; however longitudinal data on the relationship between these factors is lacking.

Methods: This is a secondary analysis of data from the longitudinal Depression in Alzheimer Disease study. Quality of life at baseline and 3 month follow up was measured using the self- and caregiver-rated QoL-AD measures. Depression was measured using the 30-item Geriatric Depression Scale (GDS). Pearson correlations were calculated for baseline values as well as change over time.

Results: Baseline self-rated GDS scores were negatively correlated with self- and caregiver-rated QoL-AD scores. Change in self-rated GDS scores correlated with change in self- but not caregiver-rated QoL-AD scores; change in caregiver-rated QoL-AD correlated with change in caregiver-rated patient QoL-AD. Caregiver-rated QOL was more strongly correlated with caregiver-rated GDS than patient-rated GDS.

Discussion: Depression is an important mediator of self-reported QoL in AD; this is in contrast to other behavioral symptoms or functional status that have been previously shown to correlate with caregiver-rated but not self-rated QoL. Caregiver perception of patient depressive symptoms influences caregiver rating of patient QoL.

Power law exponent from resting state fMRI to measure excitatory-inhibitory imbalance in older adults with mild cognitive impairment

Niharika Gajawelli & Judy Pa

Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA

Department of Biomedical Engineering, University of Southern California, Los Angeles, CA

Objective: To explore the link between longitudinal cognitive decline in aging and the power law exponent (PLE), calculated form the power frequency of resting state functional MRI (rs-fMRI) in the hippocampus.

Background: The signal acquired from rs-fMRI is a surrogate marker for local field potentials and post-synaptic processes. Imbalance of excitatory and inhibitory synaptic inputs may contribute to cognitive decline in Alzheimer's disease. FMRI signal power content is proportional to inverse frequency (1/f) with a scaling factor (i.e. the power law exponent or PLE). The PLE reflects the relative excitation/inhibition balance in electrophysiology. In a separate study of MCI subjects, higher power, and hence smaller PLE values were observed at 0.1-0.2Hz frequency for the group with clinical dementia rating scale (CDR)=0.5 compared to the CDR=0.

Methods: The rs-fMRI data (TR=3s, 3x3x3mm3) from 154 subjects (58 with CDR=0; 96 with CDR=0.5) from the Alzheimer's Disease Neuroimaging initiative database were processed using AFNI. For both hippocampi, PLE was calculated for frequency band (0.1-0.16Hz) for all subjects. Mixed model analysis was conducted to assess the interaction between PLE, age, CDR, and time after baseline scan and two cognitive time points for the Rey Auditory Verbal Learning Test (AVLT) and the Trail-Making Test A (TMTA).

Results: For both hippocampi, a significant interaction effect was found for PLE with longitudinal change in delayed memory, but not in attention. Specifically, those individuals with greater E-I imbalance in the hippocampus had greater memory change over time.

Conclusion: Older adults with MCI have an increased risk for developing Alzheimer's disease. This may be linked to an imbalance of excitatory-inhibitory synaptic activity in the hippocampus and associated memory

ABCA-1 function of cerebrospinal fluid in Alzheimer's disease

Mia Gifford, Varun Rawat, Shengyia Wang, John Ringman and Hussein Yassine

Loss of ABCA-1 function is associated with cognitive decline. The goal of this study was to test whether cerebrospinal fluid (CSF) from participants with autosomal dominant Alzheimer's disease (ADAD) has lower ABCA-1 function. 58 participants (40 ADAD carriers and 18 non-carriers) were studied. ABCA-1 function was defined by the ability of CSF to move cholesterol from inside the cell to the media using the ABCA-1 transporter ex vivo. Nine participants were followed up longitudinally. ABCA-1 function of CSF was 9% lower in ADAD carriers but the differences did not reach statistical significance (p=0.2). In participants that were followed up with time, there was a trend for a 21% decrease in ABCA-1 functions with time in carriers but not in non-carriers (p=0.09). These results suggest that ABCA-1 activity declines rapidly in carriers of ADAD. Our findings were limited by the small sample size.

Embarking on the LEARNit trial: a randomized clinical trial on the effects of modifiable lifestyle factors on older adults at risk for Alzheimer's disease

A. Lisette Isenberg, Erin Fitzgerald, Jocelyn Argueta, Teresa Monreal, Christina Dieli-Conwright, E. Todd Schroeder, Hussein Yassine, Carolee Winstein, Beth Fisher, Daniel Nation, Peter Conti, Lon Schneider, Wendy Mack, & Judy Pa
Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA

OBJECTIVE To examine the impact of modifiable lifestyle factors (physical activity and mental activity) on physical, cognitive and blood based biomarkers in subjects with objective mild cognitive impairment.

BACKGROUND Exercise is a promising, modifiable lifestyle intervention for those at risk for Alzheimer's disease (AD) and has the potential for delaying disease onset and lowing cognitive decline. However, the therapeutic effect of exercise in patients with early MCI, a prime intervention period for treatment, is not well understood. Initiating treatment in MCI before irreversible neuronal and cognitive loss may yield the greatest benefit.

DESIGN/METHODS Sedentary older adults (<60 min/week of physical activity) are being actively recruited from the community to participate in a 6-month intervention. Early cognitive changes are objectively determined by performance on a testing battery at screen. Scores on at least one executive function or memory test must be 1 SD below that of age-matched controls. Subjects are then randomized to either moderate aerobic walking (physical activity) or health education (mental activity). The primary outcome measure is performance on an fMRI memory task and brain activity, previously shown to have good sensitivity for signs of early stage cognitive decline via memory discrimination vs. generalization (Yassa et al 2010). Additional outcome measures include blood based biomarkers, physical function, cognitive performance, and neuroimaging biomarkers of cognitive decline.

RESULTS Enrollment is ongoing and there are currently 7 active participants (mean age: 65$\pm$3.4, 42% women. The average education is 17$\pm$2.8 years; 71% are non-hispanic white and 71% report a family history of AD, The mean MOCA score was 26$\pm$2.3. Subjects are randomized by APOE4 carrier status, which is blinded to investigators. Baseline data for memory function show subjects are more likely to generalize similar objects (79%) compared to discriminate similar objects (47%). Mean baseline activity in moderate-to-vigorous physical activity is 19.6 minutes per day (range:1-37). Of the 7 enrolled subjects, 1 subject has completed follow-up testing.

CONCLUSIONS We will continue recruitment and enrollment and conduct baseline analyses when warranted by a larger sample size. Future primary analyses will follow the planned intention-to-treat approach. Results from this study may provide evidence of the effects of a modifiable lifestyle factor on brain health and cognition.

T cell TGF-beta signaling control of the immune response to cerebral Ab

Kwok W. Im, Marie-Victoire Guillot-Sestier, Alexander W Vesling, Javier Rodriguez, Kavon Rezai-Zadeh, Terrence Town.

Alzheimer's disease (AD) is hallmarked by cerebral amyloid-β (Aβ) deposition, tauopathy, neuronal loss, and chronic neuroinflammation. Presence of circulating Aβ-reactive $CD4^+$ T cells has been reported in AD patients, suggesting that these adaptive immune cells may play a role in disease pathogenesis. However, mechanisms of T cell response(s) to Aβ and implication(s) for AD etiopathology remain unclear. As a major immune regulator within the CNS, transforming growth factor-beta (TGF-β) generally acts as an nti-inflammatory cytokine to tightly control immune responses. TGF-β mRNA levels are elevated in AD patient brains, and we previously showed that blockade of macrophage TGF-β signaling activated innate immunity and licensed Aβ clearance in a mouse model of cerebral amyloidosis. TGF-β is also a master regulator of T cells. To begin to understand the impact of blocking T cell TGF-β signaling on T cell response (s) to Aβ, we bred the APPswePSEN1dE9 mouse model of cerebral amyloidosis (APP/PS1) with a dominant-negative transgenic mouse that expresses an inhibitory form of TGF-β receptor type II in $CD4^+$ T cells. We observed that $APP/PS1^+$ $CD4\text{-}DNR^+$ bitransgenic mice have reduced cerebral amyloid burden, but at the net negative consequence of early death; likely due to exuberant brain inflammation. Indeed, reduced amyloid burden in $APP/PS1^+$ $CD4\text{-}DNR^+$ brains occurs with increased $CD4^+$ T-cell numbers and increased Iba1 immunoreactivity. Furthermore, we observed significantly increased numbers of $CD45^+$ $CD3^+$ T cells in parenchyma and blood vessels in cerebral cortex and hippocampus of $APP/PS1^+$ $CD4\text{-}DNR^+$ mice. We assessed recruitment of immune cells to amyloid plaques, T cell-microglia interactions and microglial Aβ phagocytosis using our quantitative three-dimensional in silico modeling (q3DISM) technique. Our data show that inhibition of T-cell TGF-β signaling induces brain influx of peripheral T cells, recruitment of microglia and cerebral Aβ clearance. This raises the intriguing possibility that infiltrating T cells may instruct microglia to restrict amyloid burden.

Cranial pericytes derived from neural crest cells reveal a pericyte-specific functional defect in Alzheimer's Disease

Casey Griffin, Ruchi Bajpai

By the year 2050, over 100 million people worldwide are projected to have Alzheimer's Disease (AD). With no means to effectively stop, delay, or cure AD, gaining a clear understanding of the exact events leading to dementia in AD has become critical for developing novel preventive therapies. Recently, forebrain-microvasculature was found to be defective, decades before onset of dementia in AD patients. Cranial pericytes, that surround endothelial cells in microvessels, have independently emerged as critical regulators of endothelial cells functions influencing cerebral blood flow and blood-brain-barrier integrity not only in AD but also numerous other metabolic and immunological disorders affecting the CNS. To model the role of human cranial-pericytes in regulating endothelial cell functions and their role in AD, we first developed a method to recapitulate the *in vivo* ontogeny of forebrain pericytes by deriving cranial-pericyte from iPSC via a neural crest intermediate in a dish. Our studies reveal inherent functional defects in cranial-pericyte from familial AD-iPSC. We also find a similar pathophysiology in primary pericytes form sporadic-AD patients, both of which can be partially rescued *in vitro*. Thus, we provide a robust method for cranial pericyte derivation and demonstrate their utility in disease modeling for both research and in developing novel therapies.

Angiotensin II Receptor Blockers and Protective Effects on Memory Function in Hypertensive Older Adults

Jean K. Ho, M.A.[a], Daniel A. Nation, Ph.D.[a]

[a]Department of Psychology, University of Southern California, Los Angeles, CA, US

BACKGROUND: Prior work suggests some but not all antihypertensive treatments may benefit cognition and risk for Alzheimer's disease, independent of stroke. Angiotensin II receptor blockers (ARBs) have been highlighted as one antihypertensive drug class that may confer greatest benefit.

METHODS: Participants were 1,626 non-demented adults, ages 55-91, recruited from Alzheimer's Disease Neuroimaging Initiative (ADNI) sites. Three groups were compared: ARBs users (HTN-ARBs), other-antihypertensive-drug-users (HTN-Other) and Normotensives. Post-hoc analyses examined users of blood-brain-barrier (BBB)-crossing ARBs and users of non-BBB-crossing ARBs. Groups were compared on cognition, and MRI measures of brain volume and white matter hyperintensities, using ANCOVA and multilevel models.

RESULTS: At baseline, the HTN-Other group performed worse than Normotensives on Rey Auditory Verbal Learning Test (AVLT) Immediate Recall (p=.002), Delayed Recall (p<.001), and Recognition memory (p=.001), and Trails A (p<.001) and B (p=.01). ARBs users performed better than the HTN-Other group on Recognition memory (p=.04) and worse than Normotensives on Trails A (p=.04). The HTN-Other group performed worse than Normotensives on Logical Memory Immediate (p=.02) and Delayed Recall over 3-year follow-up (p=.007). Over follow-up, those taking BBB-crossing ARBs performed better than the HTN-Other group on AVLT Delayed Recall (p=.04) and Logical Memory Immediate (p=.02) and Delayed Recall (p=.05). They also had fewer white matter hyperintensities (WMH) than the HTN-Other group (p=.008) and those on non-BBB-crossing ARBs (p=.05).

CONCLUSIONS: Hypertensive participants demonstrated worse baseline memory and executive function, and greater memory decline over 3 year follow up compared to normotensives, unless they were ARBs users, who showed preserved memory compared to those on other antihypertensive drugs. Users of BBB-crossing ARBs showed superior memory performance over time compared to other antihypertensive drug users and had less WMH volume. ARBs, especially those of the BBB-crossing variety, are associated with greater memory preservation and less WMH volume, when compared to other antihypertensive medications.

Predicting Alzheimer's disease markers and clinical diagnosis

Samuel Iddi, PhD[1,2], Dan Li, PhD[1,2], Wesley K Thompson, PhD[3], Michael S. Rafii, MD[1,2], Paul S. Aisen, MD[1,2], and Michael C Donohue, PhD[1,2]

1. Alzheimer's Therapeutic Research Institute, San Diego, CA, United States.

2. University of Southern California, San Diego, CA, United States.

3. Department of Family Medicine and Public Health, University of California, San Diego, USA

The identification and recruitment of patients who are likely to benefit from treatment is crucial to the design of trials aimed at discovering new therapies to slow or halt neurodegenerative diseases such as Alzheimer's and Parkinson's. In this talk, we demonstrate the use of a data-driven approach to predict patient's future outcome trajectories and clinical diagnosis. Clinical diagnosis of mild cognitive impairment or dementia relies on a clinician's subjective impression, which makes modeling challenging. Our multiple outcome, or "joint", mixed-effect model relies on observed characteristics and outcome profiles of participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI). The approach simultaneously models longitudinal measurements of the various marker domains (cognitive, imaging and biological) accounting for the association among markers. Individual's clinical diagnosis is then derived from the predicted future markers using a random forest model. We demonstrate that the joint model exhibits improved predictive performance relative to modeling the outcomes independently. Also, we envisage that the proposed procedure can compliment existing practices in monitoring disease progression and the recruitment of patients for clinical trials.

Changes In T-cell Mitochondrial Metabolism In Pre-Dementia Stages of Alzheimer's Disease.

E.Hubbard, M.Harrington

Huntington Medical Research Institute.

The various factors which contribute to Alzheimer's disease (AD) are increasingly being viewed as belonging to a chronological framework which spans many decades preceding the development of the characteristic cognitive impairment. A significant contributing factor to AD pathology is the health, Reactive oxygen species (ROS) production, and function of mitochondria which all become abnormal in AD. However, the stage in which mitochondrial dysfunction occurs relative to Amyloid-β (Aβ) accumulation, Tau deposition, and cognitive decline is currently not well described. Recent studies have demonstrated peripheral blood cells as being a useful reporter of neuronal mitochondrial health.

In this study, we analyze T-cells from cognitively healthy patients with (CH-PAT) or without (CH-NAT) pathological Aβ and Tau, as well as patients who demonstrate cognitive decline in addition to pathological Aβ and Tau (AD). In our preliminary studies, we observe that activated T-cells from CH-PATs demonstrate a significantly higher basal respiration($p=0.042$) and proton leak ($p=0.028$) compared to AD, and a trend towards these two measurements being higher compared to CH-NATs (basal respiration $p=0.09$, proton leak $p=0.07$). We also observed that coupling efficiency was significantly increased in AD ($p=0.025$) compared to CH-PATs. Interestingly, the ATP production is not significantly varied between T-cells of the different groups.

One potential explanation is that the cells are actively producing uncoupling proteins, thereby reducing mitochondrial potential in an attempt to also reduce ROS production. This may indicate a compensatory response which occurs in CH-PATS, and subsides in AD followed by a reversion to more normal mitochondrial potential and coupling efficiency. We intend to utilize flow cytometry to analyze the cells for ROS and UCP expression, and to fully characterize which T-cell types are present in each condition. We will also use mitotracker dye to confirm the decreased membrane potential, and examine the glycolytic ability of T-cells from each condition.

ROLE OF ABCA-1 ACTIVITY IN BRAIN DHA METABOLISM

Steven Horton and Hussein N. Yassine

University of Southern California

Aims: Our goal is to identify that APOE lipidation by the lipid transporter ABCA-1 is a critical mechanism in brain docosahexaenoic acid (DHA) metabolism. We previously demonstrated that ABCA-1 activity was lower in cerebrospinal fluid (CSF) of persons with APOE4 compared with non-carriers. The mechanism of DHA metabolism and transport is not completely understood as it pertains to APOE4 and Alzheimer's pathology. Previous studies have proven the involvement of ABCA-1 as a flippase of the plasma membrane which could release DHA to an extracellular acceptor such as APOE. Other studies found extracellular ATP to be an agonist of ABCA-1. Our goal is to connect these findings using a microglial cell culture model and compare the release of DHA in astrocytes containing APOE2, APOE3 and APOE4 exclusively in order to identify the exact differences in the mechanism behind the release, transport, and metabolism of DHA involving ATP, ABCA-1 and APOE.

Methods: We utilized an astrocytic cell culture model using astrocytes containing APOE2, 3 and 4 exclusively and analyzed the amount of radioactive DHA released from these cells using efflux and scintillation counting.

Results: Using astrocytes expressing APOE2, APOE3 and APOE4, we demonstrate that APOE4 cells release less DHA into APOE4 lipoproteins compared with non-APOE4 cells. We identify lower ABCA activity as a mechanism for the lower DHA release that can be reversed by inducing ABCA-1 activity. To further understand the normal mechanism of DHA metabolism we implemented efflux experiments on astrocytes containing strictly APOE3 labeled with 14CDHA, and test ATP as an agonist for the release of DHA. We were able to demonstrate that 0.01 uM ATP increased the amount of 14CDHA released by the astrocytes to APOE as a lipid transporter.

Conclusions: Establishing that ATP induces the release of 14CDHA to APOE as an acceptor gives us the foundation of the mechanism. We can further establish the role of this function in Alzheimer's pathology by comparing the amount of ATP induced efflux in E4 carrying astrocytes to E3 and E2. We can also solidify the role of ABCA-1 by silencing it in cell culture and comparing the amount of 14CDHA efflux induced by ATP.