Aging, the Central Nervous System, and Mobility in Older Adults: Neural Mechanisms of Mobility Impairments

November 19-20, 2013
New Orleans Marriott – Salon E
New Orleans, Louisiana

A workshop in conjunction with
The Gerontological Society of America
Annual Scientific Meeting

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Aging, the Central Nervous System, and Mobility in Older Adults
2012-2014

Aims of Aging, the Central Nervous System, and Mobility in Older Adults are to:
1. Examine existing evidence from basic, epidemiological, and clinical perspectives and enhance links from animal studies to human investigation of both normal aging and disease at the individual and population level.
2. Promote collaborations among basic, epidemiological, and clinical scientists of interrelated disciplines who might not otherwise have an opportunity to work together.
3. Identify knowledge gaps, barriers to progress, alternative strategies, and prospects for future inquiry through discussions of emerging research findings.
4. Emphasize cutting-edge methodologies for central nervous system (CNS) and mobility measures.
5. Support involvement from junior investigators, women, minorities, and other underrepresented groups.
6. Encourage discussions and exchanges of ideas from workshop participants by providing ample time for interactions and using multimedia presentation formats, including videos.
7. Disseminate findings, discussions, and recommendations to investigators, clinicians, and the public through symposia at The Gerontological Society of America Annual Scientific Meeting, as well as submit coordinated individual papers to a variety of related journals (e.g., Neurology, Gait & Posture, Behavioral and Brain Functions, Movement Disorders, The Journal of Gerontology: Medical Sciences, Frontiers in Aging Neuroscience) for publication.

The scientific focuses for the 3-year program are:
- 2012 Workshop 1: Establish the best evidence to date for a relationship between the CNS and mobility in the context of other contributors, and identify state-of-the-art technology to measure CNS plasticity and mobility in older adults.
- 2013 Workshop 2: Ascertain the mechanisms and causes of mobility impairment in older adults.
- 2014 Workshop 3: Discuss implications for clinical practice, as well as prevention and intervention studies, and recommend future studies on mobility impairments in older adults.
Aging, the Central Nervous System, and Mobility in Older Adults: 
Neural Mechanisms of Mobility Impairments 
New Orleans Marriott
November 19-20, 2013
Program Committee Roster

Linda Krogh Harootyan  
Deputy Executive Director 
Senior Director, Professional Affairs  
The Gerontological Society of America  
Washington, DC

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Associate Professor of Epidemiology  
Graduate School of Public Health  
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VA Pittsburgh Healthcare System  
Pittsburgh, Pennsylvania

Wen G. Chen, PhD, Co-Chair  
Health Scientist Administrator  
Program Director, Sensory and Motor Disorders of Aging  
National Institute on Aging

Sandra E. Black, MD, Co-Chair  
Deborah Ivy Christiani Brill Chair in Neurology  
University of Toronto  
Brain Sciences Program Research Director  
Sunnybrook Research Institute

Lewis A. Lipsitz, MD, Co-Chair  
Director, Institute for Aging Research  
Harvard Medical School  
Senior Scientist, Institute for Aging Research  
Hebrew Senior Life

Farzaneh A. Sorond, MD, PhD, Co-Chair  
Director, Cerebrovascular Laboratory  
Brigham and Women’s Hospital  
Assistant Professor of Neurology  
Harvard Medical School

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Director, Geriatric Psychiatry Neuroimaging Laboratory  
University of Pittsburgh

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University of Michigan  
Director, Geriatric Research, Education, and Clinical Center, VA Ann Arbor Health Care System

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Rush University Medical Center

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Johns Hopkins Center on Aging and Health

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Beth Israel Deaconess Medical Center  
Harvard Medical School  
Professor of Medicine  
Tel-Aviv University  
Director, Laboratory for Gait and Neurodynamics  
Tel-Aviv Sourasky Medical Center

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Professor, Department of Epidemiology  
University of Pittsburgh

Joe Verghese, MB, BS  
Professor of Neurology  
Murray D. Gross Memorial Faculty Scholar in Gerontology  
Director, Division of Cognitive and Motor Aging  
Albert Einstein College of Medicine
Caterina Rosano, MD, MPH
Caterina Rosano is Associate Professor and Director of the Neuroepidemiology Area of Concentration for the Department of Epidemiology in the Graduate School of Health at the University of Pittsburgh. She received her medical degree from the University of Palermo Medical School in Italy and later received her masters of public health in epidemiology at the University of Pittsburgh. Her background includes training in geriatric neuroepidemiology and neuroscience. She has extensive experience integrating brain imaging techniques into large clinical epidemiologic studies. The goal of Dr. Rosano’s research is to investigate the interactions and synergisms between brain structure and function in relation to the aging process and to identify the modifiable factors underlying this relationship. Her work applies state-of-the-art neuroimaging methodologies, structural and functional magnetic resonance imaging, in large epidemiological studies to identify key brain structures that affect locomotion in elderly individuals. Collectively, Dr. Rosano’s studies constitute a unique and novel resource comprising large datasets of detailed brain and functional markers from several hundreds of individuals. It is expected that these data will augment our understanding of brain aging and will contribute to the discovery of new approaches to the promotion of disability-free survival. Additionally, Dr. Rosano is interested in the application and validation of advanced statistical modeling algorithms for data reduction and the study of the mechanisms underlying brain degeneration, specifically dysmetabolic processes.

Lewis A. Lipsitz, MD, Co-Chair
Lewis Lipsitz has spent most of his career in geriatric medicine at Hebrew SeniorLife, where he currently serves as Vice President for Academic Medicine and Director of the Institute for Aging Research. He holds the Irving and Edyth S. Usen and Family Chair in Medical Research. Dr. Lipsitz is also Professor of Medicine at Harvard Medical School and Chief of the Division of Gerontology at Beth Israel Deaconess Medical Center. Dr. Lipsitz’s research interests include falls, fainting, blood pressure regulation, cognitive dysfunction, and improving long-term care for disabled seniors. He has published more than 160 original research papers, numerous review articles and textbook chapters, and co-edited Quality Care in the Nursing Home and Geriatric Diabetes. He was designated one the “top doctors in Boston” by Boston Magazine in 2009. A graduate of Franklin and Marshall College, he earned his medical degree from the University of Pennsylvania School of Medicine. Dr. Lipsitz also holds a master’s degree from Harvard University. He completed his residency internal medicine and a fellowship in geriatrics at Beth Israel Deaconess Medical Center.

Anna Csiszár, MD, PhD
Anna Csiszár is Associate Professor at the Reynolds Oklahoma Center on Aging of the University of Oklahoma. She received her medical degree in 1998 from the Semmelweis University of Medicine in Budapest, Hungary, and her doctoral degree in physiology in 2003 from the same institution. Following a postdoctoral fellowship, she became a faculty member of New York Medical College. In 2009, Dr. Csiszár joined the University of Oklahoma. Her research centers on age-related cerebrovascular alterations leading to mild cognitive impairment. She and her team elucidated molecular mechanisms responsible for oxidative stress and low-grade vascular inflammation in aging by introducing novel approaches to vascular aging research, such as tools of comparative biology. Dr. Csiszár has taught courses on basic vascular physiology, cellular biology of aging, and physiological genomics. Among her awards, Dr. Csiszár was named a Beeson Scholar and College of Medicine Alumni Research Scholar of the University of Oklahoma. In addition to numerous scientific articles, she is the author of several book chapters; she also is a reviewer for several scientific journals as well as for the National Institutes of Health, American Heart Association, and American Federation on Aging Research.
Farzaneh A. Sorond, MD, PhD
Farzaneh A. Sorond is Associate Neurologist at the Brigham and Women’s Hospital and Assistant Professor of Neurology at Harvard Medical School in Boston, Massachusetts. She is clinician-scientist with expertise in cerebrovascular disease. Her research is focused on neurovascular aspects of age-related gait and cognitive disorders, where she has utilized vascular and radiographic measures to examine the impact of cerebrovascular disease on clinical outcomes in elderly adults. Dr. Sorond completed the Medical Scientist Training Program at Baylor College of Medicine in Houston, Texas, followed by a residency in neurology at the Harvard Longwood Training Program and Stroke and a fellowship in neurocritical care at the Brigham and Women’s Hospital and Beth Israel Deaconess Medical Center. She is also a Beeson Scholar.

Sandra E. Black, O Ont, MD, FRCP(C), FRSC, FAAN, FAHA
Sandra E. Black is the inaugural Brill Chair in Neurology in the Department of Medicine at the University of Toronto and Sunnybrook Health Sciences Centre. She was appointed to the Order of Ontario in 2011 and elected as a Fellow of the Royal Society of Canada in 2012. Dr. Black is a cognitive and stroke neurologist and she is the current Executive Director of the Toronto Dementia Research Alliance. She is the Sunnybrook site director and key founder of the Heart and Stroke Foundation Centre for Stroke Recovery, a multisite, public-private, nonprofit research corporation focused on maximizing stroke recovery, including covert stroke. She also is the Brain Sciences Research Program Director at Sunnybrook Research Institute. She has received awards for outstanding mentorship of junior faculty, postdoctoral fellows, and graduate students. Dr. Black’s 30-year research career has bridged dementia and stroke, exploiting advanced neuroimaging techniques for detection, differential diagnosis, monitoring outcomes and studying brain-behavior relationships, with a recent focus on interactions of aging, small vessel disease, Alzheimer’s disease, and stroke. She has authored/co-authored numerous peer-reviewed papers and invited publications and serves on a number of international advisory groups on stroke and dementia.

Ihab Hajjar, MD
Ihab Hajjar is the Section Head for Geriatrics at the University of Southern California Keck School of Medicine. He received his medical degree from the American University of Beirut, completed his residency in internal medicine at the Cleveland Clinic, and completed his fellowship in geriatrics at the Medical College of Wisconsin. He is board certified in medicine and geriatrics and is certified as a clinical hypertension specialist. After graduating in 2000, Dr. Hajjar joined the University of South Carolina working in geriatric primary care, medical education, and clinical research, and he established the Center for Senior Hypertension. In 2006, Dr. Hajjar joined Harvard Medical School and Hebrew SeniorLife, where he was the Associate Director of the Cardiovascular Research Program. His work focused on studying the effect of hypertension on brain vascular and nonvascular function. In 2011, Dr. Hajjar joined the University of Southern California, where his work centers on conducting clinical trials in older adults with hypertension to assess potential effects of various antihypertensive therapies on the aging brain. His work suggests that hypertension leads to disability. Currently, he is studying the effect of angiotensin receptor blockers as a potential treatment for cognitive disorders related to vascular risk factors. Dr. Hajjar’s research is funded by grants from the National Institutes of Health and he has published more than 50 articles and book chapters.

Anand Viswanathan, MD, PhD
Anand Viswanathan is Associate Director of the Telestroke Services and Hemorrhagic Stroke Research Program at Massachusetts General Hospital and Assistant Professor of Neurology at Harvard Medical School. He received both his medical degree and doctorate in molecular genetics from Emory University. Dr. Viswanathan is a vascular neurologist and physician scientist who studies the relationship between stroke and Alzheimer’s disease. He is an executive committee member of the Massachusetts Alzheimer’s Disease Research Center. Dr. Viswanathan’s clinical and research goals are to better understand the pathophysiological mechanisms underlying cognitive impairment and dementia associated with aging. Silent stroke and lesions due to cerebral small-vessel pathology are highly frequent in elderly adults and impact cognition. His group’s area of research focuses on these cerebral small vessel diseases of the brain which, through silent ischemic stroke and intercerebral hemorrhage, can lead to vascular cognitive impairment and dementia in elders, including cerebral amyloid angiopathy and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).
**Jeffrey Kleim, PhD**
Jeffrey Kleim is Associate Professor in the School of Biological and Health Systems Engineering at Arizona State University. He received his doctoral degree in neuroscience from the University of Illinois in 1997 and completed a postdoctoral fellowship at the University of Kansas Medical Center in 1998. Dr. Kleim held a faculty position at the Canadian Centre for Behavioural Neuroscience at the University of Lethbridge prior to joining the Department of Neuroscience and the Brain Rehabilitation Research Center at the University of Florida in 2005; he joined the faculty at Arizona State University in 2011. His work examines the neural substrates underlying motor recovery after stroke and Parkinson's disease using both animal models and human patient populations. He is funded by several national agencies to conduct research directed at developing novel therapies for movement disorders based on principles of neural plasticity. Dr. Kleim has lectured extensively both nationally and internationally and he recently authored a book titled *Neural Plasticity: Foundation for Neurorehabilitation.*

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**Wen G. Chen, PhD**
Wen G. Chen is Program Director for the Sensory and Motor Disorders of Aging portfolio in the Extramural Division of Neuroscience at the National Institute on Aging (NIA) of the National Institutes of Health. Her program provides extramural funding support for research on age-related changes in chemical senses, vision, audition, somatosensation, vestibular function and balance, multimodal sensory systems, motor systems, and sensory-motor integration via a variety of grant and funding mechanisms. The program emphasizes the following diseases or disorders: pain and neuropathic pain in aging; age-related mobility impairments and Parkinson’s disease; age-related vision disorders and diseases, including age-related macular degeneration; age-related hearing loss and presbycusis; age-related olfactory declines and taste disorders; and age-related vestibular and balance disorders. Dr. Chen received a master’s degree of medical sciences from Harvard Medical School as part of the Harvard-Markey Medical Scientist Fellowship program and her doctorate in biological chemistry and molecular pharmacology at Harvard University. Her doctoral research focused on the examination of epigenetic mechanisms involved in the regulation of neural activity-dependent gene expression in the central nervous system. After a brief postdoctoral training in proteomics at the Massachusetts Institute of Technology, Dr. Chen served as a scientific editor at *Neuron* Cell Press with a special emphasis on systems neuroscience. Prior to joining the NIA, she most recently worked in the Office of Cross-Cutting Science and Scientific Technology at the National Institute of Mental Health.

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**Clemens Scherzer, MD**
Clemens Scherzer is Director of the Neurogenomics Laboratory of Harvard Medical School and the Brigham and Women's Hospital, Co-Founder and Co-Director of the Harvard NeuroDiscovery Center Biomarkers Program, and Associate Professor of Neurology at Harvard Medical School. The goals of Dr. Scherzer’s research are to decipher how the human genome programs the brain and to determine how the normal flow of genetic information is corrupted in neurologic disease. As a physician-scientist, Dr. Scherzer envisions a future personalized medicine for patients with Parkinson's disease, where a patient’s genome, epigenome, and biome are used to shift care from a one-size-fits-all approach to precision medicine tailored to the molecular disease in an individual person. With colleagues at Harvard, he launched a biomarker incubator, the Harvard Biomarker Study, an open resource that harnesses the power of collaborations to accelerate biomarker discovery and development. More than 2,000 Parkinson’s patients, people with memory decline, and healthy individuals are participating in this longitudinal study. Dr. Scherzer is the recipient of the Dr. Paul Beeson, George C. Cotzias Memorial, and Edmond J. Safra Global Genetics Consortium Awards. He serves on the editorial boards of *Neurogenetics* and *Biomarkers in Medicine,* and chairs the Parkinson’s Disease Biomarkers Program at the National Institute of Neurological Disorders and Stroke.

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**Philip De Jager, MD, PhD**
Philip De Jager is Associate Professor of Neurology at Harvard Medical School. Dr. De Jager is a neurologist at the Brigham and Women's Hospital, where he is also Director of the Program in Translational NeuroPsychiatric Genomics in the Department of Neurology and Director of Basic and Translational Research at the Institute for the Neurosciences. He earned his doctorate in neurogenetics at Rockefeller University and received his medical degree from Cornell University. Dr. De Jager’s research focuses on understanding the role of human genetic variation in neuroimmunologic function and neurologic disease, with a particular interest in the pathophysiology and treatment of an inflammatory disease of the central nervous system, multiple sclerosis, as well as in the understanding of cognitive decline in healthy aging individuals. Dr. De Jager is on the editorial board of the *Journal of Neuroimmunology,* a frequent presenter at national and international neuroscience conferences, and the author of numerous research articles.
Sean Xiao Leng, MD, PhD
Sean X. Leng is a board certified geriatrician and Associate Professor of Medicine in the Division of Geriatric Medicine and Gerontology at Johns Hopkins University School of Medicine. He also obtained a doctorate in molecular virology and immunology at Texas A&M University Health Science Center, after which he completed a research fellowship in cytokinology and immunology at Yale University School of Medicine. In addition to providing clinical care for older patients, Dr. Leng conducts translational aging research focusing on age-related immunosenescence and its potential causes and consequences, including inflammation and immune remodulation in the geriatric syndrome of frailty, influenza immunization, chronic cytomegalovirus (CMV) infection, and HIV and aging. He has developed major international collaborative initiatives with China in geriatrics and gerontology. His research interests include aging of the innate and adaptive immune system; chronic inflammation, immune activation, and their role in the pathogenesis of frailty; cytokinology; IL-6 and other cytokine dysregulations in frail older adults; immune response to and protection from influenza immunization in frail elderly; molecular virology; assessment of chronic CMV infection and its contribution to chronic inflammation and immunosenescence in older adults; and international collaborative development of geriatrics and aging research programs.

Jeffrey M. Hausdorff, PhD
Jeffrey M. Hausdorff is a Lecturer in Medicine at Harvard Medical School, Professor in the Sackler Faculty of Medicine and the Sagol School of Neuroscience at Tel-Aviv University, and Director of the Laboratory for Gait and Neurodynamics at Tel-Aviv Sourasky Medical Center. He received a master of science degree in mechanical engineering/biomechanics from the Massachusetts Institute of Technology and doctoral degree in biomedical engineering from Boston University; he also completed a postdoctoral fellowship in the Division on Aging at Harvard Medical School. Dr. Hausdorff’s research attempts to provide new understandings into the mechanisms that contribute to gait and postural control as well as the causes of deficits associated with aging and neurological diseases. Using a multidisciplinary approach, his work focuses on gait variability and fractal physiology, falls, virtual reality–based rehabilitation, and the interplay between motor and cognitive function. He has won numerous awards for his work that integrates the fields of geriatrics, gerontology, neurology, physiology and engineering. Dr. Hausdorff has served as a study section reviewer at the National Institutes of Health (NIH) and the National Science Foundation, is a reviewer for the journals Brain, Lancet Neurology, and Nature Neuroscience, and is an associate editor of the Journal of Gerontology: Medical Sciences. He has served on the organizing committees of international conferences including meetings of the International Society of Posture and Gait Research and the International Congress on Gait and Mental Function. His work has been funded by the NIH, the Michael J. Fox Foundation for Parkinson’s Research, the American Foundation for Aging Research, and the European Union. At the 2013 Annual Scientific Meeting of The Gerontological Society of America, he will receive the Excellence in Rehabilitation of Aging Persons Award.

Paul Laurienti, MD, PhD
Paul Laurienti is Professor in the Department of Radiology and Director of the Laboratory for Complex Brain Networks at Wake Forest School of Medicine. He completed his medical degree and doctoral degree in neuroscience at the University of Texas Medical Branch at Galveston. Dr. Laurienti moved to Wake Forest School of Medicine and focused his career on research; after a research fellowship, he began his faculty career in 2002. His work has focused on the use of neuroimaging techniques to understand brain changes in older adults. He leads an interdisciplinary research group that believes it is necessary to study the brain as an integrated system. The brain, body, and social environment are highly interconnected. Dr. Laurienti believes that studies of the whole person will lead to revolutionary insights into functional health. Through his many collaborations, Dr. Laurienti has implemented and applied novel analysis techniques to study brain networks. He is currently working on studies that integrate brain and body in healthy aging and is trying to identify signature network patterns that are associated with healthy brain aging. As part of this research, he is investigating associations between brain networks and physical mobility.
**David J. Clark, ScD**

David J. Clark is a Research Health Scientist with the North Florida/South Georgia Veterans Health System and Assistant Professor in the Department of Aging and Geriatric Research at the University of Florida. He also serves as Co-Leader of the Locomotor Research Initiative for the Veterans Affairs Brain Rehabilitation Research Center at the Malcom Randall VA Medical Center. Dr. Clark completed his doctoral degree at Boston University in the program of Movement and Rehabilitation Sciences; during this time, he also worked on funded research at the Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging at Tufts University. Dr. Clark's overarching research objective is to optimize mobility function in older adults and in persons with neurological injury. He pursues this objective through a mechanistic approach, with emphasis on identification, quantification, and intervention of neural impairments underlying functional loss. His research spans the domains of motor control, biomechanics, physiology, engineering, clinical medicine, and rehabilitation.

**William McIlroy, PhD**

William McIlroy is Professor and Chair of the Department of Kinesiology, Faculty of Health Sciences, at the University of Waterloo in Ontario, Canada. Dr. McIlroy is also a Senior Scientist and Mobility Team Leader at Toronto Rehabilitation Institute and a Senior Scientist at Sunnybrook Health Sciences Centre, where he is a member of the Canadian Partnership for Stroke Recovery. He co-leads the Balance, Mobility, and Falls Clinic at Toronto Rehabilitation Institute, a leading-edge clinical research collaboration that is advancing the assessment and treatment of balance and mobility challenges after stroke. Dr. McIlroy's research involves developing understanding of nervous system control of balance and mobility in order to inform new treatments and technologies that will maximize capacity for independent mobility and reduce the risk of falling. He completed his doctoral degree in biophysics and neuroscience at the University of Florida.
Aging, the Central Nervous System, and Mobility in Older Adults: Neural Mechanisms of Mobility Impairments
New Orleans Marriott
November 19-20, 2013

Junior Investigator Late Breaker Travel Awardees and Semi-Finalists

Travel Awardees

Nicola Corbett, PhD
Postdoctoral Research Associate
Rush University Medical Center
Department of Neurological Sciences
Chicago, Illinois
Excitatory Synapses in Hippocampal CA1 Pyramidal Neurons Along the Dorsal-Ventral Axis of Aged, Behaviorally Characterized Rats

Min H. Huang, PT, PhD, NCS
Assistant Professor and Coordinator of Neurologic Post Professional Certificate Program
Physical Therapy Department
The University of Michigan–Flint
Flint, Michigan
Health-Related Quality of Life, Balance Performance, and Falls in Older Cancer Survivors

Susan Hunter, PhD
Assistant Professor
School of Physical Therapy
Western University
Elborn College
London, Ontario, Canada
The Effect of Executive Function on Postural Control: An Evaluation of Simple and Dual-Task Tests on Clinical Tests of Balance

Nimali Jayasinghe, PhD
Assistant Attending Psychologist
New York–Presbyterian Hospital
Assistant Professor of Psychology in Clinical Psychiatry
Weill Cornell Medical College
New York, New York
Gait Training Using Visual and Auditory Feedback Cues with Older Adults Fearful of Falling
Feng Yankee Lin, PhD, RN  
Assistant Professor of Nursing and Psychiatry  
University of Rochester Medical Center  
Rochester, New York  
Link of Cognition and Frailty in Middle and Old Age: Metabolic Syndrome Matters

Neelesh K. Nadkarni, MD, PhD, FRCPC  
Assistant Professor  
Division of Geriatric Medicine and Gerontology  
Department of Medicine  
University of Pittsburgh Medical Center  
Pittsburgh, Pennsylvania  
Brain Amyloid and Neuronal Injury Influences Mobility Under Dual-Task Conditions

Karl A. Rodriguez, PhD  
Postdoctoral Fellow  
The Sam and Ann Barshop Institute for Longevity and Aging Studies  
University of Texas Health Science Center–San Antonio  
San Antonio, Texas  
Rapamycin Increases Proteasome Activity in the Brain of Young and Old Mice, But Not in Liver or Visceral Fat

Andrea Rosso, PhD, MPH  
Postdoctoral Fellow  
Graduate School of Public Health  
University of Pittsburgh  
Pittsburgh, Pennsylvania  
Higher Step Length Variability Indicates Lower Grey Matter Integrity of Selected Regions in Older Adults

Renae Smith-Ray, PhD  
Research Scientist  
School of Public Health  
Center for Research on Health and Aging  
Institute for Health Research and Policy  
University of Illinois at Chicago  
Normal, Illinois  
A Randomized Trial to Measure the Impact of a Cognitive Training Intervention on Balance and Gait in Black Community-Dwelling Older Adults: Results from the Healthy Brain, Healthy Body Pilot
Nima Toosizadeh, PhD
Research Associate
Interdisciplinary Consortium on Advanced Motion Performance
Scientific Member of the University of Arizona Center on Aging
Southern Arizona Limb Salvage Alliance
University of Arizona College of Medicine
Tucson, Arizona
Frailty Assessment by Characterization of Open-Loop and Closed-Loop Strategy of Postural Control in Older Adults

Semi-Finalists

Yenisel Cruz-Almeida, MSPH, PhD
Research Assistant Professor
Pain Research & Intervention Center of Excellence
University of Florida

Madeleine E. Hackney, PhD
Research Health Scientist
Rehabilitation R&D Center of Excellence
Atlanta VA Medical Center
Assistant Professor
Division of General Medicine and Geriatrics
Emory University School of Medicine

Danielle Kauffman
Postbaccalaureate/Technical IRTA
National Institute on Aging
MedStar Harbor Hospital

Bradley D. Manor, PhD
Assistant Scientist
Institute for Aging Research
Instructor in Medicine
Harvard Medical School
Workshop Introduction and Rationale: To focus on the neural mechanisms underlying mobility impairments in older age. We will examine potential biological and physiological mechanisms elucidated from laboratory-based clinical studies, animal studies, and genetic investigations. The CNS alterations associated with mobility impairment appear to be related to ischemia, inflammation, and abnormal protein deposition; metabolic, hormonal, and neurotrophic processes; and genetic factors and other pathological processes that disrupt neural networks responsible for gait and balance. The overall objective of this workshop is to identify common precursors of mobility disability that may serve as targets for future preventive and therapeutic interventions.

Workshop Goals: The workshop consists of three sessions on the first full day and one session on the following half day. Each session ends with a group discussion. The final session on Day 2 will be devoted to the development of specific future research recommendations.

Workshop Principal Investigators
Linda Krogh Harootyan
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Senior Director, Professional Affairs
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Washington, DC

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Director of Research
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Program Director
Pittsburgh Pepper Center
Director, AOC in Geriatric Medicine
Staff Physician, GRECC
VA Pittsburgh Healthcare System
Pittsburgh, Pennsylvania

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Deborah Ivy Christiani Brill Chair in Neurology
University of Toronto
Brain Sciences Program Research Director
Sunnybrook Research Institute

Lewis A. Lipsitz, MD
Director, Institute for Aging Research
Harvard Medical School
Senior Scientist, Institute for Aging Research
Hebrew Senior Life

Farzaneh A. Sorond, MD, PhD
Director, Cerebrovascular Laboratory
Brigham and Women’s Hospital
Assistant Professor of Neurology
Harvard Medical School

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Rush University Medical Center

Wen G. Chen, PhD, Co-Chair
Health Scientist Administrator
Program Director, Sensory and Motor Disorders of Aging
National Institute on Aging

Luigi Ferrucci, MD, PhD
Chief, Longitudinal Studies Section
Director, Baltimore Longitudinal Study of Aging
National Institute on Aging

Materials
Aging, the Central Nervous System, and Mobility in Older Adults program, late breaker poster abstracts, and summary slides at www.geron.org/cns
**FINAL PROGRAM AGENDA**

New Orleans Marriott Salon E

**TUESDAY, NOVEMBER 19, 2013**

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<thead>
<tr>
<th>Time</th>
<th>Session/Activity</th>
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<tr>
<td>7:00 AM–7:30 AM</td>
<td>Breakfast</td>
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| 7:30 AM–7:40 AM | Opening Remarks  
Caterina Rosano, MD, MPH†  
Co-Principal Investigator |
| 7:40 AM–9:10 AM | Session 1: Neurovascular Mechanisms  
Moderator  
Lewis A. Lipsitz, MD†  
Harvard Medical School  
Microvascular Mechanisms of Brain Aging  
Speaker  
Anna Csiszár, MD, PhD  
Reynolds Oklahoma Center on Aging  
Cerebrovascular Mechanisms of Mobility Impairment  
Speaker  
Farzaneh A. Sorond, MD, PhD†  
Harvard Medical School  
Venous Disease and White Matter Hyperintensities  
Speaker  
Sandra E. Black, MD†  
University of Toronto  
Discussion  
Lewis A. Lipsitz, MD†  
Harvard Medical School |
| 9:10 AM–9:20 AM | Break                                                                       |
| 9:20 AM–10:50 AM | Session 2: Genetic and Metabolic Mechanisms  
Moderator  
Sandra E. Black, MD†  
University of Toronto  
The Renin Angiotensin Hypothesis of Cognitive Impairments in Aging: Therapeutic Applications  
Speaker  
Ihab Hajjar, MD  
University of Southern California  
CADASIL: Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy  
Speaker  
Anand Viswanathan, MD, PhD  
Harvard Medical School  
Neural Signals Driving Cortical Plasticity and Motor Recovery After Stroke  
Speaker  
Jeffrey Kleim PhD  
Arizona State University |
As of November 10, 2013

**Discussion**
Sandra E. Black, MD†
University of Toronto

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>10:50 AM–11:50 AM</td>
<td>Roundtable Focused Small Group Discussion of Sessions 1 and 2</td>
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<tr>
<td>11:50 AM–12:30 PM</td>
<td>Roundtable Reports to the Group</td>
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<tr>
<td>12:30 PM–1:30 PM</td>
<td>Networking Lunch</td>
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<tr>
<td>1:30 PM–3:00 PM</td>
<td>Session 3: Inflammation and Misfolded Protein Deposition</td>
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<td>Moderator</td>
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<tr>
<td></td>
<td>Wen G. Chen, PhD†</td>
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<tr>
<td></td>
<td>National Institute on Aging</td>
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<td></td>
<td><strong>Mapping the Transcriptional Landscape of Parkinson's</strong></td>
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<td>Speaker</td>
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<td>Clemens Scherzer, MD</td>
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<td>Harvard Medical School</td>
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<td><strong>Cerebral Inflammation and Immunity: Multiple Sclerosis as a Model of Brain Aging</strong></td>
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<td>Phillip De Jager, MD, PhD</td>
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<td>Harvard Medical School</td>
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<td><strong>Inflammatory Response to Stress and Immune System Alterations in Mobility Disorders: Frailty</strong></td>
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<td>Speaker</td>
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<td>Sean X. Leng, MD, PhD</td>
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<td>Johns Hopkins University School of Medicine</td>
</tr>
<tr>
<td>3:00 PM–3:30 PM</td>
<td>Partnership With the National Institute on Aging: The Future of Central Nervous System Aging and Mobility Research</td>
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<tr>
<td></td>
<td>Speaker</td>
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<tr>
<td></td>
<td>Wen G. Chen, PhD†</td>
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<td>National Institute on Aging</td>
</tr>
<tr>
<td>3:30 PM–4:30 PM</td>
<td>CNS Junior Investigator Travel Awardees Late Breaker Poster Session</td>
</tr>
<tr>
<td>4:30 PM</td>
<td>Closing Remarks and Adjournment for the Day</td>
</tr>
<tr>
<td></td>
<td>Caterina Rosano, MD, MPH†</td>
</tr>
</tbody>
</table>

**WEDNESDAY, NOVEMBER 20, 2013**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 AM–7:30 AM</td>
<td>Breakfast</td>
</tr>
<tr>
<td>7:30 AM–8:00 AM</td>
<td>Introduction and Plan for the Day</td>
</tr>
<tr>
<td></td>
<td>Sandra E. Black, MD†</td>
</tr>
<tr>
<td>8:00 AM–9:30 AM</td>
<td>Session 4: Neuromotor Control and Other Networks Studies</td>
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<tr>
<td></td>
<td>Moderator</td>
</tr>
<tr>
<td></td>
<td>Jeffrey M. Hausdorff, PhD†</td>
</tr>
<tr>
<td></td>
<td>Tel Aviv University</td>
</tr>
</tbody>
</table>

† Program Committee Member
Mobility and Resting State Networks  
Paul Laurienti, MD, PhD  
Wake Forest University

Age-Related Neuromuscular Activation Impairment  
David J. Clark, ScD  
University of Florida

Cortical Control of Balance and Mobility  
William McIlroy, PhD  
University of Waterloo

Discussion  
Jeffrey M. Hausdorff, PhD†  
Tel Aviv University

9:30 AM–10:30 AM  Roundtable Focused Small Group Discussion of Sessions 3 and 4

10:30 AM–11:00 AM  Roundtable Reports to the Groups

11:00 AM–12:00 PM  Open Group Discussion: Research Recommendations  
Moderator  
Sandra E. Black, MD†

12:00 PM  Closing Remarks and Adjournment  
Caterina Rosano, MD, MPH†

Funding for this conference was made possible in part by 5U13AG041613-02 from the National Institute on Aging. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Aging or the National Institutes of Health. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

Enjoy The Gerontological Society of America Annual Scientific Meeting  
All Aging, CNS, and Mobility in Older Adults workshop participants are invited to attend the following Wednesday sessions:

2:30 PM–4:00 PM  GSA Annual Scientific Meeting Sessions I

4:30 PM–6:00 PM  GSA Annual Scientific Meeting Sessions II

6:00 PM–8:00 PM  GSA Annual Scientific Meeting Exhibit Hall Opening & Posters I  
Face-to-Face Time: 6:00 PM–7:00 PM  
- Junior Faculty Late Breaker Poster Travel Award winners will be presenting in the Health Sciences Section poster session.
MICROVASCULAR MECHANISMS OF BRAIN AGING

Anna Csiszár, MD, PhD

Reynolds Oklahoma Center on Aging
Departments of Geriatric Medicine and Physiology
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

November 19, 2013

• The brain has high oxygen and energy requirements but very little reserves
  • 20% of the cardiac output
  • 20%-25% of O₂ and glucose consumption

• 400 miles of microvessels (with 20 m² surface area) provide adequate cerebral perfusion at all times


The functional and structural integrity of the brain depends on a healthy cerebrovasculature
Structural and functional alterations of the cerebromicrovasculature will have direct impact on higher brain function.

Age-dependent microvascular changes in the brain

1) Microvascular rarefaction $\rightarrow$ impaired regional blood flow

2) Endothelial dysfunction/ impaired neurovascular coupling $\rightarrow$ impaired regional blood flow

3) BBB disruption $\rightarrow$ neuroinflammation

4) Cerebromicrovascular inflammation

5) Microbleeds
Impaired regional blood flow
- Exacerbated by hypertension and diabetes
- Possible causes:
  - Up-regulation of anti-angiogenic factors
  - Impaired angiogenic potential
  - Endothelial apoptosis
  - Platelet aggregation in dysfunctional capillaries

Aging- and obesity-related decline in capillary density predicts cognitive decline in mice
Impaired angiogenesis in the aging brain

Lack of increases in vascular density in the AAV-VEGF-injected aged mouse brain

Neurovascular coupling is a vital mechanism of regulation of cerebral blood flow that maintains optimal microenvironment of cerebral tissue by adjusting local blood flow to local neuronal activity.

Neurovascular coupling is impaired in the elderly
Role of oxidative stress in age-related impairment of neurovascular coupling

- C57BL/6 mice
- Apocynin: inhibitor of NADPH oxidase

Role of blood-brain barrier integrity

The BBB:
- limits the entry of plasma components, red blood cells and leukocytes into the brain.
- regulates the delivery into the CNS of circulating energy metabolites and essential nutrients that are required for proper neuronal and synaptic function.
- Impaired function of endothelial cells, pericytes and astrocytes may compromise the BBB, altering neuronal function and promoting neuroinflammation.
- Role of BBB disruption in neurodegeneration:
  - Stroke
  - Neurological disorders: AD, ALS, MS, PD, AIDS
Age-related blood-brain barrier disruption

- C57BL/6 mice
- Hypertension (4 weeks): ANGII infusion

Chronic BBB disruption is associated with low-grade neuroinflammation

- CD68+ cells in the hippocampus (fold change)
Low-grade cerebrovascular inflammation

- Pro-inflammatory changes in cytokine expression profile in cerebrovascular endothelial cells
- Potential role for oxidative stress and NF-κB inflammatory transcription factor activation
- Role in neuroinflammation?
- Role in BBB disruption?
- Changes in neurogenic microenvironment?

Increased risk of developing cerebral microbleeds in aging: prevention by resveratrol treatment

- C57BL/6 mice
- Hypertension: ANGII + L-NAME (to inhibit NO synthesis)
Microbleeds

Cerebral microbleeds are increasingly recognized with new and more sensitive MRI neuroimaging in people with cerebrovascular disease and dementia, and in normal aging.

Interpretation

- Are they markers of accompanying vascular pathological change?
- What are the pathological factors that determine whether a particular bleeding event will result in a microbleed versus a macrobleed?
- Do they have direct effects on neurological function, cognition, and disability?

Vascular mechanisms altering brain function in aging

Chronic low grade inflammation

- BBB disruption
- IgG
- Microglia activation

Brain Function

- Neuroinflammation
- Nitrooxidative stress
- Microvascular rarefaction
Conclusion

- Aging-induced cerebromicrovascular alterations precede and predict impairment of higher brain function in mice.

- Age-related cerebromicrovascular impairment is potentially preventable and reversible.

Future goal

- Identify novel targets for pharmacological intervention to prevent/reverse cerebromicrovascular impairment and neuronal dysfunction in the elderly.

Acknowledgement

Zoltan Ungvari MD, PhD
Peter Toth, MD, PhD
Zsuzsanna Tucsek, PhD
Danuta Sosnowska, PhD
Tripti Gautam, MS
Stefano Tarantini, BS

William E. Sonntag, PhD
Matthew Mitschelen, BS
Julie Farley, BS
Nicholas Siefers, BS
Ferenc Deak, MD, PhD
Cerebrovascular Mechanisms of Mobility Impairment

Farzaneh A. Sorond, MD, PhD
November 19, 2013

Outline

• What we know
• What we don’t know/gaps in knowledge
• Future directions
Disclosure

• Funding
  – NIA (K23-AG030967)
  – NHLBI (R01-HL089570)
  – Mars Corp.

Vascular Risk Factors Are Associated With Impaired Mobility

**Balance and Gait in Older Adults With Systemic Hypertension**

*Jeffrey M. Hausdorff, MD, Talia Herman, MPT, Rossitza Balthadjieva, MD; Tanya Guravich, MD, and Nir Giladi, MD*

<table>
<thead>
<tr>
<th>TABLE 2 Balance and Gait Measures</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pull test (a measure of postural control; 0-4)*</td>
<td>0.2 ± 0.4</td>
<td>0.7 ± 0.5</td>
<td>0.015</td>
</tr>
<tr>
<td>Taked Up and Go test (s)*</td>
<td>7.5 ± 1.5</td>
<td>8.3 ± 0.9</td>
<td>0.028</td>
</tr>
<tr>
<td>Gait speed (m/s)</td>
<td>1.27 ± 0.21</td>
<td>1.28 ± 0.11</td>
<td>0.908</td>
</tr>
<tr>
<td>Mean stride time (s)</td>
<td>1.04 ± 0.06</td>
<td>1.05 ± 0.07</td>
<td>1.000</td>
</tr>
<tr>
<td>Stride time CV (%)</td>
<td>2.5 ± 1.1</td>
<td>2.4 ± 0.7</td>
<td>0.686</td>
</tr>
<tr>
<td>% Swing time (%)</td>
<td>33.6 ± 3.2</td>
<td>31.2 ± 4.4</td>
<td>0.166</td>
</tr>
<tr>
<td>Swing time CV (%)</td>
<td>4.9 ± 3.5</td>
<td>9.7 ± 7.2</td>
<td>0.028</td>
</tr>
<tr>
<td>Fractal scaling index of gait</td>
<td>0.97 ± 0.20</td>
<td>0.77 ± 0.24</td>
<td>0.050</td>
</tr>
<tr>
<td>Tinetti balance scale (possible range: 0-16)</td>
<td>15.8 ± 0.5</td>
<td>15.4 ± 0.5</td>
<td>0.105</td>
</tr>
<tr>
<td>Tinetti gait scale (possible range: 0-12)</td>
<td>11.0 ± 0.3</td>
<td>12.0 ± 0.0</td>
<td>0.317</td>
</tr>
</tbody>
</table>

*Two normotensives and 8 hypertensives had scores of 1.0 = normal and 1 = retropulsion, but they recovered unaided.
*As modified version of the test was used. For the pull test, Taked Up and Go, and coefficient of variation measures, lower scores are better. For the other measures, the converse is true.
CV = coefficient of variation

The American Journal of Cardiology. Vol. 91, March 1, 2003
Vascular Risk Factors Are Associated With Impaired Mobility

**High Blood Pressure Accelerates Gait Slowing in Well-Functioning Older Adults over 18-Years of Follow-Up**

Caterina Rosano, MD,* William T. Longstreth, Jr, MD,† Robert Boudreau, PhD,* Christopher A. Taylor, PhD,* Yan Du, MS,* Lewis H. Kuller, MD, DrPH,* and Anne B. Newman, MD*

Higher systolic BP was associated with faster rate of gait speed decline in this selected group of 643 participants, and results were similar in the parent cohort (N = 2,733). Participants with high BP (n = 293) had a significantly faster rate of gait speed decline than those with baseline BP less than 140/90 mmHg and no history of hypertension (n = 350). Rates were similar for those with history of hypertension who were uncontrolled (n = 110) or controlled (n = 87) at baseline and for those who were newly diagnosed (n = 96) at baseline.


---

Vascular Risk Factors Are Associated With Impaired Mobility

**Arterial Stiffness and Gait Speed in Older Adults with and without Peripheral Arterial Disease**

NL Watson†, K Sutton-Tyrrell‡, AO Youk‡, RM Boudreau†, RH Mackey†, EM Simonsick‖, C Rosano,* SE Hardy*, BG Windham‡, TB Harris†, SS Nagji*, EJ Lacatita*, HH Atkinson†, KC Johnson‡, DC Bauer‡, and AB Newman*† for the Health ABC Study

Baseline characteristics of the cohort by quartiles (range in parentheses) of PWV (cm/s)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Mean ± SD or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (312–2998)</td>
<td>n=2172</td>
</tr>
<tr>
<td>Q1 (312–636)</td>
<td>n=543</td>
</tr>
<tr>
<td>Q2 (636–800)</td>
<td>n=545</td>
</tr>
<tr>
<td>Q3 (801–1046)</td>
<td>n=541</td>
</tr>
<tr>
<td>Q4 (1047–2998)</td>
<td>n=543</td>
</tr>
<tr>
<td>p-value*</td>
<td></td>
</tr>
</tbody>
</table>

- Gait speed, m/s: 1.34 ± 0.25, 1.38 ± 0.25, 1.35 ± 0.25, 1.31 ± 0.26, 1.32 ± 0.24, <0.01
- DSST score: 36.5 ± 14.5, 39.2 ± 15.1, 37.6 ± 14.1, 34.7 ± 14.3, 34.7 ± 13.8, <0.01
- Cardiovascular disease, %: 7.4, 6.9, 6.5, 6.9, 9.3, 0.25
- AAMI, %: 12.7, 8.1, 10.3, 14.3, 18.2, <0.01

*Analysis of variance

---

In mixed-effects model adjusted for demographics, each SD (396 cm/s) higher PWV was associated with 0.015 (SE 0.004) m/s slower gait at baseline and throughout the study period in the full cohort (p < 0.001); this relationship was largely explained by hypertension and other vascular risk factors.

Am J Hypertens 2011 January; 24(1): 90–95
Cerebral Small Vessel Disease Is Associated With Impaired Mobility

**Impact of White Matter Lesions on Physical Functioning and Fall Risk in Older People**

*A Systematic Review*


---

Cerebral Small Vessel Disease Is Associated With Impaired Mobility

**Gait in Elderly With Cerebral Small Vessel Disease**

Karlijn F. de Laat, MD; Anouk G.W. van Norden, MD; Rob A.R. Gons, MD; Lucie J.B. van Oudenhoven MSc; Inge W.M. van Uden, MD; Bastiaan R. Bloems, MD, PhD; Marcel P. Zwiers, PhD; Frank-Erik de Leeuw, MD, PhD

*Stroke.* 2010;41:1652-1658

---

Figure. Dose-effect relation of cerebral SVD and gait velocity. Adjusted for age, sex, height, TBV, and number of lacunar infarcts. (A) or WMH (B) with SEs.
Brain Structural Changes Are Associated With Impaired Mobility

Microbleeds Are Independently Related to Gait Disturbances in Elderly Individuals With Cerebral Small Vessel Disease

Karlijn F. de Laat, MD; Helen A.C. van den Berg, BS; Arie W. van Norden, MD; Rob A.R. Gows, MD; Marcel G.M. Oude Rikkert, MD, PhD; Frans-Erik de Leeuw, MD, PhD

Stroke. 2011;42:494-497

Table 2. Association Between Number of Microbleeds and Gait

<table>
<thead>
<tr>
<th>N of Microbleeds</th>
<th>Gait Velocity (cm/sec)</th>
<th>Slide Length (m)</th>
<th>Cadence (steps/min)</th>
<th>Stride Width (cm)</th>
<th>Double-Support Percentage (%)</th>
<th>Timed-Up-and-Go Test (sec)</th>
<th>Timed-Reach Test (cm)</th>
<th>Clinical Rating Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>-0.84 - 0.15</td>
<td>-0.03 - 0.17</td>
<td>-0.07 - 0.06</td>
<td>0.13 - 0.32</td>
<td>-0.24 - 0.23</td>
<td>0.22 - 0.23</td>
<td>0.22 (0.17)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.59 - 0.15</td>
<td>-0.08 - 0.14</td>
<td>-0.05 - 0.04</td>
<td>0.21 - 0.11</td>
<td>0.45 (0.14)</td>
<td>0.22 (0.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>-0.60 - 0.15</td>
<td>-0.07 - 0.03</td>
<td>-0.02 - 0.02</td>
<td>0.12 (0.05)</td>
<td>-0.10 (0.17)</td>
<td>0.01 (0.14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are regression coefficients (standardized p values). Model 1 represents the unadjusted relation between the N of microbleeds and gait; model 2 is with adjustment for age, gender, height, total brain volume, and the N of basal infarcts; and model 3 is with additional adjustment for white matter lesion volume and the N of lacunar infarcts.

*P<0.05
**P<0.01
***P<0.001
For several variables, the logarithm is presented.

Brain Structural Changes Are Associated With Impaired Mobility

Microbleeds Are Independently Related to Gait Disturbances in Elderly Individuals With Cerebral Small Vessel Disease

Karlijn F. de Laat, MD; Helen A.C. van den Berg, BS; Arie W. van Norden, MD; Rob A.R. Gows, MD; Marcel G.M. Oude Rikkert, MD, PhD; Frans-Erik de Leeuw, MD, PhD

Stroke. 2011;42:494-497

Table 3. Association Between Location of Microbleeds and Gait

<table>
<thead>
<tr>
<th>N of Microbleeds</th>
<th>Gait Velocity (cm/sec)</th>
<th>Slide Length (m)</th>
<th>Cadence (steps/min)</th>
<th>Stride Width (cm)</th>
<th>Clinical Rating Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>-0.07 - 0.06</td>
<td>-0.02 - 0.06</td>
<td>-0.09 - 0.02</td>
<td>0.28 - 0.15</td>
<td>0.01 (0.17)</td>
</tr>
<tr>
<td>Frontal</td>
<td>-0.05 - 0.10</td>
<td>-0.06 - 0.12</td>
<td>-0.10 - 0.01</td>
<td>0.26 - 0.05</td>
<td>0.00 (0.17)</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.03 - 0.04</td>
<td>-0.05 - 0.05</td>
<td>0.14 - 0.05</td>
<td>0.16 - 0.05</td>
<td>0.01 (0.05)</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.03 - 0.04</td>
<td>0.03 - 0.04</td>
<td>0.20 - 0.04</td>
<td>0.18 - 0.05</td>
<td>0.01 (0.14)</td>
</tr>
<tr>
<td>Temporal</td>
<td>-0.16 - 0.17</td>
<td>-0.16 - 0.16</td>
<td>-0.16 - 0.06</td>
<td>0.28 - 0.06</td>
<td>0.09 (0.15)</td>
</tr>
<tr>
<td>Deep</td>
<td>-0.05 - 0.08</td>
<td>-0.05 - 0.11</td>
<td>0.13 - 0.03</td>
<td>0.68 - 0.25</td>
<td>0.03 (0.15)</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>-0.13 - 0.07</td>
<td>-0.16 - 0.11</td>
<td>0.21 - 0.02</td>
<td>0.64 - 0.25</td>
<td>0.01 (0.15)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>-0.01 - 0.03</td>
<td>0.04 - 0.06</td>
<td>0.15 - 0.02</td>
<td>0.68 - 0.25</td>
<td>0.01 (0.15)</td>
</tr>
<tr>
<td>Intermesial</td>
<td>-0.05 - 0.06</td>
<td>-0.02 - 0.02</td>
<td>0.13 - 0.01</td>
<td>0.24 - 0.28</td>
<td>0.01 (0.15)</td>
</tr>
</tbody>
</table>

Data are regression coefficients (standardized p values). Adjusted for age, gender, height, total burden of lesions, and the N of basal infarcts, and white matter lesion volume. Significant after Bonferroni correction (P<0.005).

For several variables, the logarithm is presented.
Cerebrovascular Mechanisms of Mobility Impairment: Conceptual Model

- Vascular and Genetic Risk Factors
  - Small Vessel Structure Change
    - Loss of smooth muscle cells
    - Wall thickening
    - Fibroid necrosis
    - Lipohyalinosis
  - Small Vessel Functional Change
    - Rupture
    - Occlusion
      - CMB
      - Lacune
      - WMH

Mobility Impairment
Vascular Biomarkers: TCD Measures

- CBF to rapid changes in CO$_2$
  - Cerebral Vasoreactivity (VR)
- CBF to neuronal activation
  - Neurovascular Coupling (NVC)
- CBF response to rapid changes in CPP
  - Dynamic Cerebral Autoregulation (DCA)
- Cerebrovascular Compliance
  - Pulsatility Index (PI)
### Cerebral Vasoreactivity: Slow Gait

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>95% Confidence limits</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoreactivity (unadjusted analysis)</td>
<td>0.0487</td>
<td>-0.0063 - 1.1038</td>
<td>0.083</td>
</tr>
<tr>
<td>Vasoreactivity (adjusted analysis)</td>
<td>0.0552</td>
<td>0.0027 - 0.1076</td>
<td>0.039</td>
</tr>
<tr>
<td>Vasoreactivity (adjusted analysis) Quintile 1</td>
<td>-0.0818</td>
<td>-0.1496 - -0.0139</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>-0.0416</td>
<td>-0.1094 - 0.0262</td>
<td>0.315</td>
</tr>
<tr>
<td></td>
<td>-0.0754</td>
<td>-0.1407 - -0.0102</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>-0.0295</td>
<td>-0.0946 - 0.0355</td>
<td>0.411</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Adjusted for: age, gender, race (white-ref.), diabetes, stroke, hypertension, hyperlipidemia.

Quintile 5 is the referent quintile.


### Cerebral Vasoreactivity: Falls

![Falls by Vasoreactivity](image)

Neurovascular Coupling: Gait Speed

![Graphs showing changes in cerebral blood flow and correct responses.](image)


Neurovascular Coupling: WMH & Gait Speed

<table>
<thead>
<tr>
<th>GAIT SPEED</th>
<th>WMH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Fast</td>
<td>7.81% (7.99)</td>
</tr>
<tr>
<td>Slow</td>
<td>-1.27% (8.48)</td>
</tr>
</tbody>
</table>

The odds of being a slow walker with a high burden of white matter hyperintensity was significantly higher if neurovascular coupling also was impaired (14.5 [CI95%: 2.3-91.1; p=0.004]).

Dynamic Cerebral Autoregulation: WMH

Fractional Anisotropy (FA)  Mean Diffusivity (MD)


Pulsatility Index: WMH

Take-Home Message

- Vascular risk factors are associated with mobility impairment
- Surrogate MRI measures of cerebrovascular disease also are associated with mobility impairment
- But:
  - Our knowledge is limited to the end-stage disease
  - Many steps in the causal pathway from vascular risk factors to MRI lesions to mobility impairment are unknown
  - Contribution of other factors such as inflammation, BBB breakdown, or edema are not really known

Future Directions

- Shift to preclinical biomarkers of cerebrovascular disease
  - What are the physiological manifestations of structural changes in the cerebral vessels? (Cerebral hemodynamics)
    • TCD
    • NIRS
  - Identify surface molecules that target diseased vessels to develop PET tracer studies
    • Nanoparticles
    • Inflammatory cells
Future Directions

• Assess these preclinical measures as therapeutic targets
  • Preserve/improve vascular biomarkers (VR, NVC, and DCA)
    • Flavanol-rich compounds
    • HIF-1 activators
  • Determine if preserving/improving vascular biomarkers translates into better mobility

Questions
Venous Disease and White Matter Hyperintensities

Sandra E. Black O.Ont., MD, FRCP(C), FRSC, FAHA, FAAN
Brill Professor of Neurology, Dept of Medicine, Sunnybrook HSC, U of Toronto
Executive Director, Toronto Dementia Research Alliance
Site Director, HSF Canadian Partnership in Stroke Recovery
GSA Workshop on Neural Mechanisms of Mobility Impairments
New Orleans, November 19, 2013

Disclosure of Potential Conflict of Interest

Principal Investigator for Clinical Trials: Elan, Pfizer, Novartis, GlaxoSmithKline, Roche,
Investigator initiated: GE Healthcare, Lilly-Avid

CME Lecturer: Pfizer, Novartis, Eisai

Advisory Boards/Consultant: Pfizer, Novartis, Bristol Myers Squibb, Elan, GE Healthcare,

No stock or equity interests

No conflicts relevant to this presentation
Outline

1. Summarize new standards for reporting cerebral small vessel disease (SVD) and the need to simultaneously measure SVD and brain atrophy

2. Review the roles of occlusive arteriolar and venular pathologies in SVD

3. Consider possible relationships of SVD and amyloidosis in the aging brain

#3: Gait in Relation to SH in mild AD and NC

- F(3,70)=4, p<0.001
- F(3,70)=5, p<0.01
- F(3,70)=5, p<0.01

2013 CNS Workshop: Session 1
Tuesday, November 19, 2013
The neurogliavascular unit (+microglia)

Small Vessel Disease: the commonest pathology of human brain aging

Iadecola Acta Neuropathol 2010
COEN Consensus Panel on Small Vessel Disease

Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration


Why Standards for Imaging of SVD and Why Now?

MR has become imaging standard in most research settings

Advances in image acquisition

Major progress in image post-processing

Recognition that harmonizing imaging and analytical protocols will facilitate pooling of data, performing meta-analyses, and cross-study comparisons

Growing appreciation of the impact of vascular factors in neurodegeneration and in other conditions
**Cerebral Small Vessel Disease Is Common**

Common cause of
Lacunar stroke
Intracranial hemorrhage
Cognitive impairment
Behavioral deficits
Gait disturbance

Okudera, Neuropathology 1999

Medullary veins Penetrating arterioles
Multiple Faces of Small Vessel Disease

Hypertensive Microbleeds

Siderosis

Courtesy E. Smith.

Courtesy Ben Lam.
Variable Fate of Lesions

STRIVE: Standards for Reporting and Imaging of Small Vessel Disease

<table>
<thead>
<tr>
<th>Example Image</th>
<th>Schematic</th>
<th>DWI</th>
<th>FLAIR</th>
<th>FLAIR</th>
<th>T2</th>
<th>T1/FLAIR</th>
<th>T2* /GRE</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Usual diameter</th>
<th>≤ 20 mm</th>
<th>variable</th>
<th>3-15 mm</th>
<th>≤ 2 mm</th>
<th>≤ 10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comment</td>
<td>best identified on DWI</td>
<td>located in white matter</td>
<td>usually have hyperintense rim</td>
<td>usually linear without hyperintense rim</td>
<td>detected on Gd-DTPA, round or oval, blooming</td>
</tr>
<tr>
<td>DWI</td>
<td>↑</td>
<td>← ↔</td>
<td>↔ (↑)</td>
<td>↔</td>
<td>↔  (↑)</td>
</tr>
<tr>
<td>FLAIR</td>
<td>↑</td>
<td>↑ ↑ ↑ ↑</td>
<td>↑ ↑ ↑ ↑</td>
<td>↑ ↑ ↑</td>
<td>↑ ↑ ↑</td>
</tr>
<tr>
<td>T2</td>
<td>↑</td>
<td>↑ ↑ ↑ ↑</td>
<td>↑ ↑ ↑ ↑</td>
<td>↑ ↑ ↑</td>
<td>↑ ↑ ↑</td>
</tr>
<tr>
<td>T1</td>
<td>↓</td>
<td>↓ ↑ ↑ ↑</td>
<td>↓ ↑ ↑ ↑</td>
<td>↓ ↓ ↑</td>
<td>↓ ↓ ↑</td>
</tr>
<tr>
<td>T2* /GRE</td>
<td>↔</td>
<td>↑ ↑ ↑ ↑</td>
<td>↔ (↑)</td>
<td>↔</td>
<td>↑ ↑ ↑</td>
</tr>
</tbody>
</table>

(COEN Group, manuscript in preparation)
Can we quantify both vascular pathologies and atrophy in the same brain?

**Individualized Tissue Segmentation**

Step 1 – Co-register in T1-acquisition space

Step 2 – Head from Brain (HfB)

Step 3 – T1-segmentation algorithm (Kovacevic et al., 2002)

Step 4 – Ventricular CSF reassignment (and cerebellum removal for SABRE)

Dark Grey Voxels -> Grey matter
Light Grey Voxels -> White matter
Blue voxels -> CSF
Yellow voxels -> vCSF

Kovacevic et al. Neuroimage 2002
Dade et al Neuroimage 2004
Combined T1-segmentation, parcellation, subcortical lesion analysis (lacunes, deep and periventricular white matter hyperintensities)

Tissue and lesion segmented volumes (7 tissue types) for 26 brain regions based on individualized landmark identification

Kovacevic Neuroimage 2002; Dade Neuroimage 2004; Ramirez Neuroimage 2011

Small Vessel Disease: a dual threat from arteriolar and venular occlusive disease
Okudera et al, Neuropathology 1999

<table>
<thead>
<tr>
<th>Status</th>
<th>Age</th>
<th>Sex</th>
<th>Disease Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitively Normal</td>
<td>71</td>
<td>Female</td>
<td>NC</td>
</tr>
<tr>
<td>Elderly Control</td>
<td>72</td>
<td>Female</td>
<td>VaMCI</td>
</tr>
<tr>
<td>Mild White Matter Disease</td>
<td>79</td>
<td></td>
<td>VaMCI</td>
</tr>
<tr>
<td>Moderate White Matter Disease</td>
<td>72</td>
<td>Female</td>
<td>VaMCI</td>
</tr>
<tr>
<td>Severe White Matter Disease</td>
<td>88</td>
<td>Female</td>
<td>AD+CVD</td>
</tr>
</tbody>
</table>
Atlas of normal cerebral WM perfusion on SPECT

Holland et al Stroke 2008

SPECT Perfusion Map from 50 normal elderly
(masked using 70% WM probability mask)

Makedonov et al Eur J Neuro 2013
Perfusion Gradient out from the ventricles in a sample of 61 AD and 50 age-matched controls

A) Watershed areas and selected vectors

B) Perfusion plotted as a function of distance from ventricle in one normal control

C) Averaged data from 61 AD and 50 controls (slope difference P<.05)

Makedonov et al Eur J Neuro 2013

Arteriolar pathology

Severely disturbed cortical vascular network in AD

Suter et al, *Stroke* 2002
Histology and 3D distribution of watershed cortical infarcts in AD

Severely disturbed cortical vascular network in AD
**Arteriolar Disease**

- Focal Hyperintensity on Proton Density MRI
- Small lacunes on T1 Weighted MRI

*SBlack, SHSC, UToronto*
Gradient Echo: Microbleeds
Amyloid Angiopathy

Cerebral intramedullary venular abnormalities and white matter hyperintensities
Venular Pathologies

Leukoaraiosis
Cerebrovascular Reactivity

T1 FLAIR CVR

SBlack, SHSC, UToronto

Courtesy D Crane

The Deep Medullary Veins

Courtesy of FQ Gao
Cerebral intramedullary venular abnormalities and white matter hyperintensities
Severe pvWMH case example

- 74 y.o. woman with 4 yr hx of mild memory problems since her TIA (left leg weakness)
- Risk factors: hypertension, Peripheral Vascular Disease, Angina --ASA, ticlopidine and metoprolol
- Cognition/Behaviour: dysexecutive syndrome, poor memory retrieval; irritability with emotional outbursts, and mild gait difficulty
- Treatment: galantamine 6 years into her course
  - By 6 months follow-up- improved, much calmer and more active, with better scores on cognition, mood, and IADLs
- Maintained response until developed and died within a few weeks of rather sudden onset Congestive Heart Failure
VCI Case Example: Post Mortem

- Braak and Braak stage IV Alzheimer’s pathology (with sparing of isocortical association areas)
- No macroscopic or microscopic evidence of cerebral infarction, no amyloid angiopathy or lipohyalinosis of small vessels, no demyelination
- Clasmatodendrosis—swollen astrocytes with beaded processes was the main pathological correlate of her pvWMH

A recent review of her pathology also showed significant stenosis of the large deep periventricular venules using trichrome staining (greatest around the frontal horns-70%)

Small Vessel Disease and Amyloid: additive or synergistic?

Mechanisms for elimination of Aβ from the brain

- Neprilysin and Insulin degrading Enzyme in Brain Parenchyma
- Degradation of Aβ by Microglia and Astrocytes
- Perivascular (Lymphatic) Drainage of Interstitial Fluid and Solutes including Aβ
- Absorption into blood via low density lipoprotein receptor-related protein-1 (LRP1) and P-glycoprotein mediated mechanisms
- CSF pathways
Perivascular (lymphatic) drainage of interstitial fluid and solutes along basement membranes of capillaries and arteries

Weller RO et al Brain Pathology 2008

Prevalence of Amyloid Positivity in Subcortical Vascular Dementia

• Thirty-one (68.9%) of 45 patients with SVaD were negative for cortical PiB binding

• Significant differences between PiB-positive and PiB-negative groups in:
  – Age (79.5 vs 71.9 years)
  – Mini-Mental State Examination score (18.6 vs 22.6)
  – Number of lacunes (3.9 vs 9.0)
  – Visual rating scale of hippocampal atrophy (3.1 vs 2.3)

• PiB-negative SVaD patients performed better on delayed recall of both the verbal and visual memory test than the PiB-positive ones

Lee et al Neurology 2011
Key Findings, Gaps, Opportunities, and Future Directions
Summary of Key Points:

1. Small vessel disease is complex and heterogeneous
2. There is emerging evidence that both arteriolar and venous wall disease play a role in SVD including periventricular confluent disease
3. New insights into the relationship of SVD to vascular cognitive impairment, to gait and balance, and to amyloidosis, and neurodegeneration, are also emerging
4. Many studies have already established that SVD relates not only to cognition but also mobility

Gaps

1. Need for standardization of reporting of SVD, for core imaging acquisitions to capture the pathology, including microbleeds, and for imaging pipelines that simultaneously account for SVD as well as atrophy
2. Need for more correlative pathology studies, in normal, stroke, and dementia populations, including investigation of vessel walls
3. Need for more studies to better understand relationships of amyloid and SVD in relation not only to cognition but also mobility and their cerebral localization
Recommendations

1. Move from gap analysis to implementation and testing of consensus terminologies, imaging protocols, and more comprehensive quantitative structural pipelines for correlative studies of gait and cognition

2. Continue to explore advanced imaging methods such as DTI, SWI, ADL, rsfMRI, MRS, MTR, and CVR in normal appearing and hyperintense areas, including molecular ligands for tau, amyloid, and neuroinflammation

3. Use multivariate analysis techniques to explore regional brain-behavioural correlations in all of the above

4. Combine forces across clinical-pathological correlations to better understand neurovascular substrates and develop relevant animal models

5. Combine forces in collecting blood samples for genomic analysis given evidence for hereditary factors in SVD

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\[\begin{align*}
&\text{• Brill Chair in Neurology; Brain Sciences Research Program and Dept of Med, SHSC and SRI, U of Toronto} \\
&\text{• Toronto Dementia Research Alliance, U of T} \\
&\text{• Canadian Partnership for Stroke Recovery}
\end{align*}\]

Peer-reviewed funding
\[\begin{align*}
&\text{• Canadian Institutes of Health Research} \\
&\text{• Heart and Stroke Foundation Canada} \\
&\text{• Alzheimer Society of Canada} \\
&\text{• Alzheimer Association US} \\
&\text{• National Institutes of Health}
\end{align*}\]

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\[\begin{align*}
&\text{• LC Campbell Foundation, Odette, Slaight and Levy families}
\end{align*}\]
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- Ljubica Zotovic
Neural Mechanisms of Mobility Impairments

Session 1 Summary:
Neurovascular Mechanisms

Lewis Lipsitz, MD
Harvard Medical School

Faraco, Hypertension, 2013.
Cerebral Intramedullary Venular Abnormalities and White Matter Hyperintensities

Gao, Black, Keith, et al. in prep.
What We Know

- Vascular risk factors that accumulate with aging impair numerous cerebrovascular regulatory processes, including:
  - Cerebral autoregulation
  - Neurovascular coupling
  - Endothelial function
  - Blood-brain barrier disruption
  - Inflammation
  - Microbleeds
  - Venous outflow abnormalities (collagenosis, edema)
- Micro- and macro-vascular damage in certain brain regions are associated with impaired mobility

What We Don’t Know: Questions for Future Research

- Sequence of events and causal pathways leading to structural brain damage (Cause or effect?)
- Are functional changes early biomarkers?
- How to measure early cerebrovascular changes (TCD, NIRS, MRI, PET)?
- What are the contributing factors: genes (e.g., APO-E), epigenetic effects, inflammation, amyloid, oxidative stress, etc.?
- Compensatory mechanisms (neurovascular coupling, redistribution of cerebral blood flow, angiogenesis, antioxidants)?
Additional Knowledge Gaps

• Need to standardize terminology and definitions for microvascular disease, including imaging and neuropathological criteria and its cognitive and functional manifestations

• Need to better understand associations between abnormalities found on advanced imaging techniques such as ASL, CVR, DTI, MTR, and resting state fMRI, and abnormalities in gait, balance, and cognitive function
The Renin Angiotensin Hypothesis of Cognitive Impairments in Aging: Therapeutic Applications

Ihab Hajjar, MD, MS
University of Southern California

Vascular contributors to cognitive decline

**Risk factors**
- Hypertension
- Diabetes Mellitus
- Obesity
- APOe

**Potential vascular contributors**
- Cerebral hypoperfusion
- Decreased cerebrovascular reserve
- Blood Brain Barrier integrity
- Endothelial dysfunction and vasculogenesis
- Stiffness/Atherosclerosis (CIMT)
- Vascular inflammation

**Structurally**
- White matter lesions, atrophy, microbleeds, microinfarcts, loss of connectivity (DTI, DTT, r-fMRI)

**Cognitive disorders**
- Vascular cognitive impairment,
- Neurodegenerative dementias (AD)
- MCI, Other D/O
HTN (vascular)-related brain injury

- Brain side:
  - Atrophy, large infarcts, microinfarcts, cortical thinning
  - White matter hyperintensities, decreased connectivity
  - Amyloid deposition/angiopathy
- Vascular side:
  - Lost of BBB integrity
  - Endothelial dysfunction
  - Loss of reactivity/reserve (dynamic assessments)


Higher BP and lower perfusion measured by ASL-MRI

![Graphs showing changes in blood pressure and perfusion across different brain regions.

N=84; Covariate adjustment: age, race, BMI, education, and intra-cranial cavity volume

Hypertension is associated with impaired CO\textsubscript{2}-vasoreactivity

Baseline, hypercapnia, hypocapnia, recovery

- **Normotensive**
- **Hypertensive**

Hypertension and Cerebral Vasoreactivity

ASL-MRI

Globally: hypertensives: VR= 0.43; Normotensives 1.11, p= 0.0012. And regionally:

**Covariate adjustment:** age, race, BMI, gender, WMH, and intracranial cavity

Hajjar, I et al. Hypertension 2010
Brain renin angiotensin system

- There is an independent brain RAS involved in most brain functions
- RAS is involved in the regulation of multiple steps and elements of the vascular factors/contributors to cognitive disorders
- RAS is also involved in amyloid pathways and neurodegeneration
- There are opposing effects of RAS: a deleterious arm and a protective arm

The multiple personalities of brain RAS

AT$_2$-activation: angiotensin receptor blockers have a superior cognitive effect compared with other antihypertensive medications.

Decrease inflammation
Increase Endothelial regeneration
restore BBB breaches
may decrease amyloid deposition

Ang II vs Ang IV infusion and CBF

AGT-gene is associated With CO₂-VR

N=335 white participants, adjusted for age, gender, BMI, antihypertensives and MAP

Higher AGT levels

AGT-M235T and WMH the Rotterdam scan study

van Rijn M J E et al. J Neurol Neurosurg Psychiatry 2007;78:1083-1087
Anti-hypertensives and vascular, endothelial, and cognitive function (AVEC) trial in older adults with HTN and executive cognitive impairment

• First study to examine the effect and mechanisms of ARBs on executive function in those with cognitive impairment
• Hypotheses: ARBs are superior to ACEI or diuretic on cognition, CBF and CO$_2$-vasoreactivity (a marker of brain endothelial function)
• Explore role of blood pressure, CBF, VR, and RAS (serum aldo/renin) in the cognitive effects

Protocol

■ Double-blind simple randomization
■ 3 arms: lisinopril, candesartan, HCTZ
■ Additional agents if needed
■ Inclusion: >60 years, HTN, and executive dysfunction: <10 on the executive clock draw test (CLOX1)
Outcome measures

- Cognitive function:
  - Trail Making Test parts A, B, and B-A (adjust for motor component)
  - Digit Span Test (Forward, Backward)
  - Hopkins Verbal Learning Test (HVLT)
- BP: Seated (x2) and standing (1 and 3 min) BP/HR
- Blood flow velocity continuously measured at the MCA using TCD ultrasonography [rest, sit-to-stand (autoregulation), and CO₂ enriched air]

Participants

[Flowchart diagram showing the process and outcomes for eligible participants, with numbers and treatment groups indicated.]
Baseline measures in the 3 groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Lisinopril</th>
<th>Candesartan</th>
<th>Hydrochlorothiazide,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>73±6</td>
<td>72±9</td>
<td>71±7</td>
</tr>
<tr>
<td>Female, %</td>
<td>59%</td>
<td>47%</td>
<td>69%</td>
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<tr>
<td>African American, %</td>
<td>29%</td>
<td>12%</td>
<td>31%</td>
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<tr>
<td>White, %</td>
<td>60%</td>
<td>82%</td>
<td>62%</td>
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<tr>
<td>Education, %</td>
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</tr>
<tr>
<td>High school</td>
<td>18%</td>
<td>24%</td>
<td>15%</td>
</tr>
<tr>
<td>College education</td>
<td>82%</td>
<td>76%</td>
<td>84%</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean±SD</td>
<td>29.1±5.9</td>
<td>28.1±5.1</td>
<td>29.0±5.9</td>
</tr>
<tr>
<td>Baseline cognitive function, mean±SD</td>
<td>20±2</td>
<td>20±2</td>
<td>23±2</td>
</tr>
<tr>
<td>Executive Clock Drawing test, 9±2</td>
<td>9±2</td>
<td>9±2</td>
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<tr>
<td>Baseline functional and mood measures, mean±SD</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Gait speed, m/s</td>
<td>1.17±0.21</td>
<td>1.12±0.38</td>
<td>1.03±0.21</td>
</tr>
<tr>
<td>Instrumental activities of daily living</td>
<td>8±0</td>
<td>8±0</td>
<td>8±0</td>
</tr>
<tr>
<td>Physical Activity Scale in the Elderly</td>
<td>179±59</td>
<td>156±61</td>
<td>175±52</td>
</tr>
<tr>
<td>Revised Karasek Scale: Depression Subscale</td>
<td>8±7</td>
<td>8±7</td>
<td>6±6</td>
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<td>Poststudy antihypertensive medication, %</td>
<td></td>
<td></td>
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<tr>
<td>Diuretics</td>
<td>41%</td>
<td>24%</td>
<td>31%</td>
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<tr>
<td>Angiotensin-converting enzyme inhibitor, %</td>
<td>29%</td>
<td>29%</td>
<td>31%</td>
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<tr>
<td>Angiotensin receptor blocker</td>
<td>29%</td>
<td>0%</td>
<td>23%</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>0%</td>
<td>18%</td>
<td>8%</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>24%</td>
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<td>30%</td>
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<td>Cerebral hemodynamics</td>
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<tr>
<td>Sitting BPV, mmHg</td>
<td>28.1±6.2</td>
<td>29.1±5.7</td>
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<td>CO₂ vasoreactivity, slope</td>
<td>0.56±0.20</td>
<td>0.51±0.16</td>
<td>0.59±0.41</td>
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<tr>
<td>CO₂ vasomotor range</td>
<td>0.61±0.22</td>
<td>0.60±0.22</td>
<td>0.72±0.41</td>
</tr>
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Executive and memory measures

Least-square mean over study period in the 3 groups. A, Trail-Making Test (TMT), part B; B, Adjusted TMT (part A-part B); adjusted for age and baseline Mini-Mental State Examination. V0-V1 indicates change from baseline to 6 months; V0-V2, change from baseline to 12 months; and V1-V2, change from 6 months to 12 months.
Least-square mean over study period in the 3 groups adjusted for age. V0-V1 indicates change from baseline to 6 months; V0-V2, change from baseline to 12 months; and V1-V2, change from 6 months to 12 months.

**Change in BFV in the 3 groups**

**A: All sample (n=47)**

**B: Only those with blood flow velocity <27.6 cm/sec at baseline (n=23)**

Least-square mean over study period in the 3 groups adjusted for age. Within-group p-value obtained from linear mixed models (SLICE subcommand).

**Progression of vasoreactivity and VMR in the 3 groups**

Least-square mean over study period in the 3 groups adjusted for age. Within-group p-value obtained from linear mixed models (SLICE subcommand).
Higher serum aldosterone and lower BFV and CO$_2$-vasoreactivity: cross-sectional data

Results obtained from non-linear regression (proc NLIN): Y= predicted values from the fit model, N=42 subjects in AVEC trial after 3 weeks of washout period off anti-hypertension therapy

Candesartan vs lisinopril effects on the brain and endothelial function in executive MCI (CALIBREX)

- Larger study than AVEC trial with 2 arms specifically testing the $AT_2$-hypothesis
- Neuroimaging includes ASL, CO$_2$-vasoreactivity, DTI, and resting-fMRI
- Biomarkers include inflammatory panel, VCAM, ICAM, atherosclerosis (CIMT) and stiffness
- Newer endothelial marker: endothelial progenitor cells
The endothelial progenitor cells

Risk factor → Injury → Number and function ↓ → EPC

EPC count correlates with degree of WMH

Reduced circulating EPC in Alzheimer’s disease

[Graph showing reduced circulating EPC in Alzheimer's disease]

Lee et al., Neurology. 2009;72(21):1858-1863

Lower EPC in vascular-cognitive impairment

[Graph showing lower EPC in vascular-cognitive impairment]

J Cereb Blood Flow Metab. 2007
Ang II decreases EPC

Candesartan increases EPC

Jun J Y et al. Hypertension 2012;60:1316-1323

APP

A\beta_{40/42}

C99

sAPP\alpha

sAPP\beta

ADDL

BBB

BRAINBLOOD

Aggregation

Degradation

ACE

RAS involvement in the amyloid cascade

ADOL: amyloid-beta derived diffusible ligands, APP: Amyloid precursor protein, BACE: \beta-site amyloid precursor protein cleaving enzyme 1, IDE: insulin-degrading enzyme, LRP: Lipoprotein receptor-related protein, NEP: Neprilysin, RAGE: receptor for advanced glycation end products, sAPP (\alpha,\beta): soluble \beta-Amyloid Precursor Protein \alpha, \beta, C99: C-terminal fragment

RAS: Renin-angiotensin system.
**ARBs reduce risk of dementia and AD**

- N= 819, 491 predominantly male veterans (98%) aged 65 or more with cardiovascular disease.
- ARB vs ACEI: 0.81 (0.73 to 0.90)
- ARB vs control: 0.81 (0.73 to 0.90)

Li, N.-C. et al. BMJ 2010;340:b5465

**ARBs and amyloid deposition in an autopsy study**

- The National Alzheimer’s Coordinating Center: data collected from the 29 Alzheimer’s Disease Centers; used the data available as of June 2011
- Data elements:
  - Uniform Data Set elements (UDS) including demographic, social, and medical information and blood pressure measurement
  - Medications (used within 2 weeks of the visit): antihypertensive medication class
  - Neuropsychiatric assessment and a clinical diagnosis of the cognitive disorder made by a consensus team or physician

Hajjar, et al JAMA Neurol. 2012 Dec;69(12):1632-8
Analysis

• Sample: HTN subjects (self-report, BP ≥140/90 mm Hg, or receiving antihypertensive meds during at least one visit), those with available brain autopsy data, medication information and BP measurements from at least one visit

• Group classification: ARBs: received any ARB during at least one visit, “Other antihypertensive treatment”: treated but never been exposed to ARBs, and “Untreated”: HTN but never reported using antihypertensive medication at any visit

Sample description

- 89,703 total cases in NACC 2011 dataset
- 1,543 known autopsies with UDS + NP data
- 1,275 with ‘complete’ data
- Evidence of cognitive impairment or abnormal brain pathology n=1,229
- Normal cognition and normal brain pathology n=46
- Normotension n=319
- HTN n=890
- Treated n=710
- Untreated n=180
- ARBs n=133
- Other n=577
### Comparisons of the 3 groups

<table>
<thead>
<tr>
<th></th>
<th>ARBS</th>
<th>Other Anti-HTN</th>
<th>No Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>133</td>
<td>577</td>
<td>180</td>
<td>890</td>
</tr>
<tr>
<td>Mean age at death, years (SD)</td>
<td>82.6(9.6)</td>
<td>82.3(10.7)</td>
<td>76.7(12.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (%women)</td>
<td>49%</td>
<td>42%</td>
<td>42%</td>
<td>0.35</td>
</tr>
<tr>
<td>Race (%white)</td>
<td>96%</td>
<td>94%</td>
<td>96%</td>
<td>0.42</td>
</tr>
<tr>
<td>Education, % ≥12</td>
<td>95%</td>
<td>90%</td>
<td>94%</td>
<td>0.22</td>
</tr>
<tr>
<td>Marital Status (%married)</td>
<td>60%</td>
<td>58%</td>
<td>70%</td>
<td>0.09</td>
</tr>
<tr>
<td>Family history of dementia</td>
<td>60%</td>
<td>60%</td>
<td>63%</td>
<td>0.74</td>
</tr>
<tr>
<td>APOe (%e4)</td>
<td>41%</td>
<td>46%</td>
<td>50%</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>38.5(33.2)</td>
<td>34.1(25.6)</td>
<td>30.2(16.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean MMSE (SD)</td>
<td>19.7(9.0)</td>
<td>16.6(9.6)</td>
<td>15.7(9.2)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>46%</td>
<td>44%</td>
<td>14%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>20%</td>
<td>17%</td>
<td>10%</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24%</td>
<td>11%</td>
<td>4%</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Mean # of Anti-HTN Medications (SD)</td>
<td>2.5(1.2)</td>
<td>1.7(0.9)*</td>
<td>0</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

Except as indicated, p-values are obtained from chi-square or ANOVA tests, comparing differences among the 3 study groups. * indicates p<0.05 for the 2 groups-comparisons ARB vs other antihypertensive medications.

### AD and vascular-related pathology in the 3 groups

#### 2A

<table>
<thead>
<tr>
<th>BRAAK &amp; BRAAK</th>
<th>ARBS</th>
<th>Other Anti-HTN</th>
<th>No Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (none, Stages I-II)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>1 (Stages III-IV)</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>2 (Stages V-VI)</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

#### 2B

<table>
<thead>
<tr>
<th>CERAD Neuritic Plaques</th>
<th>ARBS</th>
<th>Other Anti-HTN</th>
<th>No Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>none-sparse</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>moderate</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>frequent</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
</tr>
</tbody>
</table>

#### 2C

<table>
<thead>
<tr>
<th>CERAD Infarcts*</th>
<th>ARBS</th>
<th>Other Anti-HTN</th>
<th>No Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Mild</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Moderate</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
</tr>
</tbody>
</table>

#### 2D

<table>
<thead>
<tr>
<th>Atherosclerosis</th>
<th>ARBS</th>
<th>Other Anti-HTN</th>
<th>No Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>None Mild</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Moderate</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
</tr>
</tbody>
</table>

* CERAD: Consortium to Establish a Registry of Alzheimer’s Disease; Anti-HTN: antihypertensive medications
  **: Large Artery Infarcts
  ***: Micro Infarcts/lacunes
  **: Moderate-Severe
### Risk of neuropathological markers

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>ARBs vs other Antihypertensive medications</th>
<th>ARBs vs Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate*</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>CI</td>
</tr>
<tr>
<td>CERAD Criteria</td>
<td>0.51(0.34-0.82)</td>
<td>0.47 (0.27-0.81)</td>
</tr>
<tr>
<td>ADRDA/Khachaturian Criteria</td>
<td>0.51 (0.28-0.93)</td>
<td>0.43 (0.21-0.91)</td>
</tr>
<tr>
<td>BRAAK and BRAAK</td>
<td>0.57 (0.38-0.87)</td>
<td>0.52 (0.31-0.86)</td>
</tr>
<tr>
<td>CERAD: Neuritic Plaques Score</td>
<td>0.64 (0.43-0.94)</td>
<td>0.59 (0.37-0.96)</td>
</tr>
<tr>
<td>Large artery infarcts**</td>
<td>1.78 (1.02-3.09)</td>
<td>2.37 (1.15-4.89)</td>
</tr>
<tr>
<td>Micro infarcts/lacunes**</td>
<td>1.01 (0.67-1.52)</td>
<td>1.03 (0.63-1.68)</td>
</tr>
<tr>
<td>Hemorrhage**</td>
<td>2.16 (1.13-4.11)</td>
<td>2.31 (1.11-4.78)</td>
</tr>
<tr>
<td>Atherosclerosis**</td>
<td>1.08 (0.66-1.78)</td>
<td>0.99 (0.52-1.88)</td>
</tr>
<tr>
<td>Arteriosclerosis**</td>
<td>1.18 (0.68-2.03)</td>
<td>1.57 (0.76-3.03)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, systolic blood pressure, BMI, stroke, APOe

**Also adjusted for anticoagulants/Aspirin

---

### Comparison of ARBs vs ACEI (n=362)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate</th>
<th>Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>CI</td>
</tr>
<tr>
<td>CERAD</td>
<td>0.51 (0.30-0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>ADRDA/Khachaturian Criteria</td>
<td>0.62 (0.30-1.29)</td>
<td>0.20</td>
</tr>
<tr>
<td>BRAAK Staging</td>
<td>0.69 (0.42-1.12)</td>
<td>0.13</td>
</tr>
<tr>
<td>Neuritic Plaques</td>
<td>0.61 (0.39-0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Large artery infarcts</td>
<td>1.62 (0.80-3.30)</td>
<td>0.18</td>
</tr>
<tr>
<td>Micro infarcts/lacunes</td>
<td>0.78 (0.49-1.26)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2.18 (0.95-5.01)</td>
<td>0.07</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>0.99 (0.49-1.99)</td>
<td>0.97</td>
</tr>
<tr>
<td>Arteriosclerosis</td>
<td>0.86 (0.46-1.61)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, systolic blood pressure, BMI, stroke, APOe

---

Hajjar, et al. JAMA Neurol. 2012 Dec;69(12):1632-8

CERAD: Consortium to Establish a Registry of Alzheimer’s Disease; ADRDA: Alzheimer’s Disease and Related Disorders Association;

*Adjusted for age, gender, systolic blood pressure, BMI, stroke, APOe

**Also adjusted for anticoagulants/Aspirin
Summary

- RAS is involved in both vascular and amyloid contributors to cognitive disorders in aging.
- Our work suggests that use of ARB is a promising intervention for executive dysfunction and possibly AD.
- The mechanisms underlying these effects are still under investigation but we have clues to a role of the endothelium, reactivity, and perfusion.

RAS-based therapy targets: beyond ARBS

- ANG 1-7: potentiates the AT$_2$ and MAS axis (currently completing a three group mice AD model experiment: candesartan, ANG1-7, candesartan+ang 1-7).
- AT$_2$-receptor agonist: compound C21.
- AT$_4$ has an inhibitory effect on AT$_4$-receptor, also the insulin-regulated aminopeptidase (IRAP): IRAP inhibitors are potent memory enhancers.
Coauthors/Collaborators

1. Lewis Lipsitz, MD, Harvard Medical School, BIDMC, and Hebrew SeniorLife
2. Vera Novak, PhD, MD, Harvard Medical School and BIDMC
3. Meaghan Hart, BS, Hebrew SeniorLife
4. William Milberg, PhD, GRECC, Boston VA, and Harvard Medical School
5. Wendy Mack, PhD, Preventive Medicine and Biostatistics, USC
6. Helena Chui, MD, Neurology, USC
7. Kathlyn Rogers, PhD, Pharmacy, USC

Funding

This work is supported by grants K23AG030057, 1R01AG042127 and a pilot sub-study from the USC-Alzheimer’s Disease Research Center
CADASIL: Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

Anand Viswanathan, MD, PhD
Stroke Service and Memory Disorders Unit
Hemorrhagic Stroke Research Group
Massachusetts General Hospital, Boston, Massachusetts

Case Presentation

- A gentleman with no vascular risk factors first developed right-sided weakness and clumsiness with slurred speech at the age of 45. MRI revealed lacunar infarctions of the basal ganglia and extensive white matter disease.

- Over the following several years, the patient had several exacerbations of his neurologic condition (worsening gait, weakness, fatigue). One of these episodes led to hospitalization and repeat MRI. This revealed a new lesion near the posterior limb of the left internal capsule.

- Detailed evaluation with genetic testing diagnosed the small vessel arteriopathy CADASIL.
Cerebral Distribution of Small Arteries of the Brain

- Long perforating arteries
  - HTN-related SVD, CADASIL

- Short perforating arteries
  - Leptomeningeal arteries
  - Amyloid angiopathy
Conventional MRI Markers of Small Vessel Disease

White Matter Hyperintensities (WMH)

Lacunar Lesions (LL)

Cerebral Microbleeds (CMB)

CADASIL

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

- Mutation of Notch3 genes (chromosome 19)
- Ischemic stroke or dementia
- MRI markers of small vessel disease: white matter lesions, lacunar infarcts, cerebral microhemorrhages, and brain atrophy
CADASIL versus Sporadic SVD


Histopathologic and Electron Microscopic Characteristics of CADASIL
CADASIL-Associated Notch3 Mutations


CADASIL: Natural History

Chabriat et al., Lancet. 2009.
Domain-Based Cognitive Performance by Age

![Graph showing domain-based cognitive performance by age](image)

Buffon et al., J Neurol Neurosurg Psychiatry. 2006.

CADASIL Subjects Have Impaired Processing Speed Due to Dysfunction in Frontal-Cortical Circuits

![Graph showing neuropsychological performance profile of CADASIL subjects](image)

Duering et al., Brain. 2011.
CADASIL Subjects Have Impaired Processing Speed Due to Dysfunction in Frontal-Cortical Circuits

Duering et al., *Brain*. 2011.

---

**Apathy Is a Common Neuropsychiatric Symptom in CADASIL**

- Apathy has been classically defined as a lack of motivation but it can be defined in a more operational way as a quantified and observable behavioral syndrome consisting in a quantitative reduction of voluntary (or goal-directed) behavior.

- These changes are not dependent on environmental or physical factors and can occur independently of mood disorders, dementia, or altered awareness.

- Apathetic patients typically show deficits in the generation, initiation, persistence, planning, and monitoring of behavior with a reduction of participation in normal purposeful behavior.

- They also can present with reduced interest in their environment, indifference, a flattening of affect, or lack of emotional reactivity.
Behavioral Disturbances and Apathy in CADASIL

Reyes et al., Neurology. 2009;72(10):905-10

<table>
<thead>
<tr>
<th>Behavioral disturbance</th>
<th>Cohort (n = 132)</th>
<th>Apathetic (n = 54)</th>
<th>Neuroathetic (n = 78)</th>
<th>p</th>
<th>p'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression/Sadness, % (n)</td>
<td>46.2 (81)</td>
<td>61.1 (23)</td>
<td>35.9 (29)</td>
<td>0.0040</td>
<td>0.02</td>
</tr>
<tr>
<td>Disturbed sleep, % (n)</td>
<td>44.7 (56)</td>
<td>64.8 (35)</td>
<td>30.8 (24)</td>
<td>0.0001</td>
<td>0.31</td>
</tr>
<tr>
<td>Inability to fulfill, % (n)</td>
<td>43.1 (57)</td>
<td>64.8 (55)</td>
<td>26.2 (22)</td>
<td>0.0001</td>
<td>0.0003</td>
</tr>
<tr>
<td>Anxiety, % (n)</td>
<td>37.1 (49)</td>
<td>40.7 (23)</td>
<td>34.6 (27)</td>
<td>0.47</td>
<td>0.71</td>
</tr>
<tr>
<td>Apathy, % (n)</td>
<td>41.0 (34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitated aggression, % (n)</td>
<td>20.5 (29)</td>
<td>53.7 (29)</td>
<td>7.7 (8)</td>
<td>0.0003</td>
<td>0.0001</td>
</tr>
<tr>
<td>Disturbed appetite, % (n)</td>
<td>16.0 (21)</td>
<td>31.5 (17)</td>
<td>5.1 (4)</td>
<td>0.0001</td>
<td>0.003</td>
</tr>
<tr>
<td>Disinhibition, % (n)</td>
<td>13.7 (19)</td>
<td>27.8 (15)</td>
<td>3.9 (4)</td>
<td>0.0001</td>
<td>0.006</td>
</tr>
<tr>
<td>Euphoria, % (n)</td>
<td>7.9 (10)</td>
<td>14.0 (8)</td>
<td>2.5 (2)</td>
<td>0.009</td>
<td>0.20</td>
</tr>
<tr>
<td>Averbent motor behavior, % (n)</td>
<td>6.0 (8)</td>
<td>14.8 (9)</td>
<td>0.0 (0)</td>
<td>0.0005</td>
<td>0.0007</td>
</tr>
<tr>
<td>Delusions, % (n)</td>
<td>2.2 (3)</td>
<td>9.7 (2)</td>
<td>1.3 (1)</td>
<td>0.36</td>
<td>NA</td>
</tr>
<tr>
<td>Hallucinations, % (n)</td>
<td>0.7 (2)</td>
<td>1.0 (1)</td>
<td>0.0 (0)</td>
<td>0.23</td>
<td>NA</td>
</tr>
</tbody>
</table>

Rayes et al., Neurology. 2011;76:1472-77

Behavioral Disturbances and Apathy in CADASIL

Figure 2: Suli in which morphology was associated with apathy in our cohort

Rayes et al., Neurology 2011;76:1472-77
CADASIL: Cortical Pathology in a Pure Subcortical Vascular Dementia

Subcortical lesions are extensive and are strongly associated with cognition and disability

- Microbleeds
- Lacunes
- White matter damage

Jouvent et al, Brain. 2008;131(Pt 8):2201-8

CADASIL: Cortical Pathology in a Pure Subcortical Vascular Dementia

Individual sulci morphology can be identified and measured and may represent a region specific measure of brain atrophy

- Right central sulcus
- Surface Area
- Sulcal Depth

Jouvent et al, Brain. 2008;131(Pt 8):2201-8
CADASIL: Cortical pathology in a pure subcortical vascular dementia

Atrophy Is a Function of Subcortical Lesion Burden in CADASIL

Low Subcortical Lesion Burden

High Subcortical Lesion Burden


Jouvent et al, Brain, 2008 Aug;131(Pt 8):2201-8

Cortical Neuronal Apoptosis in patients with large subcortical lesion burden may account for cerebral atrophy CADASIL

Jouvent et al, Brain, 2008 Aug;131(Pt 8):2201-8

Secondary Cortical Neurodegeneration After Subcortical Ischemia in CADASIL


Weight of MRI lesions in CADASIL

White Matter Hyperintensities (WMH)  
Cognitive Impairment & Disability  
Lacunar Lesions  
Brain Atrophy  
Microhemorrhages  
Diffusion Changes
### Weight of MRI lesions in CADASIL

#### Global Cognitive Function (MDRS)

<table>
<thead>
<tr>
<th>Step</th>
<th>Variables</th>
<th>Beta</th>
<th>P-value</th>
<th>Total Explained Variance</th>
<th>Standardized Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BPF</td>
<td>1.37</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>0.40</td>
</tr>
<tr>
<td>2</td>
<td>LL</td>
<td>-53.8</td>
<td>0.0057</td>
<td>0.42</td>
<td>-0.21</td>
</tr>
<tr>
<td>3</td>
<td>Mean-ADC</td>
<td>-2.73</td>
<td>0.0117</td>
<td>0.45</td>
<td>-0.21</td>
</tr>
</tbody>
</table>

#### Disability (mRS)

<table>
<thead>
<tr>
<th>Step</th>
<th>Variables</th>
<th>Beta</th>
<th>P-value</th>
<th>Total Explained Variance</th>
<th>Standardized Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BPF</td>
<td>-0.12</td>
<td>&lt;0.0001</td>
<td>0.38</td>
<td>-0.46</td>
</tr>
<tr>
<td>2</td>
<td>LL</td>
<td>6.19</td>
<td>&lt;0.0001</td>
<td>0.51</td>
<td>0.33</td>
</tr>
<tr>
<td>3</td>
<td>CM</td>
<td>0.05</td>
<td>0.0017</td>
<td>0.55</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Viswanathan et al., Neurobiol Aging 2008 Oct 14

### Multiple Cerebral Infarctions in CADASIL

Multiple Cerebral Infarctions in CADASIL


Auriel E et al. Neurology 2012;79:2335-2341

Multiple Cerebral Infarctions in CADASIL

Lobar ICH
Nonacute
Acute

Deep ICH
Nonacute
Acute
Intracortical Infarctions in CADASIL

Current Understanding of CADASIL: What we know

- CADASIL is a common genetically inherited small-vessel disease of the brain and is due to mutations in the Notch 3 gene. The disease remains underdiagnosed.

- Patients suffer from attacks of migraine, ischemic stroke or transient ischemic attacks, and multi-domain cognitive impairment.

- Mood disorders such as apathy or depression are common.

- Executive dysfunction is common in the disease.

- Degree of brain atrophy in the disease is the most important factor in disease-associated cognitive impairment and disability.
Future Directions: What we don’t know

- Further understanding of the mechanism of cerebral atrophy in this subcortical vascular disease.
- Relationship of migraine to small vessel pathology?
- Further elucidation of clinical factors that influence prognosis (blood pressure)
  - Design of a clinical therapeutic trial?
- The reasons for high variability of disease severity even within families with the same Notch3 mutation.
- Further understanding the mechanism for development of WMH in the disease
- Relationship of disease pathology to other measures such as gait function, apathy, depression.
- Impact of disease pathology on patient quality of life.
Neural Signals Driving Cortical Plasticity And Motor Recovery After Stroke

Jeffrey A. Kleim, Ph.D.
Associate Professor
School of Biological and Health Systems Engineering
Arizona State University

jakleim@asu.edu

Medical Advances: Last 100 years


Insulin  Penicillin  Influenza Vaccine  Polio Vaccine  Heart Transplant  AIDS Virus Identified  Genome Mapped

Neurorehabilitation?
Advances In Neuroscience

The Paradigm Shift In Neurorehabilitation

- Neural Plasticity
- Neurorehabilitation

Chart showing the number of papers published from 1965 to 2010, with a significant increase in papers focusing on neural plasticity and neurorehabilitation in recent years.
Rehabilitation Is A Relearning Process

Neurorehabilitation: Exploiting Neural Plasticity

Behavioral Signals
Neurorehabilitation

Neural Signals
Neurorehabilitation

Neural Plasticity

Functional Improvement

(Klein, 2012)
The Most Powerful Driver of Plasticity Is Experience

"Training a stroke patient to walk again is like training you for the Olympics".

......except we are encouraged to use performance enhancers.

Clinically Exploiting Neural Signals

Neurophysiological:
- rTMS
  - TDCS

Neuropharmacological:
- L-DOPA
  - Fluoxetine
Motor Map Plasticity

Control  |  Saline  |  LM22A-4

Genetic Influences On The Capacity For Plasticity

*Human BDNF Val/Met\(^{66}\) Polymorphism:*

- 20% population is val/met (heterozygous)
- 4% population is met/met (homozygous)
- results in aberrant BDNF transport/release
Is The BDNF Polymorphism Associated With Abnormal Experience-Dependent Cortical Plasticity?

Map 1 → 30 Mins Training → Map 2


Val/Val  Val/Met  Met/Met
Pre-training

Post-training

Map Area

<table>
<thead>
<tr>
<th></th>
<th>Pre-training</th>
<th>Post-training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val/Val</td>
<td>12.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Val/Met</td>
<td>9.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Met/Met</td>
<td>15.0</td>
<td>12.0</td>
</tr>
</tbody>
</table>

*Significant difference

Met Allele is associated with impaired motor skill learning

(McHughen et al, 2010)
BDNF Polymorphism and Stroke Recovery

(Kim et al., 2013)
APOE Polymorphism and Stroke Recovery

(Cramer et al., 2013)

Constellation Of Genetic Markers

Extracellular Signaling:
- BDNF
- NGF
- Dopamine
- Serotonin

Intracellular Signaling:
- Phosphodiesterase Inhibitors
- ACE
- CREB
- CamKII
- MapK
- ERK
Mapping the Transcriptional Landscape of Parkinson’s

Clemens Scherzer, MD
Director, The Neurogenomics Laboratory
Co-Director, NeuroDiscovery Biomarkers Program
Associate Professor of Neurology
Harvard Medical School
Brigham & Women’s Hospital

What if you could know all the data?
Goal: Data-driven decisions about disease, diagnosis, and treatment

Genes (22,000+)

RNAs (130,000+)

Proteins (> 10^6)

Metabolites (3 x 10^3)

Transcription

Translation

Enzymatic reactions

Clinical Phenotypes

History, Exam, Environment, Imaging, Scales (500?+)

Personalized Neurology

Transcriptomics: neck to neck with chip performance

Number of transcripts per assay


Moore's law
Meta-analysis of 522 gene sets across 322 human brains identifies ten molecular pathways associated with PD


Zheng et al., Science Translational Medicine, 2010

Ten gene sets pinpoint defects in mitochondrial electron transport and biogenesis --- regulated by the peroxisome proliferator-activated receptor γ coactivator-1α, PGC-1α

<table>
<thead>
<tr>
<th>Gene set</th>
<th>Stage 1 (GSE4846)</th>
<th>Stage 2 (GSE6809)</th>
<th>Stage 3</th>
<th>All</th>
<th>Activin data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondrial complex I</td>
<td>-2.26</td>
<td>-1.62</td>
<td>-1.19</td>
<td>-1.72</td>
<td>1.02</td>
</tr>
<tr>
<td>Target of the proliferator-activated receptor γ</td>
<td>-2.19</td>
<td>-1.47</td>
<td>-0.86</td>
<td>-1.54</td>
<td>1.06</td>
</tr>
<tr>
<td>Mitochondrial electron transport</td>
<td>-2.27</td>
<td>-1.51</td>
<td>-0.92</td>
<td>-1.62</td>
<td>1.07</td>
</tr>
<tr>
<td>Mitochondrial membrane</td>
<td>-0.91</td>
<td>-0.56</td>
<td>-0.28</td>
<td>-0.66</td>
<td>1.04</td>
</tr>
<tr>
<td>Mitochondrial complex II-IV, complex V</td>
<td>-0.45</td>
<td>-0.22</td>
<td>-0.07</td>
<td>-0.26</td>
<td>1.03</td>
</tr>
<tr>
<td>Nuclear receptor D</td>
<td>-0.44</td>
<td>-0.20</td>
<td>-0.06</td>
<td>-0.24</td>
<td>1.03</td>
</tr>
<tr>
<td>NADH:ubiquinone oxidoreductase</td>
<td>-0.43</td>
<td>-0.20</td>
<td>-0.06</td>
<td>-0.24</td>
<td>1.03</td>
</tr>
<tr>
<td>Pyruvate dehydrogenase</td>
<td>-0.42</td>
<td>-0.20</td>
<td>-0.06</td>
<td>-0.23</td>
<td>1.03</td>
</tr>
<tr>
<td>Ubiquitination pathway</td>
<td>-0.41</td>
<td>-0.20</td>
<td>-0.06</td>
<td>-0.22</td>
<td>1.03</td>
</tr>
</tbody>
</table>

*Activin data for each gene set is shown above.
The electron transport chain in dopamine neurons of patients with Parkinson’s disease

Transcriptomics: Stage 1 in motor PD neuropathology
The nuclear-encoded electron transport chain in dopamine neurons of patients with Parkinson’s disease

Symptomatic PD
Increased
Decreased

The nuclear-encoded electron transport chain in dopamine neurons of patients with Parkinson’s disease
Transcriptomics: *Stage 2 in pre-motor Lewy body neuropathology*

Powerless in Parkinson’s --- possibly *before* symptoms become manifest
A molecular switch: *PGC-1α* regulates the electron transport chain

*PGC-1α* regulates mitochondrial target genes through specific occupancy of conserved ERRα motifs
PGC-1α blocks A53T-α-synuclein-induced dopamine neuron loss

PGC-1α blocks A53T-α-synuclein-induced dopamine neuron loss --- in primary cultures ... 

... but what about animal models of Parkinson’s?
PGC-1α modulates MPTP- and mutant parkin-induced degeneration of nigral neurons —— in mice

Expression analysis of dopaminergic neurons in Parkinson’s disease and aging links transcriptional dysregulation of energy metabolism to cell death

Mariana Eliazar, Christopher N. Yeates, Sabrina Deol, Andreas Bender, Olga Melcher, Evdokia Janiak, Thomas Kruppel, Thomas Merkle, Benjamin M. Rothbard, Helene Frackowiak

Transgenic expression and activation of PGC-1α protect dopaminergic neurons in the MPTP mouse model of Parkinson’s disease

Ciara C. Mcgill, Johannes Malik, Valentina El Liber, Timothy El Tabet, Melinda Gilmore, Peter Dupree, Eve Belknap, Amanda Milbank, Alain Bertin, Dominique Belknap, Jean A. Girard, Laura Kaburaki, Nicole Roberz, Don Ladd-Bruno

St. Pierre et al., Cell, 2008

PGC-1α knock-out enhances MPTP-induced dopamine neuron loss in mice

St. Pierre et al., Cell, 2008
Reduced PGC-1α activity in PD: causal effects of genetics, aging, and environment

- Age-dependent telomere dysfunction
- Physical inactivity
- Parkin mutations
- Environmental exposure


But wait --- what about inflammation?
Muscle-specific knock-out of \( \text{PGC-1}\alpha \): increased expression of select cytokines as well as circulating serum IL-6

A hypothesis: a second role for \( \text{PGC-1}\alpha \) in chronic inflammation?

Handschin et al., J Clin Invest, 2007

The Brain Cell Encyclopedia: charting the flow of information from the entire human genome into a prototype brain cell-type
LC-RNA-Seq: a new tool for cell-specific RNA-sequencing

Laser-capture

Massively parallel, sequence the entire RNA content

Reconstruct the whole transcriptome without limitation to known genes

Discover and translate in health and disease

The Brain Cell Encyclopedia: charting the flow of information from the entire human genome into a prototype brain cell-type

Input:
General genetic variation encoded in 130 human genomes

Output:
522 Pathways
30,000 mRNA isoforms
~30,000 “Dark Matter” RNAs
Cell-type-specific transcription

~30,000 “Dark Matter” RNAs
The Neurogenomics Laboratory: located at the intersection of genomics, computing, and neurology

The Neurogenomics Laboratory

Bioinformatics Group
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The Laboratory for Neurogenomics

2013 CNS Workshop: Session 3
Tuesday, November 19, 2013
Inflammatory response to stress and immune system alterations in mobility disorders: frailty

Sean X. Leng, MD, PhD
Associate Professor of Medicine
Division of Geriatric Medicine and Gerontology
Johns Hopkins University School of Medicine

Sean X. Leng, MD, PhD

Disclosures

November 19, 2013

The above presenter has no relevant financial relationships with commercial interests and will not reference unlabeled/unapproved uses of drugs or products in his presentation.
Inflammation: classic definition

Acute versus chronic inflammation

Stress/Infection → Response → Healing/resolution → Time

IL-6

CRP

Chronic Inflammation

Age-related
Pro-Inflammatory State

Acute Inflammatory Reaction
The frailty syndrome

- Frailty phenotype criteria:
  - Slow walking speed by gender and height
  - Low grip strength by gender and BMI
  - Subjective exhaustion
  - Low levels of physical activity
  - Unintentional weight loss*
- Frail = 3-5/5; pre-frail = 1-2/5; non-frail = 0
  *Obesity (“fat”) frailty: weight loss criterion does not apply

Chronic inflammation in frailty

- Elevated IL-6 and CRP levels in frailty
- High IL-6, low hemoglobin and IGF-1 in frailty
- Increased total WBC and its specific subpopulations (neutrophils, monocytes, and CCR5+ T cells) in frailty
- High WBC and low IGF-1 in frailty
- Elevated neopterin levels in frailty

Leng SX, et al. Aging Clin Exp Res 2004 a, b
Inflammatory pathway in frailty: monocytic expression of stress responsive genes

**Table:**

<table>
<thead>
<tr>
<th>Genes</th>
<th>A. GIArray* (mean ± S.D.)</th>
<th>B. QPCR (mean ± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transcription factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hic-5</td>
<td>5.4 ± 2.1</td>
<td>3.4 ± 1.2</td>
</tr>
<tr>
<td>GRF1</td>
<td>26.7 ± 21.9</td>
<td>1.6 ± 1.5</td>
</tr>
<tr>
<td>PADD</td>
<td>7.9 ± 4.8</td>
<td>1.7 ± 1.0</td>
</tr>
<tr>
<td><strong>Signal transduction proteins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAPK10</td>
<td>4.6 ± 1.9</td>
<td>3.4 ± 1.3</td>
</tr>
<tr>
<td>MAP2K7</td>
<td>2.9 ± 0.9</td>
<td>4.4 ± 2.2</td>
</tr>
<tr>
<td><strong>Chemokines &amp; receptors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXCL10</td>
<td>3.8 ± 0.8</td>
<td>4.2 ± 1.1</td>
</tr>
<tr>
<td>VCAM-1</td>
<td>12.6 ± 7.5</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td>CCR10</td>
<td>10.5 ± 8.4</td>
<td>1.8 ± 1.7</td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β</td>
<td>2.9 ± 0.6</td>
<td>3.1 ± 0.9</td>
</tr>
<tr>
<td>IL-1A</td>
<td>4.3 ± 2.4</td>
<td>4.3 ± 2.1</td>
</tr>
<tr>
<td>IL-11</td>
<td>5.1 ± 2.9</td>
<td>UD^2</td>
</tr>
</tbody>
</table>

CXCL10 expression vs chronic inflammation

**Graph:**

Frail-over-non-frail Ratios of CXCL10 Expression Levels

Qu T, et al. *Cytokine* 2009

Frail-over-non-frail Ratios of IL-6 Levels

Response to influenza immunization as an immune challenge in frailty

Post-/pre-vaccination GMT Ratios

<table>
<thead>
<tr>
<th></th>
<th>All (n=71)</th>
<th>Nonfrail (n=22)</th>
<th>Prefrail (n=32)</th>
<th>Frail (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H3N2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rates of ILI (%)
P = .005

Rates of influenza (%)
P = .03

Etiology for chronic inflammation?

Chronic Inflammation

IL-6
CRP

Time

Chronic CMV infection in older adults: diagnosis and T-cell immunity

Chronic CMV infection and its health impact in older adults

Leng SX, et al. *AGE* 2011
Questions for discussion

• Is chronic inflammation important for CNS and mobility impairment, beside the frailty syndrome (neck above and below question)?
• How does chronic inflammation affect CNS, muscle, and balance (mechanisms, pathways, etc.)?
• What are etiologies and mechanisms for chronic inflammation in older adults?
• Targets for potential intervention?

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• China Medical Board, USA
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BrAnN NetWOrKs AnD mObilItY DIsAbilItY

Paul J. Laurienti
Wake Forest
Movie Time!
SPPB Score

High  Mid  Low

Motor Neighborhood

High SPPB Young
Age-Related Neuromuscular Activation Impairment

David J. Clark, ScD
Malcom Randall VA Medical Center
Brain Rehabilitation Research Center
&
University of Florida
Institute on Aging

Overview

Neuromuscular activation impairment is:

- Present in some, but not all, older adults
- Most evident during rapid/dynamic contractions
- Evident prior to decline of mobility
- Associated with decline of strength/power
- Associated with decline of mobility
- Partially restored by power resistance training
• Isometric EMG is similar across groups
• Isometric specific torque is similar across groups
• Major differences were only evident during dynamic contractions!


Rate of EMG Rise

Electromyography (EMG): detects the bioelectrical signals generated by the nervous system to elicit muscle contraction.

Rate of EMG Rise: quantifies how quickly the EMG signal increases during the onset of a maximal effort contraction.
Longitudinal Decline of Neuromuscular Activation

- 16 healthy older adults (age 75.0 ± 4.0 years)
- Quadriceps Rate of EMG during leg press
- Decline in Rate of EMG Rise (-28%) and power (-17%)
- Walking speed did not change (1.36 versus 1.39 m/s)
- SPPB did not change (11.1 versus 10.6 points)
- Activation impairment precedes functional decline

Activation Impairment and Onset of Mobility Deficits

400m walk
“Faster” Group 1.33 ± 0.15
“Slower” Group 1.10 ± 0.11
SPPB
11.8 ± 0.6
10.1 ± 1.2

Groups did NOT differ for: age, weight, height, BMI, Berg Balance Test or Mini-Mental State Exam
Activation Impairment and Overt Mobility Deficits

<table>
<thead>
<tr>
<th></th>
<th>Middle Aged</th>
<th>Age</th>
<th>SPPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older High Function</td>
<td>73.9 ± 3.5</td>
<td>11.7 ± 0.5</td>
<td>11.0 ± 0.9 (range 10-12)</td>
</tr>
<tr>
<td>Older Mobility Deficits</td>
<td>77.4 ± 4.8</td>
<td></td>
<td>7.9 ± 1.3 (range 5-9)</td>
</tr>
</tbody>
</table>


Intervening on Activation Impairment

- 27% gain in Rate of EMG Rise
- 2% gain in Muscle Mass
- 37% gain in Leg Press Power
- 1.5 point increase in SPPB

Reid KF, et al. Comparative effects of low and high resistance power training for improving lower extremity power and physical performance in mobility-limited older adults. Under review.
Mechanisms and Interventions?

**Central**
- Excitatory/inhibitory balance
- Neurotransmission
- Structural atrophy
- Behavioral networks

**Peripheral**
- Loss/remodeling of motor units
- Neurotransmission
- Neuromuscular junction
- Reflex pathways
Mobility, cortex, and cognitive function

Dual task evidence
- Consistent evidence of link between control of mobility and cognitive/executive function using ‘dual-task’ paradigms

Cognitive tasks
- reaction time tasks
- discrimination tasks
- tracking tasks
- working memory tasks
- verbal fluency tasks
- others

Walking
- velocity*
- spatiotemporal
- step variability

Mobility, cortex, and cognitive function

Evidence from ‘lesion’ studies

- Changes in control of mobility common sign/symptom of neurologic injury/disease (for example…)


Complexity of bipedal mobility

- Walking has many elements that likely demand high-level cortical processing
  - Navigation
    - Micro – obstacle avoidance/affordance
    - Macro – way finding
  - Transitions (intent)
    - Horizontal (e.g., speed changes) and/or vertical
  - Sensorimotor control
    - Locomotor control (e.g., limb placement)
    - Dynamic stability control*
Navigation

- Important dependence on visuospatial processing and internal representations for navigation


Navigation

- Parietal (area 5) important in memory of obstacle position during locomotion

Transitions (intent)

- Regional changes in cortical activation associated with control of gait speed
- Highlight involvement of:
  - Prefrontal
  - Supplementary motor area
  - Medial sensorimotor cortex

Sensorimotor (limb movement)

- Pyramidal tract neurons discharge temporally associated with phasic locomotor activity


Dynamic stability during walking

- Continuous regulation of relationship between 'centre–of-mass' (COM) and 'base-of-support' (BOS)

- Each step is an elegant combination of need for progression and stability

- Role for predictive and reactive balance control

A focus on reactive balance

- Reactive balance control, as automatic as it may seem, is dependent on and influences high-level cortical processes.
- The continuous need for reactive balance control is likely one important reason for the link between mobility and cognition.

Basics of reactive balance control

- Latency: 100 ms
- Amplitude: scaled
- Direction: tuned
- Task/environment specific
- Multi-sensory/multi-muscle

Age-related changes

- Older adults increased dependence on change-in-support reactions

**BUT**

- Older adults reveal increased inability to execute effective stepping response to instability

- Challenges could be associated with:
  - Timing
  - Direction/scaling
  - Restabilization

---

**Maki BE, McIlroy WE. (2006) Control of rapid limb movements for balance recovery: Age-related changes and implications for fall prevention. Age Ageing. 35:i12-i18.**

---

Age-related changes

- Healthy older adults reveal differences in controlling stabilization at foot-contact during voluntary stepping

- Potentially related to reactive control capacity during ongoing movement

---

**Singer et al. (2013) Age-related changes in mediolateral dynamic stability control during volitional stepping. Gait Posture. 35:679-83.**
Balance control and cognition

- Considerable evidence of the interference between cognitive function and reactive balance control

Temporal dynamics of attention shifts

- Time varying changes in balance control and need for rapid responses leads to rapid resource shifting (attention shifts)
- Attention shift onset is delayed, on average, by 67% in the healthy older adults
Potential importance of autonomic contributions

- Phasic autonomic reactions temporally coupled to balance reactions
- Initial studies point to ANS influence on processing speeds and related slowing with aging and brain injury


Perturbation-evoked cortical potentials

- Perturbation evoked reactions associated with significant frontocentral negativity (N1)
- Postural set (preparatory activity) also represented frontocentrally
- Amplitude of cortical activity:
  - Proportional to amplitude of instability
  - Augmented with increased difficulty

Independence of effectors

- Negativity and spatial location was independent of type of perturbation and effectors (e.g., same for bilateral lower limbs and unilateral upper limb).


N1 versus ERN dipole location

- Note: N1 topography independent of effectors used
- Cortical potential evoked during balance reaction localized to SMA as opposed to cingulate (ERN).

  • Marlin et al. (2013) Localizing evoked cortical activity associated with balance reactions. Does the anterior cingulate play a role? (Submitted)
Cortical activity linked to reactive control when standing still

- Frontocentral negativity time-locked to instability is evident even in stationary stance (self-generated instability)
- Amplitude scaled to amplitude of reactions

Concluding points

- Multiple aspects of natural walking are linked to cortical function and can account for link between cognition and mobility
- Reactive balance control is dependent on cortical activity and is associated with cognitive function
- Reactive balance ‘reserve’ is likely a critical determinant of the age-related changes in the association between mobility and cognition
- Age-related changes in ‘reactive-balance reserve’ and ‘cognitive-reverse’ are likely associated (and certainly increase risk of instability and falls)
Future directions

• Reveal the CNS networks participating in the control of the human walking (e.g., locomotor, balance, navigation)
• Map the CNS networks for shared involvement between balance/mobility and cognition
• Evaluate training of reactive control and cognitive function to counter age-related change in mobility
• Increased attention to the temporal characteristics of CNS processing to both assess and counter age-related changes in mobility and cognition
• Need to address age-related changes ANS reactivity/activity as a potential modulator of cortical processing for mobility

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Gerontologists make connections and study connections in many aging-related areas. We assess unstable molecular bonds in cells and study enduring human ones in families. We test for relationships among variables and examine them among retirement community residents. Our research generates alliances that improve community services and policies for older adults and their families.

The 2014 conference theme challenges researchers to present their best evidence on aging-related connections they investigate. The call for abstracts will be available mid-December, start planning now.