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Scientific Symposium and Poster Session: Friday, November 3, 2017
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4 Tribute to Dr. William R. Markesbery
On behalf of the Sanders-Brown Center on Aging, UK HealthCare, and the symposium planning committee, I am pleased to welcome you to the 7th annual “Markesbery Symposium on Aging and Dementia.”

The symposium is named in honor and memory of the late William R. Markesbery, MD, founding Director of the Sanders-Brown Center on Aging and Alzheimer’s Disease Center at the University of Kentucky. Dr. Markesbery’s legacy of groundbreaking research at the Center on Aging has formed the bedrock for our quest to understand and treat Alzheimer’s disease and to improve the quality of life of the elderly. We have no doubt that Bill Markesbery’s work will live on for generations to come as we continue the work he started here almost four decades ago.

Over the next two days, in sessions for both the scientific and community audience, you will have the opportunity to hear clinicians and researchers from the University of Kentucky and other institutions share current findings, trends, and latest updates on dementia and aging disorders, particularly as related to Alzheimer’s disease.

In addition to the presentations conducted by some of the world’s leading scientists, we have invited investigators to display posters of their current research on aging and dementia. Please take some time to visit the research poster gallery on display in the atrium and discuss these ongoing studies with the researchers.

We are honored that so many of you have chosen to join us in seeking to expand our knowledge and friendships. I hope the symposium will be both scientifically rewarding and enjoyable.

Sincerely,

Linda J. Van Eldik, Ph.D.
Director, Sanders-Brown Center on Aging & Alzheimer’s Disease Center

Symposium Planning Committee:

Elizabeth Head, PhD
Jose Abisambra, PhD
Steven Estus, PhD
Donna Wilcock, PhD

Linda Van Eldik, PhD
Jessie F. Nelson
Paula Thomason
Fredrick Schmitt, PhD

Beverly Baesler
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The Sanders-Brown Center on Aging gratefully acknowledges the support of our sponsors. Their support enables us to provide the highest quality programming.

The mission of the Sanders-Brown Center on Aging is to improve the health of the elderly through research, education, outreach and clinical programs.
Location: Auditorium and Atrium of the Albert B. Chandler Hospital, Pavilion A, 1000 S. Limestone, University of Kentucky Campus

9:00 am  Check-in begins: Receive poster assignment number, ID badge, & program

10:00 am  Welcome and Tribute to William R. Markesbery, MD
Steven Estus, PhD
Professor of Physiology and Sanders-Brown Center on Aging
Linda J. Van Eldik, PhD
Director, Sanders-Brown Center on Aging and Alzheimer’s Disease Center

10:15 am  Dementia and Resilience in the Oldest-old: the 90+ Study
Claudia Kawas, MD, University of California Irvine; Professor, Neurology School of Medicine; and Professor, Neurobiology and Behavior, School of Biological Sciences

11:15 am  Box Lunch and Judged Poster Session (Atrium)

12:45 pm  Research at the Sanders-Brown Center on Aging: An update
Moderator - Dr. Elizabeth Head, Professor, Department of Pharmacology & Nutritional Sciences and Sanders-Brown Center on Aging
Daniela Moga, MD, PhD  Medications and their role in brain health – can we optimize treatment in older adults?
Fred Schmitt, PhD  Risks and prevention efforts in dementia
Creed Pettigrew, MD, MPH  Vascular dementia
Ai-Ling Lin, PhD  How the gut microbiome affects genetic risk factors for Alzheimer’s disease?

2:00 pm  Epidemiology of Dementia in Real World Populations: Clues from Health Over the Lifecourse
Rachel Whitmer, PhD, Senior Scientist Kaiser Permanente Division of Research, Professor of Epidemiology and Biostatistics, University of California San Francisco

3:00 pm  Poster award presentations and closing remarks
Linda J. Van Eldik, PhD
“Dementia and Resilience in the Oldest-old: the 90+ Study”

Claudia Kawas, MD
University of California Irvine

Claudia Kawas, MD, The Al and Trish Nichols Chair in Clinical Neuroscience and Professor of Neurobiology & Behavior and Neurology, at the University of California, Irvine, is a geriatric neurologist and researcher in the areas of aging and dementia. Her work is concentrated on the epidemiology of aging and Alzheimer's disease, the determinants of successful aging, longitudinal and clinical pathological investigations, clinical trials, and most recently, studies in cognitive and functional abilities of the Oldest Old (over 90 years of age). Dr. Kawas is a graduate of Swarthmore College (Pennsylvania), and completed her medical studies at the University of Louisville (Kentucky) and neurology residency training and a fellowship in dementia and aging at Albert Einstein College of Medicine, Bronx, New York.

After 15 years on the faculty at Johns Hopkins School of Medicine, Dr. Kawas moved to the University of California, Irvine in 2000. She is Principal Investigator of The 90+ Study and Associate Director of the UCI Institute for Memory Impairments and Neurological Disorders. Dr. Kawas serves on committees for the National Institutes of Health and the Scientific Advisory Board of several organizations, including the Medical and Scientific Advisory Council of the National Alzheimer’s Association, The Dana Foundation, and the United States Food & Drug Administration. Over the past 25 years, Dr. Kawas has published more than 100 peer-reviewed manuscripts and has worked on numerous longitudinal studies of aging and dementia, including the Bronx Aging Study, the Baltimore Longitudinal Study of Aging (NIA), and most recently, The 90+ Study, a population based sample of more than 1,400 people aged 90 years and older. In November 2016, Dr. Kawas’ 90+ study was featured on CBS 60 minutes special on Alzheimer’s disease.
“Epidemiology of Dementia in Real World Populations: Clues from Health Over the Lifecourse”

Rachel Whitmer, PhD
Kaiser Permanente Northern California Division of Research

Rachel Whitmer, PhD, is a Senior Research Scientist at the Kaiser Permanente Division of Research. Dr. Whitmer received her BS in Psychology/Neuroscience Magna Cum Laude from the University of Massachusetts, Amherst, her PhD in Human Development from the University of California, Davis, and Fellowship in Cardiovascular Epidemiology at the School of Public Health, University of California, Berkeley. Dr. Whitmer was a K12 scholar through the NIH Office of Research in Women's Health Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program, administered by the Division of Research at Kaiser Permanente and the University of California, San Francisco, from 2003-2005. She was a Fulbright Faculty Mentor in 2010-11.

Dr. Whitmer leads a laboratory of population-based science in brain aging. Her group focuses on three major themes: 1) Ethnoracial disparities and diversity in cognitive aging and dementia outcomes; 2) Early-life contributions to brain health and dementia risk; and 3) Metabolic and vascular influences on brain aging. Her group utilizes life course methods to address these themes. Dr. Whitmer is Principal Investigator of several studies, among them the SOLID (Study of Longevity in Diabetes), a cohort study of 1200 individuals with diabetes mellitus; KHANDLE (Kaiser Healthy Aging and Diverse Life Experiences), a multiethnic cohort of 1,800 elderly individuals; and Kaiser STAR (Study of Healthy Aging in African Americans), a cohort of 700 African Americans age 50 and older. The primary objective of her research program is to identify and understand risk and protective factors for cognitive and brain aging in populations at high risk for dementia, including ethnic minority groups and those with chronic disease such as diabetes mellitus.

Dr. Whitmer is also a Professor at University of California, San Francisco, in the Department of Epidemiology and Biostatistics and is core faculty on the department's Chronic Disease and Aging Epidemiology T32, and the PhD program in Epidemiology and Translational Sciences. Multiple mentoring opportunities exist through this and other mechanisms.
“Medications and Their Role in Brain Health: Can We Optimize Treatment in Older Adults?”

Daniela Moga, MD, PhD
University of Kentucky

Dr. Moga is an Assistant Professor in the Department of Pharmacy Practice and Science. She also holds a joint appointment as Assistant Professor in the Department of Epidemiology; and is a Faculty Associate with Sanders-Brown Center on Aging and the Institute for Pharmaceutical Outcomes & Policy. Dr. Moga received her MD and residency training in Epidemiology and Public Health at the University of Medicine and Pharmacy in Cluj-Napoca, Romania, and her PhD in Epidemiology from the University of Iowa.

Dr. Moga’s research interests include pharmacoepidemiology and health outcomes. Currently, her focus is on evaluating potentially inappropriate medication use and its effects among complex patients, such as older adults with different levels of cognitive function and multiple comorbid conditions. She is also investigating ways to improve health outcomes, including brain health through interventions targeting inappropriate medications use.

“Risks and Prevention Efforts in Dementia”

Fredrick Schmitt, PhD
University of Kentucky

Fred Schmitt is a professor in the department of Neurology and Sanders-Brown Center on Aging at the University of Kentucky. Dr. Schmitt is the Neuropsychology section chief in the Department of Neurology and Kentucky Neurosciences Institute. Throughout his career, Dr. Schmitt has developed and evaluated statistical and cognitive methodologies for the early detection of Alzheimer’s disease and other dementias and the statistical assessment of various treatment interventions. A prolific applied researcher with over 150 publications, Dr. Schmitt’s research interests are in the area of HIV dementia Alzheimer’s disease, Down syndrome, life-span neurocognition, clinical trial assessments, and biostatistics. His current NIH funded research includes statistical models of dementia risk and associated neuropathology and the evolution of Alzheimer’s disease in Down syndrome.
“Vascular Dementia”

Creed Pettigrew, MD, MPH
University of Kentucky

L. Creed Pettigrew MD, MPH is a professor in the department of neurology at the University of Kentucky Neurosciences Institute and Sanders-Brown Center on Aging. He received his medical degree from the University of Texas Medical School, Galveston and completed his neurology residency and fellowship at the University of Texas Health Science Center, Houston. He is board certified by the American Board of Psychiatry and Neurology in vascular neurology and neurology. Dr. Pettigrew studies acute stroke therapy using neuroprotective drugs and novel thrombolytic agents, alternative approaches to prevention and vascular dementia (vitamin therapy, drugs designed to overcome insulin resistance), and treatment of cerebral amyloid angiopathy, which causes brain hemorrhage.

“How the Gut Microbiome Affects Genetic Risk Factors for Alzheimer’s Disease”

Ai-Ling Lin, PhD
University of Kentucky

Dr. Ai-Ling Lin completed her PhD and Postdoctoral training as a medical physicist from the University of Texas Health Science Center at San Antonio. She is currently an Assistant Professor in the Sanders-Brown Center on Aging, Department of Pharmacology and Nutritional Sciences, and Department of Biomedical Engineering of the University of Kentucky. She has developed and applied translational neuroimaging methods to determine brain vascular and metabolic physiology. Her research has focused on using neuroimaging to identify effective pharmacological and nutritional interventions to slow down brain aging and/or prevent Alzheimer's disease (AD). She recently extended her research to include gut microbiome analysis to identify brain-gut interactions in brain aging and AD. It is her goal to use neuroimaging as surrogate biomarkers to identify effective interventions to preserve brain functions in aging via brain-gut axis.

Dr. Lin has numerous peer-reviewed articles, book chapters and poster awards to her credit, and directs or co-directs grants from such prestigious institutions as the U.S. Department of Defense, the National Institutes of Health/National Institute on Aging, and the American Federation for Aging Research.
Signaling and expression of a truncated, constitutively active human insulin receptor in hippocampal neurons

Hilaree Frazier, MS • Katie Anderson • Shaniya Maimaiti, PhD • Adam Ghoweri • Susan Kraner, PhD • Gabriel Popa, PhD • Michael Mendenhall, PhD • Christopher Norris, PhD • Olivier Thibault, PhD

1Pharmacology and Nutritional Sciences, University of Kentucky • 2Sanders-Brown Center on Aging, University of Kentucky • 3Molecular and Cellular Biochemistry, University of Kentucky

Student

Objectives
Insulin signaling is indispensable in the periphery and it is becoming clear that insulin is also important for normal brain function. Early stage clinical trials report a positive impact of intranasal insulin on memory recall in young subjects and patients with mild cognitive decline or Alzheimer’s disease (AD). To address alternative strategies for enhancing insulin signaling in the brain, we have conducted a series of experiments using a constitutively active human insulin receptor (IR). Prior to in vivo experimentation with AAV delivery, lentiviral clones were derived and used to evaluate functional characteristics in rat primary mixed hippocampal cultures.

Methods
Cells were infected with either a mammalian expression plasmid encoding a red fluorescence protein (ires-dTomato), or a construct containing the truncated human IR beta subunit (HA-IRβ-ires-dTomato) via a targeted lentiviral system. A synapsin promoter was included to limit expression to neurons. Immunocytochemistry assays using antibody against HA-tagged IRβ confirmed expression of the lentiviral plasmid to neurons. The expression level and effect of IRβ on insulin signaling was confirmed by performing immunocytochemistry and Western immunoblots measuring pAkt/Akt ratio. Whole cell calcium currents were recorded in cultures infected with lentivirus using patch-clamp techniques. Different recording protocols were used to test for specificity of the effect to a subtype of voltage-gated calcium current. To more thoroughly characterize associations between calcium homeostasis and the IR, calcium imaging experiments using Fura-2 were performed. Other outcome measures included direct measures of glucose utilization rates using 2-NDBG.

Results and Conclusions
Lentiviral infection of mixed primary hippocampal cultures was successful for all our constructs. Western blots of infected mixed hippocampal cultures provide evidence that transfection with the truncated IRβ plasmid confers elevated IR signaling compared to controls. Immunocytochemistry shows the presence of the HA tag in nearly 80% of infected cells. Constitutive activity was also detected. Patch-clamp recordings show calcium currents are a target of insulin receptor activity in IRβ-expressing hippocampal neurons. Calcium levels at rest and during synaptic activity were not altered between the two groups indicating little impact of insulin signaling on resting conditions. Glucose utilization was altered with expression of the constitutively active IR. This characterization provides insights into future intervention approaches to combat cognitive decline in AD and/or aging using molecular methods to enhance insulin signaling.
Novel applications of MRI techniques in the detection of neuronal dysfunction before tangle pathology in tau transgenic mice

Ryan Cloyd 1 • Sarah Fontaine, PhD 1 • Shelby Meier 1 • David Powell, PhD 2 • Moriel Vandsburger, PhD 3 • Jose Abisambra, PhD 1

1 Physiology, University of Kentucky • 2 Anatomy and Neurobiology, University of Kentucky • 3 Bioengineering, University of California at Berkley

Student

Background: Tauopathic patients have significant cognitive decline accompanied by severe, irreversible brain atrophy. Neuronal dysfunction is thought to occur years before diagnosis. A major obstacle in the treatment of tauopathies is that current diagnostic tools are ineffective at detecting pre-pathological changes. We previously developed a MEMRI (manganese-enhanced magnetic resonance imaging) protocol coupled with R1-mapping to measure the extent of neuronal dysfunction that occurs before appearance of cognitive deficits and tau pathology associated with the rTg4510 tau model. In this study, we performed MEMRI with mangafodipir, an FDA-approved contrast.

Methods: We used MEMRI to measure neuronal dysfunction in rTg4510 mice tau transgenic mice at 2 months (no pathology/cognitive deficits), and 3 months (presymptomatic pre-tangle pathology detectable). We measured MEMRI R1 changes before (baseline) and after (time-course) injecting mangafodipir (50mg/kg) intraperitoneally. We focused on the superior cortex and hippocampal sub-regions.

Results: We found mangafodipir to be an effective contrast for MEMRI of mouse brains. Optimal enhancement of the cortex and hippocampus occurs 12-24 hours post-injection. We found APT imaging to be highly reproducible.

Conclusions: This study builds upon our previous work showing that MEMRI (with MnCl2) reveals important functional differences between tau transgenic and non-transgenic mice. Here we found that mangafodipir is as effective as MnCl2 in performing MEMRI. Mangafodipir exhibits less toxicity than MnCl2 due to structural similarity to EDTA (used to treat manganese toxicity), making mangafodipir a target for translation of MEMRI for tauopathy into human subjects.
Small molecule inhibition of p38α-mediated neuroinflammatory response to traumatic brain injury

Josh Morganti, PhD 1 • Claudia Spaeni, PhD 2 • Danielle Goulding 2 • Linda Van Eldik, PhD 1

1Neuroscience, University of Kentucky • 2Sanders-Brown Center on Aging, University of Kentucky

Faculty

Traumatic brain injury (TBI) initiates a multitude of cellular responses in the brain following the primary injury. Aberrant neuroinflammatory signaling cascades are one of these hallmark responses. Consistently, dysregulation of neuroinflammation has been linked with propagating neurodegenerative sequelae following TBI. The p38α mitogen activated protein kinase (MAPK) is a key signaling kinase that drives inflammatory responses in many CNS disorders. Therefore, we are exploring the role of p38α MAPK in regulating inflammatory-linked responses to TBI via therapeutic inhibition and cell-specific genetic deletion. In the current study, we compartmentalized the cell-specific deletion of p38α by creating two genotypes of mice; p38αΔCX3CR1-CreERT2 and p38αΔLyzM-Cre bone marrow chimera, which restricted the genetic deletion of p38α to microglia and circulating myeloid cells, respectively. Focal contusion TBI was generated in the mice using the controlled cortical impact method. Mice were examined at acute (1d post injury) and subacute (7d post injury) timeframes for peripheral macrophage recruitment using flow cytometry and for inflammatory response using multiplex ELISA and qRT-PCR gene expression assays. Collectively, our data demonstrate differential roles of p38α in regulating both microglia and peripheral macrophage contributions to TBI-induced neuroinflammatory sequelae.
In vivo neuronal and astrocytic high-resolution calcium in aging and a model of AD

Chris Gant, PhD • Bob Sompol, PhD • Philip Landfield, PhD • Christopher Norris, PhD • Olivier Thibault, PhD

1Pharmacology and Nutritional Sciences, University of Kentucky • 2Sanders Brown, University of Kentucky

Staff

Measuring fluorescence using traditional epifluorescence microscopes and charge-coupled devices has long been the standard for quantifying ion changes in neurons and astrocytes during bouts of activation. This technique is well aligned with electrophysiological approaches such that the ion indicator can be delivered to a single cell during the recording process. Even when combined with confocal microscopy, and increased signal to noise, however, this approach lacks in temporal resolution needed to lock imaging with individual action potentials at physiologically relevant frequencies (3-50 Hz). Perhaps more importantly, this approach limits recording and imaging to a single cell. However, the field of neuroscience has been stepping away from single cell recording and imaging, and has moved toward collection of data from multiple cells and cell ensembles, both in vivo and ex vivo using multiphoton microscopy.

In order to provide higher resolution data on the relationship between cells that are activated in the brain and form the neurovascular unit, with assistance from Scientifica we performed experiments on young and aged rats as well as mice (2x transgenic APP/PS1 mice) both ex vivo and in vivo. We investigated the relationship between neurons and astrocytes, neurons and blood vessels, astrocytes and blood vessels. Because the temporal and spatial relationships between these arrays are best characterized during periods of activity with stimulated some of the tissues at different frequencies (3-50 Hz). Following stereotaxic delivery of GCaMP6s (neurons) and GCaMP6f (astrocytes) 4-6 weeks prior to imaging, and in combination with acute tail vein delivery of rhodamine dextran red, we conducted frequency tuning curves in hippocampal slices from young and aged animals, and examined the relationship between blood vessels and astrocytes in vivo.

We describe our results and analysis strategy and also report on the methods used to image calcium changes in young and aged animals, as well as calcium changes in somatosensory cortex of the mice (neurons and astrocytes). For the ex vivo work, we focus our analysis on basilar and apical dendrites during activation. The frequency tuning curves for these areas are reported for young and aged animals. For the in vivo work in mice, we were able to record spontaneous events in astrocytes and examine the relationship of the astrocytes to the vascular system. These preliminary results demonstrate the feasibility of this approach for studies of aging and AD.
Therapeutic targets in vascular cognitive impairment and dementia: neuroinflammation and endothelial dysfunction

David Braun, PhD • Adam Bachstetter, PhD • Danielle Goulding • Donna Wilcock, PhD • Linda Van Eldik, PhD

1Sanders-Brown, University of Kentucky

Other

Vascular cognitive impairment and dementia (VCID) is recognized as the second leading cause of dementia behind Alzheimer’s disease (AD). Although a distinct clinical entity from AD, VCID has many similar pathological dysfunctions and risk factors. Pathogenic mechanisms responsible for VCID are diverse and overlapping, however two major contributors can be broadly identified: dysregulated inflammatory processes, and endothelial dysfunction. Hyperhomocysteinemia (HHcy) is defined by elevated plasma homocysteine levels, and it is an established risk factor for cardiovascular disease, VCID, and AD. Mice fed a diet deficient in folate, vitamin B6, and vitamin B12, and supplemented with excess methionine, develop HHcy. This corresponds with microhemorrhages, neuroinflammation, and cognitive deficits, and is therefore a useful animal model of VCID. Using this HHcy model, we have explored several potential approaches to ameliorate pathological damage: pharmacological attenuation of glial pro-inflammatory cytokine expression with a highly brain-penetrant small molecule, genetic knockout (KO) of p38α mitogen activated protein kinase (MAPK) from myeloid cells, and reducing permeability of the blood brain barrier by KO of myosin light chain kinase (MLCK) from endothelial cells. Pharmacological inhibition of glial cytokine release did not attenuate pathology. Loss of p38α MAPK, however, reduced neuroinflammatory changes and microhemorrhage, as did KO of MLCK from endothelial cells. Taken together, our data suggest that targeting peripheral or vascular-associated inflammation, and in particular reducing leukocyte infiltration into the brain, may be a useful approach in ameliorating VCID-associated neuropathology.
Leukemia inhibitory factor-loaded nanoparticles with enhanced cytokine metabolic stability & anti-inflammatory activity for ischemic stroke treatment

Stephanie Davis, PhD • Derek Reichel, PhD • Younsoo Bae, PhD • Keith Pennypacker, PhD

1Neurology, University of Kentucky • 2Pharmaceutical Sciences, University of Kentucky

Fellow

Purpose: To prolong the stability and both neuroprotective and anti-inflammatory activities of leukemia inhibitory factor (LIF), an anti-inflammatory cytokine that has shown promise as a therapeutic agent for permanent ischemic stroke.

Methods: LIF was packaged in nanoparticles made of poly(ethylene glycol)-poly(lactic acid) (PEG-PLA) polymer to form LIF-loaded nanoparticles (NanoLIF). The surface of NanoLIF was also modified with the CD11b antibody (CD11b-NanoLIF) targeting activated peripheral macrophages to increase cytokine delivery to inflammatory macrophages. ELISA was used to quantify bioactive cytokine inside and releasing from NanoLIF. NanoLIF biological activity was measured using the M1 murine leukemia cell proliferation assay.

Results: NanoLIF and CD11b-NanoLIF had diameters of approximately 30 nm, neutral surface charge, and physicochemical stability retaining biological activity of the cytokine during incubation at 25°C for 12 h. NanoLIF particles released LIF relatively fast from 0-6 h after incubation at 37°C followed by slow release from 24-72 h according to a two-phase exponential decay model. NanoLIF and CD11b-NanoLIF significantly decreased M1 cell proliferation over 72 h compared to free LIF.

Conclusions: NanoLIF and CD11b-NanoLIF preserved the metabolic stability and biological activity of LIF in vitro. These results are promising to improve the therapeutic potential of LIF in treating neurodegenerative and inflammatory diseases.
Mitochondrial and protein-degrading RNA transcripts are selectively reduced with worsened total RNA quality in post-mortem human prefrontal cortex

Eleanor Johnson • Eric Blalock, PhD

Pharmacology and Nutritional Sciences, University of Kentucky

RNA can become degraded for many reasons, including post-mortem interval, tissue of origin, sample preparation, storage duration, etc. The degree to which RNA degradation prior to quantification (e.g., via polymerase chain reaction, in situ hybridization, RNA sequencing, and microarray technology) can adversely impact measurement has been studied. Agilent technologies introduced the RNA Integrity Number (RIN; ranging from 1 worst to 10 best) to help standardize and quantify the degree of degradation in samples across studies. While some studies have used RIN measures to investigate potential causes of deterioration and how to correct for them (Catts et al., 2005; Gallego Romero, Pai, Tung, & Gilad, 2014), the scientific community has not reached a clear consensus on acceptable RIN values for study (Lee, Hever, Willhite, Zlotnik, & Hevezi, 2005). Some authors have taken the position that no samples with a RIN below 7 should be used (Ibberson, Benes, Muckenthaler, & Castoldi, 2009), though this is not yet a standard throughout the community. Relatively little work has examined whether the expression levels of subsets of genes may be more selectively associated with poor RNA quality. Therefore, in the present work, we used bioinformatic approaches to analyze the association between gene expression and RIN level across four published studies, and report a consistent influence of lower RIN values on genes associated with mitochondrial and protein-degrading processes, suggesting that pockets of subcellular RNA close to mitochondria and lysosomes may be more adversely affected during the course of RNA degradation.
Factors influencing Alzheimer’s disease (AD) caregiver stress and coping ability

Elizabeth Spencer

1Communication and Information, University of Kentucky

Student

With the pervasive nature of AD, the number of family members taking on the role of unpaid caregiver is rapidly growing (CDC, 2015; AA, 2017). Family members are taking more ownership in the caregiving process, however, many are not trained or prepared for the challenges. Social science research has investigated the complexities surrounding access to and perceptions of social support. Social support is contextualized as integration in social networks as well as perceived access to helpful people and services (MacGeorge, Feng, & Burleson, 2011). Examining AD caregivers (N = 160) from the Caregiving in the U.S. 2015 data set from the National Alliance for Caregiving and AARP (2016) unveiled variables for a multivariate examination of caregiver stress. Statistical analyses compared relationships between length of time providing care and caregiver stress; coping strategies used by caregivers and emotional stress, caregiver stress, and burden; and provider communication and emotional stress. This investigation unveiled intriguing findings. The variables examined relating to communicative behavior of healthcare professionals and actions that caregivers themselves are taking appear to not be reducing stress for AD caregivers. In fact, as this sample indicated, the current communicative and actions by healthcare organizations are positively associated with increased caregiver stress. Findings bear theoretical implications for caregiver stress theory (Tsai, 2003), which posits that caregiver physical, emotional, and socio-psychological wellbeing is impacted by chronic caregiving. Examining the relationship between length of time providing care and caregiver stress revealed a positive correlation. The largest ecologically significant finding relates to problem and emotion-focused coping strategies. Caregivers that reported asking for help to manage their own emotional and physical stress had significantly greater caregiver stress. Similarly, caregivers who reported acknowledging a need for help to manage challenging patient behavior resulted in significantly greater levels of burden. Of the 42 participants who indicated they had used a respite service, their level of burden was not significantly influenced. Only 35 caregivers indicated that a healthcare professional had ever asked what they need to meet their own needs. Those 35 indicated significantly more emotional stress. This could indicate that the manner in which healthcare professionals are asking is drawing attention to unmet needs and high stress. While necessary and beneficial, social support can also entail costs (Goldsmith, 2004). Identifying and strengthening resources and finding ways to bridge healthcare provider knowledge is imperative for lay caregivers to address the challenges of AD care (Roth, et al., 2005). Practical implications can help inform healthcare professionals and organizations in understanding ways to better meet the needs of patients and their family member caregivers.
Targeting p38α MAPK signaling after TBI: Importance of therapeutic window

Claudia Spâni, PhD • Josh M. Morganti, PhD • Adam D. Bachstetter, PhD • David J. Braun, PhD • Danielle S. Goulding • Edgardo Dimayuga • Linda J. Van Eldik, PhD

Sanders-Brown Center on Aging, University of Kentucky

Background: A key mechanism driving pathophysiological progression in many neurodegenerative diseases is the neuroinflammatory response, especially from microglial cells. Suppression of the p38 mitogen-activated protein kinase α (p38α), a major contributor to microglial inflammatory processes, could potentially prevent detrimental overproduction of proinflammatory cytokines responsible for subsequent neuronal damage. Establishing a therapeutic window for this intervention is essential to achieve optimal benefit from selective p38α inhibitors following traumatic brain injury (TBI).

Methods: In this study we investigated the use of MW150, a CNS-penetrant, selective p38α-inhibitor in two different mouse models of TBI: closed head injury (CHI) and controlled cortical impact (CCI) models. In both models, MW150 was administered i.p. (5mg/kg) at 3 and 6 hours post-injury. Biochemical and histological analyses were performed at 9h and 24h post-CHI. In the CCI model, myeloid cells from the injured area were isolated and gene expression was analyzed 24h after injury.

Results: MW150 administration in the CHI model mildly reduced proinflammatory cytokine levels, but slightly elevated microgliosis. Axonal damage, as evaluated by APP staining, was unchanged due to treatment. Myeloid gene expression analysis of mice that underwent CCI showed that MW150 treatment increased proinflammatory factors such as CCL2, IL-1β and TNFα in comparison to vehicle treated mice.

Conclusion: The results of this study show that inhibition of p38α as early as 3h and 6h after a TBI does not seem to be beneficial and may even elevate injury-associated pathologies. These results suggest that an initial p38α-dependent inflammatory response is essential for recovery, and therefore the therapeutic window for p38α inhibitor treatment must be carefully defined for effective intervention after TBI.
Q134R, A novel neuroprotective compound supresses calcineurin /NFAT signaling in neural cells

Susan Kraner, PhD 1 • Melanie Pleiss, PhD 1 • Pradoldej Sompol, PhD 1 • Irina Artiushin 1 • Laszlo Puskas, PhD 2 • Orsolya Huzian, PhD 3 • Christopher Norris, PhD 1

1Sanders Brown Center on Aging, University of Kentucky • 2Avidin Ltd. • 3Avidin Ltd

Staff

The protein phosphatase calcineurin (CN) and its transcription factor substrate, NFAT, exhibit hyperactivity at early stages of cognitive decline associated with Alzheimer’s disease (AD). Numerous studies show that inhibition of CN/NFAT signaling by genetic or pharmacologic means leads to beneficial effects on amyloid pathology, neuroinflammation, neuronal viability, synaptic physiology, and cognitive function in mouse models of AD. Though classic CN-inhibiting drugs (e.g. tacrolimus and cyclosporine) have neuroprotective properties in experimental models, their use in neurodegenerative disease has been limited by other adverse effects. Q134R, a recently developed small molecule that has successfully finished Phase I clinical trials, appears to inhibit NFAT signaling, without inhibiting CN activity per se. When given orally at low doses, Q134R is well-tolerated and readily crosses the blood-brain barrier, resulting in improved cognition in rodent models. Studies are underway to validate mechanisms of action for Q134 in different neural cell types and to investigate efficacy in mouse models of AD.
Calcineurin/NFAT signaling in activated astrocytes drives network hyperexcitability in Aβ-bearing mice

Pradoldej Sompol, PhD ¹ • Jennifer Furman, PhD ¹ • Melanie Pleiss, PhD ¹ • Susan Kraner, PhD ¹ • Irina Artiushin ¹ • Seth Batten ² • Jorge Quintero ² • Linda Simmerman ³ • Tina Beckett ¹ • Mark Lovell, PhD ¹ • M. Paul Murphy, PhD ¹ • Greg Gerhardt, PhD ² • Christopher Norris, PhD ¹

¹Sanders-Brown Center on Aging, University of Kentucky • ²Center for Microelectrode Technology, University of Kentucky • ³Spinal Cord and Brain Injury Research Center, University of Kentucky

Hyperexcitable neuronal networks are mechanistically linked to the pathologic and clinical features of Alzheimer’s disease (AD). Astrocytes are a primary defense against hyperexcitability, but their functional phenotype during AD is poorly understood. Here, we found that activated astrocytes in the 5xFAD mouse model were strongly associated with proteolysis of the protein phosphatase calcineurin (CN) and the elevated expression of the CN-dependent transcription factor nuclear factor of activated T cells 4 (NFAT4). Intrahippocampal injections of adeno-associated virus vectors containing the astrocyte-specific promoter Gfa2 and the NFAT inhibitory peptide VIVIT reduced signs of glutamate-mediated hyperexcitability in 5xFAD mice, measured in vivo with microelectrode arrays and ex vivo brain slices, using whole-cell voltage clamp. VIVIT treatment in 5xFAD mice led to increased expression of the astrocytic glutamate transporter GLT-1 and to attenuated changes in dendrite morphology, synaptic strength, and NMDAR-dependent responses. The results reveal astrocytic CN/NFAT4 as a key pathologic mechanism for driving glutamate dysregulation and neuronal hyperactivity during AD
Astrocytic calcineurin/NFAT signaling mediates neuronal dysfunction in a mouse model of vascular cognitive impairment

Christopher Norris, PhD • Melanie Pleiss, PhD • Pradoldej Sompol, PhD • Irina Artiushin • Susan Kraner, PhD • David Powell, PhD • Vikas Bakshi • Ai-Ling Lin, PhD • Peter Nelson, MD, PhD • Donna Wilcock, PhD

1Sanders Brown Center on Aging, University of Kentucky

Faculty

The contribution(s) of astrocytes to neuropathophysiology is highly complex. Our lab and others have observed increased expression/activation of the protein phosphatase calcineurin (CN) and its target transcription factor NFAT in activated astrocytes associated with several different forms of injury and disease, where it regulates key deleterious processes, including neuroinflammation, excitotoxicity, and synapse dysfunction. Vascular contributions to cognitive impairment and dementia (VCID) is comorbid with many neurodegenerative diseases, especially Alzheimer’s disease (AD). While astrocyte activation is clearly associated with a variety of vascular pathologies, no studies that we know of have investigated whether these changes are linked to astrocytic CN/NFAT signaling. In this study, we have found that 1) CN/NFAT signaling parameters are elevated in astrocytes associated with vascular pathology in humans, 2) Hyperactivation of CN in astrocytes is sufficient to disrupt synapse function in healthy rodents and 3) Blockade of CN/NFAT signaling in astrocytes protects synapse function, cerebral blood flow, and neuronal viability in a mouse model of VCID.
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Lead exposure, age-related dementia, and Alzheimer's disease

Misty Hobbs 1 • Antonela Rodriguez 1 • Lindsey R. Farris 1 • Dana M. Niedowicz, PhD 1 • Tina L. Beckett 1 • Alex Helman 2 • Katharina Kohler 1 • Teresa Macheda 1 • M. Paul Murphy, PhD 3

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Student

Lead (Pb) exposure as a dangerous entity has re-entered the public consciousness following the recent events in Flint, Michigan. Exposure to Pb is a major public health problem that could occur through contaminated air, food, or water, either during the course of everyday life, or while working in hazardous occupations. Although Pb has long been known as a neurotoxic agent in children, a recent and growing body of epidemiological research indicates that cumulative, low-level Pb exposure likely drives age-related neurologic dysfunction in adults. In fact, environmental Pb exposure in adulthood (for example, in individuals working in automotive repair) has been linked to risk of late-onset Alzheimer’s disease (AD) and dementia. Although the biological mechanism underlying this link is unknown, it has been proposed that Pb exposure may increase the risk of AD via altering the expression of AD-related genes and, possibly, activating the molecular pathways underlying AD-related pathology. Over the past few years, our lab has gathered evidence that this is not the case, but that the most likely mechanism is via the promotion of deleterious interactions between typical AD-pathology and developing cerebrovascular disease (CVD). Our data convincingly shows that a short window of Pb-exposure in adult mice impairs cognitive function, and that this effect is amplified in mice with AD mutations in the absence of any increase in typical AD-related pathology or changes in AD-related gene expression. However, Pb-exposure did cause significant hypertension, a well known risk factor for both dementia and CVD. This raises the intriguing possibility that the consequences of Pb-exposure could be mitigated simply by treating hypertension. Moving forward, these results have the potential to significantly improve our understanding of the role of environmental toxins in neurologic disease, and to have significant implications for the treatment and prevention of age-related complications of AD.
Hyperhomocysteinemia induced gene expression changes in the cell types of the brain

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High levels of homocysteine, termed hyperhomocysteinemia, is a risk factor for vascular cognitive impairment and dementia, which is the second leading cause of dementia. While hyperhomocysteinemia induces microhemorrhages and cognitive decline in mice, the specific effects of hyperhomocysteinemia on each cell type remains unknown. We took separate cultures of astrocytes, microglia, endothelial cells and neuronal cells and treated them with moderate levels of homocysteine for 24, 48, 72 and 96 hours. We then determined the gene expression changes for cell-specific markers and neuroinflammatory markers including the matrix metalloproteinase 9 system. Astrocytes had decreased levels of several astrocytic end feet genes such as aquaporin 4 and an ATP-sensitive inward rectifier potassium channel up to 72 hours as well as an increase in matrix metalloproteinase 9 at 48 hours. Gene changes in microglia indicated a peak in pro-inflammatory markers at 48 hours followed by a peak in the anti-inflammatory marker, interleukin 1 receptor antagonist, at 72 hours. Endothelial cells had reduced occludin expression at 72 hours and neuronal cells had increases in kinases and phosphatases known to alter tau phosphorylation states. This suggests that hyperhomocysteinemia induces early pro-inflammatory changes in microglia and astrocytic changes relevant to their interaction with the vasculature. Overall, the data show how hyperhomocysteinemia could impact Alzheimer’s disease and vascular cognitive impairment and dementia.
Influence of drug intervention on acute stress (psychosocial stress) in young and aged rats

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Psychosocial stress occurs when a non-noxious stimulus (e.g., loss of a loved one or solitary confinement) provokes a physiological response and has the potential to negatively affect numerous systems (e.g., corticosterone level, sleep and cognition). Prior studies from our lab have investigated the consequences of psychosocial stress on deep sleep and cognition through aging. Young animals have demonstrated to be sensitive to stress, in particular having poor performance in a probe trial. On the other hand, aged animals suffered cognitive deficits compared to young, but were interestingly hyporesponsive to both acute and chronic stress. Because deep sleep is important for cognition and decreases relative to age, our lab was interested in investigating the influence of a pharmacological intervention on the stress response in young and aged animals. We hypothesized that a deep sleep promoting drug, such as Gaboxadol, would improve cognition. To test this, young (3 mos) and aged (19 mos) male Fischer 344 rats were divided into four different groups: control (vehicle and drug) and stress (vehicle and drug). Half of the animals underwent acute restraint stress (3h/ day, 4 days) before all animals were trained in the Morris water maze. Behavior, activity, and plasma hormone levels were used to determine Gaboxadol’s influence on the stress response. In line with previous work in our lab, young animals suffered cognitive deficits, however the drug did improve cognition in the young stressed animals, while maintaining no effect on cognition in the absence of stress. Aged animals were hyporesponsive to stress, even in the presence of Gaboxadol. Taken together, Gaboxadol could be used to improve stress resiliency in young.
Utilization patterns and predictors of opioid use in persons with dementia

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Background: Inappropriate treatment with opioids is associated with adverse events, especially in elderly with comorbidities and polypharmacy. Patients with dementia are more vulnerable due to inherent difficulties in assessing and treating pain.

Objectives: To assess opioid use patterns and predictors in persons with dementia.

Methods: Data were extracted from the National Alzheimer’s Coordinating Center Uniform Data Set (2010-2014). Using a cross-sectional design, we examined opioid use (any opioid, or strong opioids) among participants age 65+ diagnosed with dementia or normal cognition (NC). We used generalized estimating equations, adjusted for demographics and comorbidities, to estimate odds ratios (OR) with 95% confidence intervals. Backward selection identified significant predictors of opioid use in participants with dementia.

Results: Among 13,126 participants (age: 76.53±7.73 years, male: 40.81%), 1,120 (8.53%) used any opioids and 331 (2.52%) used strong opioids. The crude OR for any opioid use (dementia vs. NC) was 0.91 (0.80, 1.04) and was 1.18 (0.93, 1.50) for strong opioid use; adjusted ORs were 0.66 (0.56, 0.77) and 0.70 (0.52, 0.94), respectively. Among those with dementia, factors associated with any opioid use included age (1-year difference) (ORadj: 1.02 (1.00,1.03)), female sex (ORadj: 1.78 (1.43, 2.22)), black vs. white race (ORadj: 1.58 (1.17, 2.13)), residing in assisted living vs. single family (ORadj: 2.03 (1.64, 2.51)), depression (ORadj: 1.49 (1.24, 1.78)), hypertension (ORadj: 1.30 (1.04, 1.63)), and urinary incontinence (ORadj: 1.29 (1.06, 1.57)). Factors associated with strong opioid use included female sex (ORadj: 1.90 (1.27, 2.83)), residing in assisted living (ORadj: 2.48 (1.65, 3.73)), depression (ORadj: 1.50 (1.12, 2.00)), and urinary incontinence (ORadj: 1.52 (1.01, 2.29)).

Conclusions: Opioid use (any, or strong opioids) was rare overall but less frequent among those with dementia. This may indicate under treatment among this group. Given that opioid use among participants with dementia was more likely in the presence of comorbidities, further studies are needed to evaluate the risk associated with opioid use in this population.
Targeting P-glycoprotein in a mouse model of Alzheimer’s disease: Insights from a long-term study

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INTRODUCTION Accumulation of amyloid beta (Aβ) in Alzheimer’s disease (AD) is due, in part, to impaired clearance of Aβ across the blood-brain barrier. P-glycoprotein (P-gp) is a blood-brain barrier efflux transporter that is critical for clearing Aβ from the brain. In AD, however, P-gp is substantially reduced, which contributes to impaired Aβ clearance. Despite the importance of P-gp for Aβ clearance, there is currently no strategy available to restore P-gp. The current study was a 2-year cross-sectional study with a longitudinal component that was designed to 1) restore P-gp levels by activating the nuclear receptor PXR and 2) evaluate the therapeutic benefit of this strategy on reducing Aβ brain load and slowing cognitive decline.

METHODS Three-month old hAPP mice (over-expressing human amyloid precursor protein; Tg2576 model) received a diet containing the PXR activator pregnenolone-16α-carbonitrile (PCN; 50 mg/kg). Age-matched wild-type (WT) and hAPP control mice received purified diet alone. In the cross-sectional study, mice underwent a battery of motor and cognitive testing at 3, 9, 12, 15, and 18 months of age. The longitudinal component was comprised of a subsection of mice from the cross-sectional study and received testing at 15, 18, and 21 months of age. After testing, we isolated brain capillaries to determine P-gp expression and transport activity levels.

RESULTS The cross-sectional study showed that, prior to treatment with PCN, 3-month old hAPP mice had significantly reduced brain capillary P-gp activity levels compared to WT mice. Within 6 months of treatment brain capillary P-gp activity levels in PCN-treated hAPP mice were restored to P-gp activity levels measured in capillaries isolated from WT mice. P-gp activity in PCN-treated hAPP mice remained comparable to WT mice until the completion of the study at 18 months of age. However, PCN treatment had no significant effect on cognition. In the longitudinal component, brain capillary P-gp activity levels were similar between WT and PCN-treated hAPP mice, and both of these levels were higher than those in hAPP mice. PCN treatment selectively alleviated deficits in behavioral flexibility and memory that manifested as an increase in accuracy under a reversal-learning paradigm in the 8-arm radial water maze.

CONCLUSION The data suggest that restoring blood-brain barrier P-gp via PXR activation may offer select neurobehavioral protection from Aβ neurotoxicity.
Repeated daily doses of intranasal insulin aspart in young and aged F344

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In an attempt to combat decreased insulin signaling in the brain of Alzheimer’s disease (AD) patients, several groups have used intranasal insulin in clinical and pre-clinical settings. Results show improved memory in young volunteers, patients with mild cognitive impairment, as well as in animal models of aging, diabetes or AD. We have previously reported that intranasal delivery of different insulin formulations (short and long acting), under either acute (single dose) or short term (9 doses) conditions, can enhance insulin signaling in the brain, alter cerebral blood flow and enhance memory recall. Here, we tested whether long term intranasal insulin (>60 doses) provided a greater enhancement in memory and recall in young and aged animals, or if the continued presence of the ligand might cause receptor downregulation or desensitization. Further, it is not clear how intranasal insulin alters functional communication, improves learning, or facilitates memory retrieval, particularly in animal models of aging. Our study was therefore designed to address these limitations.

We characterized the impact of long-term (3 months, > 60 daily doses) intranasal insulin aspart (NovoLog®) on behavior using the Morris water maze (MWM) as well as on insulin receptor levels using autoradiography and immunohistochemistry. We also investigated the role of long term daily doses of insulin on hippocampal RNA species using microarray analyses. Saline (0.9%) or insulin aspart (equivalent to 10 IU/day) delivery was accomplished on non-anesthetized animals as previously published by our group (10 uL total volume per day). Learning and memory were evaluated using the classical MWM in young and aged F344 (n=23/age). MWM training started on the 59th dose and study was terminated after the 62-64th dose. As previously shown, young (5 months) and aged (21 months) rats showed differences in learning and memory. Long term intranasal insulin did not raise peripheral blood glucose levels but did ameliorate aspects of memory recall in the aged animals.

These studies address the impact of repeated daily doses across 3 months in young and aged animals and directly test whether measurable changes in insulin signaling/sensitivity/binding occur across age and under conditions which should normally give rise to receptor desensitization. The results further highlight differences in insulin signaling between the brain and the periphery. We suggest that chronic changes in brain insulin using intranasal delivery can inform on therapies designed to increase insulin signaling and redress cognitive decline with aging.
Vascular risk factors in older adults are correlated with brainwave patterns of learning and memory

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Background and Objectives – Vascular cognitive impairment (VCI) is considered the second most common cause of dementia after Alzheimer’s disease (AD). Currently, there is limited understanding on cerebrovascular disease (CVD) risk and neural correlates of cognitive functions. Using electroencephalography (EEG) and cognitive event-related potentials (ERPs), we tested the hypothesis that vascular risk factors are associated with alteration of neural mechanism underlying short-term memory (explicit working memory and implicit repetition learning).

Methods – 19 older adults (mean age = 75.3 years old) from the community-based aging cohort, University of Kentucky Alzheimer’s Disease Center were included in the study. The Framingham 10-Year Risk Percentage and Hachinski Ischemic Score (HIS) were used to estimate the cardiovascular risk of an individual. Systolic Blood Pressure (BPSYS) was used as a proxy to the extent of small vessel disease. Scalp EEG during resting and cognitive ERP during working memory retrieval and repetition at 14 electrode sites were tested. We further conducted a robust regression which accounted for potential effect of an outlier.

Results – We found that Framingham 10-year risk scores were negatively correlated with cognitive ERP patterns indexing better working memory at the left frontal sites (p=0.02 ~ 0.04). Other sites did not show significant correlations. Also, HIS and BPSYS did not correlate with the left frontal ERP, nor machine learning based EEG markers during resting state. In contrast, BPSYS was positively correlated with the right frontal (F4) neural repetition during retrieval of targets (p=0.02) and non-targets (p=0.03). Similar results were seen at F4 for 10-year Framingham stroke risk and the repeated match and non-match (p=0.04). Also, BPSYS was positively correlated with the neural repetition learning (i.e. enhanced repetition learning as BPSYS increased). HIS did not show any correlation.

Conclusion – The present results revealed that the left-frontal cognitive ERP (working memory related brainwave patterns) were correlated with the 10-year risk percentage, but not HIS. Additionally, BPSYS was correlated with neural repetition at the bilateral frontal during implicit learning. Our results suggest that various vascular risk factors reflecting stroke or small vessel disease in older adults are associated with different types of short-term memory.
TREM2 activating antibody, recruit microglia, reduce beta amyloid deposition and improve cognition in a rodent model of Alzheimer's disease.

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Triggering receptor expressed on myeloid cells-2 (TREM2), is a lipid and lipoprotein binding receptor, that activate innate immune cells. Homozygous TREM2 loss of function mutations cause early onset progressive prehensile dementia while heterozygous, function reducing, point mutations, triple the risk of Alzheimer’s disease (AD) and increase the risk of amyotrophic lateral sclerosis, Frontotemporal dementia (FTD) and essential tremor, in part due to a reduction in microglia survival, proliferation, and phagocytic activity. These mutations also double the rate of brain atrophy, triple the risk of AD and decrease the age of AD onset by 3-6 years. Although, human genetic findings support the notion that loss of TREM2 function exacerbate neurodegeneration, it is not clear whether activation of TREM2 in disease state would lead to therapeutic benefits. To determine the viability of TREM2 activation as a therapeutic strategy, we undertook to identify and characterize an agonistic TREM2 antibody and test its efficacy and mechanism of action in an aggressive model of AD.

Here we show that chronic activation of TREM2, in the 5XFAD mouse model of AD, by weekly intraperitoneal (IP) injection of a TREM2 agonistic antibody, lead to a reversal of AD gene expression signature, recruitment of microglia, decrease in the area occupied by amyloid plaques and, improvement in spatial learning and novel object recognition memory.

Taken together, these finding support the idea that TREM2 gain of function therapies may be beneficial for AD and other neurodegenerative disorders.
Prebiotics for the gut microbiota as an Intervention for Alzheimer’s disease prevention in APOE4 carriers

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Student

Objectives: Alzheimer’s disease (AD) is the most common form of dementia and a growing disease burden. Risk factors include the APOE4 allele, Familial Alzheimer’s Disease (FAD) mutations, and alterations in the gut microbiota, all potentially leading to increased amyloid-ß (Aß) aggregation. It has been suggested that preventative measures such as a healthy diet may be a way in preventing AD for APOE4 carriers. Prebiotics are one potential measure and are fermented into metabolites such as short chain fatty acids, which have been demonstrated to improve metabolic and brain health. Thus, we hypothesized that modulating the gut microbiota with the prebiotic inulin would prevent AD-like symptoms such as altered brain metabolites and metabolic function and increased anxiety in a mouse model using either target-replacement APOE4 or APOE3 allele and 5xFAD mutations (E4FAD or E3FAD).

Methods/Results: At 3 months of age the mice were fed for 4 months with either control or inulin diet. We utilized 16S rRNA amplification and sequencing for determining gut microbiota diversity and species variations, magnetic resonance spectroscopy (MRS) for determining metabolites in the hippocampus, glucose tolerance testing for measuring glucose sensitivity, and a rodent anxiety test. Our results indicate that E4FAD mice had significantly different gut microbiota diversity and taxonomy compared to E3FAD mice. Further, the prebiotic inulin increased scyllo-inositol by 386% and glutamine by 936% in the hippocampus, both demonstrated to decrease Aß aggregation, improved glucose sensitivity, and reduced anxiety in E4FAD mice.

Conclusions: We suggest that prebiotics can modulate the gut microbiota leading to improved metabolic health, decreased Aß and anxiety, and abolished AD-like symptoms. Our approach in this study is translatable and potentially an actionable preventative measure for APOE4 carriers.
Cerebral amyloid angiopathy and microhemorrhages in the occipital cortex of aging adults with Down syndrome

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Background:
People with Down syndrome (DS), or trisomy 21, consistently have sufficient neuropathology for a diagnosis of Alzheimer’s disease (AD) by age 40, including both amyloid plaques and neurofibrillary tangles. Cerebrovascular pathology is a known contributor to sporadic AD, but has been virtually unexplored in people with DS who have AD. This is because people with DS are often thought to be protected from vascular risk factors, like atherosclerosis and hypertension. However, cerebral amyloid angiopathy (CAA) is consistently seen in brains of people with DS as they age and studies from our lab have shown that people with DS have significant microhemorrhages in the frontal cortex. Additionally, preliminary imaging studies from our Aging in Down syndrome cohort show significant microbleeds in the occipital cortex. Therefore, we hypothesized that there may be an age-dependent increase in CAA in the occipital cortex in people with DS and that this is driving an increase in microhemorrhages in this region.

Methods:
We counted the number of microhemorrhages in the occipital cortex using Prussian Blue stained slides in several autopsy groups: DS without AD, DS with AD, sporadic AD, and their age matched controls. This tissue was also stained for total amyloid (6E10) and CAA severity was scored.

Results:
Microhemorrhage counts in DS cases without AD were not significantly different from their age-matched controls. However, sporadic AD cases did have significantly higher microhemorrhage counts than their age matched controls. Additionally, DS with AD cases had the highest overall microhemorrhage counts compared to all other groups, and had comparable counts to the AD group, despite a large age difference. This data matches what we have seen in the frontal cortex. Additionally, we saw that the DS with AD group had higher amounts of CAA than other groups.

Conclusions:
Our results suggest a high frequency of microhemorrhages in DS adults with AD, similar to that seen in sporadic AD. This along with the increased amount of CAA suggests that cerebrovascular pathology may be an under-recognized, yet significant contributor to aging and the development of dementia in people with DS.
APOE, metabolism and cognitive function: An assessment via indirect calorimetry

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Both genetic factors and metabolic disturbances are associated with declines in cognitive performance and increased risk of dementia. The gene Apolipoprotein E (APOE) encodes for three isoforms in the human population (E2, E3, and E4), and the E4 isoform – carried by approximately 1/5 of the population – is the strongest genetic risk factor for late onset Alzheimer’s Disease (AD). Both AD and E4 have been associated with inefficient brain glucose uptake and impaired metabolism. Interestingly, our preliminary data show that aged mice expressing human E4 demonstrate a metabolic “shift” compared to those expressing human E3. This is reflected as a preference of E4 mice for lipids vs carbohydrates as a fuel source. As the brain relies primarily on glucose as an energy source, these data suggest that E4 may negatively influence metabolic pathways which are critical for cognitive function. We hypothesize that similar apoE differences are present in cognitively normal individuals, and therefore aim to translate these exciting findings to human subjects. We believe an E4-directed shift away from glucose utilization may represent a critical step in the progression of cognitive decline, and thus a potential novel biomarker for AD risk. To test our hypotheses, we aim to measure metabolic rate and respiratory quotient (RQ) – a reflection of substrate preference – using indirect calorimetry (IC). Metabolic analyses employing IC are commonly used in clinical settings and exercise studies. However, while technically feasible, to our knowledge, IC has never been applied to investigate biomarkers of cognitive impairment. Thus, repurposing IC to study the metabolic effects of an AD risk factor such as E4 represents a simple and cost-effective new approach. In the current study, real-time metabolic measures will be assessed in individuals with various APOE genotypes – both at rest and during a cognitive and dietary challenge. Accuracy and interpretation of RQ will be aided by measuring adiposity, blood glucose, and urinary urea nitrogen (for estimation of protein oxidation). Our initial feasibility studies show measurable increases in RQ during a cognitive challenge (novel object, novel location test), as well as a trend toward increased resting energy expenditure (REE). Additionally, an acute dietary challenge (sugar water drink) resulted in a steady increase in RQ following ingestion. Recruitment of ~75 young, cognitively normal subjects is scheduled to begin in October 2017. We hope to expand our methods in future studies to measure elderly subjects (cognitively normal, mild cognitive impairment and AD), as well as potential collaborative efforts in other areas of neuroscience.
Effects of cognitive reserve on memory and executive functioning in the ADNI dataset: A longitudinal analysis

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Many individuals are interested in identifying strategies that they can take to avoid late life cognitive decline. Cognitive reserve theory claims that lifelong cognitive experiences can help to stave off cognitive decline, yet little information exists in the literature to describe how this effect is differentially related to the separate cognitive domains of memory and executive functioning.

We correlated brain pathology measures and cognitive reserve (CR) markers with memory testing and executive functioning testing in the ADNI dataset using adjusted regression modeling. Screened brain pathology measures included volumes of major brain structures, FA values of major white matter tracts, white matter hyperintensities, and Tau/Amyloid-beta pathology. Screened CR markers included Education, and AMNART exam scores. An N=203 participants were examined over a 24 month time period.

CR markers were not significantly associated with memory testing scores in cognitively normal individuals. However, CR markers were significantly associated with memory testing scores in cognitively impaired individuals (p<0.05). CR markers were significantly associated with executive function testing scores in both cognitively normal and cognitively impaired individuals (p<0.01 and p<0.05, respectively).

These data suggest that CR markers may not influence all domains of brain function in the same way. Future intervention studies are needed to determine the role that CR might play in avoiding or delaying cognitive decline in different domains.
Limiting amylin dyshomeostasis improves brain function in AD rats

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Student

Mutations in Aβ and/or in proteins participating in the processing mechanisms were linked to the development of familial Alzheimer’s disease (F-AD). We found that, in addition to Aβ pathology, brains of patients suffering with F-AD have large deposits of amylin, a pancreatic hormone that makes pancreatic amyloid in patients with diabetes. To elucidate the pathobiology of the amylin-Aβ interaction, we crossed human amylin-expressing (HIP) rats with AD (TgF344-19) rats to generate AD-HIP rats. Elevated aggregated human amylin in the periphery greatly accelerated behavior changes in HIP-AD rats compared to AD and HIP rats. In the attempt to stabilize the circulating aggregated amylin, we found that upregulation of epoxyeicosatrienoic acids (EETs), which are formed by endothelial cells and have anti-aggregation properties, lowers brain amylin accumulation ameliorating brain dysfunction in HIP-AD rats.
Amyloid pathology and hypertension are associated with white matter injury through different mechanisms as assessed by FLAIR and DTI MRI

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Background: Patients with Alzheimer’s disease (AD) often have hypertension (HTN). Whether these diseases have an additive or synergistic effect on the development of subcortical white matter injury is uncertain. We evaluated the potential additive and/or synergistic impact of AD pathology and HTN on the microstructural integrity of normally appearing white matter (NAWM) and the development of macrostructural subcortical white matter injury.

Methods: Cerebrospinal fluid amyloid levels (Aβ1-42), HTN status, and quantitative MRI measures of WMH volume and diffusion tensor imaging (DTI) fractional anisotropy (FA) were collected on 62 participants. Relationships between these measures were investigated using partial correlations controlling for age, sex, and years of education. Preacher and Hayes mediation and moderation analyses were used to test models exploring the independence/interdependence of AD pathology and HTN on measures of WM after adjusting for age, gender, and education.

Results: Both HTN (r=0.325, p<0.05) and greater Aβ1-42 pathology (r=-0.353, p<0.01) were correlated with higher WMH volume and with lower NAWM-FA (HTN r=-0.238, p=0.03; Aβ1-42 r=0.371, p=0.004). Increasing WMH volume was also associated with NAWM-FA (r=-0.516, p<0.001). Multiple mediation analyses found that neither HTN nor Aβ1-42 mediated the relationship between the other variable and WMH volume or NAWM-FA. Both HTN and Aβ1-42 were directly associated with WMH and NAWM-FA.

Conclusion: Results from this study indicate that HTN and amyloid are independently associated with WM damage, manifested as either overt WMHs or microstructural alterations in NAWM. These results suggest that alterations to WM observed in AD and vascular dementia likely operate in an additive rather than a synergistic manner, and thus treatment of mixed disease states will likely require interventions aimed at both processes in order to achieve maximal clinical efficacy.
Progress elucidating the PIB binding site on synthetic amyloid beta fibrils

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The initial causes of Alzheimer’s disease (AD) are unknown and progression is characterized by cognitive decline, synaptic loss, and formation of amyloid beta (Aβ) plaques and neurofibrillary tangles. Only a subset of fibrillar Aβ in AD brain binds PET imaging agent 11C-Pittsburg Compound B (PIB) with high affinity. Synthetic Aβ fibrils recapitulate PIB binding with a significantly lower probe:Aβ ratio compared with brain. We have employed photo-affinity probes to elucidate the nature of the PIB binding site on synthetic amyloid beta 1-40 and 1-42 fibrils and hypothesize that only a subset of synthetic fibrils bind PIB. Analogs of PIB and chalcones that compete for PIB binding were prepared with both an alkyne click handle and a photo-reactive moiety. Photolysis of these probes in the presence of Aβ fibrils covalently attaches them to their binding site. Multiple rounds of photolysis increase amount of probe insertion into binding site. We have identified separate populations of PIB binding and non-PIB binding fibrils via flow cytometry. Biotin conjugation to the click handle enabled affinity enrichment of the photolabeled Aβ fibrils. Low resolution epitope mapping of affinity purified, photoreacted Aβ suggested the PIB binding site is in or near residues 18-22. Mass spectrometry will be employed in future studies to identify the specific PIB binding site.
Less is not always more: Differential inhibition of ER stress response protein PERK confers altered tau clearance in vitro

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Alzheimer’s disease and other tauopathies are neurodegenerative disorders hallmarked by pathological accumulations of tau, a protein involved in regulating microtubule dynamics. These tau species lead to increased endoplasmic reticulum stress, activating cellular proteostasis machinery such as the unfolded protein response (UPR). Protein kinase RNA-like endoplasmic reticulum kinase (PERK) regulates protein synthesis to allow protein clearance mechanisms to “catch up” with the unfolded protein load, but also indirectly increases apoptosis under chronic activation. Recently, a novel PERK inhibitor (GSK2606414, 414 herein) has been used to investigate the therapeutic outcomes of PERK inhibition. Here, we report in vitro evidence that differential PERK inhibition leads to altered tau clearance in modified HEK293 cells over-expressing PERK, human tau, or a mutated human tau species (P301L) implicated in tauopathies. These data support an acute-chronic dichotomy of PERK inhibition via treatment with 414, providing valuable proof-of-concept evidence for novel tauopathy therapies.
Rapamycin treatment increases cerebral blood flow and attenuates anxiety in APOE4

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Objectives: The ε4 allele of apolipoprotein E gene (APOE4) is the strongest genetic risk factor for Alzheimer’s disease (AD). A hallmark of AD is amyloid beta (Aβ) aggregation, however Aβ detected too late in the aging process. Human neuroimaging studies have indicated that APOE4 carriers develop vascular deficiency several decades prior to Aβ deposition, which further leads to neurometabolic deficits, neuronal loss, and dementia. In this study we investigated effect of Rapamycin, a FDA approved drug, on genetically modified AD mice with Human APOE3 and APOE4 alleles, as a preventative therapeutic for AD.

Methods/Results: Using neuroimaging and behavior testing, we assessed the efficacy of Rapa. After 16 weeks, Rapamycin (rapa) treated mice showed significant increase in Cerebral Blood Flow (CBF) when compared to control mice (p<0.024). E3-rapa and E4-rapa mice, showed a non-significant trend of higher CBF. Female mice show a significant increase in CBF after rapa treatment, when compared to Female-control (p<0.027) and Male-rapa (p<0.028). In our behavioral assessment, E4 mice showed significantly decreased physical activity when compared to E3 mice in control (p<0.0009) and rapa (p<0.0001), as well as a trend toward increased anxiety.

Conclusions: In conclusion, Rapa restored brain vascular and cognitive functions in pre-symptomatic AD mice. These results show the potential of Rapa as an effective intervention to prevent AD for pre-symptomatic APOE4 carriers.
Prediction of cognitive impairment and amyloid deposition through metabolic and vascular deficits in ADNI cohorts

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Objectives: Recent research has been focused on developing predementia biomarkers and early diagnostic methods based on amyloid-β and tau. However, metabolic and vascular changes have been shown to pre-date amyloid or tau deposits by several decades. The aim of this study was to exploit the coupling between glucose uptake in aerobic glycolysis and cerebral blood flow to produce a flow glycolytic index (FGI) that can serve as a surrogate biomarker for metabolic dysfunction and anticipate amyloid-β deposition. Specifically, we repurposed clinical MRI and PET data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI).

Methods: Multimodal neuroimaging data (MRI and PET) from 193 patients ranging from normal cognition (n = 63) to mild cognitive impairment (n = 101) to Alzheimer’s disease (n = 29) were obtained from ADNI, and analyzed for fluorodeoxyglucose uptake, cerebral blood flow, and florbetapir concentration (amyloid-β indicator). FGI was produced by the residuals of the linear regression of cerebral blood flow on glucose uptake. A four-layer perceptron neural network was constructed with two hidden layers in SPSS.

Results: FGI was negatively correlated with florbetapir concentration across the left inferior parietal, right inferior parietal, posterior cingulate, left inferior temporal, and right inferior temporal regions of the brain in gender-matched patients (p < 0.01). This suggests that physiologically, a decrease in glucose uptake in the presence of stable cerebral blood flow is spatially correlated with an increase in amyloid-β deposition. Furthermore, the neural network achieved 71.0% accuracy in identifying mild cognitive impairment patients with a receiver operating characteristic of 0.722.

Conclusions: These results suggest that uncoupling between metabolic and vascular function could drive amyloid-β deposition. Regions that exhibit abnormal FGI could serve as future regions of pathological inquiry, and FGI can be used to non-invasively assess the efficacy of pharmaceutical interventions in clinical trials.
Characterizing the role of PERK-mediated ER Stress in traumatic brain injury: A study of feasibility

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Background:
The endoplasmic reticulum (ER) offers an optimal environment for proper protein folding to occur. However, chronic ER stress may alter protein folding; in turn, excessive production of misfolded proteins leads to formation of protein aggregates, which is a classical hallmark of many neurodegenerative disorders. While the primary effects of traumatic brain injury (TBI) involve tissue damage, recent data suggest that secondary effects induce ER stress. In response, the unfolded protein response (UPR) is triggered causing activation of the kinase PERK. Chronic PERK activity promotes cell death, and this phenomenon has been reported in various diseases of tau aggregation. The goal of this study is to investigate the role of PERK-mediated ER stress in TBI and to determine whether PERK is a viable therapeutic target for TBI. We hypothesize that PERK inhibition provides benefits after TBI.

Methods:
To test this hypothesis, we used PERK conditional knockout and knockdown mice. These mice received open head controlled cortical impact injuries with a stereotaxic apparatus. MRI scanning was conducted at 5, 19, and 28 days post-injury using a 7T ClinScan small animal scanner at the UK MRISC, and mice were anesthetized with 2% isoflurane during the procedure. T2 analysis was conducted using ImageJ volumetric analysis software. To harvest tissue, animals were transcardially perfused using 1% saline, brains were fixed in 4% paraformaldehyde for 24 hours, and they were sunk in 30% sucrose. Sections were taken coronally using a sliding microtome at 25μm. Sections were immunohistochemically stained for active PERK (pPERK Thr981). Imaging was performed using a Cytation5 Cell Image Reader. Images of CA1, CA3, and DG hippocampal regions, as well as specific cortical regions were taken.

Conclusions:
We found, with one sample per group, that head injury causes significant reduction of brain volume in mice with a genetic reduction of PERK levels. These data also suggest that the effects of brain atrophy occur within the first 19d. Injury also showed broad alterations to the UPR. These very preliminary data show feasibility of injuring a genetically modified PERK mouse model and performing longitudinal non-invasive brain imaging measurements. This approach has not been previously performed, and it could offer extrinsic merit by impacting multiple fields of neurodegeneration and other types of injury.
PERK as a tau kinase: From a cell free assay to in vitro evidence

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**Background:**
Alzheimer’s disease (AD) is one of 25 known crippling neurodegenerative disorders that are characterized by the aberrant intracellular deposition of the microtubule-associated protein tau. Tau’s function has largely been ascribed to the promotion and stabilization of microtubules. Consequently, mechanistic studies of tauopathies focus primarily on alterations to microtubule dynamics. We discovered that a vast amount of soluble tau associates with the endoplasmic reticulum in AD brains. Additionally, we found that pathological tau species activate the ER stress sensor PERK. We recently established that inhibiting PERK abrogates hyperphosphorylated tau levels. However, the mechanism by which PERK inhibition reduces tau phosphorylation is unknown. Recent work suggests that PERK is indirectly linked to tau via activation of GSK3b, a major tau kinase. However, the PERK-GSK3b-tau association has not been completely established. Since manipulating PERK activity rapidly changes phosphorylated tau levels, we hypothesized that PERK directly phosphorylates tau.

**Methods:**
First, we performed kinase assays using recombinant tau as a substrate in combination with PERK, GSK3b, or Hsp27 as a control. Then, utilizing an inducible WT tau HEK293T cell line, we knocked down GSK3β by transfecting siRNA while simultaneously overexpressing PERK. We also induced tau expression in the same cells while knocking down PERK and GSK3b with siRNAs. Finally, we measured changes in protein levels using Western blots.

**Results:**
Our in vitro data show that PERK phosphorylates tau albeit at a modest level compared to GSK3b. In cells, we effectively knocked down PERK and GSK3b. We found that these manipulations altered the levels of various phosphorylated tau species.

**Conclusions:**
These data support the connection we previously established between tau and the PERK pathway. It also provides more information on the direct relationship between tau and PERK. The phosphorylation of tau by proteins in the PERK pathway with a subsequent feedback by hyperphosphorylated tau’s interference of ER function could be a possible explanation for neuronal loss. The PERK pathway could then be a possible therapeutic target for tauopathies. These data suggest that tau and PERK engage in a pathological cycle of PERK activation and tau toxicity, where tau induces PERK activation by inducing ER stress and active PERK further phosphorylates tau.
Post-injury PERK inhibition reduces astrocyte reactivity without reducing tissue loss

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Background: Traumatic brain injury (TBI) is defined as a head injury that causes interference in normal brain function. TBI affects an average of 1.4 million Americans each year, with at least 50,000 reported injuries resulting in death. TBI is a prominent risk factor for neurodegenerative disorders like Alzheimer’s disease and Parkinson’s disease. PERK, an endoplasmic reticulum kinase involved in the unfolded protein response, becomes active very early after TBI. Activation of PERK reduces overall protein synthesis through phosphorylation of an initiation factor called eIF2α. Reduction in protein synthesis can be problematic, especially for neurons as they are highly sensitive to changes in protein expression. We hypothesized that PERK inhibition would increase tissue sparing and improve overall outcomes in a mouse model of TBI.

Methods: Wild type mice were injured using the controlled cortical impact (CCI) model of TBI. One hour after injury we began treatment with a PERK inhibitor (GSK2606414), and then continued treatment once a day for 3 days or 30 days. Magnetic resonance imaging (MRI) was performed at 28 days post-injury to measure brain volume. Levels of pPERK, peIF2a, and GFAP were measured using immunofluorescent staining.

Results: We found that PERK activation occurred primarily in neurons as early as 30 minutes post-injury. Following treatment with GSK2606414, we found that activation of PERK and its downstream target, eIF2a, was reduced. Additionally, we found that treatment with the PERK inhibitor reduced GFAP positive staining after injury. Using T2 MRI, we found that 30-day treatment with the PERK inhibitor decreased tissue sparing as measured by brain volume, but that 3-day treatment did not.

Conclusions: Our data provide novel insight into the role of PERK in the physiological mechanisms of TBI response, and they suggest that PERK plays an important role in injury progression and cellular response. Additionally, these data suggest that PERK inhibition is not limited to cells with active PERK. Overall, we show that the need for further exploration of PERK in TBI and that PERK inhibition could be an attractive therapeutic option after parsing out correct dose timing.
Timing is everything: determining the therapeutic window of PERK inhibition in a mouse model of tauopathy

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Progressive neurodegenerative disorders, like Alzheimer’s diseases, involve the accumulation, aberrant localization, and propagation of the misfolded microtubule protein tau. Despite considerable study, there is no effective therapy or cure for these disorders involving tau, known as tauopathies. To address this, we have turned to previous findings that tau impairs a specific type of organelle protein homeostasis (endoplasmic reticulum associated degradation, ERAD) and upregulates the unfolded protein response (UPR), a stress response that leads to attenuation of protein translation and eventual apoptosis if the stress persists. One branch of the UPR, mediated by the ER kinase PERK, is linked to tau-induced ER stress. PERK activity can be modulated by small molecules, and there may be some benefit to their use in tauopathies. However, mechanistic and practical holes in previous studies have slowed progress of a PERK-based tau therapy. To address this, we show the effects of a short term (acute) and long term (chronic) treatment paradigm of PERK inhibition in rTg4510 mice, an aggressive model of tauopathy. Mice were treated with GSK2606414 for either 2 or 30 days by oral gavage. Changes in broad neuronal function were measured by manganese enhanced MRI. We also employed an in vivo adaptation of Surface Sensing of Translation (SUnSET), to measure changes in the levels of translation. We used in vivo SUnSET to determine the effects of PERK inhibition in advanced tauopathic mice on nascent protein synthesis, a critical cellular process. Finally, the effects ER stress/PERK pathway on pathological tau levels were quantified. Together, we demonstrate distinct differences in treatment length and disease severity. These results provide the foundation for further work defining the appropriate intervention scheme for ER stress relief in tauopathies.
MRI volumetric quantification method: sources of variability

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Background: Magnetic resonance image quantification of neuroimaging variables (MRI-Q) is a valuable method for research studies in the area of degenerative disease including standardized T1 volumetric measurements, T2 hyper-density measurements, DTI, ASL, MRS and other acquisition sequences. Disparate research centers use seemingly identical MRI-Q techniques that may seem uniform and yet may lead to significant variability depending on a number of confounding variables. These confounds have been overcome partially by studies such as ADNI that utilize a central processing protocol. However, most centers and studies, irrespective of adhering to ADNI, or other standardized, protocols for image acquisition, rely on site-specific image processing procedures that may be a significant source of variability. The extent of this variability has not been fully explored.

Method: In this preliminary study, we sought to explore sources of variability inherent in image processing of T2 hyper-density volumes, thought to be primarily related to the subcortical ischemic vascular disease. Raw FLAIR imaging sequences from 17 randomly selected subjects were analyzed using variations of near-identical techniques, including choice of image center, computer processor and system software, and imaging software versions. Fifty subjects were used to validate the new refined protocol.

Result: Images processed identically with variation only in the choice of image center showed a variance of 10.7% attributed to this confounding variable. Identical images processed with a standard center, using the same software package, but with different thresholding, analysis method demonstrated a variance of 2.8%. Lastly, identical images processed using identical centers and computer operating systems, but with different software versions of the same program showed a variance of -28.17%. The refined protocol showed a 0.23% variance.

Conclusions: Quantitative metrics of conventional imaging data are often assumed to be standardized across sites and studies, and yet our data demonstrate that significant variability in MRI-Q measurements, as high as 14.78%, that may be more common across studies than previously thought. Recognition and correction of sources of variability in MRI-Q data will allow cross-site and study comparisons necessary for reliable interpretation of data, conclusions, and hypothesis testing in relation to MRI-Q as a biomarker for diagnosis and or progression of any degenerative disease state.
Synaptic plasticity and neuron excitability changes that accompany tauopathies can be modulated through intervention in the unfolded protein response

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Long term potentiation (LTP), an electrophysiological measurement associated with the formation of memory, strengthens synapses after high frequency stimulation. This can occur through increased neurotransmitter output, increased sensitivity to neurotransmitter, often from increased AMPA receptor density, and in late stage, by structural changes such as dendrite and axon sprouting. While many researchers study these later changes, there are few examples of extended electrophysiological recordings that span over what is called late LTP. The counter process, long term depression (LTD), decreases synaptic efficacy as a result of low frequency or non-simultaneous pre and post synaptic action potentials. These two processes are subject to modulation by secondary messengers and levels of protein translation.

Chronic activation of the unfolded protein response (UPR) is a common characteristic of many neurodegenerative diseases. By activation of PERK, a mediator of the UPR, protein translation is attenuated for an indefinite period of time. While previous studies have identified PERK as a possible therapeutic target, there is little knowledge of the functional impact that inhibition of PERK would have on learning and memory. Here we have examined a neurodegenerative model of tauopathy, rTg4510 mice, by electrophysiological field recordings using low frequency and multiple high frequency stimulus trains to induce LTD and long lasting LTP. Recordings were also taken to observe synaptic strength parameters, as well as paired pulse facilitation. Surprisingly, results suggest a higher efficacy for late LTP in Tau transgenic tissue over litter-mate controls.

To observe the impact of UPR inhibition, the PERK inhibitor GSK2606414 was perfused into ACSF before stimulation. When treated with inhibitor, a remarkable decrease in long term potentiation was observed, as well as an increase in long term depression in both genotypes. Synaptic strength measurements revealed a decrease in fiber volley from the disease model indicative of reduced excitability of pre-synaptic neurons. The lack of deviation between baseline EPSPs from both genotypes suggests the inhibitor exclusively affects presynaptic terminal activity. Results may also suggest increased post-synaptic sensitivity to neurotransmission and tetanic stimulation in rTg4510 brain tissue. This data supports UPR intervention as a potential target for conditions characterized by LTD deficits.
The Sanders-Brown Center on Aging (SBCoA) was established in 1979, and received funding as one of the original ten National Institutes of Health Alzheimer’s Disease Centers in 1985. Internationally acclaimed, the SBCoA is recognized for its contributions to the fight against brain diseases that are associated with aging.

Our vision: The University of Kentucky Sanders-Brown Center on Aging will be recognized locally and nationally as a premier, vitally productive and innovative aging center that effectively translates research findings into interventions and information that will benefit older adults.

ALZHEIMER’S DISEASE FACTS

- Someone in the US develops Alzheimer’s disease every 66 seconds.
- Alzheimer’s disease is the 6th leading cause of death across all ages in the USA, and the 5th leading cause of death for those aged 65 and older.
- An estimated 5.3 million persons in the U.S. have Alzheimer’s disease.
- By 2050, as many as 16 million Americans will have Alzheimer’s disease; a new case will be diagnosed every 33 seconds.

“I spent more than 50 years in health care and know the difference that research has made in our lives.” – Mrs. Doris Engles (with her husband Morris), one of our healthy research volunteers.
More than 100 faculty and staff pursuing the following areas of research:

- Basic and clinical research in Alzheimer’s disease
- Neurodegenerative disorders
- Stroke
- Normal brain aging

A global pioneer in Alzheimer’s disease research, the Center has over thirty years of published work and 800 study volunteers (some with the disease and some without). These individuals are studied over time and plan to donate their brains upon death. Our cutting-edge research focuses on identifying problems as early as possible, before memory loss develops, so that Alzheimer’s disease can be prevented or delayed.

The ultimate goal of the Center on Aging is to catalyze innovative and outstanding brain research while ensuring a more rapid rate of progress toward new therapies to delay or prevent age-related brain diseases such as Alzheimer’s disease, so that our volunteers, patients and caregivers become the beneficiaries of our advances in knowledge.

Unless science finds a way to slow the progression of this devastating disease, the United States will see a nearly 50 percent increase in the number of victims by 2030. In addition to the direct impact on the patient, Alzheimer’s disease also affects the lives of family members and friends.

Alzheimer’s disease is the leading cause of dementia, and affects 1 in 10 people aged 65 and older.

2017 marks the first year total annual payments for caring for individuals living with Alzheimer's or other dementias will surpass a quarter of a trillion dollars > $259 billion

No cure or preventive measure currently exists for Alzheimer’s disease, but a number of promising therapies are being developed and tested, including several at the University of Kentucky.

By investing in the development of therapies now, we can save billions of dollars and heartache in the future. You can help through financial donations, or by participating in one of our research programs.

The Center is directed by Linda J. Van Eldik, PhD, Professor, Department of Anatomy and Neurobiology, Director, Alzheimer’s Disease Center and Associate Director, Kentucky Neuroscience Institute

From the 2017 Alzheimer’s Association Facts and Figures publication.

Please help us today in our fight against Alzheimer’s disease. For more information on research, clinical trials and ways to get involved, contact us at 859-323-6040 or visit our website www.centeronaging.uky.edu
WILLIAM R. MARKESBERY, MD (1932-2010)

The Markesbery Symposium on Aging and Dementia is named in honor of William R. Markesbery, MD, a gifted scientist and internationally recognized neurologist and neuropathologist. Dr. Markesbery’s creativity and commitment to aging research provided the impetus for the University of Kentucky to establish the Sanders-Brown Center on Aging in 1979 and name him as the first director. He held that position until his death in January 2010.

In 1985, Bill Markesbery became the director of the Alzheimer’s Disease Research Center, one of the original 10 National Institute on Aging (NIA)-funded centers in the United States, with a primary focus on neuropathology. After more than 30 years, the Alzheimer’s Disease Center continues to be funded by NIA, a remarkable achievement that demonstrates the strength and caliber of this program. During his academic career, Dr. Markesbery published more than 400 scientific papers and was one of the world’s leading experts on Alzheimer’s disease and oxidative stress. He will always be remembered as a compassionate and caring physician, a brilliant researcher, and an inspirational leader.