Aging, the Central Nervous System, and Mobility in Older Adults: Prevention and Intervention

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Washington Marriott Marquis Archives Room
Washington, DC

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

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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.
Program Committee Roster

**Linda Krogh Harootyan**  
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Senior Director, Professional Affairs  
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Chief, Longitudinal Studies Section  
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Associate Professor  
Johns Hopkins Bloomberg School of Public Health  
Associate Director  
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Murray D. Gross Memorial Faculty Scholar in Gerontology
Director, Division of Cognitive and Motor Aging
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Caterina Rosano, MD, MPH
Co-Principal Investigator and Workshop Co-Chair
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 master's degree in 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.

Stephanie Studenski, MD, MPH
Co-Principal Investigator and Workshop Co-Chair
Stephanie Studenski recently joined the National Institute on Aging as Director of the Longitudinal Studies Section and the Baltimore Longitudinal Study on Aging. Trained as a nurse and a physician, she is board certified in internal medicine, rheumatology, and geriatrics, based on training at Duke University in North Carolina. She also completed a master’s degree in public health at the University of North Carolina. Throughout her career, Dr. Studenski has practiced geriatric medicine and taught young health professionals. With over 30 years of experience in aging research, her work is focused on longitudinal studies and clinical trials involving community-dwelling older persons. As principal investigator of multiple research programs funded by National Institute on Aging, she works with multidisciplinary teams to examine aspects of mobility across the lifespan, with a special focus on the neural control of movement.

Michelle Carlson, PhD
Workshop Program Co-Chair
Michelle Carlson is Associate Professor at the Johns Hopkins Bloomberg School of Public Health. She leads observational and randomized controlled trial research to evaluate both environmental and pharmacologic preventive interventions of cognitive and functional declines and dementia risk. Dr. Carlson serves as the Johns Hopkins site primary investigator of the national Cardiovascular Health Study. She has 10 years of experience in leading large-scale clinical trials, having served as the primary investigator of the Johns Hopkins site of the Ginkgo Evaluation of Memory randomized controlled trial and as leader of two projects on the Baltimore Experience Corps Trial to evaluate the impact of high-intensity service on older adults’ cognitive, brain, and functional health. Dr. Carlson and her team are evaluating the mechanisms through which Experience Corps impacts older adults’ activity and health using neuroimaging, biomarkers, and objective step activity. To more precisely measure function in daily life, Dr. Carlson is using wearable devices to objectively
Richard Camicioli, MD
Richard Camicioli is Professor of Medicine (Neurology) at the University of Alberta and a geriatric neurologist. He trained in medicine and neurology at McGill University and completed training in geriatric neurology at the Portland VA Medical Center. Dr. Camicioli directs the Geriatric and Cognitive Neurology Clinic at the University of Alberta and is Interim Director of the Movement Disorders Program. His focus of his research is the interface between aging and neurological disorders and impairments. His work has examined the relationship between mobility and age-related cognitive decline and dementia and conversely the impact of Parkinson’s disease and vascular disease on cognitive risk. He has collaborated with Roger Dixon applying procedures pioneered in the Victoria Longitudinal Aging study to examine reaction time variability as a biomarker for cognitive decline in Parkinson’s disease. He also has developed dual cognitive-motor tasks as a probe of cognitive motor interaction and predictor of risk in aging, mild cognitive impairment, and in Parkinson’s disease. His imaging studies using magnetic resonance methods have shown that brain structural changes (atrophy and diffusion tensor imaging change) as well as metabolic changes (spectroscopy) are part of the Lewy body spectrum extending to Parkinson’s disease.

Olivier Beauchet, MD, PhD
Olivier Beauchet is Chair of the Division of Geriatric Medicine, Department of Neuroscience, and Director of the Memory Clinic of Angers University Hospital and the Center for Research on Autonomy and Longevity (CeRAL). He completed his medical degree in neurology and geriatrics (1995–2000) at Saint-Etienne University, France. He worked at the Geneva University Hospital, Switzerland, until 2005. During this period, he participated in the creation of the European GAITRite Network and drafted the European recommendations for proper use and harmonization of gait analysis. In 2005, he obtained his doctorate in human motor function and disability with his pioneering work on gait variability and dual-task paradigm in older adults. He was appointed Associate Professor of Medicine and Biology of Aging in 2005 and Professor in 2008 at Angers University, France. His research focuses on gait, balance, and cognitive disorders in older adults, specifically in the interaction between mobility and cognition under the dual-task paradigm. The main clinical implications are that cortical-related changes in gait could be used to improve the early diagnosis of dementia and become an integral part of a new rehabilitation approach. He is also interested in the effects of vitamin D on cognition and gait in older adults. With more than 220 peer reviewed publications in high-impact journals, Dr. Beauchet is both a leading researcher in the field of gait disorders and dementia in the elderly and a clinical scientist who has learned to efficiently combine clinical practice and well-reasoned research.

Manuel Montero-Odasso, MD
Manuel Montero-Odasso is Associate Professor of Medicine, Epidemiology, and Biostatistics at the University of Western Ontario, Canada, and Director of the Gait and Brain Lab at Parkwood Hospital in London, Ontario. Dr. Montero-Odessa received his medical and doctoral degrees from the University of Buenos Aires in Argentina and completed a postdoctoral fellowship at McGill University in Canada. He is an internist, geriatrician, and a clinician scientist who is aiming to understand the mechanisms and potential treatment of age-related mobility and cognitive decline. He focuses on gait performance research as methodology to early detect mobility and cognitive decline and future prevent the development of frailty, falls, and dementia. He leads the Gait and Brain Study, a longitudinal study aimed to assess the role of gait disturbances in the absence of overt disease as early predictor of dementia and mobility decline. He is also conducting clinical trials using cognitive enhancers and physical and cognitive exercises to improve mobility. He leads of the Mobility, Exercise, and Cognition Team, as part of the Canadian Consortium in Neurodegeneration and Aging, which is delivering standardized terminology and protocols to integrate cognitive and mobility assessments and treatments across Canada. Dr. Montero-Odasso has established a successful research program on Gait and Brain Health while remaining an active clinician. His research has received peer-reviewed funding, and he has published in high-impact journals, established collaborations with expert colleagues worldwide, and received several research accolades including the American Geriatrics Society New Investigator Award (2009), the Schulich Clinician Scientist Award (2008–2011), and the New Investigator Award.
from the Canadian Institute of Health and Research (2012–2017). He serves as editorial board member of aging journals including The Journal of Gerontology: Medical Sciences, Geriatrics, and Journal of Alzheimer’s Disease. He has been invited to give more than 40 international presentations.

**Emily A. Keshner, PT, EdD**
Emily Keshner is Professor and Chair of the Department of Physical Therapy and Director of Research Strategy in the College of Health Professions and Social Work and Professor of Electrical Engineering and Computer Science at Temple University. She is Director of the Virtual Environment and Postural Orientation Laboratory at Temple University, which was developed for both experimental and clinical testing of postural reactions within a simulated dynamic visual environment. She received her doctorate in movement science at Columbia University followed by a postdoctoral fellowships with Dr. Marjorie Woollacott at the University of Oregon, Dr. John Allum at Kantonsspital Basel, Switzerland, and Dr. Barry Peterson at Northwestern University. Her research focuses on identifying and facilitating sensory selection during multimodal disturbances of posture in older individuals and in patients with neurologic disorders. Dr. Keshner has been the recipient of numerous awards from the National Institutes of Health and is an associate editor of the Journal of NeuroEngineering and Rehabilitation. She is past-president of both the International Society for Virtual Rehabilitation and the International Society for Posture and Gait Research.

**Steven C. Cramer, MD**
Steve Cramer is Professor of Neurology, Anatomy & Neurobiology, and Physical Medicine & Rehabilitation at the University of California, Irvine. Dr. Cramer is also Vice Chair for Research in Neurology, Clinical Director of the Stem Cell Research Center, and Associate Director of the University of California, Irvine, Institute for Clinical & Translational Science. He graduated from the University of California, Berkeley; received his medical degree from the University of Southern California; did a residency in internal medicine at the University of California, Los Angeles, and a residency in neurology and a fellowship in cerebrovascular disease at Massachusetts General Hospital. He also earned a master’s degree in clinical investigation from Harvard Medical School. His research focuses on brain repair after central nervous system injury in humans, with an emphasis on stroke and recovery of movement. Treatments under examination include robotic, stem cell, brain stimulation, pharmacologic, and telehealth methods. A major emphasis is on translating new drugs and devices to reduce disability after stroke, and individualizing therapy for each person’s needs. Dr. Cramer co-edited the book Brain Repair After Stroke, is an assistant editor at the journal Stroke, and is the author of over 200 articles and chapters.

**Jessie VanSwearingen, PhD, PT**
Jessie VanSwearingen is Associate Professor in the Department of Physical Therapy at the University of Pittsburgh. She completed a bachelor of science degree in physical therapy at the University of Delaware, a master of science degree in physical therapy at The Ohio State University, and a doctoral degree in neurobiology, anatomy, and cell science at the University of Pittsburgh School of Medicine. Her research and clinical interests are the neural science of movement control, and motor skill–based interventions and outcomes for improving walking and activity and participation in older adults with mobility limitations.

**Brad Manor, PhD**
Brad Manor is Director of the Mobility and Brain Function Program at the Institute for Aging Research and an Instructor in Medicine at the Beth Israel Deaconess Medical Center and Harvard Medical School. His career goal is to alleviate the burden of balance decline that often accompanies biological aging into senescence. He directs an interdisciplinary, translational research program in the fields of human balance and rehabilitative medicine. This program combines biomechanical instrumentation with advanced medical imaging, brain stimulation, and signal processing techniques to: (1) study the complex control systems underlying human balance during standing and walking, and how these systems adapt to impairments associated with biological aging and/or disease; and (2) design rehabilitative interventions that improve balance via optimization of control systems and the exploitation of their adaptive properties.
David Knopman, MD
David Knopman is Professor of Neurology, Mayo Clinic College of Medicine, a consultant in neurology at the Mayo Clinic, and a co-investigator in the Mayo Alzheimer’s Disease Research Center. His research and clinical interests have been in dementing illnesses. He is a 1972 graduate of Dartmouth College and a 1973 graduate of Dartmouth Medical School, and he received his medical degree in 1975 from the University of Minnesota Medical School. Dr. Knopman did his internship at Hennepin County Medical Center, Minneapolis, a neurology residency at the University of Minnesota, and a fellowship in behavioral neurology at Hennepin County Medical Center and the University of Minnesota. He was a faculty member at the University of Minnesota from 1980 to 2000. Dr. Knopman joined the Department of Neurology at the Mayo Clinic in Rochester, Minnesota, in 2000. He is an author on over 350 articles on various topics in dementia including aspects of vascular dementia, frontotemporal dementia, and Alzheimer’s disease. He is Deputy Editor of Neurology. He was the senior author on the 2001 American Academy of Neurology Practice Parameter on the Diagnosis of Dementia and was co-chair of the National Institute on Aging–Alzheimer’s Association committee that drafted the revised criteria for Alzheimer’s disease dementia. In 2012, he became a member of the Medical and Scientific Advisory Council of the Alzheimer’s Association.

Frank R. Lin, MD, PhD
Frank Lin is Associate Professor of Otolaryngology, Geriatric Medicine, Mental Health, and Epidemiology at the Johns Hopkins University School of Medicine and the Bloomberg School of Public Health. He completed his medical education, residency in otolaryngology, and doctorate in clinical investigation at Johns Hopkins and completed further otologic fellowship training in Lucerne, Switzerland. Dr. Lin’s clinical practice is dedicated to otology and the medical and surgical management of hearing loss. His epidemiologic research focuses on how hearing loss impacts the health and functioning of older adults and the role of hearing rehabilitative strategies in potentially mitigating these effects. In particular, his research group has demonstrated that hearing loss in older adults is strongly and independently associated with the risk of cognitive decline, incident dementia, impairments in physical functioning and mobility, and greater health care resource utilization in multiple epidemiologic studies. Dr. Lin collaborates extensively with researchers across multiple fields including gerontology, cognitive neuroscience, audiology, and epidemiology, and he has collaborative working relationships with individuals in industry, government, and non-profit advocacy organizations. In January 2014, he co-chaired for the Institute of Medicine and the National Research Council a 2-day workshop on hearing loss and healthy aging in Washington, DC.

Pradeep Yammanuru Ramulu, MD, PhD
Pradeep Ramulu is Associate Professor of Ophthalmology at Johns Hopkins University School of Medicine. He is interested in functional outcomes in older individuals who have vision loss, with a long-term goal of rehabilitating the disability associated with vision loss. Part of his time is spent as a clinician and surgeon, where he interacts with patients and gets direct insights into how they are affected by their disease. His research is focused on developing a detailed understanding of how vision loss disables older individuals, particularly with regard to reading and mobility. In the domain of mobility, Dr. Ramulu has brought in techniques used outside ophthalmology to characterize the real-world mobility patterns of individuals with age-related macular degeneration (AMD) and glaucoma. He worked with Drs. Luigi Ferrucci and Chris Durso as part of his Dennis W. Jahnigen Award project, in which he used accelerometers to demonstrate that physical activity levels are lower in patients with decreased central vision from AMD and decreased peripheral vision from glaucoma. He also has validated and used tracking technology to demonstrate that AMD and glaucoma patients travel outside the home less. Dr. Ramulu’s other work has demonstrated that individuals with both AMD and glaucoma are more likely to restrict/stop driving and have significantly greater fear of falling. Dr. Ramulu’s current work focuses primarily on understanding the reasons for falls and mobility restriction among individuals with irreversible vision loss. His goals are to create customized programs to prevent falls and improve mobility in visually impaired individuals, and to understand how these programs need to be tailored to older adults with different patterns of vision loss.
**Lewis A. Lipsitz, MD**

Lewis Lipsitz is Director of the Institute for Aging Research at Hebrew SeniorLife, Chief of the Division of Gerontology at Beth Israel Deaconess Medical Center, and Professor of Medicine at Harvard Medical School. 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. His research is focused on age-related alterations in blood pressure and cerebral blood flow regulation and their relation to falls, syncope, and cognitive dysfunction. Dr. Lipsitz has served as principal investigator of a National Institute on Aging (NIA)-funded Program Project Grant for 26 years, an Older American Independence Center Grant for 15 years, and a Hartford Foundation Center of Excellence in Geriatric Medicine for 15 years. In these roles, he has assembled multidisciplinary teams from multiple academic institutions and laboratories to study the mechanisms and management of several important clinical geriatric syndromes, including falls, syncope, dementia, delirium, and frailty. He is currently principal investigator of an NIA Merit Award to study the physiologic mechanisms of frailty in old age and an R01 from the NIA to study cerebrovascular mechanisms of falls. His recent translational research includes demonstrations that Tai Chi exercise can improve physical function and balance control in frail elderly people, vibrating insoles based on the principal of stochastic resonance can improve gait and balance in older people, and the treatment of hypertension with ACE inhibitors can improve cerebral blood flow and executive function.

**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.

**Joe Verghese, MB, BS**

Joe Verghese is Professor of Neurology and Medicine, Murray D. Gross Memorial Faculty Scholar in Gerontology, and Director of the Resnick Gerontology Center at Albert Einstein College of Medicine in Bronx, New York. He is Chief of the Integrated Divisions of Cognitive and Motor Aging (Neurology) and Geriatrics (Medicine). He graduated from St. Johns Medical College, Bangalore, India, in 1989. Dr. Verghese did his postgraduate training in internal medicine and neurology in the United Kingdom, and he completed his neurology residency and fellowship training in neurophysiology as well as aging and dementia at the Albert Einstein College of Medicine. He also received a master of science degree in clinical research methods. He is board certified in neurology. Dr. Verghese is a recipient of the Beeson Award from the National Institute on Aging and the Outstanding Scientific Achievement for Clinical Investigation Award from the American Geriatrics Society. His research interest is the effects of disease and aging on mobility and cognition in older adults. He has more than 100 peer-reviewed publications and several federally funded grants in this area. His current projects include studying the influence of cognitively stimulating activities on reducing risk of dementia, the role of divided attention tasks such as walking while talking in predicting outcomes such as disability and cognitive decline, cognitive interventions, and global health.
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 received the Excellence in Rehabilitation of Aging Persons Award.

Teresa Liu-Ambrose, PhD, PT

Teresa Liu-Ambrose is Associate Professor, Canada Research Chair, and a physical therapist at the University of British Columbia Department of Physical Therapy. She directs the Aging, Mobility, and Cognitive Neuroscience Laboratory and the Vancouver General Hospital Falls Prevention Clinic. Her research program focuses on defining the role of exercise to promote healthy aging, with a particular focus on cognitive and neural plasticity, as well as mobility. She received her doctorate from the University of British Columbia in 2004. She completed a 2-year postdoctoral fellowship in cognitive science funded by both the Canadian Institutes of Health Research (CIHR) and the Michael Smith Foundation for Health Research (MSFHR) and joined the University of British Columbia Department of Physical Therapy in 2006. Dr. Liu-Ambrose is a recipient of the Royal Society of Canada’s Alice Wilson Award (2006), CIHR Institute of Aging Recognition Prize in Research in Aging (2005 and 2011), MSFHR Career Investigator Award (2006), and CIHR New Investigator Award (2011).

Farzaneh Sorond, MD, PhD

Farzaneh 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.
Travel Awardees

Nicole Armstrong, MPH: Derivation of a High-Quality Summary Factor of Physical Functioning Scaled to NIH PROMIS Norms
Nicole Armstrong is a second-year predoctoral fellow in the Epidemiology of Aging track at Johns Hopkins Bloomberg School of Public Health. She earned a master’s degree in public health from Columbia University Mailman School of Public Health in 2013. Her research interests lie in cognitive aging and physical functioning.

Duane Benjamin Corbett, PhD: Association Between Perceptual Effort During Mobility and Executive Function in Older Adults
Duane Corbett is a postdoctoral fellow at the University of Florida Institute on Aging in the Department of Aging and Geriatric Research. He is currently working on several large NIH-funded clinical trials, including the Lifestyle Interventions and Independence for Elders (LIFE) Study. Previously, Dr. Corbett was a research assistant at Kent State University, where he managed several research projects related to mobility and aging. He has given research presentations at the national level and has had several papers published, some of which were focused on improving cognition and mobility in individuals with Parkinson’s disease.

Gurtej Singh Grewal, PhD: Exergaming in Diabetics With Peripheral Neuropathy: A Randomized Controlled Trial
Gurtej Grewal has been a postdoctoral fellow for 4 years in the field of bioengineering, working on clinical trials and development of innovative exercise training regimens using body-worn sensors. His experience also includes virtual reality for neuro-rehabilitation of older adults. Over the years, Dr. Grewal has been translating his engineering knowledge to real-world scenarios for accurately measuring postural balance and gait. He has authored 15 journal articles, has been listed as a key investigator in four grant projects, and has contributed significantly in more than 10 nationally and internationally funded research projects.
Kristin A. Lowry, PhD: Motor Imagery Ability in Persons With Parkinson’s Disease: Does Physical and Cognitive Status Matter?

Kristin Lowry is Assistant Professor at Des Moines University, where she teaches neuro-rehabilitation content to physical therapy students and maintains an active motor control research laboratory. Her ongoing studies are: (1) A task-oriented motor learning intervention for improving walking skills in persons with Parkinson’s disease (PD): A consideration of concept study; and (2) The use of motor imagery for gait rehabilitation in older adults and persons with PD. The aims of the first project are to determine the feasibility of implementing the task-oriented motor learning intervention in persons with PD and to determine mobility outcomes following completion of the program. The motor imagery pilot project examines whether focused use of motor imagery of walking impacts walking ability and freezing of gait, and examines the associations among executive function, physical function, and imagery ability in both older adults and individuals with PD. Dr. Lowry’s work includes examining gait control in older adults and persons with PD, and is closely aligned with her primary research objectives to improve measurement and assessment of walking skill and to develop/examine interventions that optimize walking skill in older adults and persons with PD. As a postdoctoral fellow (NIH T32 training grant under the mentorship of Dr. Stephanie Studenski), she assisted with two Pittsburgh Pepper Center funded pilot studies, one examining gait variability, smoothness, and stability in older adults and persons with PD, and the other examining the effects of two exercise interventions on gait and cognition in older adults. Her experience includes acceleration-based gait analysis and she has published articles examining the smoothness of walking.

Martina Mancini, PhD: Continuous Monitoring of Turning Mobility Is Related to Fall Risk and Cognitive Function

Martina Mancini is Senior Research Associate in the Department of Neurology at Oregon Health and Science University (OHSU). She received her doctoral degree in bioengineering at the Alma Mater Studiorum University of Bologna in Italy and completed a postdoctoral fellowship in the Department of Neurology at OHSU. Her translational biomedical research focuses on objectively characterizing, understanding, and monitoring mobility impairments in patients with neurological disorders with wearable sensors in order to develop tailored rehabilitation interventions, such as biofeedback-based solutions. She has presented at national and international meetings on topics related to gait and balance impairments in persons with Parkinson’s disease and parkinsonisms. Her efforts involve active collaborations with researchers at the Department of Electrical, Electronic, and Information Engineering (“Guglielmo Marconi”) at the University of Bologna, the Neurology Department of Sant’Anna Hospital in Ferrara, Italy, the University of Michigan, and OHSU. She recently received an NIH K99-R00 award from the National Center for Medical Rehabilitation Research to characterize the physiology of gait disturbances during locomotion with body-worn sensors and to determine whether vibrotactile biofeedback improves such gait disturbances in Parkinson’s disease in a laboratory and home environments.

Neelesh K. Nadkarni, MD, PhD, FRCPC: The Relationship Between Inflammatory Burden, Mobility, and Cognition Is Influenced by White Matter Characteristics in Older Adults: Secondary Analysis of the Health, Aging, and Body Composition (Health ABC) Study.

Neelesh Nadkarni is Assistant Professor of Medicine in the Division of Geriatric Medicine at the University of Pittsburgh Medical Center. His early career goal is to become an independent investigator studying the interrelationship between age-associated changes in the brain, cognition, and mobility in older adults; his long-term goal is to develop novel multidisciplinary and multipronged interventions that target mobility impairment and delay functional decline. Dr. Nadkarni’s clinical training is in internal medicine, geriatric medicine, and geriatric and behavioral neurology, including clinical issues in the assessment and management of cognitive and mobility impairments in older adults. Dr. Nadkarni’s research training also includes a doctorate in medical sciences and neurosciences focused on addressing the interaction between mobility, cognition, and small-vessel disease in older adults with and without Alzheimer’s disease. He has studied which type of gait interventions for older adults with mobility impairments could be more beneficial in face of small-vessel disease in the brain. This work has borne two articles, one published in the Journal of the American Geriatrics Society and the other accepted in the Archives of Physical Medicine and Rehabilitation. Dr. Nadkarni is studying the relationship between mobility and changes in the aging brain such as amyloid deposition, neurodegeneration, and inflammation. His goals are to better understand the heterogeneity in brain plasticity in aging, hypothesize which mobility interventions may be more suited than others based on underlying brain characteristics, and contribute to a dialogue on personalized approach to gait rehabilitation.
Andrea Rosso, PhD, MPH: Small Vessel Disease of the Brain and Peripheral/Sensory Impairments Have Similar Contributions to Poor Mobility

Andrea Rosso is Assistant Professor in Epidemiology and Clinical and Translational Sciences at the University of Pittsburgh. Her research interests largely focus on prevention of disability in older adults, with a primary focus on mobility disability and community mobility. Her previous research has focused on two areas: (1) mobility, disability, and physical function in relation to geriatric syndromes, cardiovascular disease, social engagement, and neighborhood characteristics; and (2) laboratory and clinical neurology, with a primary focus in dementias and pain. Dr. Rosso’s current research is focused on the aging brain and mobility. She is particularly interested in how multisystem problems can impact functioning and, specifically, the neurologic contributions to these problems. Her interests also include the contributors to resilience to physical impairments, both physiologic and environmental, in the prevention of functional declines and disability.

Michael Schwenk, PhD: Effectiveness of Exergaming for Improving Balance in People With Mild Cognitive Impairment: A Randomized Controlled Trial

Michael Schwenk is a postdoctoral research associate at the interdisciplinary Consortium on Advanced Motion Performance at the University of Arizona. With a doctoral degree in exercise science and postdoctoral training in biomedical engineering, he has more than 6 years of experience in developing exercise regimens for training and assessment of motor-cognitive performances in geriatric patients. His area of focus is the development of dementia-specific exercise programs.

Renae Smith-Ray, PhD: Improvements in Gait and Balance Following Cognitive Training Are Moderated by Age: Differential Impact for Old-Old and Young-Old Adults

Renae Smith-Ray is a research scientist at the Institute for Health Research and Policy’s Center for Research on Health and Aging at the University of Illinois Chicago. Her areas of focus are gerontological public health, cognition, health promotion interventions for older adults, and dissemination and implementation of health promotion programs. She has worked on health behavior change research interventions targeting physical activity and cognitive health and most recently has focused her efforts on fall prevention interventions for older adults. Dr. Smith-Ray has been principal investigator on two pilot randomized trials testing the viability of a computer-based cognitive training intervention to improve balance and reduce falls among older adults. She also is a member of the research team that developed and tested Fit and Strong!, an evidence-based physical activity/behavior change program for older adults. During her doctoral training, she received an individual dissertation award from the Agency for Healthcare Research and Quality (AHRQ R36). She has been the recipient of numerous awards including the University of Illinois Dean’s Scholar Award and was named the Paul D. Doolen Scholar for the Study of Aging. Dr. Smith-Ray is currently funded by a 1-year career development award (KL2) to examine the link between the central nervous system and balance in older adults.

Vijay R. Varma, MPH: The Effect of Experience Corps on Lifestyle Physical Activity

Vijay Varma is a doctoral student at the Johns Hopkins Krieger School of Arts and Sciences. He earned an MPH from the Johns Hopkins Bloomberg School of Public Health in 2010. His research focuses on public health approaches to preventing or slowing cognitive decline and Alzheimer’s disease in disadvantaged older adults at elevated risk for cognitive and functional decline due to sociodemographic factors. He is particularly interested in exploring the relationship between physical activity and cognitive decline using novel devices to measure physical activity; including accelerometers, GPS units, and smartphones; his interests also include imaging biomarkers of cognition. His research vision is to elucidate the factors that drive cognitive health disparities in population-dense urban areas and work toward interventions that may positively impact cognitive and physical function outcomes in later life.
Semi-Finalists

**David M Gundermann, PhD: Community Mobility and Working Memory in Non-Demented Elders**
Postdoctoral Research Associate
Department of Aging and Geriatric Research
University of Florida College of Medicine

**Katie Marie Kietzmann, BA: Kinship Caregivers: Predicting the Likelihood of Adopting the Child/ren in Their Care**
Graduate Assistant
Syracuse University

**Heather Leutwyler, RN, PhD, FNP-BC, CNS: Older Adults With Schizophrenia Have Poor Mobility and Are in Need of Interventions to Improve Their Mobility**
Assistant Professor
Department of Physiological Nursing
University of California, San Francisco

**Erin Olson, PhD: Association Between Inattention, Impulsivity, and Physical Function in Older Adults With Type 2 Diabetes**
Postdoctoral Research Fellow—T32 Translational Research in Aging
Harvard Medical School
Hebrew Senior Life
Beth Israel Deaconess Medical Center

**Javad Razjouyan, PhD: An Objective Method for Fall Risk Assessment in Hospitalized Older Adults Using Wearable Technology**
Postdoctoral Research Fellow
Interdisciplinary Consortium for Advanced Motion Performance
Southern Arizona Limb Salvage Alliance
Associate Member, Arizona Center on Aging
University of Arizona College of Medicine

**Rachel E. Ward, PhD, MPH: Neuromuscular Impairments Among Primary Care Patients With and Without Mild Cognitive Impairment**
Postdoctoral Fellow
Spaulding Hospital Cambridge

**Melissa Y. Wei, MD, MPH: Multimorbidity and Mortality in Two Prospective Cohorts of Older Adults: Simple Counts, Charlson, and a Novel Quality of Life-Weighted Index**
Fellow
Division of General Medicine and Primary Care
Beth Israel Deaconess Medical Center
Department of Epidemiology
Harvard School of Public Health
This workshop—Aging, the Central Nervous System, and Mobility in Older Adults: Prevention and Intervention—builds on evidence from the first two workshops demonstrating that physical activity and dietary factors modify multiple risk factors associated with mobility disability, including obesity, cardiovascular disease, metabolic dysregulation, and sedentary lifestyle. We will critically evaluate intervention designs that target these modifiable risk factors using methods to more precisely measure the mechanistic pathways of potential benefit, identified in Workshop 2 (e.g., increasing cerebral blood flow, anti-inflammatory response). We will further consider how variations in intervention exposure periods and dose inform understanding of potential benefits in both central nervous system (CNS) and peripheral mobility function. Finally, interventions will be examined for primary and tertiary efficacy and effectiveness in community-based and clinically at-risk samples.

We will review the strengths and limitations of various intervention designs and approaches to address gaps in understanding of the three following factors: (1) Evaluation: To review evidence and proof of concept for methods that evaluate the efficacy and effectiveness of interventions using integrated approaches to measure changes in CNS and peripheral mobility; (2) Exposure: To better understand the minimum exposure periods and doses needed to elicit beneficial changes, or plasticity, in the CNS and mobility function, and whether such benefits are maintained post-exposure; (3) Translation: To understand the motivational messages that lead to the effective design and dissemination of large-scale interventions that target community-dwelling older adults and promote sustainability.

**Workshop Principal Investigators**

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Harvard Medical School
Boston, Massachusetts

As of October 28, 2014

Program Committee Member
TUESDAY, NOVEMBER 4, 2014

8:00 AM–8:30 AM Breakfast

8:30 AM–8:40 AM Opening Remarks
Stephanie Studenski, MD, MPH†
Co-Principal Investigator and Workshop Co-Chair

8:40 AM–8:50 AM Overview of the Workshop
Caterina Rosano, MD, MPH†
Co-Principal Investigator and Workshop Co-Chair
Michelle Carlson, PhD†
Workshop Program Co-Chair

8:50 AM–10:00 AM Session 1: Pharmacology and Diet
Moderator and Table Monitor
Richard Camicioli, MD†
University of Alberta, Canada

Changes in Gait Performance Related to Anti-dementia Drugs: Which Drug for Which Walking Condition? A Meta-analysis
Olivier Beauchet, MD, PhD
Center for Research on Autonomy and Longevity
Angers University Hospital, France

Improving Cognition to Improve Mobility: The Role of Donepezil on Gait in Older Adults
Manuel Montero-Odasso, MD, PhD, AGSF, FRCPC
Gait and Brain Lab, Parkwood Hospital
The University of Western Ontario
Lawson Research Institute

Discussion
Moderator and Table Monitor
Richard Camicioli, MD†
University of Alberta, Canada

10:00 AM–11:30 AM Session 2: Exercise and Electrical Stimulation
Moderator and Table Monitor
Emily A. Keshner, PT, EdD
Temple University

Neuroplasticity and Gait in Stroke Recovery
Steven C. Cramer, MD
University of California, Irvine
Motor Skill Training: Coaching the Brain in Walking
Jessie VanSwearingen, PhD, PT
University of Pittsburgh

Noninvasive Brain Stimulation: A New Tool for Understanding and Enhancing the Cortical Control of Mobility
Brad Manor, PhD
Harvard Medical School

Discussion
Moderator and Table Monitor
Emily A. Keshner, PT, EdD
Temple University

11:30 AM–1:00 PM  Roundtable Focused Small Group Discussion of Sessions 1 and 2 and Networking Lunch
1:00 PM–1:30 PM  Roundtable Reports to the Group

1:30 PM–3:00 PM  Session 3: Sensory Stimulation/Deprivation
Moderator and Table Monitor
David S. Knopman, MD
Mayo Clinic

Planning a Randomized Controlled Trial to Determine if Hearing Loss Treatment Reduces the Risk of Cognitive Decline in Older Adults
Frank R. Lin, MD, PhD
Johns Hopkins University

Mobility Deficits and Visual Impairment: What Should Our Interventions Address?
Pradeep Yammanuru Ramulu, MD, PhD
Johns Hopkins Medicine

Noise-enhanced Somatosensation, Gait, and Balance in Elderly People
Lewis A. Lipsitz, MD
Harvard Medical School

Discussion
Moderator and Table Monitor
David S. Knopman, MD
Mayo Clinic

3:00 PM  Partnership with the National Institute on Aging: The Future of Central Nervous System Aging and Mobility Research
Wen G. Chen, PhD
National Institute on Aging

3:30 PM  Closing Remarks and Introduction of CNS Junior Investigator Travel Awardees
Michelle Carlson, PhD
Johns Hopkins Bloomberg School of Public Health

As of October 28, 2014
† Program Committee Member
WEDNESDAY, NOVEMBER 5, 2014

7:00 AM–7:30 AM  Breakfast

7:30 AM–8:00 AM  Introduction and Plan for the Day
Stephanie Studenski, MD, MPH† and Michelle Carlson, PhD†
Workshop Program Co-Chairs

8:00 AM–10:00 AM  Session 4: Multi-Modal Activity
Moderator and Table Monitor
Joe Verghese, MB, BS†
Albert Einstein College of Medicine

Virtual Reality Treadmill Training: Effects on Gait, Cognition, and Brain Function
Jeffrey M. Hausdorff, PhD†
Tel Aviv Sourasky Medical Center

Experience Corps on Activity, Brain, and Mobility
Michelle Carlson, PhD†
Johns Hopkins Bloomberg School of Public Health

Cognitive and Neural Correlates of Improved Mobility With Targeted Exercise Training
Teresa Liu-Ambrose, PhD, PT
University of British Columbia

Other Emerging Multimodality Interventions for Brain and Mobility
Stephanie Studenski, MD, MPH†
National Institute on Aging
University of Pittsburgh

Discussion
Moderator and Table Monitor
Joe Verghese, MB, BS†
Albert Einstein College of Medicine

10:00 AM–11:00 AM  Roundtable Focused Small Group Discussion of Sessions 3 and 4

11:00 AM–11:15 AM  Break

11:15 AM–12:00 PM  Roundtable Reports to the Groups

12:00 PM–1:00 PM  Summarize Findings from the Workshop and Future Directions
Michelle Carlson, Stephanie Studenski, Caterina Rosano, Farzaneh Sorond

1:00 PM  Closing Remarks and Adjournment
Caterina Rosano, MD, MPH†

As of October 28, 2014
† Program Committee Member
Enjoy The Gerontological Society of America Annual Scientific Meeting
All participants of Aging, the Central Nervous System, and Mobility in Older Adults 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.

THURSDAY, NOVEMBER 6, 2014

10:00 AM–11:30 AM    Aging, the Central Nervous System, and Mobility Preconference Series: Findings and Future Plans

5:30 PM–6:30 PM    Brain Interest Group (BIG)
Co-conveners: Caterina Rosano, MD, MPH, and Veronica Galvan, PhD

Spotlight on the top GSA presentations on CNS
Guest speaker: Joe Verghese, MB, BS

As of October 28, 2014
† Program Committee Member
Changes in Gait Performance Related to Anti-dementia Drugs:
Which drug for which walking condition?
Meta-analysis

Olivier Beauchet, MD, PhD

Department of Neuroscience
Geriatrics Division and Memory Clinic
Angers University Hospital and School of Medicine
Centre for Research on Autonomy and Longevity (CeRAL) and Biomathics

DISCLOSURE OF INTERESTS

Potential conflict of interests: No
Relations that could be relevant for the talk: No
Payment or other remuneration: No
Shareholder: No
Other relation: No

… Hopefully, my talk will not be without “interest”
OUTLINE

- Objective of talk:
  To determine whether anti-dementia drugs may change significantly gait performance

- Outline:
  1) **Gait control** (what are we talking about here?)
  2) **Facts** on the association between gait performance and dementia (which type of dementia, gait parameters and walking conditions?)
  3) **Results** of two meta-analyses which examined anti-dementia drugs related gait changes
  4) **Take home messages**

GAIT // Which control?

<table>
<thead>
<tr>
<th>PARADOXICAL MOTOR BEHAVIOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple execution</td>
</tr>
<tr>
<td>Complex biomechanics (dynamic balance)</td>
</tr>
<tr>
<td>« Hard » motor behavior:</td>
</tr>
<tr>
<td>Automatic = Propulsion / Balance</td>
</tr>
<tr>
<td>« Flexible » motor behavior:</td>
</tr>
<tr>
<td>Adaptation = Navigation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LEVELS AND TYPES OF CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORTICAL LEVEL:</td>
</tr>
<tr>
<td>Initiation and adaptation of gait</td>
</tr>
<tr>
<td>At steady walking, without stimulation and straight (gait propulsion condition): involvement of cortical level in gait control</td>
</tr>
</tbody>
</table>

| SUBCORTICAL LEVEL:         |
| Modulation of automatic movements |

| SPINAL LEVEL:              |
| Gait patterns generation of automatic, regular and rhythmic movements |

- SLR: Subthalamic locomotor region
- MLR: Mesencephalic locomotor region
- CLR: Cerebellar locomotor region
- PMRF: Pontine and medullary reticular formations
- CPG: Central pattern generators
Main clinical hallmark of dementia: cognitive decline

Motor disorders:
- Not prominent but commonly described in later stages (bradykinesia, extrapyramidal rigidity, resting tremor and gait disorders)
- Related to basal ganglia, cerebellum and primary motor areas lesions (neurodegenerative ± ischemia)
- Also describe in early stages
- Related to central (cortical & subcortical) misprocessing of information underscoring the close relationship between gait and cognitive functioning

Gait:
- Not an action performed “in vacuo”
- Involvement of executive functions (attention, planning, updating – PFC as well as memory [hippocampus])

GAIT DISORDERS & DEMENTIA // Facts

- Prevalence of gait disorders:
  - 90%: PDD
  - 80%: VaD
  - 75%: DLB
  - 75%: DLB
  - 7%: Control

GAIT DISORDERS & DEMENTIA // Which dementia?

Prevalence and Severity of Gait Disorders in Alzheimer's and Non-Alzheimer's Dementias

OBJECTIVES: To compare the prevalence, severity, and type of gait and balance disorders in Alzheimer's disease (AD), vascular dementia (VaD), Parkinson’s disease with dementia (PDD), dementia with Lewy bodies (DLB), Parkinson’s disease without dementia (PD), and age-matched controls.

DESIGN: Cross-sectional.

SETTING: Secondary care clinics in geriatric psychiatry, neurology, and geriatrics.

PARTICIPANTS: Two hundred forty-five participants aged 65 and older (AD, n = 40; VaD, n = 39; PDD, n = 46; DLB, n = 52; PD, n = 46; and controls, n = 42).

MEASUREMENTS: Prevalence and severity of gait and balance disorders were assessed using the Tinetti gait and balance scale. The types of gait disorders in each diagnostic group were classified using the Nutt et al. classification.
- **Slow walking speed:**
  - Unspecific in demented patients
  - Specific in non-demented individuals: presence of cognitive complaints + slow gait (1SD below age- and sex-specific gait speed means) = higher risk of developing dementia (Motoric cognitive risk syndrome)

- **Increased gait variability:**
  - Fluctuations from stride-to-stride with time (magnitude +++)
  - Stride time (i.e., gait cycle duration) = Measure of the reliability of lower limb movements (biomarker of the rhythmic stepping mechanism)
  - Specific of:
    - Involvement of cognitive function in healthy individual (information updating)
    - Gait of patients with mild cognitive impairment and dementia

- **Discrepancy** between time of realized and of imagined

**Timed Up & Go test:**
- Delta time [realized - imagined]
- Performed slower than imagined = cognitive decline

---

**GAIT DISORDERS & DEMENTIA // Which gait parameters?**

- Aim: 1) to determine **which gait parameters** (slower gait speed, higher gait variability and Timed Up & Go test delta time) were most strongly associated with lower performance in two cognitive domains (i.e., episodic memory and executive function)
- Design: cross-sectional
- Population: 934
  - 934 (70.3±4.9 years; 52.1% female)
  - Community-dwellers without dementia + memory decline

The highest magnitude of association was found for higher stride time variability (effect size = -0.74, P<0.001)
Aim: 2) to quantitatively synthesize the association between stride time variability and cognitive decline (i.e., mild cognitive impairment and dementia)

Design: systematic review and meta-analysis

Results:

Higher stride time variability is a motor phenotype of patients with MCI (effect size=0.48) and dementia (effect size=1.06)

Results underscored that:

1) Involvement of cognitive resources (attention+++),
2) Highest gait control level: cortical (too high in older adults with neuropsychiatric disorders)
3) Ability or not to properly allocate cognitive resources
ANTI-DEMENTIA DRUGS & CHANGES IN GAIT // Why?

- Synthesis:
  - Gait disorders: component of all subtypes of dementia, whatever the stage
  - ♦ stride time variability: motor phenotype of cognitive decline (from MCI to dementia)
  - Gait assessment: single & dual (accentuation of disorders) tasking

- Facts:
  - Anti-dementia drugs: Acetylcholinesterase inhibitors (AChEIs) (i.e., donepezil, galantamine and rivastigmine) and NMDA receptor antagonist (i.e., memantine) = symptomatic drugs for the treatment of patients with Alzheimer’s disease and related disorders
  - To temporarily stabilize and/or to delay cognitive and functional declines

- Question: anti-dementia drugs = gait improvement?

- Objective: systematically review and meta-analysis pharmacological-related changes in gait among demented patients with Alzheimer’s disease and related disorders

CHANGES IN GAIT VARIABILITY WITH ANTI-DEMENTIA DRUGS // A systematic review and meta-analysis

- English Medline search conducted in November 2013 using the Medical Subject Heading terms “pharmaceutical preparations” combined with delirium, dementia, amnestic, cognitive disorders, AND gait, gait disorders, neurologic, gait apraxia

- First result = paradoxical situation:
  - ↑ studies exploring gait disorders in demented patients but ↓ studies on drugs-related changes in gait performance... Only 4 studies for systematic review and 3 for meta-analysis!
Qualitative systematic review underscored mixed results:
- 2 studies with significant between-visit improvements in STV (one study with donepezil and another one with memantine)
- 1 study found no significant change
- 1 study with memantine-related significant decrease in STV but no effect of AChEIs

Quantitative analysis demonstrated a non-significant decrease in STV following the use of anti-dementia drugs, whatever comparisons
CHANGES IN GAIT VARIABILITY WITH ANTI-DEMENTIA DRUGS // A systematic review and meta-analysis

- **Inconclusive results** should be considered with caution due to:
  - Methodological issues of selected studies (non-randomized, non-blinded comparative trials)
  - A focus on stride time variability under single task
  - The respective mechanisms of action and efficacy of the different anti-dementia drugs

- To address these issues and due to the recent publication of new studies:
  - **Updated** meta-analysis (from 3 to 5 studies)
  - To examine the effects of anti-dementia drugs on the mean value and the coefficient of variation of stride time among patients with Alzheimer’s disease and related disorders while taking into account:
    - The type of drugs (i.e., AChEIs versus memantine)
    - The walking conditions (i.e., single versus dual-task)

WHICH DRUGS FOR WHICH WALKING CONDITIONS // A systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Walking Conditions</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Total Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>AChEIs</td>
<td>0.89</td>
<td>0.93</td>
<td>0.95</td>
<td>1.2</td>
</tr>
<tr>
<td>Memantine</td>
<td>0.72</td>
<td>0.58</td>
<td>0.81</td>
<td>1.2</td>
</tr>
<tr>
<td>AChEIs with memantine</td>
<td>0.65</td>
<td>0.73</td>
<td>0.82</td>
<td>1.2</td>
</tr>
</tbody>
</table>

- **Comparison of the final stride time parameters** in intervention and in control groups
- **Summary measure of the mean difference**
- **Mean value** of stride time
- **Result**: no significant difference
WHICH DRUGS FOR WHICH WALKING CONDITIONS //
A systematic review and meta-analysis

Table 3. Pooled analysis exploring changes in stride parameters of stride time pooled together (i.e., mean value plus coefficient of variation) under single task and dual task conditions following the use of anti-dementia drugs in intervention group

<table>
<thead>
<tr>
<th>Walking condition / anti-dementia drug</th>
<th>Effect size*</th>
<th>95%CI</th>
<th>Q test</th>
<th>P-value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single task</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AChEIs</td>
<td>0.01</td>
<td>[0.19, 0.22]</td>
<td>0.001</td>
<td>0.80</td>
<td>68</td>
</tr>
<tr>
<td>Memantine</td>
<td>0.67</td>
<td>[0.47, 0.86]</td>
<td>0.79</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dual task</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AChEIs</td>
<td>0.54</td>
<td>[0.20, 0.88]</td>
<td>0.65</td>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>Memantine</td>
<td>0.28</td>
<td>[0.17, 0.74]</td>
<td>0.05</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

- Effect size / stride time parameters pooled
- Before-after in users of anti-dementia drugs
- Results:
  - Memantine-related gait improvement (single task)
  - AChEIs-related gait improvement (dual task)
WHICH DRUGS FOR WHICH WALKING CONDITIONS //
A systematic review and meta-analysis

- **AChEIs cognitive effect**: because higher levels (i.e., the subcortical and cortical levels) of gait control are closely linked to cerebral neural networks integrity and efficiency, supplementing the cholinergic loss with AChEIs may improve cognition and, in consequence, gait too.

- **Memantine motor effect**: memantine may act as an agonist of dopamine D2 receptors with consecutive gait improvement.

TAKE HOME MESSAGES

- **Gait disorders**:
  - Highly prevalent… *Whatever stages* of dementia
  - Cognitive decline-related central impairment
  - Stride time variability = motor phenotype & outcome for the evaluation of anti-dementia drugs on gait performance

- **Paradox**:
  - ↑ studies on type and mechanism of gait disorders
  - ↓ studies on *anti-dementia drugs effects* (3 & 5)
  - ... So, results of meta-analysis should be taken with caution

- **Anti-dementia drugs-related changes in gait**:
  - Improvement
  - Stride time variability and not mean value
  - Specific effect:
    - Memantine: *single-task/* "motor" effect
    - AChEIs: *dual-task/* "cognitive" effect
Improving Cognition to Improve Mobility
The Role of Donepezil on Gait in Older Adults

Manuel Montero-Odasso MD, PhD, AGSF, FRCPC
Professor of Medicine, Epidemiology and Biostatistics
Director, Gait and Brain Lab, Parkwood Hospital
Division of Geriatric Medicine, The University of Western Ontario
Scientist, Lawson Health Research Institute, London ON

Disclosures:
• No financial interest related to this presentation

Objectives:
• To demonstrate that improving cognition can be seen as a complementary treatment to reduce risk of falls

• To review the role of donepezil - an acetylcholinesterase inhibitor- for gait improvement and reducing risk of falls in older adults with cognitive impairment
Bipedalism, Encephalization and Gait

Bipedalism

It was a fundamental evolutionary adaptation

It happened 1 M years before encephalization

Necessary step for encephalization (creation of tools, etc.)

It was key in making humans the predominant species
Bipedalism, Encephalization and Gait

There is a “ontogenetic”
Gait and Cognition decline

Falls in the Cognitively Impaired

- Falls are very common: 1/3 of seniors/year
- Falls are two fold in people with Dementia
- Seniors with Dementia have ↑ risk of Falls injuries & Fractures

Multifactorial fall prevention programs are not successful in the cognitively impaired

Meta-analysis, falls RR Reduction 0.92 (0.82-1.03)

Shaw FE. Prevention of falls in older people with dementia. J Neurol Neurosurg Psychiatry 2007; 78:1239-1244
Falls in the Cognitively Impaired

Age and Aging (1978), 7, Supplement

ARE FALLS A MANIFESTATION OF BRAIN
FAILURE?

B. IsACS

The probability that members of this audience will reach the age of eighty is about one in three. The probability that, having done so, they will suffer a damaging fall is about the same. Self-interest alone therefore dictates an active thrust towards fall prevention. Yet is the ability to prevent falls in old age a realistic research objective for the physician or for the pharmacologist? Can anything practical be done other than the avoidance of external hazards and unsuitable drugs?

In the hope of answering these questions I propose to review briefly some aspects of falls in old people; to put forward a classification of falls based on mechanical principles; to discuss the research implications of this classification; and to speculate on a possible pharmacological approach to fall prevention.

Questions

• Why are falls so common in the cognitively impaired?

• Why does fall prevention not work in this population?

• Are we missing a treatment component?
Gait and Cognition: A Complementary Approach to Understanding Brain Function and the Risk of Falling

1a. Traditional view of parallel decline of gait and cognitive function with aging. Gait performance and cognitive function deteriorate with aging yielding two geriatric entities: falls and dementia.

1b. Alternative, emerging view. Cognition predicts mobility decline and falls, on the one hand; and, on the other hand, mobility decline and slow gait predict cognitive deterioration. These phenomena occur in a concurrent manner.
Key points:

1. Cognitive impairment (MMSE<26) confers high risk of serious injury from a fall. RR= 2.13 (1.56, 2.90)

2. Executive dysfunction was associated with an increased fall risk. OR=1.44 (1.20,1.73)

3. Executive dysfunction can be present despite normality in “global cognition”

4. EF assessment should be part of a falls risk evaluation

**Summary value 2.13 (1.56, 2.90)**

Heterogeneity: $q=0.46$, $df=2$  $p=0.796$; $I^2=0.0%$

**If we improve cognition, can we improve gait & reduce fall risk?**

**Pharmacological treatment**
Pharmacological intervention for dementia: Donepezil, Rivastigmine, Galantamine

- Modest effect on cognition but they delay placement
- Mechanism is assumed to be related to cognitive improvement
- It is unknown if it is due to an effect on mobility

• Open-Label Pilot Study

• N=6 pt with mild AD (67%♀, age 79.9±5)
  8 pt with MCI (64%♀, age 75.6±6)

• 5mg/day donepezil for 1 month, 10mg/day for 3 months. Follow-up of 4 months

• Donepezil improved gait velocity and variability


Cognitive Enhancers & Gait Phase II Study

Objective
To determine the efficacy of donepezil, a cognitive enhancer that improves cholinergic activity, on gait in older adults newly diagnosed with AD.

Methods
Design: Phase II clinical trial
Participants: 43 seniors with mild AD received donepezil.
Outcomes
- Primary outcome: Gait velocity (GV) and stride time variability (STV) under single and dual-tasking using an electronic walkway.
- Secondary outcomes: Attention and executive function.

Intervention: 5 mg/day of donepezil for 1 month
10 mg/day for the subsequent 3 months. Total follow-up of 4 months.


Cognitive Enhancers & Gait Phase II Study

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait Velocity (mean, SD cm/s):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single gait</td>
<td>108.38 (18.56)</td>
<td>113.28 (19.54)</td>
<td>4.90 (11.90)</td>
<td>0.010*</td>
</tr>
<tr>
<td>Counting backwards by 1s</td>
<td>96.33 (19.62)</td>
<td>98.87 (22.70)</td>
<td>2.53 (14.11)</td>
<td>0.246</td>
</tr>
<tr>
<td>Naming animals</td>
<td>80.62 (22.96)</td>
<td>85.31 (22.34)</td>
<td>4.69 (13.36)</td>
<td>0.028*</td>
</tr>
<tr>
<td>Counting backwards by 7s</td>
<td>70.78 (23.93)</td>
<td>74.25 (21.70)</td>
<td>3.47 (24.59)</td>
<td>0.372</td>
</tr>
<tr>
<td>Stride Time Gait Variability (CoV, %):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single gait</td>
<td>3.53 (1.37)</td>
<td>3.43 (1.42)</td>
<td>-0.11 (1.86)</td>
<td>0.594</td>
</tr>
<tr>
<td>Counting backwards by 1s</td>
<td>6.28 (6.86)</td>
<td>6.22 (6.59)</td>
<td>-0.07 (7.55)</td>
<td>0.711</td>
</tr>
<tr>
<td>Naming animals</td>
<td>9.85 (13.77)</td>
<td>8.26 (8.31)</td>
<td>-1.59 (13.24)</td>
<td>0.954</td>
</tr>
<tr>
<td>Counting backwards by 7s</td>
<td>11.38 (13.09)</td>
<td>9.84 (12.61)</td>
<td>-1.54 (18.32)</td>
<td>0.442</td>
</tr>
</tbody>
</table>

Table 2. Paired sample t-test; statistical significance is denoted with * and was set at p<0.05

Montero-Odasso, M et al. "Donepezil Improves Gait Performance in Older Adults with Mild Alzheimer’s Disease: A Phase II Clinical Trial." Journal of Alzheimer’s Disease (2014).
### Table 3. Secondary Outcomes

Cognitive test changes (mean and SD) after 4 months of follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trail Making Test A</strong></td>
<td>69.05 (36.81)</td>
<td>57.98 (29.82)</td>
<td>-11.08 (32.73)</td>
<td>0.030*</td>
</tr>
<tr>
<td><strong>Trail Making Test B</strong></td>
<td>237.09 (138.85)</td>
<td>189.35 (139.09)</td>
<td>-51.22 (107.38)</td>
<td>0.001*</td>
</tr>
<tr>
<td><strong>Trail Making Test B-A</strong></td>
<td>158.18 (110.07)</td>
<td>120.15 (100.32)</td>
<td>-38.04 (101.17)</td>
<td>0.042*</td>
</tr>
<tr>
<td><strong>Digit Span Test – Forward</strong></td>
<td>8.74 (1.83)</td>
<td>9.15 (2.03)</td>
<td>0.41 (1.93)</td>
<td>0.051</td>
</tr>
<tr>
<td><strong>Digit Span Test – Backward</strong></td>
<td>5.32 (1.75)</td>
<td>4.91 (1.60)</td>
<td>-0.41 (1.21)</td>
<td>0.273</td>
</tr>
</tbody>
</table>

Note: Statistical significance is denoted with * and was set at p<0.05.  
A Final score is total time in seconds to complete task.  
B Final score is the sum of points from each correct trial.  
Maximum score is 16.

---

**Cognitive Enhancers & Gait Phase II Study**


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**BMC Neurology**

**Can cognitive enhancers reduce the risk of falls in older people with Mild Cognitive Impairment? A protocol for a randomised controlled double blind trial**

Manuel Montero-Odasso *1,2,3*, Jennie I. Wells1,3, Michael J Borrie1,3 and Mark Speechley2,3

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Email: Manuel Montero-Odasso* - Manuel.Montero-Odasso@uwo.ca; Jennie.I.Wells - Jennie.Wells@uwo.ca; Michael.J.Borrie - Michael.Borrie@uwo.ca; Mark.Speechley - Mark.Speechley@uwo.ca

* Corresponding author

---

ClinicalTrials.gov Identifier: NCT00514551
Division of Geriatric Medicine

Approached to be in Study (n=216)

Ineligible (n=78)
- Screen failed
- Did not meet inclusion

Consented (n=46)

Refused (n=72)
- Not interested
- Withdrew from the screening

Randomized (n=46)

Allocated to Donepezil (n=24)
- Baseline Assessment (T0) (n=23)
- 1 month Assessment (T1) (n=19)
- 6 month Assessment (T6) (n=19)

Ineligible (n=78)
- Screen failed
- Did not meet inclusion

Allocated to Placebo (n=22)
- Baseline Assessment (T0) (n=20)
- 1 month Assessment (T1) (n=20)
- 6 month Assessment (T6) (n=19)

Included in Preliminary Analysis (n=19)

Consort Diagram

ClinicalTrials.gov Identifier: NCT00934531

<table>
<thead>
<tr>
<th>Cognitive Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=19)</td>
</tr>
<tr>
<td>Donepezil (n=19)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trail Making Test A (sec)</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>50.10(13.85)</td>
<td>48.86(9.94)</td>
<td>1.49</td>
<td>60.00(19.22)</td>
<td>59.06(15.29)</td>
<td>0.94</td>
<td>0.08</td>
</tr>
<tr>
<td>Donepezil</td>
<td>53.17(14.16)</td>
<td>54.57(14.88)</td>
<td>1.40</td>
<td>63.90(21.82)</td>
<td>62.79(13.12)</td>
<td>11.8</td>
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</table>

<table>
<thead>
<tr>
<th>Trail Making Test B (sec)</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>67.84(49.74)</td>
<td>66.52(43.24)</td>
<td>1.32</td>
<td>79.02(59.66)</td>
<td>76.49(56.10)</td>
<td>22.54</td>
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<tr>
<td>Donepezil</td>
<td>70.88(53.84)</td>
<td>70.12(47.84)</td>
<td>0.76</td>
<td>81.80(67.84)</td>
<td>79.39(63.12)</td>
<td>22.54</td>
<td>0.64</td>
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<table>
<thead>
<tr>
<th>Digit Span Test: Forward</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10.81(2.01)</td>
<td>10.75(2.61)</td>
<td>0.06</td>
<td>10.58(2.68)</td>
<td>10.57(2.67)</td>
<td>0.01</td>
<td>0.91</td>
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<tr>
<td>Donepezil</td>
<td>10.81(2.01)</td>
<td>10.75(2.61)</td>
<td>0.06</td>
<td>10.58(2.68)</td>
<td>10.57(2.67)</td>
<td>0.01</td>
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<table>
<thead>
<tr>
<th>MoCA (mean, SD)</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>21.73(7.73)</td>
<td>23.33(8.80)</td>
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<td>0.46</td>
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<tr>
<td>Donepezil</td>
<td>22.75(7.38)</td>
<td>23.00(7.85)</td>
<td>0.25</td>
<td>13.75(1.28)</td>
<td>14.83(1.52)</td>
<td>0.08</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Linear regression analysis for the between group differences at post-intervention (6 months).

*Adjusted for baseline gait, age, sex and history of falls in the past year.

<table>
<thead>
<tr>
<th>Gait Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=19)</td>
</tr>
<tr>
<td>Donepezil (n=19)</td>
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</table>

<table>
<thead>
<tr>
<th>Parameter</th>
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<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Donepezil</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6 month Assessment (T6)</th>
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</thead>
<tbody>
<tr>
<td>Placebo (n=19)</td>
</tr>
<tr>
<td>Donepezil (n=19)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Digit Span Test: Backward</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.08(0.20)</td>
<td>0.06(0.18)</td>
<td>0.02</td>
<td>0.02(0.18)</td>
<td>0.01(0.16)</td>
<td>0.29</td>
<td>0.54</td>
</tr>
<tr>
<td>Donepezil</td>
<td>0.08(0.20)</td>
<td>0.06(0.18)</td>
<td>0.02</td>
<td>0.02(0.18)</td>
<td>0.01(0.16)</td>
<td>0.29</td>
<td>0.54</td>
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</table>

<table>
<thead>
<tr>
<th>MoCA (mean, SD)</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>21.73(7.73)</td>
<td>23.33(8.80)</td>
<td>1.60</td>
<td>25.00(2.30)</td>
<td>25.75(2.03)</td>
<td>0.75</td>
<td>0.46</td>
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<tr>
<td>Donepezil</td>
<td>22.75(7.38)</td>
<td>23.00(7.85)</td>
<td>0.25</td>
<td>13.75(1.28)</td>
<td>14.83(1.52)</td>
<td>0.08</td>
<td>0.03</td>
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<table>
<thead>
<tr>
<th>Boston Naming Test</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12.75(1.38)</td>
<td>13.00(1.85)</td>
<td>0.25</td>
<td>13.75(1.28)</td>
<td>14.83(1.52)</td>
<td>0.08</td>
<td>0.03</td>
</tr>
<tr>
<td>Donepezil</td>
<td>12.75(1.38)</td>
<td>13.00(1.85)</td>
<td>0.25</td>
<td>13.75(1.28)</td>
<td>14.83(1.52)</td>
<td>0.08</td>
<td>0.03</td>
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<table>
<thead>
<tr>
<th>Letter Number Sequence</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>Baseline</th>
<th>6 mo follow-up</th>
<th>Change</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>20.13(2.05)</td>
<td>20.70(2.39)</td>
<td>0.58</td>
<td>20.13(2.05)</td>
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<td>0.15</td>
</tr>
<tr>
<td>Donepezil</td>
<td>20.13(2.05)</td>
<td>20.70(2.39)</td>
<td>0.58</td>
<td>20.13(2.05)</td>
<td>20.70(2.39)</td>
<td>0.58</td>
<td>0.15</td>
</tr>
</tbody>
</table>

2014 CNS Workshop: Session 1
Tuesday, November 4, 2014
Donepezil and Gait in MCI: An RCT. Preliminary Results

Conclusions

• Donepezil modestly improved GV and reduced Gva

• Changes are in the range 5 cm/s (minimum clinical significant) but it is still considered clinically meaningful and similar to the gait improvement seen after exercise intervention protocols

• Changes were of higher magnitude in dual-task gait

• More stable walking pattern in the intervention group

• Improvements were found early, 1 month, and sustained during 6 months

• Dose-response pattern
Regulation and Neural Control of Gait

Goal direct system: must reach the goal and avoid impeding objects

Motor system
1. Basal ganglia & Brain stem Level
2. Spinal Level: Central Pattern Generator (CPG)

Postural system and peripheral limbs
1. Muscle and Joints
2. Vestibular
3. Ocular

Cortical
Subcortical
Spinal

Regulates propulsion and navigation
Generates propulsive movement
Provides cadence and rhythm
Helps to position center of gravity
Provides propulsion

History of falls in Parkinson disease is associated with reduced cholinergic activity.


<table>
<thead>
<tr>
<th></th>
<th>PD fallers (n=17)</th>
<th>PD non-fallers (n=27)</th>
<th>Group Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical AChE</td>
<td>0.0264</td>
<td>0.0281</td>
<td>P=0.005</td>
</tr>
<tr>
<td>Thalamic AChE</td>
<td>0.0572</td>
<td>0.0617</td>
<td>P=0.006</td>
</tr>
</tbody>
</table>

No significant difference in nigrostriatal dopaminergic activity between PD fallers and non-fallers

Thalamic AChE activity represents cholinergic output of the pedunculopontine nucleus (PPN), a key node for gait control.

Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease.


• Randomized, crossover, double-blind. 6 w+3 w washout+6 w placebo
• N=23 pt with Parkinson disease
• When compared with placebo, donepezil reduced falls by 50%
  • From: 0.25 per day
  • To: 0.13 per day
Galantamine improves gait performance in patients with Alzheimer's disease.


<table>
<thead>
<tr>
<th></th>
<th>Single-task gait</th>
<th>Dual-task gait</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stride time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEFORE treatment</td>
<td>1123(85) ms</td>
<td>1450(251)ms</td>
</tr>
<tr>
<td>AFTER treatment</td>
<td>1166(175)ms</td>
<td>1279(227)ms</td>
</tr>
</tbody>
</table>

$p=0.01$

Potential Mechanisms

1. **Cognitive mediated:**
   - Supported by a) Executive function and attention improvements
   - b) Changes were higher magnitude in dual-task gait.

2. **Motor mediated:**
   - Potential action on *supraspinal locomotor centers*: PPN and basal forebrain center -Nucleus of Meynert-

3. **Vascular mediated:**
   - Cholinesterase inhibitors may improve brain vascular flow
Conclusions

• Donepezil improves gait velocity and variability, particularly under dual-tasking

• Changes are modest, in the range of 5 cm/s

• Mechanism seems to be cognitive mediated: improvement in attention and executive function, higher magnitude of changes seen while dual-task gait

• Can be other mechanisms involved: improving neurotransmission in supraspinal locomotor centers and improving of vascular flow

• Exiting preliminary results which can complement existing strategies, including exercise and cognitive remediation

• Caution: publication bias, small studies. Preliminary results of the large RCT are encouraging

• Further studies should include imaging/ neurovascular coupling assessment to decipher potential non-cognitive mediated mechanisms
Acknowledgments

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Dr Tim Doherty
Dr Michael Borrie
Dr Jennie Wells

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Dr Cedric Anweiller - Univ of Angers

Montreal Collaboration
Dr Howard Chertkow- McGill University
Dr Louis Bherer- Concordia University

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The Physicians Services Incorporated Foundation (PSI)
The Drummond Foundation
Canadian Institute of Health & Research (CIHR)

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Lawson Health Research Institute (LHRI)
Ontario Ministry of Research and Innovation
The Physicians Services Incorporated Foundation (PSI)
The Drummond Foundation
Canadian Institute of Health & Research (CIHR)
Motor skill training: coaching the brain in walking

Jessie VanSwearingen, PhD, PT
University of Pittsburgh
Motor skill: smooth, efficient automatic movement

- goal-oriented, minimal attention to individual components of action
- repeated practice results in progressive mastery; automaticity & efficiency
- many usual life tasks are motor skills – once difficult became easier with practice (e.g. using a spoon, walking, riding a bike)

(Brooks, 1986; Seidler et al, 2010; Milton et al, 2004; Donchin et al, 2003; Wulf et al, 2010; Doyon, 2005)

Motor skill training induces brain reorganization: neuroplasticity

- walking is a motor skill, acquired through motor learning
- preprogrammed neural circuitry underlie the automaticity and efficiency of walking
- age-related changes disrupt the neural circuitry, and disrupt automatic and efficient walking
- the brain and body systems work harder; the energy cost of walking is greater
Motor learning approach to make walking easier and reduce brain work

* older adults can learn motor tasks
* motor learning exercise has made walking better [and less work]

? motor learning exercise may be less work for the brain
? motor learning exercise may lead to walking that is less work for the brain

Seidler et al, 2010; Rowe et al, 2006; VanSwearingen et al, 2009; Brach et al, 2011; Daselaar et al 2003; Doyon et al, 2007

Motor learning involves behavioral & neural refinements: results in motor behavior that is preplanned, organized, spatially & temporally more accurate

<table>
<thead>
<tr>
<th>novice movement</th>
<th>skilled movement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>peripheral factors</strong></td>
<td><strong>central factors</strong></td>
</tr>
<tr>
<td>multiple muscles; prolonged cocontraction</td>
<td>multiple muscles; brief bursts</td>
</tr>
<tr>
<td>variable movement sequence</td>
<td>preplanned motor sequence</td>
</tr>
<tr>
<td>movement subsegments; stops and starts</td>
<td>movement starts &amp; stops programmed together</td>
</tr>
<tr>
<td>guided, discontinuous movement; irregular velocity profile</td>
<td>non-guided, continuous movement; smooth velocity profile</td>
</tr>
<tr>
<td>practice builds motor program</td>
<td>practice sustains motor program</td>
</tr>
<tr>
<td>fronto-parietal [cortical-cortical] circuitry</td>
<td>cortical-basal ganglia or -cerebellar circuitry</td>
</tr>
<tr>
<td>sustained, generalized brain activity</td>
<td>brief, specific ‘efficient’ brain activity</td>
</tr>
<tr>
<td>high cingulate motor area activity</td>
<td>reduced cingulate motor area activity</td>
</tr>
</tbody>
</table>

Practice leads to motor expertise

- feedback during practice leads to automaticity
- automaticity: individual constructs and applies internal maps that represent the interface of self and environment; frees brain resources and energy
- motor skill & automaticity decline without practice; experts regain skill more rapidly

(Milton et al, 2004; Wulf et al, 2010; Wu et al, 2008)

As motor skill develops, brain activity & performance become more efficient

<table>
<thead>
<tr>
<th></th>
<th>novice / pre</th>
<th>intermediate / mid</th>
<th>expert / post</th>
</tr>
</thead>
<tbody>
<tr>
<td>performance</td>
<td>poor</td>
<td>good</td>
<td>good</td>
</tr>
<tr>
<td>work/effort</td>
<td>high</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>brain activity</td>
<td>high</td>
<td>high</td>
<td>low</td>
</tr>
</tbody>
</table>
Walking is more than stepping
Walking is the integration of stepping with postures & phases of gait to translate the body over ground
*co-occurrence of heel strike with opposite limb push off smooths changes in the direction of limb movement during forward progression

Neural control evolved to coordinate timing of steps, postures & phases and modulate postural reflexes

The result is a reproducible, adaptable and efficient gait pattern, and walking performance that is smooth and automatic; ‘an inverted pendulum’
(Polcyn et al, 1998; Earles et al, 2001; Capaday, 2002; McGibbon, 2003)

Capturing the skill: the integration of stepping with postural adjustments and automaticity

Do measures represent the integration of multiple body systems? the motor skill in walking?
✓ combined speed, accuracy and amplitude
✓ smoothness of walking
✓ energy cost of walking

(Capaday, 2002; Dickinson et al, 2000; Lay et al, 2002; Brach et al 2011; Boyd et al, 1999)
Energy cost of walking: a measure of motor skill and efficiency, affected by ‘how’ a person walks

- energy expenditure of the integration of all body systems for walking
- rate of oxygen consumption (work) / workload
- can be compared over time and across individuals who walk at different speeds

energy cost - how much work it is to walk
- minimized at preferred speed; higher cost at all other speeds, ‘J-curve’
- abnormalities shifts curve up and left

(Age, 2004; Zarrugh et al, 1974; Martin et al, 1992; VanSwearingen & Studenski, 2014)

Age & disease disrupt the inverted pendulum for walking; energy expensive effects

Energy cost 2-4 times greater for older adults with disordered walking compared to usual adult cost, .15ml/kg/m

Age-related changes in biomechanics alter pendulum action; in neuromuscular alter strategies to initiate & continue walking

<table>
<thead>
<tr>
<th>Increase energy cost</th>
<th>Energy cost savings/efficiency lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>cocontraction</td>
<td>degradation of internal motor maps</td>
</tr>
<tr>
<td>changed trajectory of body</td>
<td>lose stepping signal; energy capture</td>
</tr>
<tr>
<td>altered strategies to advance</td>
<td>reduced rate of momentum generation</td>
</tr>
<tr>
<td>prolonged force development</td>
<td>less ATP produced/oxygen consumed</td>
</tr>
<tr>
<td>slow, guided movements</td>
<td></td>
</tr>
</tbody>
</table>

(Kuo et al, 2013; McGibbon, 2003; Wert et al, 2010; Dickinson et al, 2000; Hortobagyi et al, 2011; Lanza & Nair, 2010)
Flexed trunk disrupts neural control; leads to less automaticity & greater energy cost of walking

• altered sensory input / feedback
• modulation of postural reflexes inappropriate for walking
• trailing limb not loaded
• reduced propulsion; trajectory of ground reaction forces more vertical; sacrifice momentum
• limited or no hip extension/extensor moment
• neural signal for walking reduced

(Kuo et al, 2013; McGibbon, 2003; Wert et al, 2010; Dickinson et al, 2000; Hortobagyi et al, 2011; Lanza & Nair, 2010)

Loss of motor skill in walking, reversion to novice-like motor skill

• why? reduced practice? increased intentional control? changes in internal maps? alone and in combination
• degraded internal maps, loss of automaticity, person perceives increasing gap between actual and intended performance
• to rebuild maps requires trial & error practice; risky for persons with altered central & peripheral neuromotor systems; alternative use greater intentional control

(Donchin et al, 2003; Wu et al, 2010; Doyon et al, 2009; Kleim, 2011)
Age-related brain changes may explain the loss of motor skill, automaticity & efficiency

Diffuse processes involving prefrontal & parietal association areas, putamen, cerebellum, & connecting tracts

**Changes related to motor skill performance:**
- inefficient patterns of brain activity; more activity, greater regions
- greater local connectivity; reduced distal connectivity
- reduced dopamine and norepinephrine in striatum & cerebellum – disrupt timing and reward-based mechanisms
- reduced cholinergic function interferes with motor learning/skill acquisition

The brain changes can interfere with central processing important in motor skill acquisition & motor plan selection for walking; and the brain works harder to walk.

Motor learning exercise is goal-oriented, accurately practiced, reward-based learning

movements become linked to a task goal; become automatic and efficient
- **position** – facilitates motor task sequence, appropriate recruitment & accuracy
- **define goal** – limits degrees of freedom; links motor sequence to a neural circuit for the intended task
- **accurate practice** – repetitive and increasingly accurate; promotes experience dependent changes in neurons (synaptic plasticity)
- knowledge of **success in performance** – enhances motor skill outcomes; reward-based motor learning sustains the learning

Brain challenged to optimize motor sequence for the task, which facilitates adaptations of the internal map

(Cramer et al, 2011; Kleim, 2011; Brooks, 1986; King et al, 2013)
The brain organizes voluntary motor actions about an overarching ‘motor behavioral goal’ for walking: impacts intervention, performance & neural network assessment

**stability & efficiency**
- brain estimates the tradeoff of motor actions for stability against motor actions that promote energy efficiency
- wider base support; train over track

**maneuverability & efficiency**
- responses to perturbation first promote the intended action; followed by voluntary movement to restore path
- Narrower base of support; stick balancing on a finger

Kuo & Donelan, 2010; Huang & Almed, 2011; Hasan, 2005

Motor learning exercise benefits automaticity; may facilitate ability to select & modify motor programs; expand movement repertoire and lead to improved daily activities

*Task-oriented; motor learning – learning, integrative, adaptive*
- visual feedback of the center of mass of the body during treadmill walking
- task-oriented stepping and walking patterns to improve timing & coordination in walking
- indicated walking speed goal & feedback
- task-oriented exercise training for walking

Coaching the aging CNS to enhance motor skill in walking: gaps, needs, barriers & some paths

Gaps

- Integrated body-environmental system view of walking: **walking is a whole body behavior**
- Underlying mechanisms of walking motor behavior: **behavioral goal drives assessment and intervention**
- Optimal interventions that reduce compensation and enhance motor skill & efficiency in walking: **training for motor expertise in walking**

Walking is a behavior: intent is linked to interaction with the world

Energy cost of walking influences behavior

- distinguish efficient, motor skilled from compensated gait: assess both performance and energy cost; relate better motor skill to more efficient walking; indicators of behavioral pattern in motor skill acquisition

- define the brain’s role in optimizing skill & efficiency of walking: what drives acquisition of motor skill & optimal walking efficiency; functional brain activity changes with changes in motor skill; methods to examine functional neural networks of walking – fmri imagined walking, nirs, eeg
Motor behavior goal of walking impacts performance

• represent the motor behavioral goal of walking in gait & brain activity measures: account for center of movement changing with position & task; for multiple types of variability or planes of smoothness; brain activity representation of behavior; identify tasks that challenge the brain to optimize performance under either goal

• use technology to enhance motor skill & efficiency in walking: impact of assistive devices on motor skill & efficiency; explore devices to assist navigation & facilitate the intent of walking; define the energy cost of walking that prohibits performance of daily activities

Motor skill training as a part of an exercise approach: motivation & rewards of practice VIP

• Combined aerobic with motor learning exercise intervention - building a bigger and a better engine for walking: comparison of mobility outcomes of aerobic, motor learning & combined; optimal dose & format of combined; relation of improved motor skill & efficiency to improve activity & participation; process of motor skill re-acquisition may influence payoff and intent; role of reward-based motor learning, success may sustain the motor skill; what are appropriate motor tasks/goals to rebuild internal maps for walking in the world
Summary of challenges to coaching the aging CNS to enhance motor skill in walking

• capture behavior: energy cost of walking,…
• represent the motor behavioral goal: maneuverability / stability [or the problems of multiple variability; multiple smoothness]
• performance and neural networks: connectivity differences with performance differences; neural network changes in relation to motor learning induced changes in motor skill
• define combined interventions: building a bigger and a better engine for walking; strategies for sustaining skill – safe but challenging experiences; practice in a world full of choices

Motor skill is essential to efficient walking, often lost with aging, and can potentially be restored through types of goal-oriented motor learning walking practice

....by increasing motor skill & decreasing energy cost, we can make walking easier, attractive for older people, despite health-related limitations ...[and might even make it possible for the older person to think and dream while walking too]
Acknowledgment

Stephanie Studenski, Jennifer Brach, Subashan Perera, Kristin Lowry, Caterina Rosano, Howard Aizenstein, David Wert, Wennie Huang, Patrick Sparto, Ted Huppert, Ervin Sejdic, Kirk Erickson and the Pittsburgh Pepper Center investigators and participants

Pittsburgh Claude D. Pepper Older Americans Independence Center, grant # P30 AG024827; Departments of Physical Therapy, Division of Geriatrics, University of Pittsburgh
Noninvasive brain stimulation: A new tool for understanding and enhancing the cortical control of mobility

Brad Manor, PhD
Harvard Medical School
Standing and walking are dependent upon supra-spinal control.

- Which brain elements and networks are involved?
- What can we do to optimize them?

Rosano et al., J Gerontol, 2008
Do we ever just stand or walk?

Dual Task Paradigm

Standing

Standing + Counting

Dual task “cost”
Dual task costs suggest that the involved tasks are processed using shared brain networks.

- The extent of interference is dependent upon the difficulty and type of unrelated task.

Fig. 2. Changes in gait speed and motor cost during preferred-speed walking. This figure shows changes in gait speed (A) and motor cost (B) in walking only (ST), visuomotor reaction time (VMT), word list generation (W), serial subtraction (SS) and Stroop task (STR) dual-task conditions. Significant differences in gait speed and motor cost between conditions are indicated by different letters. Same letters indicate no difference in gait speed or motor cost between these conditions. Significance level was set at $p = 0.05$.

Patel et al, Neuroscience, 2014

- Is there a “dual task” brain network?

Neuroimaging can help us determine which networks are involved.

Table 1

<table>
<thead>
<tr>
<th>H</th>
<th>Anatomical Region</th>
<th>BA*</th>
<th>cluster size (in number of voxels)</th>
<th>MNI coordinates</th>
<th>Cluster pFWE</th>
<th>T-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>Middle frontal gyrus</td>
<td>106</td>
<td>32</td>
<td>$-24 -4 50$</td>
<td>0.001</td>
<td>0.75</td>
</tr>
<tr>
<td>L</td>
<td>Premotor cortex</td>
<td>6</td>
<td>139</td>
<td>$-26 -6 50$</td>
<td>&lt;0.0001</td>
<td>3.15</td>
</tr>
<tr>
<td>L</td>
<td>Middle frontal gyrus, DLPFC, premotor cortex</td>
<td>6</td>
<td>246</td>
<td>$10 0 50$</td>
<td>&lt;0.0001</td>
<td>7.62</td>
</tr>
<tr>
<td>L</td>
<td>IPS, superior parietal lobe, precuneus</td>
<td>70</td>
<td>94</td>
<td>$-18 -70 54$</td>
<td>&lt;0.0001</td>
<td>7.17</td>
</tr>
<tr>
<td>L</td>
<td>IPS, superior parietal lobe, precuneus</td>
<td>70</td>
<td>584</td>
<td>$22 -56 42$</td>
<td>&lt;0.0001</td>
<td>0.30</td>
</tr>
<tr>
<td>R</td>
<td>STG, precuneus</td>
<td>70</td>
<td>584</td>
<td>$22 -56 42$</td>
<td>&lt;0.0001</td>
<td>0.30</td>
</tr>
</tbody>
</table>

*H: hemisphere; R: right; L: left; IPS: intraparietal sulcus; DLPFC: dorsolateral prefrontal cortex; pFWE: family-wise error correction for multiple comparisons; MNI: Montreal Neurological Institute.

Deprez et al, Neuropsychologia, 2013
Strategies that modulate cortical excitability may help to understand and optimize balance.

- How can we modulate brain activity?
  - Pharmacological interventions
  - Cognitive effort or physical exercise
  - Non-invasive brain stimulation

We can use electricity or magnets to safely modulate cortical activity.

Transcranial Magnetic Stimulation

Transcranial Direct Current Stimulation (tDCS)
tDCS modulates cortical excitability.

Batsikadze et al, J Physiol, 2013

![Graph](image)

**Time course after tDCS**

Rampersad et al, 2014

Anode: F3

Cathode: Orbit

Nitsche et al, Brain Stimulation, 2008

---

tDCS targeting the prefrontal cortices acutely improves cognitive function.

- Selective attention
- Declarative memory
- Short-term memory
- Problem solving
- Executive function
Our study: The effects of a single session of tDCS on balance and brain function.

20 younger and 40 healthy older women and men

- Dual task Assessment
- tDCS (Real or Sham)
- Dual task Assessment

- fMRI
- tDCS (Real or Sham)
- fMRI

- tDCS: Facilitate excitability in left prefrontal cortex
- Successfully double-blinded
- No adverse events were reported

72-year-old female

A: Post Sham tDCS
- Undisturbed Standing
- Dual Task Standing
- Dual Task Cost

B: Post Real tDCS
- Anteroposterior Displacement (cm)
- Mediolateral Displacement (cm)
tDCS improves the ability to dual task.

- Figure A: Dual Task Cost and Postural Sway Area
  - Graphs showing the improvement in dual task performance and reduction in postural sway area with tDCS compared to sham.

- Figure B: Gait Speed and Dual Task Cost
  - Graphs showing the increase in gait speed and decrease in dual task cost with tDCS compared to sham.

2014 CNS Workshop: Session 2
Tuesday, November 4, 2014
tDCS also reduced the dual task costs to gait and postural control in younger adults.

Transcranial direct current stimulation reduces the cost of performing a cognitive task on gait and postural control

Junhang Zhou,1 Ying Hao,1,2 Ye Wang,1 Azizah Jordan,1,3 Alvaro Passua-Leone,1,4 Jue Zheng,1,5 Jing Fang1,5 and Brad Manor1,5,6
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2Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA
3Department of Neurology, Benaroya-Hiller Center for Nervous Brain Stimulation, Beth Israel Deaconess Medical Center, Boston, MA, USA
4College of Engineering, Peking University, Beijing, China
5Institute for Aging Research, Hebrew SeniorLife, Roslindale, MA, USA

Dual task capacity is modifiable and dependent upon prefrontal cortical excitability.

• Functional implications are potentially significant!
  • How long does the effect of one session last?
  • What about multiple sessions?
  • Sports, mobility, falls...
  • Other populations?
Which brain networks were actually affected?

- We targeted the left prefrontal cortex, but tDCS is diffuse.

Right superior frontal gyrus

Courtesy of Dana Brooks, College of Engineering, Northeastern University

Which brain networks were actually affected?

- fMRI: The right superior frontal gyrus is connected to:

Cognitive control

execution network

motor control

Li et al, Neuroimage, 2013
The effects of tDCS are diffuse, which makes things easy…and hard.

- **The easy**: We might not have to be very accurate to induce changes in performance.

- **The hard**: Difficult to determine the exact mechanisms that change performance.

![Diagram](https://example.com/diagram.png)

- **fMRI**: Structural, resting-state connectivity, resting-state perfusion, BOLD block design

---

**tDCS modulates the cortical response to walking-related somatosensory stimuli**

Hao, Manor et al, *MRM*, 2012
Take home messages

• Proof-of-concept: Modulation of prefrontal excitability improves dual tasking in healthy younger/older adults.
  ➢ Validate
  ➢ Optimize

• Modeling electrical flow may help us to understand, and individualize, tDCS.

• Neuroimaging + tDCS may enable elucidation of the mechanisms of tDCS and dual tasking.

Thank you!

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Azizah Jor‘dan, Ph.D.

Peking University
Jue Zhang, Ph.D.
Junhong Zhou
Ye Wang
Hao Ying, Ph.D.

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National Institute on Aging (K01)
National Natural Science Foundation of China
Planning a Randomized Controlled Trial to Determine if Hearing Loss Treatment Reduces the Risk of Cognitive Decline in Older Adults

2016-2021

Prepared by
Frank R. Lin, MD, PhD
Johns Hopkins University
In partnership with Josef Coresh, MD, PhD, and the ARIC Investigative Team

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NHLBI with ancillary studies by
NCI, NEI, NIA, NIAAA, NIDCR, NIDDK, NIEHS, NINDS, NCRR & NIH Roadmap

Outline – Hearing-Cognition RCT

1. Pathways & current evidence linking hearing & cognition
   • Mechanistic pathways linking hearing loss (HL) & cognition suggest a role for HL treatment in reducing cognitive decline/dementia

2. Integration of trial within the Atherosclerosis Risk in Communities-Neurocognitive Study (ARIC-NCS)

3. Trial design
   • Powered to detect 0.25 effect size difference in rates of cognitive decline between tx & watchful waiting groups over 3 years of follow-up
**Mechanistic Pathways**

Age-related hearing loss, present in nearly 2/3 of all adults > 70 years, results in poor fidelity in peripheral encoding of sounds

- **Hearing Loss**
  - Changes in brain structure
  - Reduced Social Engagement

  **Common Cause**
  (e.g., aging, microvascular disease)

  Impaired Cognition & Dementia

HL interventions could plausibly reduce the cognitive load of processing degraded auditory signals, provide increased auditory stimulation, and improve social engagement.

- Role of HL as potentially modifiable, late-life risk factor

**Current Evidence**

Audiometric HL has been independently associated with:
- 2-5 fold increased risk of incident dementia Neurology 2012; Arch Neuro 2011
- Accelerated cognitive decline on 3MS and digit symbol test Arch Int Med 2013
- Accelerated whole brain and lateral temporal lobe atrophy NeuroImage 2014

Determining the role of HL tx in attenuating cognitive decline/dementia in observational studies is not possible
- Individuals choosing to use hearing aids differ substantially from those who do not; adequacy, quality, & duration of HL treatment unable to be determined from observational data; etc.

Only 1 prior RCT of HL treatment exploring outcomes beyond speech and QoL has ever been conducted (n = 192 veterans) Ann Intern Med 1990
- Improved communicative and emotional functioning and cognitive function (using a cognitive screener) observed at 4 months post-tx
- Results have never been confirmed in a larger trial with longer follow-up
ARIC Cohort: 1987-present; n=15,792

ARIC Investigators: Neurocognitive Study (NCS)

Data Coordinating Center: University of North Carolina (UNC, PI: David Couper; Lisa Wruck)
Analysis Workgroup (Chairs: Karen Bandeen-Roche & Richey Sharrett)
Field Centers: UNC & Wake Forest (PI: Gerardo Heiss, Wake PI: Lynne)
Univ. of Minnesota (PI: Alvaro Alonso)
Johns Hopkins Univ. (PI: Josef Coresh, study co-chair; Richey Sharrett)
Univ. of Mississippi (PI: Thomas Mosley, study chair)
Lipid Laboratory: Baylor Univ. (PI: Christie Ballantyne)
Genetics Laboratory: Univ. of Texas, Houston (PI: Eric Boerwinkle; Fornage & Bressler)
Biochemistry Laboratory: Univ. of Minnesota (PI: John Eckfeldt)
MRI reading center: Mayo Clinic (PI: Cliff Jack)
Neurology unit: Johns Hopkins (Marilyn Albert, Rebecca Gottesman, Guy McKhann)
Mayo Clinic (subcontract to: David Knopman)
Specialty labs: Mayo Clinic (subcontract to: Steven Younkin)
Large ancillaries: PET (PI: Gottesman), Brain Vasculature (PI: Wasserman/Suri + K99:Ye), AAA (Tang)

Supported by National Institutes of Health, NHLBI, NINDS, NEI and NIA
ancillary studies funded separately
Integration of RCT within ARIC-NCS

**ARIC Timeline**

- **Exam 1**: n=15,792
- **Exam 2**: n=14,348
- **Exam 3**: n=12,860
- **Exam 4**: n=11,656
- **Car. MRI**: N=2,066
- **Exam 5**: n>6,538

Cohort Follow-up: Annual calls (semi-annual from 2011) + Hospitalization Abstraction

Community CHD Surveillance

Community Heart Failure Surv.

Dementia Surveillance


- Community representative; age 45-65 years; 25% African-American; spouse invited n~4500

Integration of RCT within ARIC-NCS

RCT will be nested within the ongoing ARIC-NCS

- ARIC provides an existing, well-characterized, and racially diverse cohort of participants
- Established research protocols for neurocognitive assessments, dementia adjudication, & other outcomes
- Recruiting ARIC participants offers substantial power in investigating how HL tx affects trajectories of decline

Estimated number of ARIC participants in 2017 eligible for RCT

<table>
<thead>
<tr>
<th>Age in 2016</th>
<th>Estimated N in 2017</th>
<th>Estimated N without dementia</th>
<th>Estimated N with MMSE&gt;24</th>
<th>Estimated N with hearing loss &amp; without hearing aid</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 – 84 y</td>
<td>4475</td>
<td>3482</td>
<td>3074</td>
<td>1721</td>
</tr>
</tbody>
</table>

* Estimated prevalence of MCI 0.26, 0.30, and 0.4 for 70-74y, 75-79y, & 80-84y, respectively
Integration of RCT within ARIC-NCS
Responsive to Calls for Research

Current 2014 Senate Appropriations Bill for Health and Human Services:
“In addition, NIH is urged to take advantage of existing well-characterized, longitudinal, population-based cohort studies to provide new insights into risk factors and protective factors related to cognitive decline and dementia. The NIH is encouraged to support additional research in minority populations that are at particularly high risk for cognitive decline and dementia.”

http://www.appropriations.senate.gov/sites/default/files/LHHS%20Report%20w%20Chart%2007REPT.PDF

Proposed trial is directly responsive to recommendations made in NHLBI's workshop on Embedding Clinical Interventions into Observational Studies (April 2013). Specifically:
Rec. #1: Develop opportunities for embedding clinical trials within established observational registries and cohort studies.
Rec. #2: Build on the cohort study infrastructure for the implementation of the intervention study


Trial Design
Overview

• Planning for RCT currently underway from 2014-2016 funded by an NIA R34 Clinical Trial Planning grant (R34AG046548)

• Participants: 70-84 y.o., healthy, cognitively normal community-dwelling adults with untreated mild-moderate HL

• ~766 individuals to be recruited across the 4 ARIC field sites from 2016-17. ~50% likely to be recruited directly from existing ARIC participants with the rest recruited de novo from the community

• Participants to be randomized to best-practices hearing rehabilitative treatment vs. no-contact control group and followed for 3 years

• Study powered to detect 0.25 effect-size difference in rates of cognitive decline between the two groups at 3 years post-randomization
R34 Hearing-Cognition Clinical Trial Planning
Organizational Structure

Trial Design

Aims

• **Aim #1** To determine the effects of best-practices hearing rehabilitative treatment on rates of cognitive decline (primary outcome measure) in 70-84 year-old well-functioning and cognitively normal older adults with hearing loss.

• **Aim #2** To determine the effects of best-practices hearing rehabilitative treatment on secondary outcome measures of health-related quality of life, social/leisure activities, daily functioning, mobility, and longitudinal brain atrophy on structural MRI.

• **Aim #3** To investigate the mechanistic pathways through which hearing rehabilitative treatment affects cognitive functioning by studying longitudinal changes in proximal/mediating outcome measures in relation to cognitive trajectories.
**Trial Design – Conceptual Model**

**Intervention**
- Best-Practices Hearing Rehabilitative Treatment

**Proximal/Mediating Outcomes**
- Audibility of speech & environmental sounds
- Enhanced verbal communication & social engagement

**Primary Outcome**
- Cognitive Functioning

**Secondary Outcomes**
- HRQL
- Social/Leisure Activities
- Daily Functioning
- Mobility
- Brain Volume Changes on MRI

---

**Trial Design**

**Hearing Rehabilitative Intervention**

- **Visit 1**
  - Comprehensive Evaluation, Baseline Measures & Goal Setting
  - 1-2 Weeks
    - Hearing Aid Fitting and Hearing Aid Orientation
  - 1st Follow Up and Begin Aural Rehabilitation (AR) Program (Individual/Group)
  - 4-6 Weeks of AR Program
    - Outcome Visit 1; Determine Assistive Listening Device (ALD) Need (Based on Goal Attainment)
  - 12-16 Weeks
  - Outcome Visit 2

- 2-3 Weeks
  - ALD Check
**Trial Design**

**Study Outcomes**

- Outcomes to be assessed at baseline and annually post-randomization for at least 3 years

---

**Trial Design**

**Pilot Study 2015**

- A pilot study* of ~50 participants recruited at Univ. S. Florida and Johns Hopkins/Comstock Field Site will be conducted in 2015
- Participants will receive tx & be followed for 6 months
- Abridged set of outcome measures focusing on proximal/mediating outcomes
- Pilot study objectives:
  - Assess for efficacy signal/potential of hearing intervention on key proximal outcomes
  - Assess feasibility of delivering study intervention and rates of participant follow-up/compliance

---

* Pilot study funded through discretionary and foundation grants and not by the R34 mechanism
Mobility Deficits and Visual Impairment
What should our interventions address?

Pradeep Ramulu, MD, PhD
Johns Hopkins University
GSA Workshop
November 4, 2014

Funding/Disclosures

Active
R01 EY022976
Research to Prevent Blindness

Supported this work
K23 EY018595
Dennis W. Jahnigen Award

Disclosures
Carl Zeiss Meditec Inc.
Mobility Deficits & Visual Impairment

- Visual Impairment
  - Refractive
    - Myopic
    - Hyperopic
  - Non-Refractive
    - Correctable
    - Non-Correctable
    - Acuity
    - Contrast
    - Color
    - Peripheral
    - Stereo
Refractive vs. Non-refractive Impairment

Different implications regarding treatment

Distinct functional implications

2014 CNS Workshop: Session 3
Tuesday, November 4, 2014
Several independent visual abilities

- High Contrast Visual Acuity
- Contrast Sensitivity
- Color Vision
- Peripheral Vision
- Stereo Vision

Most abilities better with 2 eyes

Significant prevalence of vision loss in the aged

2010 U.S. Prevalence Rates
All Vision Impairment

Vision impairment = Corrected visual acuity worse than 20/40, both eyes

Ignores impairment from:
- Visual field loss
- ↓ Color vision
- ↓ Contrast
- Poor stereoacuity

nei.nih.gov
All visual metrics decline with age

Visual impairment and mobility

Getting about
- Driving
- Walking/Activity
- Leaving Home
- Falls

Getting about safely
- Car crashes

Confidence without fear — Fear of falling
Independence relies on driving

Driving cessation → greater incident depression, entry into long-term care

Primary mode of transportation

Highly valued function in visually impaired

Glaucoma severity associated with driving cessation

Probability of driving cessation

Probability of driving cessation

100%

50%

0%

SEE
Bilateral glaucoma impact comparable to non-visual factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interval</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilat. Glaucoma</td>
<td>Present</td>
<td>2.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Age</td>
<td>5 years older</td>
<td>1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female vs. male</td>
<td></td>
<td>2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE score</td>
<td>5 points lower</td>
<td>3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>African-American vs. Caucasian</td>
<td></td>
<td>1.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>1 illness</td>
<td>1.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Severity of visual acuity loss predicts driving cessation in AMD

![Graph showing probability of no longer driving against better eye visual acuity]
Does vision also lead to “physical activity cessation”?

Less activity associated with mortality

Less activity $\rightarrow$ more heart dz, diabetes, osteoporosis

Less activity associated with lower QoL

Vision affects physical activity more than heart failure

<table>
<thead>
<tr>
<th>COPD</th>
<th>Arthritis</th>
<th>Diabetes</th>
<th>Stroke</th>
<th>CHF: 20/50 or worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>8%</td>
<td>16%</td>
<td>26%</td>
<td>26%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

48%
Dose-response between VF loss severity & PA in glaucoma patients

Leaving the home less has serious health consequences

↓ life space associated with higher mortality

↓ life space associated with increased incident risk of Alzheimer’s and cognitive decline

↓ life space → greater incident frailty
**Why not measure travel outside the home directly?**

Cellular tracker provides location every 15’ from 7a – 11p

*Daily excursions* > 1/3 mile from home measured

Rare blackout periods, sensitive, specific

---

**Glaucoma associated with modest decreases in travel outside home**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interval</th>
<th>Δ Weekly excursions</th>
<th>No excursions on given day (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaucoma</td>
<td>vs. controls</td>
<td>-1.4</td>
<td>1.82</td>
</tr>
<tr>
<td>Severe glaucoma</td>
<td>vs. controls</td>
<td>-2.1</td>
<td>2.14</td>
</tr>
<tr>
<td>African-American</td>
<td>vs. non-AA</td>
<td>+1.0</td>
<td>0.53</td>
</tr>
<tr>
<td>Female</td>
<td>vs. male</td>
<td>-1.4</td>
<td>1.39</td>
</tr>
<tr>
<td>MMSE score</td>
<td>5 points ↓</td>
<td>-1.7</td>
<td>1.49</td>
</tr>
</tbody>
</table>

Other covariates: age, education, grip strength, day of week (p>0.2)

Employment, living alone, other driver in home & comorbid illness not included as NS in age/gender adjusted analyses (p>0.3)
AMD also associated with smaller travel distances

![Bar graph showing miles traveled by controls, glaucoma, and AMD patients.]

Vision loss and mobility

Getting about

Getting about safely

Confidence without fear
Vision loss increases the risk of falls

SEE: ↑ fall risk with peripheral VF loss, not with central VF loss or visual acuity loss

2-4x ↑ risk of falls among glaucoma patients

Several studies indicating ↑ fall rate with visual acuity loss & in cataract/AMD

Balance is one presumed link between vision and falls

Greater VF loss → worse postural balance

Mixed evidence connecting visual acuity with balance

Significantly higher fall risk with multiple sensory impairment
↑ self-reported falls with ↓ visual acuity not from refractive error

Glaucoma/Visual field loss may → more car crashes

Nearly 7x ↑ in one study

Little or no effect in other studies

More Accidents with ↑ VF loss in 1 study

No clear evidence for more crashes with worse acuity
Vision loss and mobility

Getting about

Getting about safely

Confidence without fear ——— Fear of falling
Glaucoma has a large impact on FoF relative to other factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interval</th>
<th>Δ Fear of falling score (logits)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaucoma</td>
<td>Present</td>
<td>-1.20</td>
<td>0.001</td>
</tr>
<tr>
<td>VF Loss, better eye</td>
<td>5 dB worse</td>
<td>-0.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>female</td>
<td>-0.55</td>
<td>0.03</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>1 illness</td>
<td>-0.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lives alone</td>
<td>Yes</td>
<td>+1.16</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Other covariates: BMI, grip strength, age (all NS with p>0.05)

Opinion: Falls are first item to be addressed in persons with poor vision

- Alternatives to driving
- Consequences of ↓ travel/physical activity not established in this population
- Impact of fall-related injury indisputable
Geriatrics vs. ophthalmology: Fall prevention approach in poor vision

Geriatrics
- Screen VA
  - Ophthalm referral
  - Strength/balance
  - Home modification
  - Medication review

Ophthalmology
- Screen VA
  - Glasses
  - Cataract surgery
  - Other disease treatment
  - Low vision referral

Low vision services have a unique approach to improving mobility

- Sensory substitution
- Mobility training
- Lighting control
- Unique environmental modifications
Falls in Glaucoma Study (FIGS)

Unique study elements

3 year prospective collection of fall data

Accelerometer trials and GPS tracking to define fall exposure

Balance & gait measures

Formalized home assessment
GAITRite – gait parameters

Opal – wireless gait and balance system

- **Upper limb**
  - Arm swing speed
  - Arm range of motion

- **Lower limb**
  - Gait speed
  - Stride length

- **Postural Sway**
  - Sway area
  - Sway speed

- **Postural Transitions**
  - Turn duration
  - Sit/stand speed
Opal – wireless gait and balance system

Static balance
Postural sway

Dynamic balance
Timed up and go

Home assessment
Validated tool
Thorough assessment → outside home/each room
Aim 1 - VF loss and fall risk

Characterize association between VF loss severity and fall risk in glaucoma subjects

Define degree of vision loss associated with a significant fall rate – is vision loss best defined as VF loss?

Secondary analyses – VF loss and:
- Injurious falls
- Rate of falls normalized to steps taken
- In-home and out-of-home falls

Aim 2 - Modifiable risk factors for falls

Determine modifiable risk factors for falls

What can/needs to be changed to decrease falls in this group?

Secondary analyses – Intrinsic/extrinsic factors and:
- Injurious falls
- Rate of falls normalized to steps taken
- In-home and out-of-home falls
Aim 3 - Impact of falls on mobility

Determine impact of falls on mobility

Are decreased PA and less travel outside the home a consequence of falls, or do they occur for other reasons (which also may need to be addressed)?

Secondary analyses – mobility changes and:
- Injurious falls
- In-home and out-of-home falls
Noise-enhanced Somatosensation, Gait, and Balance in Elderly People

Presented by: Lewis A. Lipsitz, MD
Co-Investigators: Brad Manor, PhD, James Niemi, and Matthew Lough

Hebrew SeniorLife, Beth Israel Deaconess Hospital, Wyss Institute, and Harvard Medical School, Boston, MA

Disclosures: None

Background

• Age-related impairments in somatosensation may lead to abnormal gait, falls, and injury.
• Contrary to conventional thought, small amounts of white noise can enhance the detection and transmission of weak signals, via the mechanism of “stochastic resonance”.
• The ability to detect subthreshold mechanical stimuli is enhanced by imperceptible electrical or mechanical noise.
Somatosensation is dependent upon complex neural pathways

"Higher-level" modulation

Somatosensory cortex
Activation

Spinal circuitry

Peripheral nerves

Mechanoreceptors

We can study the cortical response to sensory input using an MRI-compatible device that simulates walking.

Manor and Hao 2012, Magnetic Resonance in Medicine
Support: Harvard Catalyst KL2, Chinese International Young Scientist Grant
Foot pressure stimuli activate specific brain regions.

Stimulation to the right foot sole activated the following regions:

- Contralateral primary somatosensory cortex (S1)
- Contralateral primary and secondary motor cortices
- Bilateral supplementary motor area
- Bilateral dorsolateral prefrontal cortex (dIPFC)
- Cerebellum

Manor and Hao 2012, Magnetic Resonance in Medicine
Support: Harvard Catalyst KL2, Chinese International Young Scientist Grant

Aging and Age-Related Diseases (e.g. Diabetes) Reduce Neural Sensory Input

Young Skin

Diabetic

Old Skin

Neuropathy
Stochastic Resonance

The application of certain amounts of white noise can be used to enhance detection of a weak stimulus.

Application to Human Sensory Systems

• Applying imperceptible mechanical noise can improve somatosensation in the soles of the feet
Enhancing Sensation with Mechanical Noise

Enhancing Balance with a Vibrating Platform

Adapted from Priplata et al., Phys. Rev Lett., 2002
Enhancing Balance with Vibrating Insoles

Vibration set to 90% of sensory threshold

Adapted from Priplata et al., Lancet 2003; 362:1123

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young</th>
<th>Elderly</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Radius</td>
<td>5.9%</td>
<td>9.1%</td>
<td>0.530</td>
</tr>
<tr>
<td>Swept Area</td>
<td>8.5%</td>
<td>12.2%</td>
<td>0.009*</td>
</tr>
<tr>
<td>Max Radius</td>
<td>4.9%</td>
<td>7.9%</td>
<td>0.291</td>
</tr>
<tr>
<td>Range AP</td>
<td>7.5%</td>
<td>4.9%</td>
<td>0.015*</td>
</tr>
<tr>
<td>Range NIL</td>
<td>-1.5%</td>
<td>14.6%</td>
<td>0.022*</td>
</tr>
<tr>
<td>$&lt;\dot{y}^2&gt;$</td>
<td>6.9%</td>
<td>20.8%</td>
<td>0.018*</td>
</tr>
<tr>
<td>$D_y$ (s°)</td>
<td>34.6%</td>
<td>21.7%</td>
<td>0.024*</td>
</tr>
<tr>
<td>$M_y$</td>
<td>12.3%</td>
<td>7.1%</td>
<td>0.281</td>
</tr>
</tbody>
</table>

* statistically significant (p < 0.05)

Balance: Center of Pressure
Testing Effects of Vibrating Sandals on Gait

- Three tactors deliver 0-100 Hz mechanical white noise
- Force sensing resistors (FSRs) record the pressure changes associated with the cyclic pattern of walking
- Large power requirements, tethered to power supply

Clinical Testing

- 12 young, 18 elderly non-fallers, 18 elderly recurrent fallers
- Vibration set at 90% of sensory threshold for one-legged, two-legged, and sitting positions
- Three 6 minute trials around a 22 m elliptical track randomized to 3 min. with and 3 min. without noise
Results

Significant reduction in stride time, stance time, and swing time variability in elderly fallers.

Galica et. al., *Gait and Posture*, 2009

Piezo-electric Vibratory Insoles – Version 2
Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Completed Subjects (n=12)</th>
<th>Failed Vibration Screening (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>73.8 ± 8.1</td>
<td>79.3 ± 7.8</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>1 (8.3)</td>
<td>8 (29.6)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>11 (91.7)</td>
<td>19 (70.4)</td>
</tr>
<tr>
<td>African-Amer., n (%)</td>
<td>3 (25)</td>
<td>Not available</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>9 (75)</td>
<td>Not available</td>
</tr>
<tr>
<td>Height (cm), mean ± SD</td>
<td>158.1 ± 10.3</td>
<td>Not available</td>
</tr>
<tr>
<td>Weight (lb), mean ± SD</td>
<td>147.5 ± 29.6</td>
<td>Not available</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>26.7 ± 4.5</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Stability of Sensory Thresholds
### Effect of Insoles on Balance

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean for Each Stimulation Level (CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>70%</td>
</tr>
<tr>
<td>Area ellipse, EO (mm²)</td>
<td>190.8 (150.8, 230.9)</td>
<td>156.2 (116.2, 196.3)</td>
</tr>
<tr>
<td>Area ellipse, EC (mm²)</td>
<td>248.6 (196.7, 300.6)</td>
<td>217.8 (165.9, 269.8)</td>
</tr>
<tr>
<td>ML average sway, EO (mm)</td>
<td>2.63 (2.26, 2.99)</td>
<td>2.29 (1.92, 2.66)</td>
</tr>
<tr>
<td>ML average sway, EC (mm)</td>
<td>2.83 (2.37, 3.29)</td>
<td>2.70 (2.12, 3.04)</td>
</tr>
</tbody>
</table>

Superscripts a & b indicate post-hoc comparisons that are statistically similar (a-a, b-b) or different (a-b).

### Effect of Insoles on Timed-Up-and-Go and Gait Variability

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean for Each Stimulation Level (CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>70%</td>
</tr>
<tr>
<td>TUG (s)</td>
<td>9.75 (9.01, 10.49)</td>
<td>9.44 (8.70, 10.18)</td>
</tr>
<tr>
<td>Stride time, right foot (CV)</td>
<td>2.65 (2.43, 2.87)</td>
<td>2.31 (2.09, 2.54)</td>
</tr>
<tr>
<td>Stride time, left foot (CV)</td>
<td>2.83 (2.61, 3.06)</td>
<td>2.32 (2.10, 2.55)</td>
</tr>
<tr>
<td>Double support (CV)</td>
<td>8.36 (7.39, 9.33)</td>
<td>6.45 (5.48, 7.42)</td>
</tr>
</tbody>
</table>

Superscripts a & b indicate post-hoc comparisons that are statistically similar (a-a, b-b) or different (a-b).
Area of Ellipse for One Subject

Challenges to Insole Version 2

- We have shown proof of principle in healthy elderly subjects, but not in clinical populations.
- Insufficient power and vibration levels to set thresholds in patients who are heavy or have severe neuropathy and cannot feel the highest settings.
- Unknown effects in reducing falls and injuries.
Conclusions

• Age- and disease-related degeneration of peripheral somatosensory receptors reduce sensory input to motor control centers of the brain and impair mobility.

• Subsensory vibratory white noise can improve the detection of weak sensory signals via the mechanism of stochastic resonance.

• High-powered vibratory insoles can improve balance and gait in healthy elderly people and patients with stroke or peripheral neuropathy.

• Many engineering challenges remain.
Virtual Reality Treadmill Training: Effects on Gait, Cognition, and Brain Function
Jeffrey M. Hausdorff, PhD
Center for the Study of Movement, Cognition and Mobility
Tel Aviv Sourasky Medical Center
Department of Physical Therapy and Sagol School of Neuroscience, Tel Aviv University
E-mail: jhausdor@tlvmc.gov.il

November 4-5, 2014 Washington, DC
2014 Aging, the Central Nervous System, and Mobility in Older Adults
Prevention and Intervention

Formula for safe gait

Cognitive Function + Motor System + Sensory System = Safe Gait

- Attention
- Executive Function
- Obstacle Negotiation
- Dual Tasking
- Decision Making
- Adaptation

Background, Preliminary Studies, Translation to Practice, Clinical Experience, Future Directions
Multi-factorial treatment approach

**Gait** training that promotes **motor learning**, while introducing graded **motor** and **cognitive** challenges **tailored** to individual subjects

---

**VR for gait training in patients with Parkinson’s disease**

20 Subjects with PD  
18 Sessions

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>67.1 ± 6.5</td>
</tr>
<tr>
<td><strong>Gender (M/F)</strong></td>
<td>14/6</td>
</tr>
<tr>
<td><strong>Disease duration (y)</strong></td>
<td>9.8 ± 5.6</td>
</tr>
<tr>
<td><strong>H&amp;Y staging (I-IV)</strong></td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td><strong>Montreal Cognitive Assessment (MoCA)</strong></td>
<td>25.7 ± 1.7</td>
</tr>
</tbody>
</table>

Mirelman et al., JGMS 2011
Example of the Effects of Training

Training with Virtual Reality week 1

Training with Virtual Reality week 6

Results

Improvement in gait measures

Usual Walking  Dual Tasking  6MWT

Pre  Post  Follow-up

* * *

Mirelman et al., JGMS 2011
Comparison of treadmill training with VR (TT-VR) to TT without VR (TT)

Herman et al., Arch Phys Med Rehab 2007

Results
Improvement in cognitive measures

Mirelman et al., JGMS 2011
VR training effects on fall risk

Training effects in patients with Multiple Sclerosis

Training effects in elderly fallers

Timed Up & Go score [sec]

Number of falls

6 months pre 3 months post 6 months post

73%

Background Preliminary Studies Translation to Practice Clinical Experience Future Directions

Translating research into practice

2014 CNS Workshop: Session 4
Wednesday, November 5
A VR clinical service

- A 5-week VR training program
- Training provided 3 times a week x 1 hour

Data analysis
Patient characteristics

<table>
<thead>
<tr>
<th>N=60</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>72.18 ± 10.39</td>
</tr>
<tr>
<td>Gender (% Women)</td>
<td>50%</td>
</tr>
<tr>
<td>Education (y)</td>
<td>14.95 ± 3.87</td>
</tr>
<tr>
<td>Number of falls in last 6 months</td>
<td>3.02 ± 5.64</td>
</tr>
<tr>
<td>Baseline gait speed (m/sec)</td>
<td>1.12 ± 0.27</td>
</tr>
</tbody>
</table>

Extrapyramidal disorders 40%
Post-stroke 10%
High level gait disorder 18%
Idiopathic faller 5%
Peripheral neuropathy 17%
Other 10%
Results
Example outcomes

“People tell me I walk better”
“I’m able to concentrate better”
“I’m more aware and pay attention while walking”
“I feel safe enough to be able to walk alone outside”
Treadmill training in VR RCT

- **V-TIME**: A single-blinded, multi-center RCT comparing treadmill training (TT) and VR augmented training

- Elderly fallers, PD, MCI

- To date, 277 subjects trained

Mirelman et al, 2013

---

Treadmill training in virtual reality: Sample outcome measures
Training effects on frontal activation during VR obstacle negotiation in PD: plasticity?

![Graph showing fNIRS HbO2 level (μmol) for Sessions 3, 9, and 18 with p-values p=0.93 and p=0.04.]

fNIRS examples: frontal activation during different walking conditions

- **Usual Walking**
- **Dual Tasking**
- **Obstacle Negotiation**

![Images showing walking conditions with corresponding fNIRS examples.]

2014 CNS Workshop: Session 4
Wednesday, November 5
fNIRS findings: effects of walking condition in healthy young adults

Background
Preliminary Studies
Translation to Practice
Clinical Experience
Future Directions

Mirelman et al JNER 2014

fNIRS findings during usual walking

Background
Preliminary Studies
Translation to Practice
Clinical Experience
Future Directions

Mirelman et al submitted
fNIRS findings during dual tasking

HbO2 level [μmol]

Healthy young
Healthy older adults
Patients with PD

Usual walk
Dual task

Healthy young
Healthy older adults
Patients with PD

fNIRS findings during dual tasking

HbO2 level [μmol]

Healthy young
Healthy older adults
Patients with PD

Usual walk
Dual task

Healthy young
Healthy older adults
Patients with PD

Usual walk
Dual task

Mirelman et al submitted

Background
Preliminary Studies
Translation to Practice
Clinical Experience
Future Directions
Training effects on frontal activation during VR obstacle negotiation in PD: plasticity?

**Discussion**

- Engaging and motivating training → 95% adherence
- Applicable to diverse patient populations
- Improvement in gait and balance and in the performance of complex tasks
  - Task specific training
  - Transfer of enhanced abilities to untrained tasks
  - Retention
Discussion

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- Lior Yeshayahu
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- Noit Inbar
- Geut Dotan

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- Dr. Tanya Gurevich

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thank you!
Experience Corps on Activity, Brain, and Mobility
Michelle C. Carlson, PhD

Department of Mental Health
Center on Aging and Health
Johns Hopkins Bloomberg School of Public Health

Experience Corps Model

- Volunteers 60 and older
- Trained and placed in public elementary schools: K-3
- Critical mass: teams of 15-20 in each school
- High intensity: 15 hours per week
- Sustained dose: full school year
- Meaningful roles; important unmet needs
- Monthly stipend to reimburse for travel, lunch, etc.

Freedman & Fried, 1997; Fried et al., 2004; Fried et al., 2013
The Experience Corps (EC) Program

- Win-Win: simultaneously creates generative roles for older adults while assisting teachers with unmet needs of children in public elementary schools.
  - 15 volunteers X 15 hours = 225 hours per week

- Results of 4-7 month pilot trial demonstrated EC-related improvements among older adults in:
  - Improved Mobility (Fried et al., 2004)
  - Increased Walking and decreased TV watching
  - Executive Function & related prefrontal brain functions among highest risk (Carlson et al., 2008; Carlson et al., 2009)

P01-funded Randomized Controlled Trial: Baltimore Experience Corps Trial

- Randomized:
  - 702 aged 60 yrs and older to EC or low-activity, wait-list control
  - 30+ public elementary schools to EC or control

- Exposure: 2 years of high-intensity service

- Primary Outcomes measured annually:
  - Physical: Mobility difficulty, Gait speed
  - Cognitive: Memory, Executive fx

- Activity: Lifestyle Activity Questionnaire (LAQ)

- Brain Health Substudy (N=115)
  - Brain MRI: Cortical & Hippocampal volumes
  - Objective Physical Activity: Step Activity Monitor (SAM)

See Fried, Carlson, McGill, Seeman, Xue ... Rebok, 2013
Characteristics of BECT Participants (N=702)

Table 1. Sociodemographic characteristics of BECT participants

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (n=702)</th>
<th>Control participants (n=350)</th>
<th>Intervention participants (n=352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (60-89)</td>
<td>67.4 (5.9)</td>
<td>67.4 (5.8)</td>
<td>67.4 (5.9)</td>
</tr>
<tr>
<td>Black/African-American</td>
<td>92</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black/African-American</td>
<td>92</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/regular partner</td>
<td>28</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>35</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Widowed</td>
<td>28</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Never married/other</td>
<td>9</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ HS/GED</td>
<td>44</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>≥ Some college</td>
<td>56</td>
<td>57</td>
<td>55</td>
</tr>
<tr>
<td>Household income (yearly all sources)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$15,000</td>
<td>30</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>≥$15,000-&lt;$25,000</td>
<td>36</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>≥$25,000</td>
<td>34</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>Currently employed</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

Results from Pathways to Mechanisms to Mobility

Conceptual Framework for the Baltimore Experience Corps® Trial

Intervention | Primary Pathways | Mechanisms | Outcomes
--------------|-----------------|------------|-----------
Experience Corps Participation (generative service) | Physical Activity | Functional parameters: + strength & balance | Physical function (mobility) |
| Social Engagement | Cognitive parameters: + cognitive reserve Changes in brain structure and function | Cognitive function |
| Cognitive Stimulation | Psychosocial parameters: + social support + self-efficacy | Psychosocial health |
|                     |                   | Health care costs (hospital & outpatient costs) |
Analytic Models

- Intention to Treat (ITT): treated as exposed following randomization
- Complier Average Causal Effect (CACE): incorporates amount of intervention exposure
- Evaluated sex/gender as interaction term or stratification variable—sex differences in risks for physical disability, chronic diseases, and in brain morphology (Fried, et al., 2013)

Did We Increase Lifestyle & Cognitive Activity?
EC volunteers report half a day/month increase in overall activity level, especially in intellectual and physical activities 12-months post-baseline. No significant interactions by sex.

<table>
<thead>
<tr>
<th>Activity Domain</th>
<th>12-month ITT B (SE)</th>
<th>12-month CACE B (SE)</th>
<th>24-month ITT B (SE)</th>
<th>24-month CACE B (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Activity</td>
<td>0.43 (0.19) *</td>
<td>0.59 (0.29) *</td>
<td>0.22 (0.19)</td>
<td>0.55 (0.31) †</td>
</tr>
<tr>
<td>Intellectual</td>
<td>0.66 (0.31) *</td>
<td>0.92 (0.42) *</td>
<td>0.59 (0.30) †</td>
<td>1.07 (0.48) *</td>
</tr>
<tr>
<td>Social</td>
<td>0.10 (0.14)</td>
<td>0.43 (0.17) *</td>
<td>-0.26 (0.16)</td>
<td>-0.16 (0.39)</td>
</tr>
<tr>
<td>Physical</td>
<td>0.43 (0.21) *</td>
<td>0.95 (0.19) *</td>
<td>0.26 (0.22)</td>
<td>0.15 (0.17)</td>
</tr>
<tr>
<td>Creative</td>
<td>0.32 (0.32)</td>
<td>0.50 (0.44)</td>
<td>0.39 (0.33)</td>
<td>0.54 (0.43)</td>
</tr>
<tr>
<td>Passive</td>
<td>0.61 (0.51)</td>
<td>1.42 (0.83) †</td>
<td>0.83 (0.51)</td>
<td>1.94 (0.95) *</td>
</tr>
</tbody>
</table>

Note. *All models adjusted for age, sex, education, major morbidities, depressive symptoms, cohort, baseline LAQ.

Parisi, Kuo, Rebok, Xue, Fried, Gruenewald, Huang, Seeman, Roth, Tanner, & Carlson, in press
Did We Increase Daily Physical Activity After Program Participation? Step Activity Monitors (N=115):

Women in Experience Corps maintained average steps/day over 24 months *post-Intervention* while Controls declined.

![Graph showing average steps/day over 24 months for Control and Intervention groups.](image)

Female EC volunteers walked about 1200 more steps/day than Controls post-EC intervention.

Varma, V et al.- see Poster here

---

Mechanisms: Brain Health

* Men and women in the control arm exhibited typical rates of atrophy.
* Men in the Experience Corps arm showed a 0.7-1.6% *increase* in brain volumes.
* Women in Experience Corps also exhibited modest gains of 0.3-0.54% by 24 months of exposure that did not reach significance.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Intervention</td>
</tr>
<tr>
<td>Percent change in brain volume</td>
<td>12 months-Baseline</td>
<td>24 months-Baseline</td>
</tr>
<tr>
<td>Cortex</td>
<td>0.20%</td>
<td>-0.14%</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0.34%</td>
<td>-3.52%</td>
</tr>
</tbody>
</table>

Note: *All models adjusted for age, education, and intra-cranial volume (ICV).*

Carlson, Kuo, Chuang, Varma, et al., under review
Brain Health

Carlson, Kuo, Chuang, Varma, et al., under review
Carlson et al., under review

Mobility:  Mean difference in EC v. Controls at 12 & 24 months

Dose-Response: Higher levels of exposure to Experience Corps (CACE models) are related to greater benefits in gait. However, differences did not reach statistical significance.

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>CACE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60th Percentile of Exposure</td>
<td>80th Percentile of Exposure</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>0.38 (0.52)</td>
<td>0.30 (1.27)</td>
</tr>
<tr>
<td></td>
<td>ES = 0.04</td>
<td>ES = 0.04</td>
</tr>
<tr>
<td></td>
<td>-0.17 (0.43)</td>
<td>-0.23 (1.68)</td>
</tr>
<tr>
<td></td>
<td>ES = -0.02</td>
<td>ES = -0.03</td>
</tr>
<tr>
<td>24 months</td>
<td>-0.79 (3.77)</td>
<td>-0.09 (3.25)</td>
</tr>
<tr>
<td></td>
<td>ES = -0.09</td>
<td>ES = -0.01</td>
</tr>
<tr>
<td>Gait speed (m/sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>0.032 (0.022)</td>
<td>0.082 (0.044)</td>
</tr>
<tr>
<td></td>
<td>ES = 0.12</td>
<td>ES = 0.30</td>
</tr>
<tr>
<td></td>
<td>0.007 (0.022)</td>
<td>0.064 (0.066)</td>
</tr>
<tr>
<td></td>
<td>ES = 0.03</td>
<td>ES = 0.24</td>
</tr>
</tbody>
</table>

*All outcome models include centered age, sex, education, income, centered depression, health status, and cohort year as covariates. Grip strength and gait speed are continuous and mobility disability is nominal.

Xue, Carlson, Betz, Barron, …Rebok, & Fried., under review
Conclusions

Experience Corps led to benefits over 2 years in:

- **Physical Activity:**
  - Self-reported leisure activity in 1st year
  - Maintenance of post-program low-intensity walking activity
- **Cognitive Activity:** increases over both years
- **Social Activity:** increases during first year
- **Biological CNS Mechanism:** maintained & increased brain volumes over 2 years
- **Primary Mobility Outcomes:** non-significant, dose-dependent trends favoring EC volunteers. Entropy?

**Q 1:** Will changes in activity and mechanisms be durable post-intervention?

**Q 2:** With changes in multiple pathways, will EC volunteers better maintain mobility with continued follow-up?

---

Where Do We Go From Here to Promote Activity?

Small Steps...
Linking Physical Activity and Brain Health

Everyday Physical Activity: Small Increases in Daily Step Activity Are Associated with Larger Hippocampal Volume

Even small increases in physical activity may matter

Average steps/day

Peak bout of daily activity

Varma et al., under review

Building Other Models to Promote Activity in Daily Life

Greatest Amount & Highest Intensity of Daily Step Activity May Occur Outdoors in Community Spaces

Carlson, Varma, Adam, Crainiceanu, & Zippunikov, under review
Does It Matter Where Walking Activity Occurs?
Answer: Activity in community spaces most strongly associated with memory & mental speed

Discussion

- **Real-world activity** as a vehicle to promote and sustain:
  - Physical and cognitive activities
  - Meaning and value in one’s life—activity in the service of a generative goal
  - Social/ Community:
    - The glue or “Stickiness” factor to sustain it
    - Novel and less routine/predictable
### It Takes a Village:

Linda Fried (PI)
Dean, Columbia Mailman School of Public Health
George Rebok (co-PI)
Erwin Tan
Elizabeth Tanner
Jeanine Parisi
Alden Gross

Teresa Seeman
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Tara Gruenewald
University of California, Los Angeles

Sylvia McGill
Greater Homewood Community Corporation

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University of Pittsburgh

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- Johns Hopkins Neurobehavioral Research Unit
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- Greater Homewood Community Corporation & Intergenerational Community Services

**For Geo-Coded Activity:**

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Cognitive and Neural Correlates of Improved Mobility With Targeted Exercise Training
Cognitive and Neural Correlates of Improved Mobility With Targeted Exercise Training

Teresa Liu-Ambrose, PhD, PT
University of British Columbia, Department of Physical Therapy
Centre for Brain Health
Centre for Hip Health and Mobility
Canada Research Chair
teresa.ambrose@ubc.ca

Overview

Context → Studies → Potential Implications → Future Directions
Context

Mobility

Physical Function

Exercise

Cognitive Function

Studies

RCTs of Exercise

Falls

Gait Speed

Mobility
Exercise Training in Older Fallers

- Presented to a health care provider (ED or GP) with a fall
- Aged 70 years and older
  
  » Liu-Ambrose et al., 2008

Baseline Measurement

74 Randomized

Otago Exercise Program (OEP)

Guideline Care (CON)

6- & 12-Month Measurement

Outcomes

- Executive Functions

- Falls
  
  - Monthly calendars

- Physiological Profile Assessment (PPA)
  
  1. Quad strength
  2. Postural sway
  3. Hand reaction time
  4. Contrast sensitivity
  5. Proprioception
Results

• At 6 months
  – No significant between-group difference in PPA scores
    • 5% improvement in OEP
    • 0% change in CON
  – A significant between-group difference in Stroop Test performance
    • 13% improvement in OEP
    • 10% deterioration in CON

• At 12 months
  – Using negative binomial regression, the unadjusted incidence rate ratio of falls in the OEP group, compared with the CON group was 0.56.
  – Adjusted incidence rate ratio = 0.47
Studies

RCTs of Exercise

- Falls
- Gait Speed

Mobility

Resistance Training in Older Women

Liu-Ambrose et al., 2010 & 2011

Baseline Measurement

155 Randomized

- 1x/week Resistance Training
- 2x/week Resistance Training
- 2x/week Balance & Tone Exercises

12-Month Measurement
12-Month Measurement
12-Month Measurement
Outcomes

- Executive processes
  - Response inhibition/conflict resolution
  - Working memory
  - Set shifting
- Gait speed (4-meter walk)
- Neuroimaging
  - Structural MRI
  - WML progression
    - Semi-automated process (expert radiologist)

Covert Ischemic

Risk factors:
- Age
- Hypertension
- Diabetes
- Dyslipidemia

White Matter Lesions
Lacunes
Cerebral Microinfarcts
Results

155 @ Baseline 
(54/88 had WML)

135 @ 12 Months 
(42/54)

Overall Exercise Compliance = 68%

Compared with BAT, 1x/week and 2x/week RT significantly improved selective attention and conflict resolution performance.
Improved cognitive performance significantly associated with increased gait speed ($r=0.24; \ p<0.01$).

<table>
<thead>
<tr>
<th>Change in Gait Speed (m/s)</th>
<th>Change in Stroop Performance (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0.4</td>
</tr>
<tr>
<td>20</td>
<td>-0.2</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>0.2</td>
</tr>
<tr>
<td>80</td>
<td>0.4</td>
</tr>
<tr>
<td>100</td>
<td>0.6</td>
</tr>
<tr>
<td>120</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Results

- At trial completion, after adjusting for baseline WML volume, 2x RT group had significantly lower WML volume compared with the BAT group ($p=0.03$).
- There was no significant difference between the BAT group and the 1x RT group at trial completion ($p=0.77$).

» Bolandzadeh et al., Submitted
Descriptive Values for WML Volume (mm$^3$) for Baseline and Trial Completion.

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Baseline</th>
<th>Trial Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>2x RT Group</td>
<td>n=13</td>
<td>n=13</td>
</tr>
<tr>
<td>Mean WMLs (SD)</td>
<td>1805.03 (2456.57)</td>
<td>1903.50 (2684.03)*</td>
</tr>
<tr>
<td>1x RT Group</td>
<td>n=18</td>
<td>n=18</td>
</tr>
<tr>
<td>Mean WMLs (SD)</td>
<td>1774.52 (2007.44)</td>
<td>1920.26 (2127.23)</td>
</tr>
<tr>
<td>BAT Group</td>
<td>n=11</td>
<td>n=11</td>
</tr>
<tr>
<td>Mean WMLs (SD)</td>
<td>810.52 (1082.03)</td>
<td>952.51 (1310.84)</td>
</tr>
</tbody>
</table>

* Significantly different from BAT Group at p=0.03.
† WML = white matter lesion; 2x RT = twice-weekly resistance training; 1x RT = once-weekly resistance training; BAT = balance and tone (i.e., control)

Reduced WML progression was associated with improved gait speed ($r=0.31$, $p=0.04$).
Results

- Exercise may positively impact mobility via improved executive functions and brain health.
- The reduction of cardiometabolic risk factors should be a focus/key consideration when designing exercise interventions to promote both cognitive function and mobility.

Potential Implications
Future Directions: Preliminary Results

- There was significant change in FPN connectivity over time between groups, with the AT increasing in FPN functional connectivity compared with CON ($p<0.05$).
- Increased FPN was associated with better SPPB performance ($r=0.45$, $p=0.03$).

Future Directions

- Studies with larger samples are needed to allow proper mediation analyses
  - Direct effects
  - Indirect effects
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