Markesbery Symposium on Aging and Dementia

November 9 & 10, 2012
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November 9, 2012

Dear Conference Participants,

On behalf of the Sanders-Brown Center on Aging, UK HealthCare, and the symposium planning committee, I am pleased to welcome you to the second annual “Markesbery Symposium on Aging and Dementia.”

The symposium is named in honor and memory of the late William R. Markesbery, M.D., 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:

Linda Van Eldik, Ph.D, Chair  Sally H. Malley
Deborah Danner, PhD       Paula Thomason
G. Steven Estus, PhD
Elizabeth Head, PhD

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Thank you to our Symposium Sponsors!

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

Educational Grant Support:

This activity is supported by educational grants from Baxter Healthcare Corporation and Lilly USA, LLC.

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Presenting Sponsor - Community Session:
2nd Annual Markesbery Symposium on Aging and Dementia
November 9, 2012 - UK Hospital Pavilion A Auditorium – Lexington, Kentucky

Thank you for attending this CME activity. No meeting is truly successful if it simply serves the purpose of transferring information. You are encouraged to pose questions to the speakers and take advantage of the time allocated for informal exchanges and networking.

• Be sure to sign in at the Registration Table.

• The Evaluation Form should be completed and turned in at the end of the activity. Information from these is very important in determining educational needs and planning future continuing education activities.

• Please notify the registration staff of any special needs you may have during the symposium so we may work to assist you.

• To enhance everyone’s learning experience, please place all electronic devices on SILENT during the presentations to limit disruptions

Accreditation

Medicine

The University of Kentucky College of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The University of Kentucky College of Medicine designates this live activity for a maximum of 2.0 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The University of Kentucky College of Medicine presents this live activity for educational purposes only. Participants are expected to utilize their own expertise and judgment while engaged in the practice of medicine. The content of the presentations is provided solely by presenters who have been selected for presentations because of recognized expertise in their field.

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Learning Objectives

Upon completion of this educational activity, you will be able to:

1. Recognize Alzheimer’s disease (AD) symptoms using the latest effective diagnostic methods;

2. Summarize how normal brain functions such as sleep may affect AD risk;

3. Describe how a prior head injury can increase AD risk and progression;

4. Explain the importance of preventing head injury as a means to lower AD risk.
Disclosure of Relevant Financial Relationships with Commercial Interests

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<td>David M. Holtzman, MD speaker</td>
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No planners or staff members have any relevant financial relationships to disclose.

Disclosure of a relationship is not intended to suggest or condone commercial bias in any presentation but it is made to provide participants with information that might be of potential importance to their evaluation of a presentation.

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IMPORTANT! The deadline to claim credit online is January 8, 2013.

If you experience problems obtaining your certificate, please call (859) 257-5320.
Scientific Session and Poster Presentations

Location: Pavilion A Auditorium and Atrium of UK Albert B. Chandler Hospital.

10:00 am Check-in begins: Receive poster assignment number, ID badge, and program

11:00 Welcome
Linda J. Van Eldik, PhD
Director, Sanders-Brown Center on Aging and Alzheimer’s Disease Center
University of Kentucky

Tribute to William R. Markesbery
Stephen Scheff, PhD, Associate Director
Sanders-Brown Center on Aging
University of Kentucky

11:15 From Concussion to Dementia: Key Roles for ApoE
Cheryl Wellington, BSc, PhD
Professor of Pathology and Laboratory Medicine
University of British Columbia

12:15 Lunch and Poster Session (Atrium)

2:00 Research at the Sanders-Brown Center on Aging: an Update
Frederick Schmitt, PhD
Professor of Neurology and Sanders-Brown Center on Aging
University of Kentucky

3:00 Alzheimer’s Disease Risk: Pathogenesis, Early Detection, and How Normal Brain Functions such as Sleep May be Important
David M. Holtzman, MD
Andrew B. and Gretchen P. Jones Professor and Chair of Neurology
Washington University School of Medicine

4:00 Poster award presentations and closing remarks
Linda J. Van Eldik, PhD

4:30 Reception

– 5:30
CHERYL WELLINGTON, BSC, PHD
UNIVERSITY OF BRITISH COLUMBIA, VANCOUVER

Cheryl Wellington obtained her PhD in Microbiology at the University of British Columbia in 1991 and received postdoctoral training at Harvard Medical School, the University of Calgary, and the University of British Columbia. She joined the Department of Pathology and Laboratory Medicine at the University of British Columbia in 2000 and was promoted to Professor in 2011. Dr. Wellington's research interests include lipid and lipoprotein metabolism in the brain and how this relates to chronic and acute neurological disorders such as Alzheimer's disease and traumatic brain injury. Dr. Wellington's group has made key contributions to the understanding of the role of apolipoprotein E (apoE) in Alzheimer's disease and traumatic brain injury. ApoE is the major carrier of cholesterol in the brain and the strongest genetic risk factor for typical Alzheimer's disease. Dr. Wellington’s laboratory has shown that the amount of cholesterol carried on apoE critically affects amyloid metabolism and cognitive function in Alzheimer’s disease. More recently, her laboratory has demonstrated a key role for apoE in promoting recovery from mild repetitive traumatic brain injury. Her laboratory is currently investigating how these pathways might be used for therapeutic application to both Alzheimer’s disease and traumatic brain injury.

“From Concussion to Dementia: Key Roles for ApoE”

Apolipoprotein E (apoE) is the most established genetic risk factor for Alzheimer’s disease (AD) and also influences recovery following a variety of acute neurological insults including traumatic brain injury (TBI). In the central nervous system (CNS), apoE is expressed by astrocytes and microglia, and functions as the brain’s major lipid carrier. ApoE receives lipids from the ATP-binding cassette transporter ABCA1. In AD mice, ABCA1 deficiency exacerbates amyloidogenesis, whereas selective overexpression of ABCA1 reduces amyloid burden. Liver-X Receptor (LXR) agonists, such as GW3965, which stimulate ABCA1 and apoE expression, reduce Aβ levels and rescue cognitive deficits in AD mice. Selective deletion of ABCA1 impairs the ability of GW3965 to protect from cognitive dysfunction in AD mice. GW3965 also promotes cognitive recovery and axonal repair after mild concussive brain injury in mice, effects that require apoE. Taken together, these observations support a major role for apoE in mediating the beneficial effects of LXR agonists for both chronic and acute CNS damage.

Supported by Canadian Institutes of Health Research and the Alzheimer’s Society of Canada.
Fred Schmitt is a Professor 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 for the statistical assessment of various treatment interventions. A prolific applied researcher with over 150 publications, Dr. Schmitt’s research interests are in the areas of HIV dementia, Alzheimer’s disease, Down syndrome, life-span neurocognition, clinical trial assessments and biostatistics. His current NIH-funded research includes studies of antioxidant supplements and dementia prevention, statistical models of dementia risk and associated neuropathology, and the evolution of Alzheimer’s disease in Down syndrome.

“Research at the Sanders-Brown Center on Aging: an Update”

Since its inception over thirty years ago, research at the Sanders-Brown Center on Aging (SBCoA) has focused on healthy and pathological brain aging. This presentation will provide a summary of early findings from SBCoA projects highlighting the roles of oxidative stress, trace metals, early attempts to treat Alzheimer’s disease, and a special group of research volunteers. Current research projects that offer insights into brain pathologies that are associated with aging, new clinical treatment targets, prevention research, and basic brain mechanisms in aging will also be reviewed. In summary, research at SBCoA continues to provide a national and international resource in the study of the aging brain.
“Alzheimer’s Disease Risk: Pathogenesis, Early Detection, and How Normal Brain Functions such as Sleep May be Important”

There is substantial evidence from both human studies as well as genetic, biochemical, and animal model evidence that the amyloid-β (Aβ) peptide plays a key role in Alzheimer’s disease (AD) pathogenesis. Recent studies from our lab and others have shown that Aβ levels are directly regulated by neuronal activity. To explore how physiological processes influence both neuronal activity, Aβ, and AD pathogenesis, we have been studying the sleep-wake cycle. We have found that levels of interstitial fluid (ISF) Aβ in the brain are highest during wakefulness and lowest during sleep. Once Aβ accumulates in the brain in mice, there is a disruption of the normal sleep-wake cycle with increased wakefulness as well as attenuation of the normal fluctuation of ISF Aβ in the brain. Both the changes in sleep and the attenuation in ISF Aβ fluctuation are blocked by actively immunizing an AD mouse model with Aβ42. This strongly suggests that Aβ accumulation is causing sleep disruption. In studying cognitively normal middle aged humans, individuals who have developed Aβ/amyloid deposition in their brain have decreased sleep efficiency compared to those without amyloid deposition. Overall, these studies suggest that the sleep-wake cycle regulates the level of a protein important in initiating AD pathogenesis and that disruption of the sleep-wake cycle may be an early functional indicator of brain dysfunction even prior to cognitive decline.
Aging attenuates Bmal1 expression in hamster hippocampus, cortex, and SCN but not skeletal muscle

Marilyn Duncan PhD, Daniel Cook, Kathleen Franklin PhD, Joshua Tyler, Jeffrey Prochot

Anatomy & Neurobiology, University of Kentucky

Faculty

Deletion of the core clock gene, Bmal1, not only ablates circadian rhythms but also induces an early aging phenotype, characterized by tissue atrophy (e.g., skeletal muscle) and deficits in cognition and memory (Kondratov et al., 2006, Kondratova et al., 2010). These finding and others suggest that Bmal1 participates in the regulation of memory and muscle function. Both of these functions exhibit deficits during aging. In this study, we tested the hypothesis that aging reduces Bmal1 expression in brain substrates for memory (e.g., hippocampus and cingulate cortex) and skeletal muscle (gastrocnemius), as well as the master circadian pacemaker (suprachiasmatic nucleus [SCN]). Young (3-5 mos) and old (16-18 mos) male hamsters (N=8-14/age) exposed to a 14:10 light:dark cycle were euthanized at zeitgeber time (ZT) 1, 6, 13, or 19 (ZT12=lights-off), to enable detection of Bmal1 rhythms. Skeletal muscle and brains were dissected and frozen. Muscle tissue was homogenized and RNA was purified for real-time RT-PCR; amplification was quantified using SYBR Green chemistry. Coronal brain sections were prepared and processed for in situ hybridization using P33-labeled oligonucleotide probes complementary to Bmal1 mRNA. X-ray films were exposed to the slides and radioactive standards to generate autoradiograms. Bmal1 expression in the SCN, cingulate cortex, and hippocampal areas (CA1, CA2, CA3, and dentate gyrus [DG]), was measured by computerized microdensitometry of the autoradiograms. The results showed that Bmal1 expression in all brain regions examined varied with time of day (P<0.05), as expected, and was lower in old hamsters (P<0.01). Only the CA2 showed a time by age interaction (P<0.05). In skeletal muscle, time of day (P<0.0001) but not age (P=0.15) nor an interaction of time and age (P=0.33) affected Bmal1 expression. In conclusion, these findings suggest that aging differentially affects Bmal1 expression in skeletal muscle and brain, and that age-related attenuation of Bmal1 expression in the hippocampus and cingulate cortex may contribute to age-related cognitive defects.
2
Increased amygdala functional connectivity during working memory among patients with mild cognitive impairment

Lucas Broster, Sarah Wing, Ruolei Gu PhD, Chunyan Guo PhD, Jessica Clark PhD, McKinley Heflin, Gregory Jicha MD, PhD, Yang Jiang PhD

Behavioral Science, University of Kentucky • Psychology, Chinese Academy of Sciences • Psychology, Capital Normal University • Psychology, National Rehabilitation Hospital • Neurology, University of Kentucky

Student

Patients with amnestic mild cognitive impairment (aMCI) recruit networks to facilitate cognition. Affective neural networks have been implicated (Broster et al., 2012). 12 older adults with normal cognitive status (NC) and 11 age- and education-matched patients with aMCI performed a modified delayed-match-to-sample task during an event-related fMRI design to test this hypothesis. Percent change in BOLD signal was analyzed at regions implicated in affective and cognitive networks. Results indicated characteristic group differences at the amygdalae such that patients' left amygdala reactions matched those of the right amygdala. Functional connectivity analysis showed that both amygdalae in patients with aMCI were associated with activity in working memory and executive function brain regions, but only the right amygdala was so associated in NC, ps < 0.001. This connectivity change is suggestive of cognitive-affective network interplay even in the earlier aMCI stage of Alzheimer disease progression.

3
Hyperhomocysteinemia as a dietary model of vascular dementia

Donna Wilcock PhD, Abigail Greenstein, Tiffany Sudduth

Sanders-Brown Center on Aging, University of Kentucky

Faculty

Vascular dementia (VaD) is the second most common cause of dementia behind Alzheimer's disease (AD). Of note, it is estimated that between 20 and 40% of AD patients also have VaD co-morbidity. We have developed a model of VaD by inducing hyperhomocysteinemia in wildtype mice. To achieve this we administered a special diet that is methionine-enriched; folate, B6, B12 and choline deficient. Mice were administered the diet for a 6 week period beginning at 2 months of age. We performed cognitive testing immediately prior to tissue harvest as well as MRI imaging. We found significant cognitive deficits and cerebrovascular abnormalities on the MRI imaging. We processed the left hemisphere of the brain for histology and the right hemisphere was dissected and flash frozen for biochemical assays. To assess for microhemorrhage presence we performed Prussian blue staining and found significant induction of microhemorrhages in the brains of the hyperhomocysteinemic mice. We also assessed markers of neuroinflammation and found elevations in the expression of IL-1β, TNFa and IL-6. In addition, both the MMP2 and MMP9 metalloproteinase systems were activated in the hyperhomocysteinemic mice. These data suggest that the neuroinflammatory response and subsequent activation of the matrix metalloproteinase systems play a significant role in the pathogenesis of VaD. Also, the development of a dietary model of VaD allows us to examine the AD-VaD co-morbidity in mouse models of AD.
Neuroinflammatory phenotype as a source of heterogeneity in early Alzheimer’s disease

Tiffany Sudduth, Frederick Schmitt PhD, Peter Nelson MD, PhD, Donna Wilcock PhD

Sanders-Brown Center on Aging, University of Kentucky

Alzheimer’s disease (AD) is defined pathologically by the presence of amyloid plaques and neurofibrillary tangles in the brain. Despite advancement in our understanding about AD pathologies, there remains unexplained variability in course, duration and therapeutic response. We hypothesize that neuroinflammatory signals in the brain are an important potential source of AD clinical and pathological variability.

In frozen brain tissue samples of frontal cortex and cerebellum from the University of Kentucky Alzheimer’s Disease Center autopsy cohort, we measured gene expression profiles from age-matched non-demented controls, early-stage AD and late-stage AD cases. We also examined the neuropathological data on these samples and performed analyses of the serum proteins. We performed gene expression analysis for genes categorizing inflammatory states termed M1 and M2. M2 can be further categorized as M2a, M2b and M2c. We also performed ELISA analysis of Aβ proteins on the same brain samples and the serum samples were analyzed for a profile of inflammatory proteins.

Striking heterogeneity was found in early AD. Specifically, early-stage AD brain samples indicated polarization toward either the M1 or M2a states when compared to age-matched non-disease control tissue. Where gene expression indicated an M1 state, there was very little expression of M2 markers. By contrast, in the presence of M2a markers, M1 markers tended to be absent. This polarization was only observed in the frontal cortex, unlike the cerebellum, a region not affected in the early stages of AD. We were able to detect both differences in neuropathological features, and changes in serum proteins that distinguished the individuals M1 versus M2a brain inflammatory polarization.

Neuroinflammatory polarization occurs early in the course of AD and is a source of variability in the population of AD patients considered for recruitment to clinical trials. It is hoped that assessment of serum proteins as biomarkers to predict the neuroinflammatory state will combine with in vivo animal studies to personalize the therapeutic approach to treatment of AD.
Dephosphorylation of the astrocytic gap junction protein, connexin 43, is increased in human hippocampus during mild cognitive impairment

Melanie Pleiss, Jennifer Furman PhD, Hafiz Mohmmad Abdul PhD, Christopher Norris PhD
Molecular and Biomedical Pharmacology, University of Kentucky • Sanders Brown Center on Aging, University of Kentucky • Molecular and Biomedical Pharmacology, Sanders Brown Center on Aging, University of Kentucky

Student

Objective:
Astrocyte activation arises early in the progression of Alzheimer’s disease (AD), possibly leading to chronic neuroinflammation, synapse dysfunction, and neurodegeneration. Pro-inflammatory cytokines inhibit intracellular communication between astrocytes by impairing the function of gap junction proteins, including connexin 43 (Cx43). Earlier work found that Cx43 is dephosphorylated and disrupted by calcineurin (CN), a protein phosphatase upregulated in activated astrocytes during AD and involved in immune/inflammatory signaling. However, the extent to which CN interacts with Cx43 during AD is not known.

Methods/Results:
In the present study, we prepared hippocampal membrane fractions from non-demented human subjects (n = 10), and subjects diagnosed with mild cognitive impairment (MCI, n =14) or AD (n =21) and used Western blot to assess levels of total and dephosphorylated Cx43. The results revealed a slight, though insignificant reduction in Cx43 in the MCI and AD groups relative to non-demented controls. In contrast, levels for the dephosphorylated form of Cx43 exhibited an ~58% increase during MCI (p < 0.01), but returned to near control levels during AD. This pattern of change was similar to that shown previously by NFAT1, another critical CN substrate found in activated astrocytes.

Conclusion:
The results suggest that neuroinflammation arising in the early stages of AD disrupts astrocytic gap junctional coupling, in part, through the activation of CN. Further studies will be done to elucidate the possible direct interaction between CN and Cx43, and the mechanism by which CN dephosphorylates Cx43.

Research Supported by the NIH: R01 AG027297
NADPH-oxidase upregulation in pre-clinical Alzheimer’s disease and mild cognitive impairment

Mubeen Ansari PhD, Scheff Stephen PhD

Sanders-Brown Center on Aging, University of Kentucky

Upregulation of reactive oxygen species production via NADPH-oxidase (NOX) has been shown to play a role in variety of neurological disorders including Alzheimer’s disease (AD). Previous work from the laboratory has shown an increase in NOX activity in both the frontal and temporal cortex as a function of the disease progression. Changes in NOX were already apparent in tissue from individuals with amnestic mild cognitive impairment (aMCI), a condition believed to be an early stage of transition in AD. Results also indicated that NOX activity may be elevated in the asymptomatic (pre-clinical) phase of the AD. In order to further explore the role of NOX activity, we investigated the hippocampal formation, a structure known to be affected very early in AD progression. Short post-mortem autopsy samples were obtained from individuals who underwent antemortem cognitive testing and postmortem histopathologic assessment to determine disease progression. The subjects were assigned to one of the following groups: 1) individuals with no cognitive impairment (NCI) and low or no AD-type pathology (LP-NCI), 2) NCI individuals with high levels of AD-type pathology (HP-NCI), and 3) individuals with aMCI. Biochemical methods were used to determine overall NOX activity as well as levels of the different NOX subunits (gp91phox, p67phox, p47phox, p40phox, and p22phox). Overall enzyme activity was significantly elevated in the hippocampus of the HP-NCI and aMCI groups compared to the LP-NCI cohort. Almost all of the subunits were significantly elevated in the aMCI subjects and the HP-NCI cohort also showed increased levels. The membrane bound p22phox subunit was the only one that remained stable, similar to that observed in the frontal and temporal cortex. Collectively, these data show that NOX is upregulated early in the hippocampus and that the HP-NCI group is a cohort in transition in the progression of AD, suggesting it may represent a pre-clinical stage of the disease.
Chemical cleavage under dissociating conditions followed by proteolytic digestion facilitates proteomic analysis of insoluble AD brain pathologies

Sergey Matveev PhD, Irfan Baig PhD, Fredrick Onono PhD, Subramanian Thangaian PhD, Stephen Scheff PhD, Haining Zhu PhD, Peter Spielmann PhD, Harry LeVine PhD

Sanders-Brown Center on Aging, University of Kentucky • Internal Medicine, University of Kentucky • Biochemistry, University of Kentucky

Staff

Amyloid plaques and neurofibrillary tangles are the hallmark brain pathologies of Alzheimer’s disease, a uniquely human disorder. The application of Aβ amyloid fibril PET ligand imaging in living patients offers promise for earlier detection of disease processes and widens the window for therapeutic intervention. The 11C-labeled benzothiazole Pittsburgh Compound B (PIB) was one of the first of these ligands used clinically. Interestingly, PIB shows a remarkable selectivity for the human Alzheimer’s disease (AD) Aβ plaque pathology. Only humans have a high density of PIB binding while animal models with comparable amounts of Aβ deposits bind little PIB. We suggest that the molecular and biological differences between humans and animal models reflected by PIB binding will provide key insights into the pathologic process that are not recapitulated in current models.

We isolated a purified brain fraction containing ~90% of PIB binding activity by a protocol developed in our lab. This fraction contains less than 1% of the initial protein and lipid, and is extremely insoluble, resisting SDS, urea, guanidine, and protease treatments. Attempts to further purify the PIB binding site destroyed PIB binding and dissociated prebound 3H-PIB. Partial solubilization of the PIB binding site material was achieved by combining 2% SDS and 8M urea. Subsequent SDS-PAGE resulted in considerable protein precipitation. Proteomic analysis of in-gel trypsin digests of the top of the stacking gel and the separating gel revealed Aβ in multiple bands.

To circumvent aggregation we took advantage of solubilization of the purified PIB binding site by high concentrations of formic acid. Combination of cyanogen bromide cleavage at methionine residues in 70% formic acid followed by neutralization with ammonium hydroxide, then trypsinization was required to completely solubilize peptides for LC-MS/MS proteomic analysis. This protocol allowed the identification of >110 proteins, predominantly of neuronal origin, while formic acid treatment followed by dilution, neutralization, and trypsinization identified only 10 proteins, a subset of those from the combined CNBr/trypsinization treatment.

We conclude that combining chemical cleavage under strongly dissociating conditions followed by proteolytic digestion is likely to be helpful in the effective analysis of the protein species present in the highly insoluble pathologies of many neurodegenerative diseases.
Oxidative DNA damage in genes of proteins modified during AD

Sony Soman MS, Mark Lovell PhD

Chemistry, University of Kentucky • Chemistry, Sanders Brown Center on Aging, University of Kentucky

Student

Multiple studies demonstrate increased oxidative DNA damage in the progression of Alzheimer’s disease (AD), although the exact site of the oxidation in the human genome remains unclear. To test the hypothesis that oxidative DNA damage is not an arbitrary process but is associated with specific locations in genes that code for proteins whose expression is altered in vulnerable regions of the AD brain, we used quantitative PCR to study nuclear DNA (nDNA) isolated from the superior and middle temporal gyrus (SMTG) and cerebellum (CER) of normal control (NC) subjects and subjects with preclinical AD (PCAD), mild cognitive impairment (MCI) and late stage AD (LAD). nDNA specimens were treated with formamidopyrimidine glycosylase (Fpg), a DNA repair enzyme with both N-glycosylase and AP lyase activities that recognizes and removes damaged bases including 8-oxoguanine, 8-oxoadenine, and 2,6-Diamino-4-oxo-5-formamidopyrimidine (fapy-guanine). The DNA strands containing single-nucleotide gaps flanked by phosphate termini at sites of guanine oxidation were then subjected to quantitative/real-time polymerase chain reaction (qPCR/RT-PCR) amplification and primers for voltage dependent anion channel proteins (VDAC) 1, 2 and 3. Previous studies suggest protein levels of VDAC 1 and 3 are altered in LAD but levels of VDAC2 are unchanged.

Analysis of the data shows significant increases in the extent of oxidative damage in nDNA from the SMTG of LAD subjects in specific amplicons of VDAC1 and VDAC 3 compared to age-matched NC subjects but no significant changes in VDAC2. Overall, these preliminary data suggest oxidative damage may be localized to particular segments of specific genes associated with protein alterations in AD and may play a role in the pathogenesis of the disease.
Loss of hippocampal synaptic proteins in pre-clinical Alzheimer’s disease

Stephen Scheff, Mubeen Ansari, Elliott Mufson

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

Alzheimer’s disease (AD) manifests severe pathological changes in the central nervous system (CNS) including increased levels of amyloid, hyperphosphorylated tau, and synaptic loss. Synaptic dysfunction is a hallmark of the disease that associates with cognitive ability and level of dementia during the progression AD. Relatively recent imaging studies, coupled with neuropathology, suggest a long asymptomatic (pre-clinical) phase to AD, with cognitive function largely maintained despite substantial AD-type amyloid and tau pathology. Previous work from this laboratory reported a loss of synapses in the hippocampus of individuals with amnestic mild cognitive impairment (aMCI), which is believed to be an early stage of transition in AD. In the present study, to test whether or not synapses were affected in the pre-clinical stage of the disease, we evaluated the hippocampal formation harvested from short post-mortem autopsy samples obtained from three different cohorts: 1) individuals with no cognitive impairment (NCI) and low or no AD-type pathology (LP-NCI), 2) NCI individuals with high levels of AD-type pathology (HP-NCI), and 3) individuals with aMCI. Changes in several different key synaptic proteins were analyzed along with possible changes in markers of oxidative stress. Compared to the age-matched LP-NCI cohort, individuals with HP-NCI and aMCI showed significant increases in numerous markers of oxidative stress. The hippocampal analysis of the HP-NCI and aMCI groups also revealed significant declines in key synaptic proteins. These results support the idea that in the pre-clinical stage of the disease, there already appears to be a defect in synaptic structure that may be related to levels of oxidative stress. The fact that the HP-NCI group continues to manifest adequate cognitive ability may be evidence for the use of cognitive reserve in this cohort. Supported by AG27219; AG14449; AG028383
Trajectories of cognitive decline by driving mobility: evidence from the Health and Retirement Study

Moon Choi PhD, Matthew Lohman MS, Briana Mezuk PhD

College of Social Work, University of Kentucky • Department of Epidemiology and Community Health, Virginia Commonwealth University

Faculty

OBJECTIVES: To examine the trajectories of cognitive decline by driving mobility.

METHODS: Using longitudinal mixed effects models and discrete-time hazard models, trajectories of cognitive decline and risk for incident cognitive impairment among adults aged 65 and older without any memory-related disease or cognitive impairment at baseline were estimated by driving status while controlling for sociodemographic and health characteristics. The data came from the 1998–2008 waves of the Health and Retirement Study, a nationally-representative panel study (N = 9,135). Cognitive function was assessed with a modified version of the Telephone Interview for Cognitive Status. Driving status and health characteristics were assessed by self-report.

RESULTS: Older adults who did not drive (former and never drivers) at baseline had lower average cognitive test scores as compared to active drivers. Former drivers at baseline experienced accelerated cognitive decline over the subsequent 10 years compared to active drivers (β = -0.35, 95% Confidence Interval [CI] = -0.43 to -0.26) even after controlling for baseline cognitive test scores and health status. Transition to non-driving among active drivers was associated with a faster cognitive decline over the 10-year follow-up period (β = -0.31, 95% CI = -0.40 to -0.22). The hazard for incident cognitive impairment was higher in former drivers than active drivers (HR = 1.86, 95% CI = 1.36 to 2.53).

CONCLUSIONS: The amount of cognitive decline over the 10-year period was modest for participants. However, older adults without driving mobility had poorer cognitive functioning and were at a higher risk for incident cognitive impairment and accelerated cognitive decline than active drivers. Targeted interventions aimed at helping older adults without driving mobility preserve cognitive functioning need to be developed.
Mild cognitive impairment: statistical models of transition using longitudinal clinical data

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Mild cognitive impairment (MCI) refers to the clinical state between normal cognition and probable Alzheimer’s disease (AD), but persons diagnosed with MCI may progress to non-AD forms of dementia, remain MCI until death, or recover to normal cognition. Risk factors for these various clinical changes, which we term “transitions,” may provide targets for therapeutic interventions. Therefore it is useful to develop new approaches to assess risk factors for these transitions. Markov models have been used to investigate the transient nature of MCI represented by amnestic single-domain and mixed MCI states, where mixed MCI comprised all other MCI subtypes based on cognitive assessments. The purpose of this study is to expand this risk model by including a clinically determined MCI state as an outcome.

Analyses show that several common risk factors play different roles in effecting transitions to MCI and dementia. Notably, APOE-4 increases the risk of transition to clinical MCI but does not affect the risk for a final transition to dementia, and baseline hypertension decreases the risk of transition to dementia from clinical MCI.
p38β MAPK deficiency fails to inhibit cytokine production or protect neurons against LPS insult in in vitro and in vivo models

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Evidence implicates that chronic neuroinflammation plays a detrimental role in the process of neurodegenerative diseases. Key to the neuroinflammatory process is the overproduction of proinflammatory cytokines, such as TNFα and IL-1β. Microglia are considered the primary cellular sources of TNFα and IL-1β in the brain. Extensive clinical data in peripheral inflammatory disorders suggests that the p38 MAPK pathway is involved in the production of TNFα and IL-1β. There are at least four isoforms of p38 MAPK, with p38α and p38β the target of most p38 MAPK inhibitor drugs. Our previous studies demonstrated that genetic deletion, or pharmacological inhibition of microglial p38α MAPK could prevent LPS-induced neurotoxicity by suppressing TNFα overproduction. However, the potential role of the p38β MAPK isoform in a CNS context is poorly understood. In the current studies, wild type (WT) and p38β KO mice were used for in vitro (primary microglia and neuron culture experiments in response to LPS), and in vivo assays (LPS injections to stimulate systemic (i.p) and central (i.c.v)) of LPS-induced neuroinflammatory responses. Following LPS stimuli, WT and p38β KO microglia/neuron co-cultures were found to have similar levels of TNFα and IL-1β production. Importantly, co-cultures of WT neurons with WT or p38β KO microglia showed no difference in LPS-induced neurotoxicity. The in vitro results were confirmed in vivo, where levels of TNFα and IL-1β in the cortex were not significantly different between WT or p38β KO mice in LPS i.p and i.c.v models. Our results suggest that, consistent with peripheral inflammation mechanisms, p38β MAPK may not play a critical role in the TNFα and IL-1β response to LPS-induced neuroinflammation.
Targeting serine-threonine protein kinases in CNS disorders: revisiting p38α MAPK

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More than 500 protein kinases (PK) are encoded by the human genome, and perturbations of diverse PK-mediated signaling pathways are implicated in disease progression. However, only about a dozen PK inhibitor drugs are approved for clinical use, mostly for non-CNS indications. Further, these drugs are multi-kinase inhibitors that mostly target tyrosine PKs. Therefore, there is a critical need to develop more specific PK inhibitor drug candidates, especially ones targeting serine-threonine (S/T) PKs, and to explore their potential to alter CNS pathology progression.

The S/T PK p38α MAPK is especially attractive as a starting point case study due to its history as a drug discovery target that regulates increased proinflammatory cytokine production. It is a critical and druggable component of an intracellular signal transduction cascade that has more recently been implicated in direct involvement in neuronal pathology. The biological role of p38α MAPK is also context dependent. Therefore, p38α MAPK offers a paradigm of a widely distributed target whose functional importance is dependent on biological context and, in the CNS, is involved in pathology progression in both involved cell types, glia and neurons.

We used a structure- and chemoinformatics-assisted, pharmacology-driven approach to develop novel, highly selective, active site-directed, small molecule p38α MAPK inhibitors. The inhibitors’ cellular mechanism of action, kinase target engagement, and linkage to cellular regulation were demonstrated in cell and slice cultures. In vivo screens in mice demonstrated promising pharmacodynamic functions related to amelioration of synaptic dysfunction and memory in two Alzheimer’s disease relevant stress models. The in vivo biological tool deliverables from this effort provide a starting point for future drug development and demonstrate the feasibility of developing single kinase-directed inhibitors with in vivo efficacy.

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Detrimental neuroinflammatory response following TBI is mediated by microglia via p38α MAPK dependent mechanism

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Neuropathologic damage following traumatic brain injury (TBI) is the result of both the immediate impact injury and secondary injury mechanisms. Post-traumatic glial activation with increased production of inflammatory molecules such as proinflammatory cytokines is a secondary injury mechanism that contributes to pathology progression in both animal models and human head injury patients. Moreover, following TBI the inflammatory response can result in persistently sensitized or “primed” microglia, which can contribute to a chronic state of neuroinflammation. We recently demonstrated using in vitro models that p38α MAPK signaling in microglia is a key event in promoting cytokine production in response to diverse disease-relevant stressors and subsequent inflammatory neuronal dysfunction. From these findings, we hypothesized that the p38α MAPK signaling pathway in microglia could be contributing to the secondary neuropathologic sequelae following a diffuse TBI. To test this hypothesis, we used a midline fluid percussion model to induce a diffuse brain injury in young adult wild-type (WT) mice or in conditional knockout mice genetically deficient in microglia p38α MAPK (p38α KO). From day 1-7 post-injury, motor coordination and balance were tested using a rotarod task. Injured WT mice showed a significant impairment on the rotarod task compared to sham-injured mice, while p38α MAPK deficiency in microglia prevented this TBI-induced impairment. Microglial activation was assessed by immunohistochemistry for three different microglial markers: IBA-1, CD45 and CD68. Mechanistically, we found that p38α MAPK was critical for microglia activation, as the p38α KO mice showed a dramatically reduced microglial activation response to the injury compared to the WT mice. The results suggest that stressor-induced activation of p38α MAPK signaling in microglia is a key event that primes microglia and leads to motor deficits following a diffuse TBI.

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Targeting proinflammatory cytokine up-regulation with a novel anti-cytokine therapeutic, MW-151, attenuates pathology in an AD mouse model

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Staff

Background: Neuroinflammation is a key contributor to pathology progression in both inherited and sporadic forms of Alzheimer's disease (AD). Increased production of proinflammatory cytokines by glia early in AD is clearly implicated in neuron damage, synaptic dysfunction and pathophysiology. Neuroinflammation covers a broad and diverse array of responses, many of which are beneficial; therefore, a rational therapeutic strategy is to specifically target excessive proinflammatory cytokine production at early stages of pathology to modify disease progression without pan-suppression of glia stress responses. The Minozac family (3-amino-6-phenylpyridazines) of experimental anti-proinflammatory cytokine therapeutics are efficacious in a variety of animal models of CNS disorders where proinflammatory cytokine overproduction is a component of neuropathology progression. We used the Minozac compound, MW01-2-151SRM (MW-151), to test the hypothesis that suppression of proinflammatory cytokine production, by treatment with MW-151, would be beneficial at reducing pathology endpoints in a mouse model of Aβ-induced AD-relevant pathology.

Methods: An APP/PS1 double knockin mouse model was used in two intervention paradigms: (1) prevention – a chronic study where MW-151 was administered (IP 2.5mg/kg) three times weekly for five months beginning at an age when pathology was just beginning; and (2) treatment – an acute study where compound was administered to older diseased mice once daily for one week. Treatments ended and pathology endpoints were measured at the same age.

Results: In the prevention paradigm, MW-151 treatment reduced proinflammatory cytokine (IL-1β) production, attenuated astrocyte and microglia activation, and suppressed neuron damage (synaptic protein loss). In the treatment paradigm, one week MW-151 treatment that started at a later point in disease development also suppressed cytokine production and neuron damage, but to a lesser extent. These beneficial responses occurred in the absence of effects on amyloid plaque load or Aβ levels as determined by immunohistochemistry.

Conclusions: The results indicate that therapeutic intervention that targets increases in proinflammatory cytokine production is a viable treatment paradigm. The results raise the possibility that if such interventions are begun early in the disease development process, AD onset or progression might be slowed.

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Increased expression of calpains 2 and 10 in Alzheimer’s disease

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Increases in intracellular calcium are thought to contribute to the two hallmark pathologic features of Alzheimer’s disease (AD): neurofibrillary tangles (NFTs) composed of aggregated tau protein; and senile plaques composed primarily of β-amyloid (Aβ) protein. These pathologies are prevalent in the hippocampus and many cortical regions, with primary motor cortex being less vulnerable. Calpains are calcium-activated proteases thought to contribute to NFT and plaque formation making them a potential target for AD prevention and treatment. Currently, seven calpain isoforms (Calpain 1, 2, 5, 7, 10, 12 and 15) have been identified in the central nervous system (CNS). Previous studies in a mouse AD model revealed increased expression of calpains 10 and 12, whereas in humans, AD causes increased expression and activation of calpain 2 (m-calpain) in AD vulnerable brain regions. However, the expression levels of other calpain isoforms have not been examined in the brain of patients with mild cognitive impairment (MCI) or AD and were the focus of this study. mRNA and protein was isolated from the cerebellum, motor cortex, pre-frontal cortex and posterior cingulate from age-matched controls (n=6), MCI (n=6) and AD (n=6) post-mortem human brain samples. Protein and mRNA expression of calpains 1, 2, 5, 7 and 10 was evaluated by western blot analysis and qPCR, respectively. In AD, but not MCI, calpain 2 mRNA and protein levels increased only in the posterior cingulate. Calpain 10 mRNA levels also increased in the posterior cingulate with AD. Calpains 1, 3, 5 and 7 mRNA levels and calpain 10 proteins levels were unaffected. N-terminal autolysis of calpain 1 occurred in AD (cerebellum, motor cortex and pre-frontal cortex) but not in MCI, suggesting its activation in AD. In summary, significant elevations in calpain 2 and 10 expression and calpain 1 activation were observed in the posterior cingulate cortex obtained post-mortem from individuals with AD, but were not altered in MCI. This suggests that the conversion of MCI to AD may involve calpain activation.
2-NBDG fluorescence imaging in hippocampal CA1 neurons with age

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Staff

We have recently adapted a fluorescent glucose imaging technique for studies of hippocampal cultures (Pancani et al., 2011). This provides sufficient spatial resolution to directly monitor glucose utilization and Ca2+ levels in live neurons. We are now using the fluorescent glucose analog 2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxyglucose (2-NBDG) for studies of brain aging. Interest in glucose imaging stems from several studies using PET scan imaging that have shown regional decreases in brain glucose utilization in AD. Also playing a critical role in the development of cognitive decline with aging and AD is the mishandling of neuronal Ca2+. Additionally, evidence suggests that intracellular Ca2+ levels can affect glucose signaling not only in the periphery but also in the brain. At the cellular level, the nature of the relationship between Ca2+ and glucose utilization in the brain is not clear, and methods such as PET and autoradiography lack spatial or temporal resolution to test the relationship. Furthermore, in animal models of aging that show increases in hippocampal Ca2+ dysregulation with age, it is not clear whether these changes can alter glucose utilization.

The technique was first developed for in vitro experiments, and was then adapted for work in acute hippocampal slices from young (3-4 months old) and aged (20-21 months old) Fischer 344 (F344) rats. We monitored neuronal glucose utilization in CA1 hippocampal neurons in response to suprathreshold repetitive synaptic stimulation (RSS). As opposed to the results obtained in cell cultures, we find that initially during RSS in the theta range (3, 7, 15 Hz), 2-NBDG fluorescence increases. This is followed by an increase in 2-NBDG disappearance (slope), which accelerates further upon termination of the stimulation. During the course of the work in culture it was shown that the glycolysis inhibitor iodoacetate was able to significantly blunt the response to depolarization (Pancani et al., 2011). In order to confirm that 2-NBDG fluorescence in slices also reports on glucose utilization, ex vivo experiments were carried out in which RSS at 7 Hz was recorded before and after iodoacetate treatment. Here, we report that iodoacetate was unable to alter the observed biphasic response in slices. Ongoing work is determining the source of the signal and its relationship to brain aging, as well as the effects of voltage, Na+ and Ca2+ on 2-NBDG fluorescence.
Over-recruitment in the aging brain reflects declining neural efficiency: A combined fMRI and DTI study

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Objectives: The present study tested whether commonly observed functional neuroimaging over-recruitment in older adults reflects decreased neural efficiency and/or neural compensation.

Methods: Twenty-eight young adults and 33 healthy older adults completed a task-switching paradigm while functional magnetic resonance imaging (fMRI) was performed. In the single task, participants made either a color or a shape decision. In the mixed task, participants switched between performing color or shape decisions. Diffusion tensor imaging (DTI) data was also collected while subjects rested. To match the task demand between groups, the present study compared the behavior and BOLD signal change in the single task in the older group versus the mixed task in the young group. Correlations were performed between BOLD magnitude in selected regions of interest (ROIs) and both behavioral performance and fractional anisotropy (FA) in each group.

Results: Age-related fMRI over-recruitment persisted in cognitive control regions even though behavioral performance was matched between the older and young adults. Critically, BOLD signal change in the ROIs within the over-recruited regions positively correlated with error rate and RT in the older group. In addition, the BOLD signal change in right dorsolateral prefrontal cortex and right insula negatively correlated with FA in both the body and genu portions of the corpus callosum in the older group.

Conclusions: These results suggest that over-recruitment reflects less efficient use of neural resources in older adults. Age-related reductions in neural efficiency appear to be based in part on age-related reductions in white matter integrity.
Redox proteomics-identified brain proteins involved in glucose metabolism: a key to understanding Alzheimer disease progression

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Faculty

Positron-emission tomography (PET) studies demonstrate that brain from subjects with Alzheimer disease (AD) and arguably its earliest form, amnestic mild cognitive impairment (MCI), have significantly decreased glucose utilization, with AD brain being more involved. In the current research, we used the techniques of redox proteomics, pioneered in our laboratory, to identify oxidatively modified proteins from hippocampus and inferior parietal lobule of subjects with AD and MCI compared to those from aged-matched controls. Brain proteins with elevated levels of protein-bound 4-hydroxy-2-nonenal (HNE), a marker of lipid peroxidation, and protein carbonyls and 3-nitrotyrosine, markers of protein oxidation, were identified. In nearly every oxidatively modified protein examined activity of the damaged proteins is decreased. Alpha-enolase, which normally has pro-survival and anti-Ab peptide properties in addition to being a glycolytic enzyme, was oxidatively modified in common between MCI and AD. This result is consistent with the notion that enolase may contribute to both the decreased PET assessed glucose utilization in MCI and AD and to the progression of this dementing disorder.

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CERAD Practice Effects and Attrition Bias in a Dementia Prevention Trial

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Objectives: Repeated cognitive measures are an important component in tracking cognitive change over time; however, practice effects and attrition bias may obscure significant clinical change over time. The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) set of tests is frequently used for such purposes in both clinical and research settings. The current study sought to examine the presence and magnitude of practice effects and the role of attrition bias in a sample of cognitively normal older men enrolled in a prevention trial.

Method: 308 participants were grouped according to whether they completed five years of follow-up (n = 182) or less (n = 126). Practice effects were examined in these participants as a whole (n = 308) and by group. Results: Findings indicate that moderate sized practice effects exist in both groups and that attrition bias likely does not play a contributing role in improved scores over time. Discussion: The current study provides evidence and support for the effect of practice on the interpretation of cognitive data gathered longitudinally.
Intranasal insulin on spatial learning and memory in the aged F344 rat

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The combination of aging and insulin resistance is associated with type 2 diabetes mellitus, and while its impact is recognized in the periphery, insulin resistance also exists in the brain. In an attempt to combat this decreased insulin signaling, several groups have used intranasal insulin delivery in clinical and pre-clinical settings. Results show improved cognition and memory in young volunteers, patients with mild cognitive impairment or Alzheimer's disease (AD), as well as in animal models of diabetes or AD. Decreased brain insulin sensitivity has been reported as a mediator of cognitive decline in brain aging and AD. While some studies have linked insulin signaling in the brain to dysregulation in tau, Ca²⁺, Abeta clearance mechanisms, excitatory neurotransmitters or synaptic plasticity, it is not clear how intranasal insulin delivery to the brain might alter functional communication, improve learning, or facilitate memory, particularly in animal model of aging.

We used the F344 rat model of aging to test the hypothesis that the insulin analog Humalog® or long-acting insulin Levimir® could improve cognition in animals at 21 months of age. Thirty aged animals received daily doses of Levimir® at 3 concentrations (10/group) equivalent to those used in several clinical trials (0.143, 0.286 or 0.571 IU/Kg/day), while ten aged received daily Humalog® doses of 0.143 IU/Kg/day. Twenty aged and 10 young-adult (3 months old) animals received saline. The experimenters were blind to the doses applied to the aged animals. Treatment lasted for 11-18 days with training on the Morris water maze spatial task starting on the fifth day. Western blots quantified insulin receptor (IR) and insulin receptor substrate-1 (IRS-1) levels in the brain and insulin levels were measured in the brain as well (ELISA). Electrophysiological characterization was also accomplished in a subset of animals.

Animals receiving the low and the high dose insulin showed a trend for improved performance on the 24 hr recall task compared to the middle dose, and the age-dependent decreases in hippocampal IR and IRS-1 levels were reversed with increasing insulin doses. Ongoing projects are clarifying whether acute or chronic effects of insulin are responsible for these results. Together with evidence that acute insulin can reduce the AHP in aged animals, our results provide further evidence that this model displays characteristics of patients sensitive to intranasal insulin administration. Once a day intranasal insulin exposure therefore, appears able to have a significant impact on hippocampal processes, partially reversing some aspects of the aging phenotype.
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Epigenetic changes in the progression of Alzheimer’s disease

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The formation of 5-hydroxymethylcytosine (5hmC), a key intermediate of DNA demethylation, is driven by the ten eleven translocation (TET) family of proteins that oxidize 5-methylcytosine (5mC) to 5hmC. To determine whether methylation/demethylation status is altered during the progression of Alzheimer’s disease (AD), levels of TET1, 5mC and subsequent intermediates, including 5hmC, 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) were quantified in nuclear DNA from the hippocampus/parahippocampal gyrus (HPG) and the cerebellum (CER) of age-matched normal controls, subjects with preclinical AD (PCAD) and late-stage AD (LAD) subjects using immunochemistry. Results show significantly (P < 0.05) increased levels of TET1, 5mC, and 5hmC in the HPG of PCAD and LAD subjects. In contrast, levels of 5fC and 5caC were significantly (P < 0.05) decreased in the HPG of PCAD and LAD subjects. Overall, the data suggest altered methylation/demethylation patterns in vulnerable brain regions prior to the onset of clinical symptoms in AD suggesting a role in the pathogenesis of the disease.

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Semi-Markov models for transitions from cognitively intact to clinically impaired

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In dementia research, cognitively intact (CI) elderly subjects enroll in cohorts where each participant volunteers for annual cognitive assessments. While all subjects are CI at baseline, future assessments may result in a diagnosis of clinical Mild Cognitive Impairment (MCI) or dementia. We consider modeling the flow of subjects through CI, clinical MCI, dementia, and the competing state of death, and investigate risk factors for these transitions using semi-Markov models. In our application to 543 subjects enrolled in the Biologically Resilient Adults in Neurological Studies (BRAiNS) cohort at the University of Kentucky’s Center on Aging, we found considerable competition for transitions to clinical MCI and dementia due to death. Results show that the holding time distributions for the states CI and clinical MCI are well-approximated by Weibull distributions with parameters depending on the final state, while transition probabilities among the states expressed as multinomial logistic models are functions of the risk factors under study.
ABCA7 and AD-associated SNPs: Translating a Mechanism into a Potential Therapeutic Target

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Genome wide association studies (GWAS) have recently identified genes with single nucleotide polymorphisms (SNPs) associated with Alzheimer’s disease (AD), including ABCA7, a lipid transporter within the brain. Here, we hypothesized that the AD-associated SNPs alter ABCA7 expression. To evaluate this hypothesis, we genotyped two AD associated SNPs, rs3764560 and rs3752246, and used qPCR to quantify ABCA7 expression in 60 human brain RNA samples. We found that the minor allele of rs3764650 was associated with decreased ABCA7 expression and increased AD risk. Agents that increase ABCA7 expression would be predicted to reduce AD risk. Currently, we are using next generation sequencing to assess allele expression imbalance (AEI) to substantiate our qPCR findings. For this work, we genotyped two exonic SNPs, rs4147914 and rs4147930, and are sequencing cDNA from heterozygous individuals to assess whether one allele is expressed at higher levels than the other allele. Additionally, we are testing ABCA7 expression in lymphocytes from humans treated with valproic acid, which induces ABCA7 in vitro. Overall, these studies will identify the mechanism of action of an AD-associated SNP and translate this mechanism into a potential therapy.
Beta-Amyloid Immunization with Behavioral Enrichment in a Canine Model of Aging: Antibody Titers and CSF Beta-amyloid

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Alzheimer’s disease (AD) is characterized by the cognitive decline of an individual and the presence of hallmark pathology, including senile plaques (SP) and neurofibrillary tangles. SPs contain β-amyloid protein (Aβ), resulting from cleavage of the amyloid precursor protein (APP). A number of therapeutic strategies being developed today are focused on reducing the production or deposition of Aβ in the brains of patients with AD. The canine model is useful for testing potential therapeutic agents. Canines produce APP that has 98% homology with human APP. In addition, canines naturally develop Aβ neuropathology and show cognitive decline with age, similar to AD patients. Recent studies have shown that active immunization for 2 years with fibrillar Aβ1-42 (IMM) in aged canines significantly decreased brain Aβ and maintained executive function, while other measures of cognition remained unchanged (Head et al., 2008). However, behavioral enrichment (BEH) improves cognition (Milgram et al 2005) without reducing brain Aβ (Pop et al., 2010). We hypothesized that IMM combined with BEH would provide larger cognitive benefits and reduce neuropathology to a greater extent, as compared to either controls or individual IMM and BEH treatments alone.

Aged beagles (10.5-13.6 y) were placed into one of four groups: controls with Alum adjuvant only, fibrillar Aβ1-42 + Alum vaccine, BEH with Alum, and combination treatment (IMM+BEH). Dogs receiving BEH were housed with a kennel mate, had novel play toys each week, and were taken for a 20 minute walk outdoors three times a week. At baseline, animals were given a series of learning tasks and a spatial memory task and matched into equivalent groups on the basis of cognitive test scores. Animals were treated for over 15 months. Fibrillar Aβ1-42 antibody titers in serum and Aβ levels cerebral spinal fluid were measured by ELISA. When compared to non-IMM groups over the first 6 months of the study, anti-Aβ1-42 IgG responses in IMM groups increased significantly (F(2,64)=3.24 p=0.046) and were maintained. No systematic effects on CSF Aβ1-42, Aβ1-40, or total Aβ have been observed in response to 12 months of treatment. On a test of spatial attention (landmark task), BEH dogs performed significantly better than IMM dogs (t(16)=2.7 p=0.016). Additional measures of cognition are being collected. Upon completion of the study, changes in brain Aβ, extent of neurogenesis, and growth factor levels will be measured using immunohistochemistry and western blot analysis.

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Laser capture microdissection reveals major upregulation of inflammatory and glial genes in the hippocampal white matter of aging rats

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Previous microarray analyses of hippocampal gene expression in aging rats point to upregulation of immune/inflammatory, myelinogenic and lipid transport programs (Blalock et al, 03; Rowe et al, 07; Kadish et al, 09), consistent with other studies of brain aging. However, relatively little is known regarding the regional distribution of these aging transcriptional changes. To address this question, we tested whether the prominent immune/inflammatory signatures typical of brain aging show white vs. gray matter tissue differences. Young and aged male F344 rats (n = 9/group) were trained on the Morris water maze. The hippocampus of each animal was then removed and sectioned, and specimens were mounted on slides for laser capture microdissection (Zeiss PALM Microbeam). Gray matter [stratum pyramidale + the upper 1/3 of stratum radiatum] and white matter [alveus + fimbria] samples were collected across multiple slides from each subject. RNA was isolated, amplified and hybridized to Rat Gene 1.0 ST arrays (Affymetrix; one array per tissue type per subject, 36 arrays). Results showed large differences in gene expression between white and gray matter. White matter exhibited much more pronounced inflammatory/gliaal gene expression changes with age than did gray matter, and also manifested the majority of age-related gene expression changes. Also, aged animals performed significantly worse on the water maze. These results point to white matter as a major locus for age-related inflammatory changes, and suggest that regional white matter-selective changes in astrocytic and oligodendrocytic gene expression may play key roles in cognitive decline.
Comprehensive behavioral characterization of an APP/PS-1 double knock-in mouse model of Alzheimer’s disease

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Genetic mutations in the amyloid precursor protein (APP) and presenilin-1 (PS-1) can cause early onset Alzheimer’s disease, and many transgenic mouse models overexpressing the mutant proteins have been developed. Although these transgenic models have provided some insight into the pathogenesis of AD, they are less physiologically relevant than ideal due to their construct of random genetic insertion into the host genome and their abnormally high levels of APP and PS-1 produced. For these reasons, genetic knock-in (KI) models involving targeted insertion of APP and PS-1 to specific locus in the mouse genome convey a more physiologically relevant disease model of AD. Here we use a double KI (APPNLh/APPNLh x PS-1246L/PS-1246L) mouse model of AD which has previously been shown to have amyloid deposition starting at 9 months of age and exhibit signs of oxidative stress in the brain of the KI mice as early as 1 month old. However, to date a comprehensive behavioral analysis of this AD model has not been completed. Here we assess the behavioral phenotype of this mouse model of AD across the time course of the disease (test groups: 7 months, 11 months, 15 months, and 24 months old). The behavioral test battery used consisted of tasks to assess motor function, anxiety-related behavior, and cognitive function. We observed no differences in motor function (grip strength, rotor-rod, & balance beam) or anxiety-related behavior (open field & elevated plus maze) between APP/PS-1 KI animals and wild type counterpart animals for any age group. Cognitive deficits in both recognition memory (novel object recognition) and spatial working memory (radial arm water maze) became apparent for the KI animals as the disease progressed. The comprehensive behavioral analysis reported here is important to the design of future studies investigating potential AD relevant therapeutics using this APP/PS-1 KI mouse model of AD.
Robust and efficient point registration based on clusters and generalized radial basis functions

Huihui Xu MS, Jundong Liu PhD, Charles D Smith MD

School of Electrical Engineering and Computer Science, Ohio University • Neurology and Sanders-Brown Center on Aging, University of Kentucky

Student

Objectives: Radial Basis Functions (RBF) are effective in modeling regularization stabilizers, and have been successfully utilized in several point-based registration algorithms. Unfortunately, the solutions usually require the inversion of a matrix or solving a linear system, whose computational cost grows rapidly with the increase of the input data size.

Methods/Results: In our work, we present a fast and robust approximation remedy for this issue. Our model formulates the registration objective function under the Generalized Radial Basis Function (GRBF) framework with respect to the cluster centers of one point set. With fewer variables, a computationally efficient registration is achieved, which updates the non-rigid transformation and the correspondence matrix simultaneously. Since the cluster centers often capture the global structure of the point sets very well, enhanced registration robustness results due to the reduced likelihood of trapping into local minima. This is especially beneficial in the context of large or/and unevenly distributed data sets. By means of experiments on real and synthetic data, we demonstrate the improvements made over several state-of-the-art solutions.

Conclusions: Point-based image registration using cluster-based radial basis functions is more efficient than linear technique by removing the need for matrix inversion, but still produces robust results.
Riemannian Shape Analysis based on Meridian Curves

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Student

Objectives: Comparing different shapes is a fundamental problem in Computational Anatomy (CA), where a rigorous and intrinsic distance metric is key for a shape analysis system to work effectively and consistently.

Methods/Results: We propose a shape comparison and classification framework that consists of two major components: (1) a meridian-based shape representation based on spectral graph theory, that possesses the merit of capturing salient structure properties along the direction of maximal shape variations, (2) After projecting the 3D meridians onto a multi-dimensional sphere, similarity/dissimilarity between shapes is computed based on a Riemannian spherical distance metric. Group statistics, as well as object classification/clustering, can be readily carried out. Use of the method is demonstrated with human hippocampus extracted from volumetric MRI images as an example.

Conclusions: Higher dimensional meridian shape characterization allows comparisons between complex 3-D shapes such as the human hippocampus on a standard sphere with a detail unavailable with simple summary variables, e.g., hippocampal volume. Future work includes comparison of hippocampi in Alzheimer’s pre-states to detect shape differences that may be present early in the pathologic process.
α5 Integrin knockout mice have reduced infarct volume following ischemic stroke

Jill Roberts PhD, Michael Kahle, Gregory Bix MD, PhD

Sanders-Brown Center on Aging, University of Kentucky

Stroke is a leading cause of long-term disability and death in the United States. While research has focused on the role of angiogenesis following stroke, relatively little is known about the role and relative importance of blood vessel cell surface receptors, such as integrins, in the post-stroke angiogenic response. Understanding their role could lead to the development of better stroke therapies that might target or modulate these receptors. In particular, brain endothelial cell α5β1 integrin, a receptor that is normally not expressed on adult brain microvasculature until after stroke, has a suggested but ill-defined role in post-stroke angiogenesis. Therefore, in the current study, we examined the role of α5β1 integrin using endothelial cell specific α5 integrin knockout (α5 KO) mice. Wild-type mice that underwent tandem ipsilateral CCA/MCA transient occlusion, a well-documented animal stroke model, showed an increase in mean infarct volume from post-stroke day 1 to 3 as expected. Importantly, we report here that while α5 KO mice had similar sized infarcts as wild-type mice after 1 day post-stroke, these infarcts did not subsequently increase in volume on post-stroke day 2 or 3. Intriguingly, as the bulk of the post-stroke angiogenic response does not occur until after post-stroke day 3, it is very unlikely that potential differences in angiogenesis due to deficient endothelial cell α5β1 integrin could explain this result. Furthermore, data suggests increased protein levels of vascular endothelial growth factor (VEGF), a key neuroprotective and pro-angiogenic factor, in the infarcted hemisphere of α5 KO mice on post-stroke day 2 and 3 compared to wild-type mice. While the possibility exists that other receptors within the brain endothelium are upregulated prior to or following a stroke in order to compensate for a lack of α5β1 integrin in the α5 KO mice, we hypothesize that the brain endothelial cell α5β1 integrin could play an important, non-angiogenesis related role in the evolution of an ischemic stroke infarct. Further characterization of the α5 KO mice will increase our understanding of the function of brain α5β1-integrin before, during and following ischemic stroke.
Noninvasive Optical Evaluation of Cerebral Autoregulation in Patients with Obstructive Sleep Apnea

Ran Cheng, Yu Shang PhD, Guoqiang Yu PhD

Center for Biomedical Engineering, University of Kentucky

Background: Obstructive sleep apnea (OSA) affects 15 million adult Americans. The surges in blood pressure and fluctuations in cerebral blood flow (CBF) that associate with OSA may impair cerebral autoregulation. We have recently developed a hybrid instrument which combines a novel near-infrared diffuse correlation spectroscopy (DCS) flowmeter for CBF measurement and a commercial tissue oximeter (Imagent, ISS Inc.) for cerebral tissue oxygen saturation (StO2) measurement. In this study, we simultaneously quantify CBF, StO2, and mean artery blood pressure (MAP) during physiological manipulations for evaluation of cerebral autoregulation in patients with OSA.

Methods: DCS measures speckle fluctuations of diffuse light in tissue, which are sensitive to the motion of red blood cells in cerebral microvasculature. The Imagent is a frequency-domain system and detects the amplitude and phase of modulated light from tissues for extraction of StO2. Eleven healthy controls and 13 patients with OSA participated in this study. A 5-minute leg cuff-occlusion protocol was used to create transient changes in MAP and CBF. The MAP was continuously monitored using a finger pulse plethysmography (Finapres). An optical probe was taped on subject's forehead for cerebral hemodynamic measurements. The baseline StO2 is estimated by averaging data before cuff occlusion. The changes of MAP and rCBF after cuff deflation are defined as $\Delta$MAP (mmHg) and $\Delta$rCBF (%), and are calculated by their mean values before cuff deflation minus minimum values after cuff deflation, respectively. Autoregulation Index (AI) is calculated by $\Delta$rCBF/$\Delta$MAP (%/mmHg).

Results: Mean baseline value of StO2 in patients with OSA (61±8%) was significantly lower (p=0.002) than that in healthy controls (73±9%). On average, significant smaller (p=0.014) $\Delta$rCBF change was found in the control group (-17±9%) compared to the OSA group (-26±8%). The OSA group had a significantly lower (p=0.005) $\Delta$MAP (-8.6±4.5mmHg) compared to the control group (-15.0±5.5mmHg). However, there was no significant difference in AI between the OSA and control groups.

Discussions and Conclusions: The StO2 in patients with OSA are lower than those of healthy subjects, indicating that OSA impacts cerebral tissue oxygenation adversely. Compared to healthy subjects, the smaller changes in MAP and rCBF after cuff deflation in patients with OSA might be due to the larger vascular resistance to blood flow caused by the potential high sympathetic nerve activity and impaired endothelial function in patients with OSA. The fact of insignificant AI difference between the two groups might be due to that the cuff deflations created relatively small changes in MAP (< 15 mm Hg), which were much less than the cerebral autoregulation range (50 - 150 mm Hg). Other manipulation protocols are being explored to create large MAP variations for testing the potential cerebral autoregulation impairment in patients with OSA.
Noninvasive Optical Evaluation of Spontaneous Low Frequency Oscillations in Cerebral Blood Flow and Oxygenation

Ran Cheng, Yu Shang PhD, Sibu Saha MD, Guoqiang Yu PhD

Center for Biomedical Engineering, Division of Cardiothoracic Surgery, University of Kentucky

Student

Background: The phase shift between the spontaneous low frequency oscillations (LFOs) around 0.1 Hz of arterial blood pressure (ABP) and cerebral blood flow velocity (CBFV) in middle cerebral artery (MCA) has been used for noninvasive assessment of cerebral autoregulation (CA) in large vessels. However, no one has directly evaluated the CA in cerebral microvasculature through quantifying the LFOs of cerebral blood flow (CBF) and oxygenation. The goal of this study is to explore the feasibility of using a newly developed hybrid optical instrument to simultaneously detect the LFOs of CBF and cerebral oxygenation.

Method: A custom-designed near-infrared (NIR) diffuse correlation spectroscopy (DCS) was combined with a commercial NIR tissue oximeter (Imagent, ISS Inc.) for simultaneous measurements of CBF and cerebral oxygenation. Two fiber-optic probes were fixed on the left and right sides of the subject’s forehead for continuous monitoring of the CBF and concentrations of oxygenated-hemoglobin (HbO2), deoxygenated hemoglobin (Hb) and total hemoglobin (THC). The ABP was noninvasively measured by a finger plethysmograph (Portapres, FMS Inc.). The ABP, CBF, HbO2, Hb, and THC were measured under three conditions sequentially: at rest, 70° head up tilting (HUT), and voluntarily breathing at 0.1 Hz. Each condition lasted for 10 minutes. Fifteen young healthy subjects participated in this study with signed IRB consent forms. The valid LFO signals were judged by the coherences of frequency signals between the ABP and each of the hemodynamic parameters, respectively. The valid criterion for coherence was set as >0.4 based on previous studies.

Results: The successful rates to obtain the valid LFOs of CBF, HbO2, Hb, and THC under three conditions were listed as follows respectively: 83%, 70%, 53%, and 73% at rest; 100%, 100%, 93%, and 97% during HUT; and 93%, 96%, 86%, and 100% during voluntarily breathing.

Conclusion: The LFOs of CBF, HbO2, Hb, and THC can be detected by the noninvasive diffuse optical techniques with different successful rates under different physiological conditions. Among all the hemodynamic parameters, the LFOs of CBF, HbO2, and THC can be detected with reasonable successful rates (> 70%). Among the three conditions, the HUT significantly enhanced the LFOs, leading to high successful rates (> 86%). Future work will quantify the cerebral autoregulation ability in patients with impaired cerebral function (e.g., stroke) using the measured differences in phase shifts between ABP and hemodynamic parameters during HUT.
Cerebral monitoring during carotid endarterectomy using near-infrared diffuse optical spectroscopies and electroencephalogram

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Fellow

Intraoperative monitoring of cerebral hemodynamics during carotid endarterectomy (CEA) provides essential information for detecting cerebral hypoperfusion induced by temporary internal carotid artery (ICA) clamping and post-CEA hyperperfusion syndrome (CHS). This study tests the feasibility and sensitivity of a novel dual-wavelength near-infrared diffuse correlation spectroscopy (DCS) in detecting cerebral blood flow (CBF) and cerebral oxygenation in patients undergoing CEA. Two fiber-optic probes were taped on both sides of forehead for cerebral hemodynamic measurements and the instantaneous decreases in CBF and electroencephalogram (EEG) alpha-band power during ICA clamping were compared to test the measurement sensitivities of the two techniques. The ICA clamps resulted in significant CBF decreases (-24.7 ± 7.3%) accompanied with cerebral deoxygenation at the surgical sides (n = 12). The post-CEA CBF were significantly higher (+43.2 ± 16.9%) than the pre-CEA CBF. The CBF responses to ICA clamping were significantly faster, larger and more sensitive than EEG responses. Simultaneous monitoring of CBF, cerebral oxygenation, and EEG power provides a comprehensive evaluation of cerebral physiological status, thus holding a potential for adoption of acute interventions (e.g. shunting, medications) during CEA to reduce the risks of severe cerebral ischemia and CHS.
Perlecan Domain V Promotes Neuroprotection and Neurorepair Following Multiple Stroke Models

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Neuroscience & Exp Therapeutics, Texas A&M Health Science Center College of Medicine • Anatomy & Neurobiology, University of Kentucky • Anatomy & Psychology, University of Otago • Anatomy & Neurobiology, Neurology, University of Kentucky

Student

The role of the extracellular matrix in ischemic brain stroke is poorly understood. Indeed, its role has largely been relegated to that of a degradation by-product after stroke, and a marker of blood-brain barrier dysfunction. However, we have recently demonstrated that perlecan domain V (DV), a proteolytic fragment of the vascular basement membrane, is persistently generated after stroke and is neuroprotective, enhances angiogenic brain repair, and inhibits chronic glial scar formation (a potential barrier to brain repair) when administered via intraperitoneal injection 24 hours post-stroke. Protection was observed in two distinct models of transient focal ischemia in mice and rats, the stereotactic injection of vasospasm-inducing endothelin-1 next to the middle cerebral artery (MCA) and the tandem ipsilateral common carotid artery and MCA occlusion models. DV treatment resulted in rapid functional recovery to pre-stroke levels in two days. Objectives: We now investigated whether DV could also be therapeutic in a permanent focal ischemia model in both young and aged (an important clinical factor as the elderly population is both more likely to suffer a stroke and potentially less well equipped to recover than younger stroke suffers) mice and whether it might enhance neurorepair by enhancing post-stroke neurogenesis, neuronal migration, and the number of these new born neurons that reach the infarct and peri-infarct sites. Results: We now report that DV treatment 6 hours after permanent focal ischemia in a mouse motor cortex photothrombotic stroke model was also neuroprotective as lesions were significantly smaller in DV-treated animals (n=7 animals per group). Importantly, this was also the case in aged mice. Furthermore, these animals had significantly improved post-stroke motor function measured by the cylinder and grid-walking tests. Additionally, DV enhanced several aspects of post-stroke neuronal regeneration including neurogenesis in the subventricular zone, migration, and repopulation and synaptic connection in the peri-infarct region and ischemic core. In vitro analysis demonstrated that DV significantly increased neurosphere size (neurogenesis), neuronal migration, and neurite sprouting, which depended on DV's alpha2beta1 integrin receptor. Conclusions: Collectively, these results suggest that DV is effective in both transient and permanent ischemic stroke models, effective in aged animals, and in addition to having significant positive post-stroke effects on existing neurons, astrocytes and neovascularature, also enhances neuronal regeneration and repair, further supporting DV as a promising novel stroke therapy.
African American Incentives and Barriers to Research Participation and Brain Donation

Tyler Schnieders MS, Deborah Danner PhD, Flores Reynolds, Caitlin McGuire

Sanders-Brown Center on Aging, University of Kentucky

Staff

Mistrust, fear, and conspiracy theories are often barriers that result in a reluctance among African Americans to participate in research. This study offers an incisive view of attitudes expressed by African Americans related to their decision to participate in research. Through a structured, educational face-to-face interview information was collected about why older African Americans would be willing to participate in research and what would keep them from participating. This interview was developed as a recruitment strategy that allowed participants to learn about our center and our normal control longitudinal program. Participants were 91 African Americans aged 65 or older who consented to in-home interviews - 54.8% of participants indicated that risk to their personal health was a significant barrier to research participation. Of those who enrolled, 61.8% indicated a benefit to self/family was a reason to participate. This finding suggests that successful recruitment should include assurances of low health risks to participants while personal benefit and benefits to family need to be emphasized to successfully recruit in the local African American community. Through involvement in research and educational programs, African Americans gained a better understanding of the importance of brain autopsy in Alzheimer’s disease research and were more likely to consent to brain autopsy over time.
Suppression of NFAT-mediated astrocyte activation reverses pathological hallmarks of Alzheimer’s disease in aged, Tg6799 APP/PS1 mice

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Pharmacology, Spinal Cord and Brain Injury Research Center, Sanders-Brown Center on Aging, University of Kentucky

Faculty

Introduction: Astrocytes are the most abundant cell type in the brain and play a critical role in maintaining healthy nervous tissue. In Alzheimer’s disease (AD), however, many astrocytes convert to an “activated” phenotype, characterized by morphological and biochemical changes that lead to a loss of protective properties and an acquisition of harmful neuroinflammatory properties. Work from several studies has shown that such astrocyte activation is largely-driven by the protein phosphatase, calcineurin (CN) and its downstream transcription factor, NFAT (nuclear factor of activated T-cells). By selectively inhibiting CN/NFAT activity with the synthetic peptide, VIVIT, the activated astrocyte phenotype is effectively suppressed. Recent work from our lab showed that treatment of AD model mice at the early stages of amyloid pathology with novel astrocyte-specific, VIVIT-expressing adeno-associated virus (AAV) constructs was sufficient to ameliorate neuroinflammation, amyloid pathology, synaptic dysfunction, and cognitive deficits in aged APPswe/PS1de9 mice, suggesting astrocytic CN/NFAT inhibition as a potential therapeutic for AD.

Objective: Here, we used the same AAV constructs to treat a different, more aggressive 5x model of AD (Tg6799). Our objective was to observe the potential for AAV-VIVIT to reverse, rather than prevent, disease pathology.

Methods: AAV was bilaterally injected into the hippocampus of transgenic mice at ~7 months-of-age, a time when amyloid pathology, neuroinflammation, and synaptic deficits are abundant and widespread in this mouse model. Three months following treatment, animals were sacrificed and several pathological outcome measures assessed.

Results: Similar to our previous study, we found that astrocyte-specific NFAT inhibition dampened several neuroinflammatory markers and reduced levels of the highly-toxic soluble Aβ1-42 peptide. Several markers of synaptic transmission and glutamate regulation were also affected by our astrocyte-targeted VIVIT treatment.

Conclusions: Results corroborate and expand upon our previous findings, although in a separate mouse model, and suggest a detrimental role of activated astrocytes in disease pathology. Moreover, results from this study further implicate activated astrocytes, in general, and astrocytic CN/NFAT activity, in particular, as plausible targets for future AD therapeutics, even during severe stages of the disease.

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The Use of Digital Pathology and Image Analysis to Rapidly Quantitate Alzheimer’s Disease Neuropathologic Changes.

Janna Neltner MD, Stephanie Denison, Ela Patel, Peter Nelson MD, PhD
Pathology, Sanders-Brown Center on Aging, University of Kentucky
Faculty

Objective: Quantitative neuropathology has been shown to be far superior to semi-quantitative measures when correlated to clinical parameters. At the Sanders-Brown Center on Aging, we have been manually counting diffuse Aβ plaques (DPs), neuritic Aβ plaques (NPs), and neurofibrillary tangles (NFTs) in multiple brain sections for every patient in our neuropathologic database for over 20 years. Such counting, however, is time consuming and involves technical challenges. We wanted to develop computer based algorithms that would minimize sources of experimental bias and standardize our database. Methods: We examined the superior and middle temporal gyri (SMTG) from 54 cases in the UK-ADC database whose AD pathological severity ranged from normal controls to end-stage AD. After performing Aβ and PHF-1 immunohistochemistry, the slides were scanned using the Aperio ScanScope XT at a 40x magnification. For amyloid quantitation, two parameters were calculated: a DP density and an overall amyloid burden, using modified algorithms from the Aperio Image Analysis Toolbox ©. To quantitate NPs and NFTs, we first utilized the Genie Histology Pattern Recognition© software to ‘teach’ the computer to identify these structures. We then used a modified positive pixel count to calculate NP burden and a modified nuclear algorithm to calculate NFT density. Results: We found good correlation between our recorded manual counts and the amyloid burden, DP density, and NFT density. We also found good correlation between NP burden and our manual counts, however such studies were somewhat confounded by the differences between the modified Bielschowsky silver stain and the PHF-1 immunohistochemical stain. Conclusion: Image analysis, using our modified algorithms, offers a more efficient and replicable, and less-biased method, relative to manual counting.

Emotion Recognition and Marital Satisfaction in Stroke

Lee Blonder PhD, Creed Pettigrew MD, Richard Kryscio PhD
Behavioral Science, Neurology, Statistics, University of Kentucky
Faculty

Deficits in the comprehension of facial and prosodic expressions are commonly associated with right hemisphere stroke. However, little is known regarding the impact of these disorders on social relations. We examined facial and prosodic processing, mood, and marital satisfaction in twelve right hemisphere damaged (RHD) stroke patients and nine controls. Results revealed significant impairments in the comprehension of facial expressions and prosody among RHD stroke patients. Non-parametric correlations in the RHD group showed significant associations between marital satisfaction and facial affect discrimination and matching, and non-affective prosody discrimination. We conclude that deficits in the recognition of non-verbal expressions are associated with reduced relationship satisfaction.
Transcription factor peroxisome proliferator-activating receptor gamma regulates microRNA-107 expression in primary brain cells

Wangxia Wang PhD, Irina Artiushin, Willa Huang, Bernard Wilfred PhD, Chris Norris PhD, Peter Nelson MD, PhD

Sanders Brown Center on Aging, University of Kentucky

Staff

MicroRNAs (miRNAs) are potent agents of CNS gene regulation. MiR-107 is a miRNA that regulates key biological and pathological processes. The association of miR-107 expression with AD pathology was first reported by our group, and was confirmed later by other laboratories. Among its verified targets, BACE1, GRN/PGRN, and Cofilin are directly linked to neurodegenerative diseases. We hypothesize that miR-107 pathways could be a therapeutic target; however, any therapeutic strategy will require more detailed understanding of miR-107 regulation in CNS cells. The gene for miR-107 resides within an intron of the pantothenate kinase (PANK) 1 gene. The PANK1 gene bears several peroxisome proliferator-activating receptor (PPAR) response elements. PPARs are nuclear receptor proteins that play essential roles in differentiation, development, inflammation, and the metabolism of lipids and glucose. Activation of PPARs has been shown to be protective in brain; however, clinical trials using PPARgamma agonists, Rosiglitazone and Pioglitazone have yielded mixed results. The current knowledge about PPAR action in the brain is incomplete, and we feel one of the missing pieces is miRNA, more specifically, miR-107. In this study, we investigate the regulation of miR-107 expression in rodent primary microglia, astrocytes, and neurons. Our study revealed that PPAR gamma agonists up-regulates miR-107 expression in primary rodent brain cells. Moreover, PPAR agonist was able to reverse decreased level of miR-107 following lipopolysaccharide (LPS) treatment in microglial cells. The fact that changes of miR-107 expression constitute a component of LPS-induced inflammation may be very significant to our understanding of neurodegenerative processes that involve neuroinflammation. This study will help to identify the specific miR-107 targets related to PPAR and inflammatory pathways in neurodegenerative diseases.
Conducting study follow-up with elders in an ancillary study

Allison Caban-Holt PhD, Erin Abner, Richard Kryscio PhD, Frederick Schmitt PhD

Behavioral Science, College of Public Health, Sanders-Brown Center on Aging, Neurology, University of Kentucky

Faculty

Introduction: Conducting research with an aging population in a longitudinal clinical trial can pose unique challenges particularly when cognitive decline is the primary endpoint. Unanticipated issues can arise due to use of data gathering methods that may be routinely used with younger research participants, but are less effective when used with older adults. Such differences may lead to false impressions of participant status and incidence of endpoints. The analysis of procedural methods that may disproportionately affect older adults if of critical importance at this time when many clinical trials are being undertaken to investigate interventions aimed at the older adult population.

Further, research challenges can be magnified when a clinical trial is undertaken as an ancillary study to another larger trial. The directions of the larger study affect the ancillary study in profound ways that may also lead to dramatic changes in research procedures.

The NIA-sponsored PREADViSE study is an ancillary study of the prostate cancer prevention trial SELECT. The goal of PREADViSE is to examine the effectiveness of the antioxidants Vitamin E and Selenium in preventing Alzheimer’s disease in older men in the United States, Canada, and Puerto Rico. The PREADViSE 2x2 factorial randomized clinical trial (RTC) was terminated due to a futility analysis (prostate cancer outcome) of the parent study (SELECT) and is now an exposure study of approximately 4,200 participants with up to seven years exposure, who volunteered for centralized follow-up. Changes to the parent study procedures resulted in major methodological and procedural changes to the PREADViSE study. The resultant procedural changes have also caused challenges to data collection and highlighted the need for awareness of sensory changes with aging that can dramatically influence the accuracy of data collection and conclusions made from the data.

Objectives: The purposes of this poster are to:

1. Discuss challenges facing an ancillary clinical trial when the parent study undergoes major changes.

2. Elucidate some of the challenges encountered with cognitive evaluations of older men via telephone contact. Such as:

   a) Logistics of contacting aging men who are still actively working outside the home

   b) Obtaining meaningful test results from participants who have sensory deficits

   c) Recognizing the impact of health issues, including recent surgery, chemotherapy, or serious illness on cognitive measurement

   d) Accelerated lost-to-follow-up, due to death, chronic illness, or placement in a nursing home.
Driving Limitations and Perceived Stress in Later Life

Lee Blonder PhD
Department of Behavioral Science and Sanders-Brown Center on Aging, University of Kentucky

Driving cessation is a major life event representing a loss of independence to many older Americans. Little has been known about the relationship between driving cessation and psychological well-being other than depressive symptoms. Recent literature has suggested that perceived stress is a distinct concept from depressive symptoms and an independent predictor of negative psychosocial outcomes. This study aims to examine the relationship between driving limitations and perceived stress.

Data come from the 2002 and 2004 waves of Health and Retirement Study. We limited our analysis to those who drove in 2002 and responded to both experimental modules in 2002 and 2004 (N: 721; 53% female; Mean age: 73.6). Of 721 active drivers at baseline, 34 stopped driving; 266 limited driving to nearby places; 421 drove on longer trips at follow-up. Analyses focused on the changes in perceived stress before and after driving limitations. Multiple logistic regression was used to assess the relationship between driving mobility changes with perceived stress.

Respondents who stopped driving were 4.22 times more likely to report high levels of perceived stress as compared to those without any driving limitations at follow-up (OR=4.22, 95% CI=1.91–9.30) even after accounting for baseline perceived stress, depressive symptoms, and functional limitations. The relationship between limiting driving to nearby places and increased perceived stress was marginally significant (OR=1.39, 95% CI=0.97–2.00).

Driving limitations are associated with increased perceived stress, independently from depressive symptoms. Results indicate the need to develop interventions that mitigate the psychosocial consequences of mobility limitations for older adults.
Community Session

Location: Thoroughbred Room, Lexington Convention Center, 430 W Vine, Lexington, KY

8:30 am  
Check-in and Continental Breakfast

9:00  
Welcome and Introductions
Linda Van Eldik, PhD
Director, Sanders-Brown Center on Aging and Alzheimer’s Disease Center
University of Kentucky

9:15  
Living Life to its Fullest: New Perspectives on What You Can Do About Alzheimer’s Disease
Cheryl Wellington, BSc, PhD
Professor of Pathology and Laboratory Medicine
University of British Columbia

10:15  
Break

10:30  
Sanders-Brown Center on Aging Faculty Research Highlights & Audience Q & A
Steven Estus, PhD: Moderator
Paul Murphy, PhD: Developing Therapies
Deborah Danner, PhD: Community Education and Outreach
Frederick Schmitt, PhD: Staying Sharp
Gregory Jicha, MD, PhD: Nutritional Supplements for Brain Health

12:00  
Closing Remarks
Linda J. Van Eldik, PhD
Speaker Presentations

CHERYL WELLINGTON, PHD
UNIVERSITY OF BRITISH COLUMBIA

Cheryl Wellington obtained her PhD in Microbiology at the University of British Columbia in 1991 and received postdoctoral training at Harvard Medical School, the University of Calgary, and the University of British Columbia. She joined the Department of Pathology and Laboratory Medicine at the University of British Columbia in 2000 and was promoted to Professor in 2011. Dr. Wellington’s research interests include lipid and lipoprotein metabolism in the brain and how this relates to chronic and acute neurological disorders such as Alzheimer’s disease and traumatic brain injury. Dr. Wellington’s group has made key contributions to the understanding of the role of apolipoprotein E (apoE) in Alzheimer’s disease and traumatic brain injury. ApoE is the major carrier of cholesterol in the brain and the strongest genetic risk factor for typical Alzheimer’s disease. Dr. Wellington’s laboratory has shown that the amount of cholesterol carried on apoE critically affects amyloid metabolism and cognitive function in Alzheimer’s disease. More recently, her laboratory has demonstrated a key role for apoE in promoting recovery from mild repetitive traumatic brain injury. Her laboratory is currently investigating how these pathways might be used for therapeutic application to both Alzheimer’s disease and traumatic brain injury.

“Living Life to its Fullest: New Perspectives on What You Can Do About Alzheimer’s Disease”

Have you ever wondered whether there is anything you can really do to live well long into your senior years and avoid or minimize the risk of Alzheimer’s disease? A great deal of scientific and medical research is indeed showing that each of us has considerable control in healthy aging. A dynamic speaker, Dr. Wellington will discuss how lifestyle factors such as exercise, diet, and “using your brain power” all help to maintain a sharp and active mind. She will also discuss how the risk of Alzheimer’s disease may share some common factors with other common concerns in the elderly, such as heart disease and diabetes.

“Sanders-Brown Center on Aging Faculty Research Highlights and Audience Q & A”

STEVEN ESTUS, PHD, MODERATOR

Steve Estus is a Professor of Physiology and Sanders-Brown Center on Aging at the University of Kentucky. Estus’ research seeks to elucidate the molecular and cellular mechanisms underlying neurodegenerative disease. Over the past several years, his focus has been the use of molecular genetics to identify genetic variants, or polymorphisms that alter gene expression or RNA splicing and thereby increase the risk of Alzheimer’s disease (AD). Since cholesterol is emerging as a possible AD modulator, Dr. Estus is currently evaluating polymorphisms in genes that encode proteins critical to cholesterol homeostasis. The overall goal of his laboratory is to use human genetics to investigate hypotheses evaluating pathways critical to AD risk and progression. These studies contribute to the fight against AD by identifying individuals at risk, identifying possible novel therapies, and tailoring therapy to individuals.
“Community Education and Outreach”

DEBORAH DANNER, PHD

Deborah Danner is an Assistant Professor of Behavior Science and Sanders-Brown Center on Aging at the University of Kentucky. Dr. Danner is the Leader of the Education and Information Transfer Core of the Alzheimer’s Disease Center at the Sanders-Brown Center on Aging. She is a developmental psychologist with an interest in the arousal and expression of basic emotional states and how the emotional lives of the elderly affect their quality of life. In 2003, with funding from the Administration on Aging, she helped create the African-American Dementia Outreach Partnership, to increase awareness of Alzheimer’s disease and the utilization of diagnostic and family services in the African-American population in the Lexington Bluegrass area.

“Developing Therapies”

M. PAUL MURPHY, PHD

Paul Murphy is an Associate Professor of Molecular and Cellular Biochemistry and Sanders-Brown Center on Aging at the University of Kentucky.

Age-related disease is a major public health problem. As global population demographics shift towards a relatively older population, these diseases will become a catastrophic burden on both health care resources and on human well-being. Dr. Murphy’s lab is interested in Alzheimer’s disease, and in the molecular pathways that it shares with other disorders. For example, the amyloid precursor protein (APP) is potentially involved in a variety of cellular processes, but is best known for its role as the source of a small peptide fragment known as the amyloid β peptide (Aβ). This peptide plays a major role in the development of Alzheimer’s disease in the brain. Aβ and APP may also be involved in the pathology of another age-related human degenerative disease – inclusion body myositis – in muscle. Recently, Dr. Murphy’s lab has also begun to explore the connections between these processes and metabolic factors involved in type II diabetes, a condition known to confer significant risk for a variety of age-related conditions, including Alzheimer’s disease. They are pursuing the idea that these seemingly disparate diseases are connected not only at the level of shared molecular pathways, but are also connected at the level of transcriptional and translational regulation; his work is centered around understanding these factors. The ultimate aim is to use the knowledge gained from these studies to refine model systems in which to develop novel therapeutic approaches. Recent studies include the use of NSAIDS (such as ibuprofen), immunotherapy, cholesterol lowering agents, and dietary modifications to modify the processes that they study, and that will hopefully one day lead to effective clinical treatments.
“Nutritional Supplements for Brain Health”

GREGORY A. JICHA, MD, PHD

Greg Jicha is an Associate Professor in the Department of Neurology and Sanders-Brown Center on Aging at the University of Kentucky (UK). Dr. Jicha serves on the Executive Committee and is the Director of the Clinical Core of the NIA-funded UK Alzheimer’s Disease Center. He also directs the Telemedicine Cognitive Clinic at UK, designed to reach out to rural populations across KY for both clinical and research-related activities in the area of Alzheimer’s disease (AD) and related disorders.

Dr. Jicha holds the Robert T & Nyles Y McCowan Endowed Chair in Alzheimer’s Research at UK. His current research interests lie in the areas of mild cognitive impairment, clinico-pathological correlations in early preclinical disease states, and clinical trials of disease-modifying therapies for AD. He is the principal investigator at UK for the National Alzheimer’s Disease Cooperative Study Group and also serves on the Clinical Task Force and Steering Committee for the National Institute of Aging Alzheimer’s Disease Center Program.

“Staying Sharp”

FREDERICK A. SCHMITT, PHD

Fred Schmitt is a Professor 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 for the statistical assessment of various treatment interventions. A prolific applied researcher with over 150 publications, Dr. Schmitt’s research interests are in the areas of HIV dementia, Alzheimer’s disease, Down syndrome, life-span neurocognition, clinical trial assessments and biostatistics. His current NIH-funded research includes studies of antioxidant supplements and dementia prevention, statistical models of dementia risk and associated neuropathology, and the evolution of Alzheimer’s disease in Down syndrome.
Sanders-Brown Center on Aging

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.

With more than 100 faculty and staff pursuing the following:

• Basic and clinical research in Alzheimer’s disease, stroke and other neurodegenerative disorders.
• Neurodegenerative disorders
• Normal brain aging

The Center is directed by Linda J. Van Eldik, PhD, Professor, Department of Anatomy and Neurobiology. Associate Director is Stephen W. Scheff, PhD, Professor, Department of Anatomy and Neurobiology.

A global pioneer in Alzheimer’s disease research, the Center has more than 30 years of published work and 700 study volunteers (some with the disease and some without). These individuals are studied over time and plan to donate their brains upon death. The 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 like Alzheimer’s disease, so that our human volunteers, patients and caregivers become the beneficiaries of our advances in knowledge.
Alzheimer’s Disease Facts

From the 2012 Alzheimer’s Association Facts and Figures publication:

• Someone in the US develops Alzheimer’s disease every 68 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.

• In 2010, 80,000 people in Kentucky were living with Alzheimer’s disease.

• An estimated 5.4 million Americans of all ages have Alzheimer’s disease in 2012.

• By 2050, as many as 16 million Americans will have Alzheimer’s disease, and a new case will be diagnosed every 33 seconds.

• Alzheimer’s disease is the leading cause of dementia, and affects 1 in 8 people aged 65 and older.

• Over 15 million Americans provide unpaid care for a person with Alzheimer’s or other dementias. Payments for care are estimated to be $200 billion in 2012.

• 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.

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 the family and friends.

Please help us today in our fight against Alzheimer’s disease.

For more information on research, clinical trials and ways to help, contact the Foundation Office. 859-323-5374 or visit our website www.centeronaging.uky.edu.
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 25 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.