Aging, the Central Nervous System, and Mobility in Older Adults: Evidence on Changes in the Central Nervous System Control of Movement Across the Lifespan and in Aging

November 12-14, 2012
Marriott Marquis & Marina
San Diego, California

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

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

Aims of Aging, the Central Nervous System, and Mobility in Older Adults are to:
1. Examine existing evidence from basic, epidemiological, and clinical perspectives and enhance links from animal studies to human investigation of both normal aging and disease at the individual and population level;
2. Promote collaborations among basic, epidemiological, and clinical scientists of interrelated disciplines who might not otherwise have an opportunity to work together;
3. Identify knowledge gaps, barriers to progress, alternative strategies, and prospects for future inquiry through discussions of emerging research findings;
4. Emphasize cutting-edge methodologies for central nervous system (CNS) and mobility measures;
5. Support involvement from junior investigators, women, minorities, and other underrepresented groups;
6. Encourage discussions and exchanges of ideas from workshop participants by providing ample time for interactions and using multimedia presentation formats, including videos; and
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.
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Marriott Marquis & Marina • San Diego, California
November 2012
Program Committee Roster

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Senior Director, Professional Affairs
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Director, Layton Aging and Alzheimer’s Disease Center
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Joe Verghese, MB, BS
Professor of Neurology
Murray D. Gross Memorial Faculty Scholar in Gerontology
Director, Division of Cognitive and Motor Aging
Albert Einstein College of Medicine
Caterina Rosano, MD, MPH
Caterina Rosano is Associate Professor and Director of the Neuroepidemiology Area of Concentration for the Department of Epidemiology in the Graduate School of Health at the University of Pittsburgh. She received her MD from the University of Palermo Medical School in Italy and later received her MPH 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. Dr. Rosano’s 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 that they will contribute to the discovery of new approaches to the promotion of disability-free survival. Additionally, Dr. Rosano is interested in and focuses on the application and validation of advanced statistical modeling algorithms for data reduction and the study of the mechanisms underlying brain degeneration, specifically dysmetabolic processes.

Jeffrey Kaye, MD
Jeffrey Kaye is Director of the National Institute on Aging (NIA)–Oregon Center for Aging and Technology (ORCATECH) and Director of the NIA–Layton Aging and Alzheimer’s Disease Center. Dr. Kaye serves as the Layton Endowed Professor of Neurology and Biomedical Engineering at Oregon Health and Science University. He also directs the Geriatric Neurology program at the Portland Veterans Affairs Medical Center in Oregon. His research has focused over the past two decades on the question of why some individuals remain protected from frailty and dependency at advanced ages while others succumb at much earlier times. This work has relied on a number of approaches ranging across the fields of genetics, neuroimaging, physiology and continuous activity monitoring. He leads several longitudinal studies on aging including the ongoing Oregon Brain Aging Study, established in 1989, and the Intelligent Systems for Detection of Aging Changes (ISAAC) study using ubiquitous, unobtrusive technologies for assessment of elders in their homes to detect changes signaling imminent decline of function. Dr. Kaye has received the Charles Dolan Hatfield Research Award for his work. He is listed in Best Doctors in America. He serves on many national and international panels and review boards in the fields of geriatrics, neurology, and technology including as a commissioner for the Center for Aging Services and Technology, Chair of the Technology Professional Interest Area Workgroup for the National Alzheimer’s Association and on the Leadership Council of the Network on Environment, Services, and Technologies for the American Society on Aging. He is the author of more than 250 scientific publications and holds several major grant awards from federal agencies, national foundations, and industrial sponsors.

Richard Camicioli, MD
Richard Camicioli is a Geriatric Neurologist with an interest in both cognitive and movement disorders. He obtained his MDCM from McGill University in 1987 and completed his neurology residency at McGill in 1991. He then began a VA Fellowship in Geriatric Neurology at the Oregon Health and Sciences University and the Portland VA Medical Center. He developed an interest in the in the relationship between motor function and cognition. This led to work with the Oregon Brain Aging Study. Since joining the University of Alberta, he has focused on cognitive decline in people with Parkinson’s disease and has continued work with older “controls.” Recently he has rekindled studying people with mild cognitive impairment in order to define clinically distinct phenotypes.
Jack Guralnik, MD, PhD, MPH
Jack Guralnik is Professor of Epidemiology and Public Health at the University of Maryland School of Medicine. He spent 25 years in research at the National Institute on Aging and was Chief of the intramural Laboratory of Epidemiology, Demography and Biometry. He received his MD from Jefferson Medical College in Philadelphia and MPH and PhD from the University of California, Berkeley. He is Board Certified in Public Health and General Preventive Medicine. Dr. Guralnik has received multiple professional awards during his career. In 2005, he was awarded an Honorary Doctorate from the University of Tampere in Finland and, in 2009, received the Nation Institutes of Health Director’s Mentoring Award. His primary areas of interest in the epidemiology of aging include the study of physical functioning and disability, the benefits of physical activity, the prevalence and impact of multiple co-existing chronic conditions, factors associated with healthy aging, methods of assessment of health and functional status, and trends in demographic and health status characteristics of the older population. He has published over 550 journal articles and book chapters in these areas of aging research and has taught and lectured extensively in the United States and abroad.

Joe Verghese, MB, BS
Joe Verghese is a 1989 graduate in medicine and surgery of St. Johns Medical College in Bangalore, India. He then completed postgraduate training in Internal Medicine and Neurology in United Kingdom. At the Albert Einstein College of Medicine, Bronx, New York, he completed a Neurology Residency in 1998 followed by Fellowship training in Neurophysiology as well as Aging and Dementia in 1999. He received a MS in Clinical Research Methods with Distinction from the Albert Einstein College of Medicine in 2001. Dr. Verghese is Board Certified in Neurology. Currently, Dr. Verghese is Professor and Director of the Division of Cognitive and Motor Aging in the Department of Neurology as well as Chief of Geriatrics in the Department of Medicine at the Albert Einstein College of Medicine. His research interest is the effects of disease and aging on mobility and cognition in older adults, and he has had several peer-reviewed publications and federally funded research grants in this area. His current projects include studying the influence of cognitively stimulating activities on reducing risk of dementia, global health studies in dementia, and cognitive control of gait and mobility.

David A. Bennett, MD
David A. Bennett is the Robert C. Borwell Professor of Neurological Sciences and Director of the Rush Alzheimer’s Disease Center, a free-standing multi-disciplinary clinical and research center at Rush University Medical Center. Dr. Bennett is internationally known for his research on the health and well-being of older persons. His main research interest is the prevention of common chronic diseases, especially neurodegenerative diseases and stroke that cause loss of cognitive and motor function in older persons, and in the identification of factors that promote health and well-being in aging. He is Principal Investigator of several studies funded by the National Institutes of Health including the Rush Religious Orders Study and the Memory and Aging Project, both cohort studies of risk factors for common aging diseases, and cognitive and motor decline, among persons enrolled without dementia who agree to organ donation at death. His studies incorporate risk factors, cognitive and motor function, functional abilities, neuropathology and neuromolecular markers of resilience, with genomics, epigenomics, transcriptomics, proteomics, and metabolomics, in addition to biofluid and neuroimaging biomarkers to understand the pathways linking risk factors to adverse health outcomes or the maintenance of well-being. He has more than 375 peer-reviewed manuscripts and serves on many national and international advisory and editorial boards.

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 particularly 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 PhD in Biological Chemistry and Molecular Pharmacology at Harvard University. Her PhD 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 post-doctoral 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.

Mark Hallett, MD
Mark Hallett obtained his MD at Harvard University, interned at the Peter Bent Brigham Hospital, and trained in Neurology at Massachusetts General Hospital. Dr. Hallett had fellowships in Neurophysiology at the National Institutes of Health and at the Institute of Psychiatry in London. From 1976 to 1984, he was Chief of the Clinical Neurophysiology Laboratory at the Brigham and Women’s Hospital and Associate Professor of Neurology at Harvard Medical School. Since 1984, he has been at the National Institute of Neurological Disorders and Stroke, where he serves as Chief of the Human Motor Control Section and pursues research on the Physiology of Human Movement Disorders and other problems of motor control. He also served as Clinical Director of the Nation Institute of Neurological Disorders and Stroke until July 2000. Dr. Hallett is Clinical Professor of Neurology at The George Washington University School of Medicine and Health Sciences, Adjunct Professor at the College of Chemical and Life Sciences at the University of Maryland, and Clinical Professor of Neurology at the Uniformed Services University of the Health Sciences. He is Past President of the American Association of Electrodiagnostic Medicine and the Movement Disorder Society. He also served as Vice President of the American Academy of Neurology. Currently, Dr. Hallett also serves on the editorial boards of Clinical Neurophysiology, Brain Stimulation, Acta Neurologica Scandinavica, Journal of Clinical Neurophysiology, Medical Problems of Performing Artists, Annals of Neurology, The Cerebellum, and Neurotherapeutics. The main work of his group focuses on the physiology and pathophysiology of movement. Dr. Hallett’s interests in motor control are wide ranging, and include brain plasticity and its relevance to neurological disorders and the pathophysiology of dystonia, parkinsonism, and myoclonus.

Olivier Beauchet, MD, PhD
Olivier Beauchet is a Full Professor of Medicine and Head of the Geriatrics Division in the Department of Neuroscience at Angers University Hospital in France. He currently holds other positions at the University of Angers including Chair of Internal Medicine and Geriatrics and Director of Memory Clinic. He has earned the following academic degrees: MD (Neurologist, Internal Medicine, Geriatrician), MS in Neuropsychology (Neuropsychologist); and PhD (Human Motricity and Handicap). Dr. Beauchet’s wide-ranging research includes gait, balance, and cognitive disorders in the elderly, and vitamin D deficiency and its neurologic adverse effects. He is a sitting member on the Laboratory of Process of Thinking and Intervention, Faculty of Medicine, at the University of Angers.

Yaakov Stern, PhD
Yaakov Stern is Professor of Clinical Neuropsychology in the Departments of Neurology, Psychiatry, and Psychology, as well as the in Sergievsky Center and the Taub Institute for the Research on Alzheimer’s Disease and the Aging Brain, at Columbia University College of Physicians and Surgeons. Dr. Stern directs the Cognitive Neuroscience Division of the Department of Neurology and is Associate Director of the Alzheimer’s Disease Research Center. He also directs the post-doctoral training program “Neuropsychology and Cognition in Aging.” Dr. Stern earned his BA in Psychology at Touro College in New York City. He earned his PhD at the Experimental Cognition program of City University of the City of New York. Dr. Stern’s research focuses on cognition in normal aging and in diseases of aging, particularly Alzheimer’s disease. A major focus of his research is understanding the factors contributing to individual differences in the cognitive and functional changes resulting from brain insult. His research approach includes classic neuropsychological and cognitive experimental techniques, as well as functional imaging. He is also conducting a cognitive intervention studies in healthy individuals, and a natural history study of Alzheimer’s disease. He has published over 400 peer-reviewed papers, numerous chapters, and edited a book on cognitive reserve.
**Gregorio Valdez, PhD**

Gregorio Valdez is Assistant Professor at the Virginia Tech Carilion Research Institute and in the Department of Biological Sciences at Virginia Tech. Dr. Valdez’s research is focused on discovering and manipulating molecules that protect synapses from the ravages of aging and age-related neurological diseases, particularly at the motor neuron to muscle synapse, the neuromuscular junction. Recently, he discovered that a life-long caloric restricted diet and exercise can slow and even reverse synaptic aging. He earned his PhD from the State University New York at Stony Brook in the lab of Dr. Simon Halegoua, where he examined the mechanisms for trafficking of growth factor receptors at developing synapses. His postdoctoral training was as a Ruth R. Kirstein National Research Service Award Fellow in the laboratory of Dr. Joshua R. Sanes at Harvard University in the Center for Brain Sciences, where he investigated the mechanisms of synaptic maintenance in aged, injured, and disease-afflicted neuromuscular junctions. Continuing this line of research, the Valdez lab aims to understand the structural changes that this undergoes during normal aging, and to seek out molecular mechanisms that function to maintain its structure and function using mice as a model system and a number of molecular and imaging techniques, including chronic in vivo imaging, genetic manipulation with viral-based approaches. The goal of his lab is to discover molecular machineries that function to protect all synapses from the insults of aging and diseases. His work has appeared in many scientific journals including *Science*, *Cell*, *PNAS*, *The Journal of Neuroscience*, and *The Journal of Cell Biology*.

**Howard Aizenstein, MD, PhD**

Howard Aizenstein is Associate Professor of Psychiatry and Bioengineering and Director of the Geriatric Psychiatry Neuroimaging Laboratory at The Western Psychiatric Institute & Clinic of the University of Pittsburgh. Dr. Aizenstein graduated from the Medical Scholars MD/PhD program at the University of Illinois in Urbana-Champaign with an MD and a PhD in Computer Science (Computational Learning Theory). He then completed residency in General and Adult Psychiatry at the University of Pittsburgh School of Medicine, where he also completed a clinical fellowship in Geriatric Psychiatry. Dr. Aizenstein’s research interests focus on structural and functional brain MRI in elderly individuals with cognitive impairment and mood disorders. His research is integrates software engineering and clinical aspects of neuroimaging and brain mapping. In clinically oriented research, he uses imaging approaches to investigate therapeutic response to antidepressant drugs in late-life depression.

**Nicolaas I. Bohnen, MD, PhD**

Nicolaas I. Bohnen is Professor of Radiology and Neurology at the University of Michigan, Ann Arbor, MI. He attended medical school in the Netherlands and completed a PhD in neuropsychology. He completed residency training in neurology (Mayo Clinic, Rochester, MN) and nuclear medicine (University of Michigan, Ann Arbor, MI). He was a fellow in movement disorders at the University of Michigan Medical Center. He holds clinical appointments in the Departments of Radiology (Division of Nuclear Medicine), Neurology at the University of Michigan and the Ann Arbor VA where he directs the movement disorders clinic. Dr. Bohnen’s research interests include the use of PET and MRI in the study of neurodegenerative disorders and normal aging. He is the Director of the UM Functional Neuroimaging, Cognitive and Mobility Laboratory where his clinical research has a focus on neurobiological correlates of mobility and cognition in normal aging and Parkinson disease and biomarker development for the diagnosis and treatment monitoring in Parkinson disease. His research is funded by grants from the NIH, the Department of Veterans Affairs, and the Michael J. Fox Foundation.

**Jeffrey M. Hausdorff, PhD**

Jeffrey M. Hausdorff received a BS in Engineering from the Cooper Union, MS in Mechanical Engineering/Biomechanics from the Massachusetts Institute of Technology (MIT), and PhD in Biomedical Engineering from Boston University. After completing a postdoctoral fellowship in the Division on Aging at Harvard Medical School, he joined the faculty, first as an Instructor in Medicine and later as an Assistant Professor. He also served as Associate Director for the Institute for Nonlinear Dynamics in Physiology and Medicine and held appointments at MIT and Beth Israel Deaconess Medical Center in Boston. Currently, he is a Lecturer in Medicine at Harvard Medical School, Professor in the Sackler Faculty of Medicine at Tel-Aviv University, and Director of the Laboratory for Gait and Neurodynamics at the Tel-Aviv Sourasky Medical Center. 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 is
particularly focused 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 cutting-edge 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 a number of journals including *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.

**Roee Holtzer, PhD**

Roee Holtzer is Associate Professor at Ferkauf Graduate School of Psychology and the Department of Neurology at Albert Einstein College of Medicine of Yeshiva University. He is also the director of the minor in Clinical Neuropsychology. Dr. Holtzer earned his PhD in Clinical Psychology with a secondary emphasis on Neuropsychology at the State University of New York at Binghamton. He completed his internship training in Clinical Psychology at the Rusk Institute of New York University. He also completed a T-32 Postdoctoral Fellowship in Neuropsychology and Cognition in Aging and Dementia at the Cognitive Neuroscience Division of the Sergievsky Center of Columbia University Medical Center. He is licensed as a psychologist in New York State. Dr. Holtzer is a recipient of the Beeson Award from the National Institute on Aging. He studies higher order cognitive functions such as attention, memory, and executive control in normal and clinical populations. Further, he is interested in studying the utility of cognitive functions as markers of disease progression or remission and as predictors of outcomes that are of major clinical and public health interest. His current funded research uses a multilevel theory-driven method integrating clinical, cognitive neuroscience, genetic, and neuroimaging approaches to identify predictors of mobility impairments in aging. The long-term goal of this translational research is to identify specific modifiable mechanisms pertinent to developing more efficient risk assessment and intervention programs of cognitive and motor decline in aging.

**Heather Allore, PhD**

Heather Allore is Director of the Yale Program on Aging and Senior Research Scientist in Medicine (Geriatrics) at the Yale School of Medicine. The focus of Dr. Allore’s research collaborations and methodological development work at the Yale Program on Aging is the investigation of geriatric health conditions in which multiple contributing factors affect multiple outcomes. Innovative designs and biostatistical methods are required to rigorously address the myriad of unanswered scientific questions related to geriatric health conditions, including multiple chronic conditions. Dr. Allore has developed and extended analytic methods to address the many challenges of aging research, and she has trained biostatisticians and clinicians in these methods. Dr. Allore’s research has focused on issues related to the design and analysis of studies of multicomponent interventions and observational studies of multifactorial geriatric condition. She has a wealth of experience conducting epidemiologic studies and is a recognized authority on longitudinal statistical methods, including extended Cox models for state transitions, generalized estimating equations, mixed effects models, latent class trajectory models, and joint models. Dr. Allore is the founder and leader of the field of Gerontological Biostatistics within the American Statistical Association. This discipline trains biostatisticians for conducting collaborative clinical research with geriatricians and gerontologists in elderly populations and provides the basis for the development of new statistical methodology.
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Movement Across the Lifespan and in Aging
Marriott Marquis & Marina • San Diego, California
November 12-14, 2012

PROGRAM AGENDA

MONDAY, NOVEMBER 12, 2012

6:00 PM–6:30 PM  Registration: Marriott Marquis & Marina Bayside

6:30 PM–6:50 PM  Welcome and Introductions
                  Linda Harootyan
                  The Gerontological Society of America

                  Caterina Rosano, MD, MPH†
                  University of Pittsburgh

6:50 PM–7:30 PM  Opening Session: Overview and Goals of Workshop
                  Jeffrey Kaye, MD†
                  Oregon Health and Science University

7:30 PM  Networking Reception

8:30 PM  Adjournment
          Enjoy a wonderful evening in San Diego on your own!

TUESDAY, NOVEMBER 13, 2012

7:00 AM–7:15 AM  Breakfast: Marriott Marquis & Marina Ballroom G

7:15 AM–7:30 AM  Opening Remarks
                  Caterina Rosano, MD, MPH†

7:30 AM–9:00 AM  Session 1: The Evidence From Epidemiological and Clinical Studies
                  Moderator
                  Richard Camicioli, MD†
                  University of Alberta, Canada

                  Evidence for a multisystem approach to mobility impairment in older adults living in the community

                  Speaker
                  Jack M. Guralnik, MD, PhD, MPH†
                  University of Maryland

† Program Committee Member
Evidence from neuroimaging and neuroepidemiology: The artificial dichotomy of cognition vs. mobility

Speakers
Caterina Rosano, MD, MPH†
University of Pittsburgh

Joe Verghese, MBBS‡
Albert Einstein College of Medicine

The evidence from epidemiological and clinical studies: Evidence from human disease-based models
Speaker
David A. Bennett, MD†
Rush University Medical Center

9:00 AM–9:30 AM Summary of Session 1 and Discussion
Moderator
Richard Camicioli, MD†
University of Alberta, Canada

9:30 AM–10:30 AM 1st Roundtable Focused Group Discussion
Evaluate the CNS effect on mobility

10:30 AM–10:45 AM Blackberry Break

10:45 AM–12:15 PM Session 2: The Evidence From Basic Science Studies
Moderator
Wen G. Chen, PhD†
National Institute on Aging

Central nervous system control of locomotion, dual tasking, and automaticity
Speaker
Mark Hallett, MD
National Institute of Neurological Disorders and Stroke

Age-related changes in cortical gate propulsion control: Evidence from human data
Speaker
Olivier Beauchet, MD, PhD
University of Angers, France

Influences on brain plasticity: Implications for cognition and mobility control
Speaker
Yaakov Stern, PhD
Taub Institute

Evidence from animal models: Effects of aging and lifestyle factors on motor synapses
Speaker
Gregorio Valdez, PhD
Virginia Tech Carilion Research Institute

12:15 PM–12:45 PM Summary of Session 2 and Discussion
Moderator
Wen G. Chen, PhD†
National Institute on Aging

† Program Committee Member
12:45 PM–2:15 PM  Working Lunch and 2nd Roundtable Focused Group Discussion

- Evaluate multisystem effects on movement

2:15 PM–2:45 PM  1st and 2nd Roundtable Reports and Feedback/Discussion
Moderators
Richard Camicioli, MD†
Wen G. Chen, PhD†

2:45 PM–3:00 PM  Blackberry Break

3:00 PM–4:30 PM  Session 3: Tools and Methods
Moderator
Howard Aizenstein, MD, PhD†
University of Pittsburgh

- Structure, neurochemistry, and function of CNS components related to mobility

  Speaker
  Nicolaas I. Bohnen, MD, PhD
  University of Michigan

- Mobility measures in the laboratory and in the field using body-worn and fixed sensor systems

  Speaker
  Jeffrey M. Hausdorff, PhD†
  Harvard Medical School

- Using neuropsychological measures, dual-task paradigms and functional near infrared spectroscopy to determine cognitive and brain mechanisms of mobility

  Speaker
  Roee Holtzer, PhD
  Albert Einstein College of Medicine

- Statistical and mathematical modeling approaches to multisystem studies

  Speaker
  Heather Allore, PhD
  Yale School of Medicine

4:30 PM–5:00 PM  Summary of Session 3 and Discussion
Moderator
Howard Aizenstein, MD, PhD†
University of Pittsburgh

5:00 PM–6:00 PM  3rd Roundtable Focused Group Discussion

- Evaluate methodological approaches to the study of CNS and mobility

6:00 PM–6:30 PM  3rd Roundtable Reports and Feedback/Discussion
Moderator
Howard Aizenstein, MD, PhD†

6:30 PM  Closing Remarks and Adjournment for the Day
Caterina Rosano, MD, MPH†

† Program Committee Member
7:00 AM–7:30 AM  Breakfast: Marriott Marquis & Marina Ballroom G

7:30 AM–8:00 AM  Introduction and Goals of Group Discussion

8:00 AM–11:30 AM  Recommendations: Group Discussion

11:30 AM–12:00 PM  Closing Remarks

12:00 PM  Adjournment

Enjoy The Gerontological Society of America Annual Scientific Meeting

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
  •  Travel Award winners will be presenting in the Health Sciences Section poster session
Questions

1. What are the issues regarding prevalence of mobility impairment in older adults? Do we have data about how prevalent mobility impairment is among the general older adult population? How does it compare with other major geriatric problems?

2. What are the significant clinical implications for mobility impairment in older adults? Are the data strong? Do we need better evidence? What other types of functional independence issues are related to mobility impairment in older adults, such as possible connections to future development of Alzheimer disease, dementia, etc.?

3. What is the socioeconomic cost of mobility impairment in older adults?

4. What are the other known non-CNS factors contributing to mobility impairment in older adults? What kind of evidence is there for those factors?

5. What extent does the CNS contribute to mobility impairment in older adults? How prevalent is it that mobility impairment in older adults is at least partially correlated with (or due to) neural dysfunction? What lines of evidence support the connections between the CNS and mobility impairment in older adults?
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Monday, November 12, 2012 to Wednesday, November 14, 2012
San Diego, California

Welcome

Linda Krogh Harootyan
Deputy Executive Director
Senior Director, Professional Affairs
The Gerontological Society of America
• 67 years strong
• Largest national/international interdisciplinary professional membership organization touching all facets of aging

GSA’s Mission
• Promote the conduct and funding of multi- and interdisciplinary research in aging
• Disseminate gerontological research findings to researchers, practitioners, decision/opinion makers, and the public
• Promote, support, and advocate for education on aging across all disciplines
• Foster the application of scientific research into the development of policy
GSA and Affiliates

- Oldest/largest international, interdisciplinary scientific organization in aging
- Association for Gerontology in Higher Education
  - Academic institutions with programs in gerontology and/or geriatrics
- National Academy on an Aging Society
  - Non-partisan policy institute

GSA Membership Overview

- Over 5,500 researchers, educators, practitioners, and other professionals in the field of aging
  - Highest growth in international membership
- Medical and Biological Sciences; Health Sciences; Behavioral and Social Sciences; Policy and Practice
- Emerging Scholar and Professional Organization (ESPO)
International Membership

- Members from 45 countries; in addition to United States, top membership includes:

  - Australia
  - Brazil
  - Canada
  - China
  - Germany
  - Hong Kong
  - Italy
  - Japan
  - Netherlands
  - South Korea
  - Sweden
  - Taiwan
  - United Kingdom

GSA’s Strategic Vision and Focus

- Our Vision
  - To be recognized as the preferred, trusted, credible partner for our research, knowledge, and unique collaborations across all disciplines leading to important innovative solutions in the field of aging

- Our Focus
  - Advancing innovation in aging to address unmet needs through our credible, trusted, respected members, affiliates, offerings, and collaborations
Acknowledgements

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The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.
Agenda Review and Introductions

Caterina Rosano, MD, MPH
Associate Professor of Epidemiology
Graduate School of Public Health
University of Pittsburgh

3-Year Workshop Overview

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

- Caterina Rosano, MD, MPH
- Stephanie A. Studenski, MD, MPH
- Howard Aizenstein, MD, PhD
- David A. Bennett, MD
- Sandra Black, MD
- Richard Camicioli, MD
- Wen G. Chen, PhD
- Luigi Ferrucci, MD, PhD
- Jack M. Guralnik, MD, PhD, MPH
- Jeffrey M. Hausdorff, PhD
- Jeffrey Kaye, MD
- Lenore J. Launer, PhD
- Lewis A. Lipsitz, MD
- Anne B. Newman, MD, MPH
- Joe Verghese, MB, BS

Junior Faculty Travel Awardees

- Benjamin D. Capistrant, ScD
- Yi-Fang Chuang, MD, PhD
- Jason R. Gerstner, PhD
- Gurtej Singh Grewal, PhD
- Azizah J. Jor’dan, PhD
- Jeannette R. Mahoney, PhD
- Ha Nguyen, PhD, MPH
- Michael Schwenk, PhD
- Sarinnapha (Fah) Vasunilashorn, PhD
- Lan Yao, PhD, RN
Agenda

MONDAY
• Opening Session
• Networking Reception

TUESDAY
• Session 1: Evidence From Epidemiological and Clinical Studies
  – Panel presentation and small group discussion
• Session 2: Evidence From Basic Science Studies
  – Panel presentation and small group discussion
• Small group reports and feedback
• Session 3: Tools and Methods
  – Panel presentation and small group discussion
• Small group reports and feedback

WEDNESDAY
• Group Discussion
• Closing Remarks

Opening Session
Overview and Goals of Workshop

Jeffrey Kaye, MD
Professor of Neurology and Biomedical Engineering
Oregon Health and Science University
Director of the Layton Aging and Alzheimer’s Disease Center
Director of the Oregon Center for Aging and Technology
Evidence for a Multisystem Approach to Mobility Impairment in Older Adults Living in the Community

Jack M. Guralnik, MD, PhD, MPH

Department of Epidemiology and Public Health
University of Maryland School of Medicine
Maintaining Mobility in Late Life
Established Populations for the Epidemiologic Study of the Elderly (EPESE)

Study Design

Baseline
10,048 screened

Mobility
7227 (72%)

Mobility-related disability
2821 (28%)

Four annual followups

Maintained mobility
3847 (53%)

Loss mobility
2526 (35%)

Died - no mobility loss in prior interviews
608 (8%)

Missing data
246 (3%)


Odds Ratios for Loss of Mobility Over Four Years in Persons Initially Mobile, EPESE

**Relative Risk for Loss of Mobility According to Number of Chronic Conditions**

Multivariate Community-Stratified Summary

<table>
<thead>
<tr>
<th>Number of Conditions</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.4</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>1.7</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>2.3</td>
</tr>
<tr>
<td>4+</td>
<td>2.9</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Change in SPPB Score Over Interval During Which Participants Were Hospitalized for Specific Events

**Women’s Health and Aging Study**

<table>
<thead>
<tr>
<th>Event</th>
<th>Change in SPPB Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Fracture</td>
<td>-3.06</td>
</tr>
<tr>
<td>Stroke</td>
<td>-2.63</td>
</tr>
<tr>
<td>MI</td>
<td>-2.3</td>
</tr>
<tr>
<td>CHF</td>
<td>-1.48</td>
</tr>
<tr>
<td>No Events</td>
<td>-0.29</td>
</tr>
</tbody>
</table>


- MI = myocardial infarction
- CHF = congestive heart failure
Chronic Conditions Associated with Disability

Heart disease
  Myocardial infarction
  Angina
  Congestive Heart Failure
  Stroke
Osteoarthritis
Hip Fracture
Diabetes
Peripheral artery disease
Chronic Obstructive Pulmonary Disease
Cancer
Visual Impairment
Depression
Cognitive Impairment


Physiologic Subsystems of Mobility

Central Nervous System

Periph. Nervous System

Muscles

Bones & Joints

Sensory input

Energy Production and Delivery

Walking

Normal
- Usual pace
- Fast Pace

Provocative
- Obstacle
- Talking
- Narrow Base
- Low light
- Retrieving an Object
- 400 m. Walk
- Weight Increase

InChianti Study
The Homeostatic Network in the InCHIANTI Study and BLSA

**Homeostatic Network**
- **Hormones**
  - Insul., Ghrelin, Leptin, Adiponectin, Resistin, IGF-1, Testosterone, Estradiol, DHEA, Cortisol, Thyroid, PTH
- **Inflammation**
  - PCR, IL-8, sIL-6r, gp130, TNF-α, TNFβ1, TNFβ2, Ig-18, Ig-15, Homocysteine
- **Autonomic**
  - Heart Rate Variability
- **Ox Stress**
  - Carbonylated Proteins
- **Nutrition**
  - Food Intake, VitD, VitB12, Folate, VitE, Albumin
- **Phys Activity**
  - Self-Report Accelerometer

**Mobility Domains**
- **CNS**
- **PNS**
- **Muscles**
- **Bone, Joints**
- **Energy**
- **Feedback**

**Outcome**
- **Mobility**

---

**Graph**

*Age Adjusted 7 m Usual Walking Speed (m/ sec)*

*Source: Ferrucci, InCHIANTI Study*
Proportion of Subjects with Functional Limitations in 1991-93 According to Grip Strength Tertiles 25 Years Earlier
(3,218 Initially Healthy 45- to 68-Year-Old Men, Honolulu)

Functional Limitations
- Walking Speed ≤0.4 m/s
- Unable to Rise from a Chair

<table>
<thead>
<tr>
<th>Grip Strength Tertiles</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest</td>
<td>25</td>
</tr>
<tr>
<td>Middle</td>
<td>15</td>
</tr>
<tr>
<td>Lowest</td>
<td>10</td>
</tr>
</tbody>
</table>


Hazard ratios and 95% confidence intervals for incident mobility limitation among men (A) and women (B) by history of obesity (body mass index ≥30 kg/m2), the Health, Aging and Body Composition Study, 7 years of follow-up.

Source: Houston D K et al. Am. J. Epidemiol. 2009;169:927-936
IL-6 and 4-Year Incident Mobility Disability

- Probability of Mobility Disability
- Ln (IL-6)
- 2.5 pg/ml
- Adjusted probability
- 95% CI
- n=633

Source: Ferrucci et al. JAGS 1999;47:639

Survival Free of Mobility Limitation by Angiotensin-Converting Enzyme Genotype and Physical Activity

Health ABC

- Physically Active
  - [Energy Expenditure ≥1000 kcal/wk]
- Not Physically Active
  - [Energy Expenditure <1000 kcal/wk]
- Genotype
  - DD
  - ID
  - II

Source: Kritchevsky et al. JAMA 2005;294:691-698
Diurnal Drop in Cortisol and Walking Speed
Halcyon Collaboration Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Sex</th>
<th>Age</th>
<th>Cortisol</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaPS</td>
<td>M</td>
<td>73</td>
<td>Salivary</td>
<td>0.05 (-0.01, 0.11)</td>
<td>14.03</td>
</tr>
<tr>
<td>Whitehall II</td>
<td>B</td>
<td>61</td>
<td>Salivary</td>
<td>0.05 (0.02, 0.08)</td>
<td>49.23</td>
</tr>
<tr>
<td>LASA</td>
<td>B</td>
<td>74</td>
<td>Salivary</td>
<td>0.08 (0.02, 0.14)</td>
<td>17.03</td>
</tr>
<tr>
<td>NSHD</td>
<td>B</td>
<td>63</td>
<td>Salivary</td>
<td>0.04 (-0.01, 0.09)</td>
<td>19.70</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%; p = 0.790)</td>
<td></td>
<td></td>
<td></td>
<td>0.05 (0.03, 0.08)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Difference in standardised walk speed per SD increase in diurnal drop adjusted for age and sex

Source: Gardner et al. Psychoneuroendocrinology 2012

Neurologic Signs Associated with Slow Gait Speed and/or Inability to Walk 1 Km, InCHIANTI

- Muscle rigidity of the knee
- Paresis of the upper extremity
- Asymmetry in hip flexion strength
- Slow pronation-supination test
- Abnormal touch sensitivity
- Abnormal hand stereognosis
- Abnormal foot stereognosis
- Diminished Achilles reflex
- Snout reflex
- Abnormal Romberg test

Walking Speed and Percent Unable to Walk 1 Km
According to Number of Neurological Signs, InCHIANTI

Walking Speed (m/sec)

Number of Neurological Signs

0.0 0.5 1.0 1.5 2.0

0 1 2 3 4 5 6 7

0.0 0.5 1.0 1.5 2.0

0 1 2 3 4 5 6 7

No Neurological Signs
(Slope: -0.8±0.4 cm/sec per year)

One or More Neurological Signs
(Slope: -1.8±0.1 cm/sec per year)

Age (years)

Walking Speed (m/sec)
Executive Function and Walking Speed
The InCHIANTI Study

Age and Sex Adjusted Walking Speed (m/sec)

4 - meter course
(usual pace)

7 - meter obstacle course
(fast pace)

Delta-TMT (sec)

TMT = Trail making test


Unraveling the Pathway to Mobility Loss
Change in Muscle Strength Explains Accelerated Decline of Physical Function in Older Women With High Interleukin-6 Serum Levels: The Women’s Health and Aging Study

Walking Speed

<table>
<thead>
<tr>
<th>Follow-up (yrs)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking Speed on 4-m Course (m/sec)</td>
<td>0.7</td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Hip Flexors Strength

<table>
<thead>
<tr>
<th>Follow-up (yrs)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength (Kg)/ Body Mass Index (Kg / mq)</td>
<td>0.21</td>
<td>0.18</td>
<td>0.15</td>
<td>0.12</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Baseline IL-6 (pg/ml)
- < 1.76
- 1.76-3.55
- ≥ 3.55


Comorbidities and Impairments Explaining the Association Between Diabetes and Lower Extremity Function

Source: Volpato et al. Diabetes Care 2002;25:678-683
Mean SPPB Scores by Neuropathy Score and Diabetes Status, Adjusting for Age and Sex

IFG = Impaired fasting glucose
**Rate of Incident Severe Walking Disability According to Balance and Strength, WHAS**


**Prevalence and Incidence of Inability to Walk 400m According to Number of Impairments**

*Impairments: leg power, nerve conduction velocity, balance, vision*
Prevalence and Incidence of Inability to Walk 400 m According to Specific Pairs of Impairments
InCHIANTI Study

Prevalence

- A = leg power impairment, B = vision impairment
- A = leg power impairment, B = balance impairment
- A = nerve conduction impairment, B = balance impairment
- A = vision impairment, B = balance impairment

3-Year Incidence

- A = leg power impairment, B = vision impairment
- A = leg power impairment, B = balance impairment
- A = nerve conduction impairment, B = balance impairment
- A = vision impairment, B = balance impairment
**Significant Age- and Sex-Adjusted Risk of Mobility Disability by Domain, InCHIANTI Study**

**CNS**
- MMSE
- CES-D
- Balance
- Executive function

**PNS - Sensory**
- Pressure sensitivity
- Graphesthesia
- Somatosensory index
- Distance visual acuity
- Contrast sensitivity

**Muscle**
- Grip strength
- Strength - knee flexion, extension; hip flexion, extension, abduction; ankle dorsiflexion, plantarflexion; muscle power

**Bones and joints**
- Passive ROM - hip abduction, flexion; knee flexion; ankle plantarflexion
- Pain - knee, back
- Knee OA, hip OA

**Energy production and delivery**
- Systolic BP, diastolic BP
- Resting heart rate
- Dyspnea
- CHF
Summary

- Multiple diseases and conditions, health behaviors, physiologic changes with aging and biological indicators are associated with loss of mobility.

- A framework that characterizes domains responsible for mobility loss is helpful in approaching this complex process.

- In an individual, impairments in multiple domains often contribute to mobility loss.

- The study of the role of the CNS in mobility loss may be enhanced by considering its relationships with other domains.
Evidence from neuroimaging: The artificial dichotomy of cognition vs. mobility

Caterina Rosano, MD, MPH
Associate Professor of Epidemiology
Center for Aging and Population Health
Graduate School of Public Health

OUTLINE

1. Conceptual model to explain mobility impairment in aging
2. Neuroimaging studies of gait: summary of evidence
3. Implications for mechanisms
4. Challenges and opportunities

Proposed conceptual model mobility impairment in older adults living in the community

(age, lifestyle, cardiometabolic and inflammatory diseases or conditions)

Brain Structure → Neural Activation → Mobility

Sensorimotor brain networks

Visuospatial attention, information processing, and memory brain networks

Peripheral contributors to mobility control (Peripheral nervous, muscle-skeletal and cardiopulmonary systems)
1. Conceptual model to explain mobility impairment in aging

2. Neuroimaging studies of gait: summary of evidence

3. Implications for mechanisms

4. Challenges and opportunities
Multimodal neuroimaging

MACRO-structure (volume)

MICRO-structure (MTI, DTI)

Function
Neuronal activation, resting activity, blood flow (task-related, resting state arterial spin labeling)

Quantitative, complementary information of network integrity.

Macro-structure  Semiquantitative ratings, total brain

In older adults living in the community, diffuse brain structural abnormalities are associated with slower gait,* balance difficulty and greater risk of physical disability, independent of other important risk factors for poor mobility.

Masdeu; 1989; Hennerici 1994; Baloh 1995; Briley 1997; Whitman 1999; Guttmann, 1999; Camicioli 1999; Guo, 2000; Carmelli, 2000; Baloh 2003; Starr 2003; Wolfson, 2005; Longstreth, 2005; Gouw 2006; Silbert, 2008; Baezner, 2008; Palm 2009; Shrikanth 2009; Soumare, 2009; Murray 2010; DeLaat, 2010; DeLaat 2012; Steinke, 2002; Thompson 1987; DeLaat, 2011.

* longer DST, longer stride length
Macro-structure

VOLUMETRIC METHODS: GM regions

Step length, double support time, bradykinesia

Sensorimotor area

temolateral retrolentiform

Sensorymotor area

CHS, n=321, 82 yo, stroke and dementia free; HBP, n=311, 84 yo, dementia free

Gait speed
Tinetti/SPPB (Kerber 1998)

Gait disturbances (UPDRS)
Stride length (Zimmermann)*

Rosano, JGMS, 2007; Rosano JGMS 2009.

NIH Public Access
Author Manuscript
Published in final edited form as:

Gait Measures Indicate Underlying Focal Gray Matter Atrophy in the Brain of Older Adults

Characteristics

Body mass index, kg/m2, mean (SD)
Hypertension, %
Impaired vibration sensitivity, %
Hypokinesia, %
Ankle area ratio, cm2, mean (SD)
Prevalence of stroke, %
Cerebral risk factors of gait abnormalities
Brain infarct, %
White matter hyperintensities, %
Total brain volume, cm3, mean (SD)
Brain fraction measures
Modified Mini Mental State Examination, mean (SD)
Digit Symbol Substitution Test, mean (SD)
CES-D score, mean (SD)
Depression, %

Gait speed, m/s, mean (SD)
Step length, m, mean (SD)
Step width, m, mean (SD)
Sway time, s, mean (SD)
Double support time, s, mean (SD)

CHS, n=321, 82 yo, stroke and dementia free; HBP, n=311, 84 yo, dementia free

CHS, n=321, 82 yo, stroke and dementia free; HBP, n=311, 84 yo, dementia free
**Macro-structure:** VOLUMETRIC METHODS, WMH by Tract

Frontal:
- SPPB [Benson, 2002]
- Sway [Novak, 2009]
- GAITRite composite [Srikanth, 2010]
- Speed / stride length [DeLaat, 2011, 2011]

Corpus callosum:
- Speed/SPPB [total* - Ryberg, 2007]
- Gait disorders [genu* - Moretti, 2005]
- Speed [splenium - Moscufo, 2011]

**Micro-structure:** DIFFUSION TENSOR– normal appearing White M.

Frontal:
- Parkinsonian signs- [DeLaat 2011]
  (n.s. in posterior horns and centrum semiovale)

Corpus Callosum:
- Tinetti - genu* [Bhadelia, 2009]
- Gaitmat measures -- splenium/genu [DeLaat, 2011]
Micro-structure: DIFFUSION TENSOR—normal appearing White M.

Eliminated in those in the 3rd tertile of atrophy
**Micro-structure:** Magnetization transfer—normal appearing white matter

Age head size, BMI, coronary artery calcium, physical activity, hip/knee, OA

*Eliminated in men after adjustment for brain infarcts and WMH.*

---

**FUNCTIONAL MRI**

*Cross-sectional*

Functional neuroimaging studies indicate a role of basal ganglia and prefrontal motor regions in relationship with gait

[Ben-Salem, 2008; Iseki, 2010; la Fougere, 2010, ……]
Findings somewhat consistent with disease-related model of mobility control

- **GM atrophy:**
  - Dorsolateral prefrontal: gait speed
  - Sensorimotor: bradykinesia/slowing
  - Medial temporal: gait disturbances

- **WMH-**
  - Frontal
  - Interhemispheric connections

- **Micro-structure:** *(in those with lower atrophy)*
  - Frontal
  - Interhemispheric connections

- Repeatability

- Integration with non-neuro measures

- Specificity of spatial distribution by mobility measures
Evidence from neuroimaging: The artificial dichotomy of cognition vs. mobility

OUTLINE

1. Conceptual model to explain mobility impairment in aging
2. Neuroimaging studies of gait: summary of evidence
3. Implications for mechanisms and interventions
4. Challenges and opportunities

Implications: Insights into mechanisms

The PFC areas associated with gait speed partially overlap with the areas related to information processing speed in aging.

- dLPFC atrophy and lower DSST score: volumetric study
- dLPFC activation and DSST

Adjustment for tests of information processing speed partially explains the associations between dLPFC volume and gait (Zheng, 2012; Carmelli, 2000; Rosano, 2008; Rosano, 2010)—cross-sectional
Implications: Strategies for intervention

fMRI 2 yrs after completing a 1-yr physical activity intervention

PA- walking intervention group

SA – Control group

Rosano et al, 2009, JGMS

Challenges and opportunities: Approach

1. Most of the evidence on networks is correlational → longitudinal studies

2. Single-modality approaches → multimodal
   → Include careful accurate assessment of non-neuro measures, including multiple time points
   → Multimodal neuroimaging of networks in light of limitations of each technique
   → Standardized mobility measured (Session 2)
Multimodal neuroimaging

MACRO-structure (volume)

MICRO-structure (MTI, DTI)

Function
Neuronal activation, resting activity, blood flow
(task-related, resting state arterial spin labeling)

ULTRA-structure
(7 Tesla, 100 micron)

Quantitative, complementary information of network integrity

Challenges and opportunities: Model

1. Current neurocognitive model does not explain maintenance of mobility → new conceptual model?


Cardiometabolic and inflammatory risk factors

Trajectories of risk factors

Rate of Accrual of Structural Abnormalities

Brain Structure

Neural Activation

Mobility

Compensation for structural brain changes
Challenges and opportunities: Model

2. Current neurocognitive models may not distinguish aging vs. disease → Hypotheses-generating studies (e.g. all brain studies-- implications for statistical analyses—S.3)
Evidence from Neuroepidemiology: 
The artificial dichotomy of cognition vs. mobility

Joe Verghese, MBBS, MS

Integrated Divisions of
Cognitive & Motor Aging (Neurology) and Geriatrics (Medicine)
Albert Einstein College of Medicine
Bronx, NY

Outline

• Where we are: Brain substrates and biology are shared between gait and cognition in aging
• Walking while talking: Mobility stress approach
• Gait & Cognition: dementia, MCR syndrome
• Cognitive-motor interventions
• Barriers
Apolipoprotein E

Poor mobility performance test results but not self-reported limitation
Worse balance and gait test performance
### Effect of APOE e4 genotype on gait speed decline and disability in aging

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Gait speed decline</th>
<th>p-value</th>
<th>N</th>
<th>Disability</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>627</td>
<td>0.47 (p = 0.37)</td>
<td></td>
<td>554</td>
<td>0.76 (p = 0.41)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>235</td>
<td>-1.16 (p = 0.04)</td>
<td></td>
<td>212</td>
<td>3.72 (p = 0.004)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>392</td>
<td>0.44 (p = 0.41)</td>
<td></td>
<td>342</td>
<td>0.77 (p = 0.46)</td>
<td></td>
</tr>
</tbody>
</table>

Einstein Aging Study

Unpublished data

---

**Dopamine**

**COMT**
**Attention/Executive** * Gait Velocity

<table>
<thead>
<tr>
<th>COMT</th>
<th>Met/ Met</th>
<th>Met/ Val</th>
<th>Val/ Val</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>51</td>
<td>144</td>
<td>94</td>
</tr>
<tr>
<td><strong>Met/Met</strong></td>
<td>0.39 (.16)</td>
<td>0.18 (.09)</td>
<td>-.09 (.12)</td>
</tr>
<tr>
<td><strong>Met/Val</strong></td>
<td>91.1 (2.8)</td>
<td>100.3 (2.1)</td>
<td>97.1 (2.3)</td>
</tr>
<tr>
<td><strong>Val/Val</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OR (95% CI) best quartile**

**MM vs. VV** 3.01 (1.2-7.7) 0.22 (0.06-0.77)

*Cognitive factor scores are standardized regression scores with a mean of 0 and SD of 1. Higher factor scores indicate better cognitive performance.

289 cognitively normal adults, mean age 80, mean edn 13.9, women 62%
Holtzer et al. Neurobiol Aging, 2010

---

**Hippocampal volume and stride length in older adults**

Opportunity 1: Can we improve cognitive risk prediction?

Change point example for gait speed in MCI converters in relation to the mean age at conversion in men and women

Survival analysis: Any dementia

Hazard Ratio 1.96 (95% CI 1.3-2.96)

*Adjusted for age, sex, education, medical illnesses, and Blessed scores.


Quantitative gait and cognition

Pace
• Stride
• Velocity

Rhythm
• Swing
• Cadence

Variability
• Stride

Verghese J, JNNP 2007
Survival analysis: Any dementia (33)

<table>
<thead>
<tr>
<th>Hazard ratio*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity</td>
<td></td>
</tr>
<tr>
<td>(unadjusted)</td>
<td>0.98</td>
</tr>
<tr>
<td>(adjusted)</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>0.96 - 0.99</td>
</tr>
<tr>
<td>0.97 - 1.06</td>
<td></td>
</tr>
<tr>
<td>Rhythm factor</td>
<td>1.48</td>
</tr>
<tr>
<td></td>
<td>1.03 - 2.14</td>
</tr>
<tr>
<td>Pace factor</td>
<td>1.30</td>
</tr>
<tr>
<td></td>
<td>0.96 - 1.78</td>
</tr>
<tr>
<td>Variability</td>
<td>1.37</td>
</tr>
<tr>
<td></td>
<td>1.05 - 1.78</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, education, and medical illnesses

Verghese J, JNNP 2007

Cognitive Domains

Pace
Blessed
Executive function (DSST, letter fluency)

Rhythm
Memory (Free recall – FCSRT)

Variability

Verghese J, JNNP 2007
Mild Cognitive Impairment (MCI) syndrome

- Subjective cognitive complaints
- Objective cognitive
- Preserved ADL
- Absence of dementia

Motoric Cognitive Risk (MCR) syndrome

- Subjective cognitive complaints
- Objective motoric: slow gait (1 SD below age and sex adjusted means)
- Preserved ADL
- Absence of dementia

J Gerontol Med Sci 2012
**Einstein Aging Study**

- 767 community residing participants
- Age 70 and above (mean 79y)
- 60% women
- Mean follow-up: 42.3 ± 27.2 months

<table>
<thead>
<tr>
<th></th>
<th>MCR, N (n = 52)</th>
<th>Controls, N (n = 715)</th>
<th>Hazard Ratio* (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>8</td>
<td>62</td>
<td>2.7 (1.2 to 5.9), 0.01</td>
</tr>
<tr>
<td>Alzheimer's Disease</td>
<td>1</td>
<td>40</td>
<td>0.6 (0.1 to 4.2), 0.57</td>
</tr>
<tr>
<td>Vascular</td>
<td>7</td>
<td>14</td>
<td>11.1 (4.0 to 30.8), &lt;0.001</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, education, medical illnesses and cognition.
### MCI subtypes

<table>
<thead>
<tr>
<th>MCI subtypes</th>
<th>Dementia</th>
<th>AD</th>
<th>VaD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Pure Amnestic MCI</td>
<td>11.7</td>
<td>13.5</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td>(6.6 to 20.7)</td>
<td>(6.4 to 28.5)</td>
<td>(3.5 to 31.9)</td>
</tr>
<tr>
<td>Pure Non-amnestic</td>
<td>2.8</td>
<td>2.6</td>
<td>4.8</td>
</tr>
<tr>
<td>MCI</td>
<td>(1.4 to 5.7)</td>
<td>(1.1 to 6.5)</td>
<td>(1.4 to 15.9)</td>
</tr>
<tr>
<td>Pure MCR</td>
<td>2.91</td>
<td>*</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td>(0.6 to 12.2)</td>
<td>(2.3 to 56.3)</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, sex, education, medical illnesses and cognition.

J Gerontol Med Sci 2012
Opportunity 2: Can we improve functional risk prediction?

Mobility Stress Test Approach
Walking While Talking Test


40 feet: sec

Complex

A, C, E...

“Old age comes with the first fall, and death with the second.”

Gabriel Garcia Marquesa
Love in the time of cholera
Mobility Stress Test Approach to Predicting Frailty, Disability, and Mortality in High Functioning Older Adults. Verghese et al. JAGS, Oct 2012

Einstein Aging Study

- SPPB
- WWT
- Gait speed
Opportunity 3: Cognitive-motor interventions

J Gerontol Med Sci 2010
**Effect on Gait Velocity**

<table>
<thead>
<tr>
<th>Time</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (baseline)</td>
<td>12/12</td>
</tr>
<tr>
<td>3 months (Post-trial)</td>
<td>10/10</td>
</tr>
<tr>
<td>6 months (3-month follow-up)</td>
<td>9/9</td>
</tr>
</tbody>
</table>

**WWT: Walking while reciting alternate alphabets**

<table>
<thead>
<tr>
<th>Time</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (baseline)</td>
<td>12/12</td>
</tr>
<tr>
<td>3 months (Post-trial)</td>
<td>10/10</td>
</tr>
<tr>
<td>6 months (3-month follow-up)</td>
<td>9/9</td>
</tr>
</tbody>
</table>
Summary

- Gait and cognition are interlinked
- Gait: A cognitive/brain process
- Gait speed is only one indicator
- Attention executive function
- WWT: Mobility stress test approach
- MCR syndrome
- Interventions

Barriers

- Cognition and Motor silos: Effect on collaborations, publications, **funding**…
- Interdisciplinary approach needed
- Most studies correlational: Longitudinal and clinical trials lacking on gait end of equation
- Motor biology and pathways not well established
- Translation of cognitive-motor knowledge to interventions
Einstein Aging Study: RB Lipton, H Buschke, M Katz, A Sanders, M Zimmerman, C Derby, C Hall.

Funding received from National Institutes on Aging (grants PO1 AGO3949, RO1 AGO25119, and R21 25572)

Einstein has patent pending on CR to improve mobility
The Evidence From Epidemiological and Clinical Studies: Evidence from human disease-based models

David A. Bennett, MD
Rush Alzheimer's Disease Center
Rush University Medical Center
Chicago, IL

Background:
- Impaired motor function is common and associated with disability and mortality

Acknowledgments

Study Participants
Rush Memory and Aging Project
Religious Orders Study

National Institutes of Health
Alzheimer’s Association
Illinois Department Public Health
Elsie Heller Brain Bank Endowment Fund
Robert C. Borwell Endowment Fund

Disclosures
No relevant disclosures

PREVALENCE OF PARKINSONIAN SIGNS AND ASSOCIATED MORTALITY IN A COMMUNITY POPULATION OF OLDER PEOPLE

Impaired motor function is common and associated with disability and mortality. Common neurologic diseases are well known to cause impaired motor function including: Stroke, PD, ALS, AD, FTD. The pathologies of these conditions are far more common than clinically diagnosed disease, including: cerebral infarctions, Lewy bodies, neuronal loss, neuritic plaques, neurofibrillary tangles, TDP-43.

**Background:**

- Impaired motor function is common and associated with disability and mortality.
- Common neurologic diseases are well known to cause impaired motor function including: Stroke, PD, ALS, AD, FTD.
- The pathologies of these conditions are far more common than clinically diagnosed disease, including: cerebral infarctions, Lewy bodies, neuronal loss, neuritic plaques, neurofibrillary tangles, TDP-43.

**Question:**
To what extent do common subclinical neuropathologies cause age-related impairment of motor function?

**Objectives:**

- Review two cohort studies of motor function that include organ donation at death.
- Consequences of impaired motor function.
- Common age-related neuropathology.
- Relation of neuropathologies to motor function.
- Risk factors for decline in motor function.
- Challenges and opportunities.

**Background:**

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- Common neurologic diseases are well known to cause impaired motor function including: Stroke, PD, ALS, AD, FTD.
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- Risk factors for decline in motor function.
- Challenges and opportunities.
The Religious Orders Study

- Began in 1993
- > 1,150 older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual clinical evaluation, blood donation at baseline, and repeated on a subset
- All agreed to brain donation
- > 275 have developed dementia
- > 400 have developed MCI
- > 550 brain autopsies

The Memory and Aging Project

- Began in 1997
- > 1,650 older persons without dementia from across northeastern Illinois
- All agreed to annual clinical evaluation and annual blood donation
- All agreed to donate brain, spinal cord, muscle, nerve
- > 250 have developed dementia
- > 375 have developed MCI
- > 450 autopsies
### Motor Function Testing

<table>
<thead>
<tr>
<th>Global Motor</th>
<th>Parkinson Signs</th>
<th>Physical Frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>Finger Tapping</td>
<td>Bradykinesia</td>
</tr>
<tr>
<td>Arm</td>
<td>Purdue Pegboard</td>
<td>Rigidity</td>
</tr>
<tr>
<td>Grip</td>
<td>Timed Walk &amp; Turn</td>
<td>Tremor</td>
</tr>
<tr>
<td>Pinch</td>
<td>Leg</td>
<td>Parkinsonian Gait</td>
</tr>
<tr>
<td>Foot</td>
<td>Balance</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

### Muscle Structure & Function

- Body mass index
- Bioelectrical impedance
- Lean muscle index
- Maximum inspiratory pressure
- Maximum expiratory pressure

### Objectives:

- Review two cohort studies of motor function that include organ donation at death
- Consequences of impaired motor function
- Common age related neuropathology
- Relation of neuropathologies to motor function
- Risk factors for decline in motor function
- Challenges and opportunities

### CHANGE IN FRAILTY AND RISK OF DEATH IN OLDER PERSONS

- Physical frailty is associated with incident Alzheimer’s disease and cognitive decline in the elderly
- Physical frailty is associated with incident mild cognitive impairment in community-based older persons
- Change in body mass index and risk of incident Alzheimer disease
- Grip strength and the risk of incident Alzheimer’s disease

### Change in Motor Function and Risk of Mortality in Older Persons

- Pulmonary function, muscle strength and mortality in old age

### Pulmonary Function, Muscle Strength, and Incident Mobility Disability in Elders

- Association of muscle strength with the risk of Alzheimer disease and the rate of cognitive decline in community-dwelling older persons
Loss of motor function is common in aging and can be measured in a variety of related ways. Parkinsonism, physical frailty, global motor function, physical activity. These complementary motor function assessments make unique contributions to a range of adverse health outcomes: Mortality, disability, MCI, AD.

Summary:
- Review two cohort studies of motor function that include organ donation at death.
- Consequences of impaired motor function.
- Common age related neuropathology.
- Relation of neuropathologies to motor function.
- Risk factors for decline in motor function.
- Challenges and opportunities.

Objectives:
- Common age related neuropathology.
- Relation of neuropathologies to motor function.
- Risk factors for decline in motor function.
- Challenges and opportunities.

Pathology:
- AD (silver stain)
- Amyloid load
- PHFtau tangles
- Amyloid angiopathy
- Macro infarcts
- Micro infarcts
- Arterial sclerosis
- Atrophy
- Lewy bodies
- TDP-43
- Microglia

Nigral Lewy bodies and neuronal loss

Nigral Tangles
Objectives:

- Review two cohort studies of motor function that include organ donation at death
- Consequences of impaired motor function
- Common age related neuropathology
- Relation of neuropathologies to motor function
- Risk factors for decline in motor function
- Challenges and opportunities

**Substantia Nigra Tangles Are Related to Gait Impairment in Older Persons**

Variable | Gait Impairment
---|---
Age (yr) | 0.30^p
M.A Sex | -0.13
Dementia | 0.19^p
Brain injury | 0.21
Cortical infarcts | 0.02
Lobar injury | 0.17
Substantia nigra tangle count | 0.20^p

*p < 0.001; ^p < 0.01; ^ ^p < 0.10

**Cerebrovascular Disease Pathology and Parkinsonian Signs in Old Age**

**Nigral Pathology and Parkinsonian Signs in Elders without Parkinson Disease**

**Microvascular Brain Pathology and Late-Life Motor Impairment**

**TABLE 3: Relation of Nigral Pathology and Global Parkinsonian Score**

<table>
<thead>
<tr>
<th>Model A</th>
<th>Model B</th>
<th>Model C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Age</td>
<td>Sex</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathology Measure</th>
<th>Pathology Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrovascular Infarcts</td>
<td>Global Parkinsonian p (SE, A)</td>
<td>Global Parkinsonian p (SE, A)</td>
</tr>
<tr>
<td>Microvascular Infarcts</td>
<td>0.404 (0.001, 0.704)</td>
<td>0.404 (0.001, 0.704)</td>
</tr>
<tr>
<td>Arteriosclerosis</td>
<td>0.053 (0.023, 0.872)</td>
<td>0.053 (0.023, 0.872)</td>
</tr>
</tbody>
</table>

**TABLE 4: Relation of Nigral Pathology, Other Common Pathology, and Global Parkinsonian Score**

<table>
<thead>
<tr>
<th>Pathology Measure</th>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Parkinsonian</td>
<td>r (SE, A)</td>
<td>r (SE, A)</td>
</tr>
</tbody>
</table>

**Microvascular Pathology**

- Hand Strength
- Manual Dexterity
- Gait
- Walking Speed

<table>
<thead>
<tr>
<th>Microvascular Pathology</th>
<th>Hand Strength</th>
<th>Manual Dexterity</th>
<th>Gait</th>
<th>Walking Speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Arteriosclerosis</td>
<td>-0.05 (0.004, 0.204)</td>
<td>0.401 (0.001, 0.704)</td>
<td>0.053 (0.023, 0.872)</td>
<td>0.053 (0.023, 0.872)</td>
</tr>
<tr>
<td>Cerebral Amyloid Angiopathy</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>


We simultaneously analyzed change in motor and cognitive function in a series of mixed-effects change point models (Laird & Ware, 1982) using a Bayesian Monte Carlo Markov Chain Approach (Gelman, et al., 2004) implemented in OpenBUGS software (Lunn, et al., 2009).

Higher level of plaques and tangles, but not Lewy bodies or cerebral infarction, associated with earlier onset of terminal motor. No pathologic measures were related to motor decline, but all 3 were related to lower levels of motor function proximate to death.
Body mass index in older persons is associated with Alzheimer disease pathology

Physical frailty in older persons is associated with Alzheimer disease pathology

Summary:
- Loss of motor function is associated with the accumulation of:
  - AD pathology
  - CVD
  - Lewy body pathology
  - TDP-43
- However, these pathology only explain a small amount of the variance of decline in motor function suggesting that other indices must be important

Objectives:
- Review two cohort studies of motor function that include organ donation at death
- Consequences of impaired motor function
- Common age related neuropathology
- Relation of neuropathologies to motor function
- Risk factors for decline in motor function
- Challenges and opportunities
Summary:
- Loss of motor function is associated with:
  - APOE
  - Diabetes
  - Loneliness
  - Physical activity
  - Psychological distress (neuroticism)
  - Social activity
  - Odor identification
- How do we conceptualize the relation of risk factors, neuropathology, and loss of motor function?

Objectives:
- Review two cohort studies of motor function that include organ donation at death
- Consequences of impaired motor function
- Common age related neuropathology
- Relation of neuropathologies to motor function
- Risk factors for decline in motor function
- Challenges and opportunities

Challenges and opportunities
- The substantia nigra is not the ony aminergic nucleus
- Are other aminergic nuclei related to motor function
- With the exception of the nigra, the brain pathology was assessed primarily in regions that subserve cognition
- Quantify neuropathology in regions that subserve motor function
- The brain is not the only part of the nervous system involved in motor function
  - Motor unit: spinal cord, nerve, and muscle
- Do humans have a locomotion central pattern generator
Locus Coeruleus Neuron Density and Parkinsonism in Older Adults without Parkinson's Disease

Impaired motor function is common in aging and associated with significant morbidity and mortality.

The common pathologies of AD, CVD, LBD, and TDP-43 account for some of the motor decline in persons without clinically diagnosed neurologic disease.

We are beginning to identify risk factors for motor decline, most of which have no pathologic footprint.

Numerous challenges and opportunities exist, including role of:

- Other brainstem nuclei besides the nigra
- Neuropathology in brain regions that directly subserve motor function
- The spinal motor unit
- The locomotor central pattern generator

Summary:
Epidemiology of Mobility

Richard Camicioli, MD
University of Alberta
rcamicio@ualberta.ca

Epidemiology

Population

E C

+ Outcome
- Outcome

Jackson R et al EBM 2006
Neuroepidemiology: Imaging - Motor

- Cross-sectional and longitudinal methods examining imaging correlates of mobility
- MRI methods include volumetrics (gray matter atrophy), white matter changes, diffusion tensor imaging, magnetization transfer, and functional imaging
- Motor measures include SPPB, sway, gait speed, stride-length, stride-width, pathologic, variability, information processing
- Interventions may lead to long-term change
- Resilience despite pathology

Caterina Rosano

Epidemiology: Imaging-Outcome

<table>
<thead>
<tr>
<th>CVH study</th>
<th>WMD</th>
<th>Vents</th>
<th>Stroke</th>
<th>Physical Impairment</th>
<th>Physical Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>+ Outcome</td>
<td>- Outcome</td>
</tr>
</tbody>
</table>
Multisystem Approach

- Population-based cohort studies (EPESE, WHAS, InChianti, Health ABC) examine mobility decline (Decline in SPPB, loss of mobility)
  - Gait relates to other measures (leg & hand power, neurological signs, ΔTMT, balance)
- General health (specific and sum of conditions) increase risk of mobility decline and disability
- Consider physiological subsystems framework (Central (Mood+Cognition) & Peripheral Nervous System, Sensory Integration, MSK, Energetics)
- Consider homeostatic systems (hormones, inflammation, autonomic, ox stress, nutrition, activity)
  - Obesity, IL-6, ACE X physical activity, drop in cortisol, diabetes/glucose intolerance

Jack Guralnik

Epidemiology

InChianti

E Sum C

<table>
<thead>
<tr>
<th>Impaired Mobility</th>
<th>Impaired Mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain Mobility</td>
<td>Maintain Mobility</td>
</tr>
</tbody>
</table>

+ Outcome

- Outcome
Probing Cognitive-Motor Interactions

- Shared substrates for gait and cognition
  - Disease
    - Parkinson's, Vascular, Alzheimer
      - Direct or indirect evidence (pathology or imaging)
    - Systemic inflammation
    - Genetic risks (Sex, ApoE, COMT)
  - WWT
    - Gait task, secondary tasks
      - Falls, frailty, disability, mortality
  - MCR
  - MCI/Dementia
    - Decreased gait speed and conversion to MCI year before
    - Gait abnormalities increase risk of dementia
      - Pace (stride/velocity), rhythm (cadence/swing)*, variability*
        » Specific correlates: Pace: Blessed, EF; Rhythm: Memory
  - Cognitive-motor interventions

Joe Verghese
Motor Measures and Correlations

- Parkinsonism, gait decline, physical frailty, strength, performance measure, and their interactions predict
  - Mortality, disability, falls, cognitive decline, dementia
  - Risk factors include smell loss, diabetes, ApoE4, physical activity, personality, loneliness, social isolation

- Religious Orders Study, Rush Memory Aging Study)
  - Recognized pathologies with clinical signatures (Alzheimer, vascular, Parkinson's, Frontotemporal dementia, ALS, neural loss)
  - Can appear at autopsy without diagnosis in life
    - Do they cause ageing related decline in motor function
      - Unrecognized pathologies….TBD

- Parkinsonism (bradykinesia, rigidity, tremor, gait)
  - Related to SN neural loss and vascular pathology
  - Gait impairment associated with
    - Substantia Nigra NFTs, vascular pathology

David Bennett

Epidemiology

Buchman AS Ann Neurol 2012
Challenges and Opportunities

• Opportunity: Communication across approaches
  – Populations, physiological measures, fluid biomarkers, imaging biomarkers, pathology
    • Multimodal approaches
    • Causality needs longitudinal view (not sufficient)
    • Novel analysis approach necessary given complexity

• Barriers
  – Separate lines of funding, publishing, meeting, communication - different “worlds”
  – Language, culture and ways of thinking
  – Biology not understood well enough
  – Interventions aren’t simple
Central Nervous System Control of Locomotion, Dual Tasking and Automaticity

Mark Hallett, MD
Human Motor Control Section
NINDS, NIH, Bethesda
(No relevant disclosures)
Hierarchy of Motor Control

- Muscle
- Alpha motor neuron
  - Segmental influences
  - Suprasegmental influences
- Primary motor cortex
  - Subcortical influences
    - Basal ganglia and cerebellum
  - Cortical influences
    - Parietal and premotor
    - Mesial motor areas
    - Limbic and frontal areas
- Consciousness (awareness of action)
Walking

• To some extent walking is automatic, but it still needs some attention
• If less automaticity, more attention is needed
• “Stops walking when talking” test can bring out abnormalities
  – Lundin-Olsson et al. 1997

Deterioration of Motor Control With Aging

• Normal age-related changes
• Cumulative development of neurologic and other disorders
• Inactivity

Seidler et al. 2010
Neurosci Biobehav Rev
Automaticity: Experimental design

- Normal subjects, young and older
- Have them learn and then practice sequences of finger taps
  - A sequence of 4 and a sequence of 12
- Studied just after beginning the learning and then again with automaticity, defined by lack of deterioration while doing a second task
  - Simple tapping with the other hand or letter counting
fMRI Study of Movement Automaticity
Sequence 12

Before Training

After Training

Wu et al. 2004

Brain Areas More Activated at Pre-training Stage Than at Automatic Stage (sequence-12)

There was less activity in bilateral cerebellum, presupplementary motor area, cingulate cortex, left caudate nucleus, premotor cortex, parietal cortex, and prefrontal cortex.

Wu et al. 2004
Brain Areas More Activated in Old Subjects Than Young Subjects at Automatic Execution of Sequence-12

Wu & Hallett 2005

Psychophysiological Interaction (PPI) From the Cingulate Motor Area (CMA) at the Automatic Stage Compared to the Novel Stage


The Journal of Physiology
Brain Area More Activated in the Dual Task of Sequence-12 and Letter Counting Compared to Single Component Tasks in Aged Subjects

Wu T, Hallett M J Physiol 2005;562:605-615

Automaticity and Dual Tasking

Conclusions

- In the young, with learning, required brain activity diminishes due to more efficient communication (supported by white matter?)
- With aging, this process is impaired, and more brain activity is required – presumably meaning less automaticity and requiring more attention
AGE-RELATED CHANGES IN CORTICAL GAIT PROPULSION CONTROL:
Evidence from human data

Pr. Olivier Beauchet, MD, PhD

Department of Neuroscience
Geriatrics Division and Memory Clinic
Angers University Hospital and School of Medicine

DISCLOSURES

- Unpaid consultant for Ipsen Pharma company
- Unpaid associate editor: *Gériatrie, Psychologie et Neuropsychiatrie du Vieillissement* (Geriatr Psychol Neuropsychiatr Vieil)
- Unpaid President of Ageing, Balance and Cognition (ABC) research group
- Paid director of Research Department of Gérontopôle des Pays de la Loire
- No relevant financial interests in this talk
### GAIT IS A COMPLEX MOTOR BEHAVIOR

#### PARADOXICAL MOTOR BEHAVIOR
- **Simple** execution
- **Complex** biomechanics (dynamic balance)
  - « Hard » motor behavior:
    - Automatic = Propulsion / Balance
  - « Flexible » motor behavior:
    - Adaptation = Navigation

#### LEVELS AND TYPES OF CONTROL
- **CORTICAL LEVEL:**
  - Initiation and adaptation of gait
- **SUBCORTICAL LEVEL:**
  - Modulation of automatic movements
- **SPINAL LEVEL:**
  - Gait patterns generation of automatic, regular and rhythmic movements

#### THE FAMOUS MANUSCRIPT FOR CLINICIANS

> "Stops walking when talking" as a predictor of falls in elderly people

![Log rank test: P < 0.001](image)

Results underscored that:
- Gait was **not only** an automatic rhythmic motor task
- Gait assessment while dual-tasking underlined:
  1) Involvement of **cognitive resources** (attention+++),
  2) Highest gait control level: **cortical** (too high in older adults with neuropsychiatric disorders)
Two main questions related to changes in the highest levels (from sub-cortical to cortical) of gait control with aging:

- **Does cortex influence gait propulsion with aging?**
  - Yes (see session #1)
- **How does cortex influence gait propulsion with normal aging (i.e., healthy older adults)?**

**Gait-related questions:**
- Which walking conditions? (see Dr. M Hallett talk)
- Which gait parameter?

**Brain-related questions:**
- Which cortical structures?
- Which cognitive function?
- Is there a specific biology?
WHICH GAIT PARAMETER IS A MARKER OF CHANGE OF CORTICAL GAIT PROPULSION CONTROL?

- **Gait variability**: Fluctuations from stride-to-stride with time
- Assessment: **Magnitude** = Variance calculated from coefficient of variation (CoV) = \( \frac{SD}{\text{mean}} \times 100 \)

\[ \downarrow \text{CoV} = \uparrow \text{Gait stability} \]

**Fig. 1.** Box plot of the CoV of gait parameters (n = 63), p value significant (< 0.014) based on the Bonferroni test calculated with a repeated-measures ANOVA.

AGE-RELATED CHANGES IN GAIT VARIABILITY

- Age-related changes in gait variability while dual tasking:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Walking Alone</th>
<th>Walking While Backward Counting</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young subjects (n = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stride length CV (%)</td>
<td>2.3 ± 0.8</td>
<td>2.7 ± 1.2</td>
<td>.398</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.3 ± 1.3</td>
<td>3.5 ± 1.6</td>
<td>.636</td>
</tr>
<tr>
<td>Old subjects (n = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stride length CV (%)</td>
<td>3.9 ± 1.6</td>
<td>10.2 ± 9.3</td>
<td>.002</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>6.8 ± 2.2</td>
<td>12.5 ± 9.2</td>
<td>.016</td>
</tr>
</tbody>
</table>

- Main results:
  - **Higher gait variability in older adults**
  - **Increase in gait variability while dual tasking only in older adults**
- Interpretation: **Involvement of cognitive resources** and thus of **cortical areas** in **gait control** with aging
PROBLEMATIC AND MAIN QUESTIONS

- Two main questions related to changes in the highest levels (from sub-cortical to cortical) of gait control with aging:
  - Does cortex influence gait propulsion with aging?
    Yes (see session #1)
  - How does cortex influence gait propulsion with normal aging (i.e., healthy older adults)?

Gait-related questions:
- Which walking conditions? (see Dr. M Hallett talk)
- Which gait parameter?

Brain-related questions:
- Which cortical structures?
- Which cognitive function?
- Is there a specific biology?

AGE-RELATED CHANGES IN CORTICAL GAIT PROPULSION CONTROL: Functional data (RMIf)

<table>
<thead>
<tr>
<th>BA</th>
<th>Cluster</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>2059</td>
<td>5.26</td>
</tr>
<tr>
<td>6</td>
<td>675</td>
<td>5.17</td>
</tr>
<tr>
<td>6</td>
<td>88</td>
<td>2.93</td>
</tr>
<tr>
<td>6</td>
<td>2059</td>
<td>2.77</td>
</tr>
<tr>
<td>7</td>
<td>115</td>
<td>2.22</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>2.77</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>2.03</td>
</tr>
<tr>
<td>155</td>
<td>32</td>
<td>2.47</td>
</tr>
</tbody>
</table>

Blood oxygen level-dependent (BOLD) signal increases during mental imagery of walking (functional magnetic resonance imaging (fMRI) in older adults compared with imagined lying, $p < 0.05$, FDR-corrected).

For comparison, a group of young subjects (age below 40 years, $n = 20$) and a group of old subjects (age over 60 years, $n = 20$) was defined.

No age-related change in locomotor brain network (premotor cortex, basal ganglia, midline cerebellum, pontomesencephalic tegmentum)

AGE-RELATED CHANGES IN CORTICAL GAIT
PROPULSION CONTROL: Functional data (IRMf)

Table 2 Correlation analysis of BOLD signal response and age

<table>
<thead>
<tr>
<th>Central hemispheres</th>
<th>BA</th>
<th>Cluster</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>R insula</td>
<td>22</td>
<td>680</td>
<td>3.61</td>
</tr>
<tr>
<td>L superior temporal gyrus</td>
<td>22</td>
<td>482</td>
<td>3.84</td>
</tr>
<tr>
<td>R middle occipital gyrus</td>
<td>19</td>
<td>73</td>
<td>3.02</td>
</tr>
<tr>
<td>L fusiform gyrus</td>
<td>117</td>
<td>2.85</td>
<td></td>
</tr>
<tr>
<td>R postcentral gyrus</td>
<td>3</td>
<td>92</td>
<td>3.19</td>
</tr>
</tbody>
</table>

More cortical activation with aging

Table 3 BOLD signal decreases in the group of younger persons (< 40 years) and older persons:

<table>
<thead>
<tr>
<th>BA</th>
<th>Cluster</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>R insula</td>
<td>22</td>
<td>482</td>
</tr>
<tr>
<td>L insula</td>
<td>399</td>
<td>3.34</td>
</tr>
<tr>
<td>R superior temporal gyrus</td>
<td>21</td>
<td>680</td>
</tr>
<tr>
<td>R middle temporal gyrus</td>
<td>21</td>
<td>73</td>
</tr>
<tr>
<td>L superior temporal gyrus</td>
<td>19</td>
<td>243</td>
</tr>
<tr>
<td>L middle temporal gyrus</td>
<td>21</td>
<td>215</td>
</tr>
<tr>
<td>Anterior cingulate gyrus</td>
<td>32</td>
<td>2568</td>
</tr>
</tbody>
</table>

Less cortical deactivation with aging

AGE-RELATED CHANGES IN CORTICAL GAIT
PROPULSION CONTROL: Interpretation

- Increase and decrease in cortical activity may reflect a compensatory mechanism due to age-related sensorimotor decline

- Previous age-related changes in motor control:
  - Decline in:
    - Unimodal sensory ability with a low sensory cortical activity response
    - Inhibitory reciprocal interaction (activity in one sensory modality suppressed activity in other modalities)
  - Enhance in cortical representation of multisensory information


Jahn K et al. NeuroImage. 2008;39:786-92
AGE-RELATED CHANGES IN CORTICAL GAIT PROPULSION CONTROL: Morphological data

- 73 healthy community dwellers
- Mean age 65.3±0.6 years
- 59.1% women
- 3D T1-weighted MRI at 1.0 Tesla
- Voxel-based morphometry performed with SPM
- CoV of stride time

Figure 1: Stride time variability related decrease in gray matter volume of the right angular gyrus

Table 1. Localization of gait-related decreases in gray matter volume adjusted for baseline characteristics of participants (n=73)

<table>
<thead>
<tr>
<th>Side</th>
<th>Cortical brain region</th>
<th>Lobe</th>
<th>BA</th>
<th>MNI coordinates</th>
<th>Cluster size</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Angular gyrus</td>
<td>Parietal</td>
<td>30</td>
<td>x, y, z</td>
<td>492</td>
<td>0.006</td>
</tr>
</tbody>
</table>

High gait variability = Parietal atrophy (age-related sensorimotor decline?)

PROBLEMATIC AND MAIN QUESTIONS

- Two main questions related to changes in the highest levels (from sub-cortical to cortical) of gait control with aging:
  - Does cortex influence gait propulsion with aging?
    - Yes (see session #1)
  - How does cortex influence gait propulsion with normal aging (i.e., healthy older adults)?

Gait-related questions:
- Which walking conditions? (see Dr. M Hallett talk)
- Which gait parameter?

Brain-related questions:
- Which cortical structures?
- Which cognitive function?
- Is there a specific biology?

*: Normal aging (healthy older adults)
- Information updating and monitoring
- Mental shifting
- Cognitive inhibition

Miyake executive-mental set

Conclusion: Gait control in healthy older adults mainly depends on information updating and monitoring (walking requires processing a flow of information in a short period to adapt gait to environmental conditions)
PROBLEMATIC AND MAIN QUESTIONS

Two main questions related to changes in the highest levels (from sub-cortical to cortical) of gait control with aging:

- Does cortex influence gait propulsion with aging?
  Yes (see session #1)
- How does cortex influence gait propulsion with normal aging (i.e., healthy older adults)?

Gait-related questions:
- Which walking conditions? (see Dr. M Hallett talk)
- Which gait parameter?

Brain-related questions:
- Which cortical structures?
- Which cognitive function?
- Is there a specific biology?

EVIDENCE FOR A SPECIFIC BIOLOGY... VITAMIN D: What do we know?

- Main anatomical localizations:
  - Hippocampus
  - Hypothalamus
  - Cerebellum

- Cellular localisations:
  - Neurons +++
  - Glial cells

- Metabolism:
  - Expression of human 1α-hydroxylase mRNA as revealed by RT-PCR

- Main vitamin D-related brain effects:
  - Neurotrophic
  - Anti-ischemic

- Brain localization of VDR:

Clinical data

**Conclusion:**
- Low serum 25OHD concentrations were associated with higher STV reflecting a disturbed gait.
- This association may be explained by a possible action of vitamin D on different components involved in gait control.

**Research question:** Is there a relationship between vitamin D deficiency and brain structures?

### Table 1
Clinical characteristics of study subjects according to serum 25OHD concentrations (n = 411)

<table>
<thead>
<tr>
<th>Serum 25OHD concentrations (ng/mL)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 (n = 64)</td>
<td></td>
</tr>
<tr>
<td>10–20 (n = 249)</td>
<td></td>
</tr>
<tr>
<td>&gt;20 (n = 46)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>71.0 ± 6.4</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>98 (58.5%)</td>
</tr>
<tr>
<td>No. of drugs taken per day, mean ± SD</td>
<td>3.1 ± 2.7</td>
</tr>
<tr>
<td>Use of psychotropic drugs, n (%)</td>
<td>12 (7.6%)</td>
</tr>
<tr>
<td>Abnormal findings, n (p/n)</td>
<td>22 (14.2%)</td>
</tr>
<tr>
<td>Cognitive impairment, n (%)</td>
<td>33 (21.6%)</td>
</tr>
<tr>
<td>Falls in the past year, n (%)</td>
<td>24 (15.0%)</td>
</tr>
<tr>
<td>CMM, mm, mean ± SD</td>
<td>232 ± 184.5</td>
</tr>
<tr>
<td>Handgrip strength, n (%)</td>
<td>33 ± 10.7</td>
</tr>
<tr>
<td>Lower limb proprioception, n (%)</td>
<td>6.7 ± 1.5</td>
</tr>
<tr>
<td>Visual acuity (n = SD)</td>
<td>6.1 ± 2.6</td>
</tr>
<tr>
<td>Stride length, cm, mean ± SD</td>
<td>1.2 ± 0.19</td>
</tr>
<tr>
<td>Stroke length variability, cm, mean ± SD</td>
<td>4.0 ± 4.6</td>
</tr>
</tbody>
</table>

---

**Brain imaging (MRI)**

- Compared to individuals with normal 25OHD, those with 25OHD deficiency (n=33) had 28% larger lateral ventricles (P=0.026).
- The ventricular enlargement involved ventricle bodies (P=0.025) but not temporal horns (P=0.112).

**Methods:** Ninety-two Caucasian community-dwellers with no clinical hydrocephalus (mean, 72.2 ± 6.2 years; 46.7% females) were divided into 2 groups according to serum 25OHD concentration (deficiency: <50 nmol/L, normal: 50–80 nmol/L). Cerebral ventricular volume was quantified using semi-automated software from three-dimensional T1-weighted MRI. Age, gender, body mass index, blood pressure, education level, Mini-Mental State Examination, white matter lesions and serum calcium concentrations were used as covariates.

Annweiler C et al. Mol Nutr Food Res 2012 (in press)
### Evidence for a Specific Biology... Vitamin D: Brain Magnetic Resonance Spectroscopy

#### Table 1. Characteristics and comparison of participants (n=20, mean age 74.6±6.2 years, 35.0% women) separated into two groups based on NAA/Cr in cPMC.

<table>
<thead>
<tr>
<th>Gait characteristics</th>
<th>Total sample (n=20)</th>
<th>NAA/Cr in cPMC</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤ 1.17 (n=9)</td>
<td>&gt; 1.17 (n=11)</td>
</tr>
<tr>
<td><strong>Gait characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stride time variability, %</td>
<td>3.9±2.4</td>
<td>4.0±2.9</td>
<td>3.7±2.0</td>
</tr>
<tr>
<td><strong>Neuromaging measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low NAA/Cr was associated with 1) Increased stride time variability and vitamin D deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low serum 25OHD was associated with reduced neuronal function in cPMC (adjusted linear regression)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White matter hyperintensities grade, 9</td>
<td>2.5±1.6</td>
<td>2.9±1.7</td>
<td>2.1±1.5</td>
</tr>
<tr>
<td><strong>Serum measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-hydroxyvitamin D concentration, nmol/L</td>
<td>110.80±45.43</td>
<td>104.22±66.66</td>
<td>116.18±17.18</td>
</tr>
<tr>
<td>Vitamin D insufficiency*</td>
<td>3(15.0)</td>
<td>3(15.0)</td>
<td>0(0.0)</td>
</tr>
</tbody>
</table>

**Methods.** Ratio of N-acetyl aspartate to creatine (NAA/Cr), a marker of neuronal health and function, was calculated in cPMC. Participants were categorized according to mean NAA/Cr. Vitamin D insufficiency was defined as serum 25-hydroxyvitamin D (25OHD)<37nmol/L. Age, gender, number of comorbidities, vascular risk, cognition, gait performance, vitamin D supplements, caudal primary motor cortex (cPMC) thickness, white matter hyperintensities grade and serum parathyroid hormone concentration were used as potential confounders.

Annweiler C et al. (in preparation)

### Take-Home Messages

- **Magnitude of gait variability of stride time** (fluctuation from stride-to-stride with time of gait cycle time):
  - A biomarker of cortical gait propulsion control
  - **Increases with aging**

- **No age-related change** in cortical brain network... but **more cortical activation** and **deactivation** (compensatory mechanism of age-related sensorimotor decline?)

- **Information updating and monitoring** = **subdomain of executive** function is involved in gait propulsion control with aging

- Serum **vitamin D** concentration is strongly related to gait propulsion control with aging
Influences on Brain Plasticity: Implications for Cognition and Mobility Control

Yaakov Stern, PhD
Columbia University
www.cogneurosci.org

Supported by the NIA

What Is Reserve?

Brain Damage \[\rightarrow\] Outcome

Reserve

Reserve may explain the disjunction between the degree of brain damage and the clinical manifestation of that damage. A set of lifestyle factors may increase reserve.
Mechanisms Underlying Reserve

- Brain reserve:
  - More neurons/synapses to lose
  - Anatomic changes on the basis of experience
- Cognitive reserve:
  - Resilience/plasticity of cognitive networks in the face of disruption
- A new possibility: Direct effect of lifestyle/activities on aging/disease pathology

Brain Reserve: Association Between Head Circumference and Alzheimer’s Disease

Brain Reserve Is Not So Simple

The literature suggests that exercise and environmental stimulation can activate brain plasticity mechanisms and remodel neuronal circuitry in the brain.

They can increase:
- Vascularization (exercise)
- Neurogenesis in the dentate
- Brain volume/Cortical thickness
- Neuronal survival and resistance to brain insult
- Brain-derived neurotrophic factor (BDNF) -- benefits brain plasticity processes

Physical Activity, Diet, and Risk of Alzheimer Disease

Nikolas Scarmeas, MD
Jose A. Luchsinger, MD
Nicole Schupf, PhD
Adams M. Brickman, PhD
Stephanie Cohen, PhD
Ming X. Tang, PhD
Yaakov Stern, PhD

Context Both higher adherence to a Mediterranean-type diet and more physical activity have been independently associated with lower Alzheimer disease (AD) risk but their combined association has not been investigated.

Objective To investigate the combined association of diet and physical activity with AD risk.

Design, Setting, and Patients Prospective cohort study of 2 cohorts comprising 1880 community-dwelling older adults without dementia living in New York, New York, with both diet and physical activity information available. Standardized neurological and neuropsychological measures were administered approximately every 1.5 years from 1992 through 2006. Adherence to a Mediterranean-type diet (scale of 0-5; dichotomized into low, moderate, or high) and physical activity (sum of weekly participation in various physical activities, weighted by the type of physical activity [light, moderate, vigorous]; dichotomized into no physical activity, some, or much) were then combined, were the main predictors in Cox models. Models were adjusted for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, body mass index, smoking status, depression, leisure activities, a comorbidity index, and baseline Clinical Dementia Rating score.

Main Outcome Measure Time to incident AD.

Results A total of 282 incident AD cases occurred during a mean (SD) of 5.4 (3.3) years of follow-up. When considered simultaneously, both Mediterranean-type diet adherence (compared with low diet scores, hazard ratio [HR] for middle diet score was 0.98 [95% confidence interval (CI), 0.73-1.33]; the HR for high diet score was 0.60 [95% CI, 0.42-0.87]; P = .008 for trend) and physical activity (compared with no physical activity, the HR for some physical activity was 0.78 [99% CI, 0.54-1.04]; the HR for much physical activity was 0.67 [95% CI, 0.47-0.95]; P = .03 for trend) were associated with lower AD risk. Compared with individuals neither adhering to the diet nor participating in physical activity (low diet score and no physical activity; absolute AD risk of 15%), those both adhering to the diet and participating in physical activity (high diet score and high physical activity) had a lower risk of AD (absolute risk, 12%; HR, 0.65 [95% CI, 0.44-0.96]; P = .03 for trend).

Conclusion In this study, both higher Mediterranean-type diet adherence and higher physical activity were independently associated with reduced risk for AD.
Lifestyle May Impact Cortical Thickness and Neuronal Density

Figure 3. Neurotrophic effects of an active cognitive lifestyle in Brodmann area 9. Exemplar mid-frontal Brodmann area 9 sections from two individuals, showing that high Cognitive Lifestyle Score was associated with increased neuronal density (A,B) and greater neocortical thickness (C,D). Part (E) depicts significant intergroup differences.

Valenzuela et al. BIOL PSYCHIATRY 2012

Can Lifetime Cognitive Engagement Impact Amyloid Development?

Figure 1. Individuals with greater cognitive engagement show reduced amyloid burden. Carbon 11-labeled Pittsburgh Compound B (11C)PIB in cognitively normal older participants (x-axis) is inversely associated with past cognitive activity (y-axis) (linear regression, \( \beta = -1.73 \times \beta = 0.47; P < .001 \)). Both variables are residual values after correcting for age, sex, and years of education.

Landau et al. Arch Neurol. Published online January 23, 2012
Advancing AD Pathology

Initiation Factors

Promoting Factors

Diagnosis

Death

Clinical Symptoms Appear

Table: Outcome of Incident Dementia

<table>
<thead>
<tr>
<th>Study</th>
<th>Education</th>
<th>High-activity (%)</th>
<th>Low-activity (%)</th>
<th>OR (95% CI estimate)</th>
<th>Weight (%)</th>
<th>OR (95% CI estimate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reform (1982)</td>
<td>29.032</td>
<td>42.149</td>
<td>2.6 (0.96-6.44)</td>
<td>2.6</td>
<td>0.74 (0.39-1.42)</td>
<td></td>
</tr>
<tr>
<td>Pekiel (1994)</td>
<td>13.776</td>
<td>36.793</td>
<td>1.8</td>
<td>1.1</td>
<td>0.60 (0.29-1.68)</td>
<td></td>
</tr>
<tr>
<td>Stein (1994)</td>
<td>35.029</td>
<td>60.026</td>
<td>3.1</td>
<td>0.60 (0.25-1.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cott (1995)</td>
<td>1.0003</td>
<td>1.0007</td>
<td>3.5</td>
<td>1.05 (0.83-1.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferina (1999)</td>
<td>0.936</td>
<td>0.9026</td>
<td>1.2</td>
<td>0.50 (0.31-0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt (1997)</td>
<td>30.949</td>
<td>30.1144</td>
<td>4.1</td>
<td>0.73 (0.52-1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donoff (1997)</td>
<td>24.512</td>
<td>70.520</td>
<td>2.7</td>
<td>0.30 (0.19-0.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elias (2000)</td>
<td>35.094</td>
<td>47.464</td>
<td>3.4</td>
<td>0.91 (0.67-1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ono (2001)</td>
<td>12.2586</td>
<td>12.2001</td>
<td>3.2</td>
<td>0.51 (0.33-0.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scannin (2000)</td>
<td>83.796</td>
<td>82.0922</td>
<td>4.6</td>
<td>0.64 (0.46-0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gao (2001)</td>
<td>35.056</td>
<td>10.76</td>
<td>3.5</td>
<td>0.66 (0.45-0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feng (2004)</td>
<td>22.2984</td>
<td>28.964</td>
<td>5.7</td>
<td>0.53 (0.46-0.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tochiki (2005)</td>
<td>65.289</td>
<td>79.252</td>
<td>3.5</td>
<td>0.54 (0.37-0.80)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Occupation

Bier (1996) | 10.153 | 24.159 | 1.4 | 0.39 (0.18-0.83) |
| Stein (1994) | 17.291 | 7.357 | 2.2 | 0.33 (0.19-0.58) |
| Pekiel (1994) | 20.234 | 20.236 | 2.1 | 1.00 (0.60-1.69) |
| Donoff (1997) | 12.565 | 50.294 | 2.4 | 0.60 (0.37-0.97) |
| Schmidt (1997) | 28.642 | 111.1296 | 3.2 | 0.44 (0.25-0.79) |
| Schmidt (1997) | 26.968 | 110.1175 | 3.5 | 0.53 (0.35-0.80) |
| Jones (1998) | 7.174 | 6.96 | 0.7 | 0.53 (0.18-0.83) |
| Elias (2000) | 4.0467 | 6.3807 | 3.4 | 0.96 (0.63-1.44) |
| Scannin (2001) | 37.425 | 120.1913 | 3.6 | 0.67 (0.40-0.99) |
| Hinde (2001) | 21.261 | 72.2929 | 2.9 | 0.59 (0.32-0.97) |
| Ati (2004) | 21.062 | 27.420 | 2.1 | 0.49 (0.26-0.87) |
| Korg (2004) | 12.7274 | 40.359 | 3.3 | 0.53 (0.39-0.98) |

Personal health

Schmidt (1997) | 64.0064 | 90.678 | 4.1 | 0.60 (0.34-0.98) |
| Elias (2000) | 23.271 | 24.271 | 2.2 | 0.54 (0.31-0.92) |

Leisure activity

Fang (2000) | 21.25 | 47.239 | 3.7 | 0.65 (0.44-0.91) |
| Scannin (2001) | 77.221 | 18.3641 | 4.5 | 0.53 (0.34-0.80) |
| Wang (2002) | 35.018 | 86.384 | 3.3 | 0.44 (0.29-0.67) |
| Vogelwiek (2003) | 14.582 | 40.57 | 2.2 | 0.33 (0.20-0.56) |

Total (95% CI)

173.312456 | 225.425468 | 100.0 | 0.54 (0.49-0.65) |

Test for heterogeneity $\chi^2=55.62, df=12, p<0.001$ | Test for overall effect $z=12.38, p=0.0001$
Controlling for clinical disease severity, there is an inverse relationship between education and a functional imaging proxy for AD pathology.
Scheme for Studying Neural Implementation of Cognitive Reserve

Neural Reserve and Neural Compensation

Steffener and Stern, Biochimica et Biophysica Acta 2012
How Would Reserve-based Interventions Work?

Aging/AD Pathology → Clinical Disease

Brain Reserve ← Cognitive Reserve

Father’s occupation
Cognition at 8 years
Education by 26 years
Own occupation at 43 years
NART at 53

Richards, JCEN 2003
Eight out of 11 studies reported that aerobic exercise interventions resulted in improvements in cognitive capacity.

The largest effects on cognitive function were found on motor function and auditory attention (effect sizes of 1.17 and 0.50 respectively).

Moderate effects were observed for cognitive speed (effect size 0.26) and visual attention (effect size 0.26).

Problems With Cognitive Interventions to Date

- Small effect size
- Poor generalization to other cognitive domains
- Poor generalization day-to-day functions or IADLs
- Questionable sustainability of effects
- Relation to rate of aging or dementia onset not established
Ongoing Intervention Trials

We have two ongoing intervention trials in healthy, cognitively intact individuals:

• Combined space fortress and aerobic exercise
  – Age 60-75
  – 3 conditions (N=30/condition): space fortress +aerobic exercise; SF + stretching/toning; computer games + S/T
  – 3 months with 12-month followup

• Long-term aerobic exercise
  – Ages 30-45 and 50-65 (N=130 for each)
  – 2 conditions: aerobic exercise vs. stretching/toning
  – 6 months with 12-month followup

What Will the Large-Scale Project to Enhance CR Look Like?

• Healthy elderly population
• Intensive, extensive, combined interventions
• Long-term follow-up
• Outcomes:
  – Rapidity of cognitive/functional decline
  – Incident dementia
Conclusions

- Epidemiologic and imaging evidence support the concept of reserve
- Reserve is malleable: it is influenced by aspects of experience in every stage of life
- The concept of cognitive reserve is applicable to a wide range of conditions that impact on brain function at all ages
- Influencing cognitive reserve may delay or reverse the effects of aging or brain pathology
- While I have focused on cognitive outcomes, all of the mechanisms discussed here apply equally to motor outcomes
Evidence from Animal Models: Effects of Aging and Lifestyle Factors on Motor Synapses
Gregorio Valdez, Ph.D.
Virginia Tech Carilion Research Institute

The motor circuit

NEUROSCIENCE 5e, Figure 16.1
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Age-related cellular and molecular changes

The functional unit of the nervous system

Aged Nervous System
- Significant biochemical changes
- Disruption of neuronal circuits
- Specific loss of neurons
- Widespread synaptic loss
Using animal models to study aging

“Brainbow” Mouse Cerebellum

**Toolbox**

- High-throughput analysis
- Imaging throughout life span
- Molecular composition of specific cells
- Genetic manipulation

Synaptic loss in old animals

Dickstein et al., 2007
Control of skeletal muscles

Motor Neuron
Spinal Cord
Muscle Fiber
Nerve Terminal

A very large synapse

Neuromuscular junction (A) and hippocampal synapses (B) to the same scale

Red = postsynaptic membrane
Green = nerve terminal
Yellow = apposition

5 μm
Age-related changes at the NMJ

Valdez G et al. PNAS 2010;107:14863-14868

Live imaging of aging muscle synapses
Effect of diet on aging muscle synapses

Caloric restriction attenuates synaptic aging
Effect of exercise on aging muscle synapses

Exercise attenuates synaptic aging

Old-Sedentary

Old-Exercised
Summary

- Aging results in the loss of synapses.
- Diet and exercise slow the decay of motor synapses.
- Animal models are necessary to understand age-related changes in the motor system.
- Genetic tools have significantly aided in discovering cellular and molecular changes.
- Optogenetics will provide valuable insights on the specific and first motor circuits affected by aging.
Session Two: Evidence From Basic Science Studies

Summary and Discussion

Wen G. Chen, PhD
National Institute on Aging
NIH, DHHS

1. Behavioral Evidence:
   • Simple Walking (automatic) vs. Complex Walking (dual-task, brain reserve, information updating band monitoring)
   • Gait measures (length, time, speed/velocity, variability, coefficient of variation or CoV)
   • Dynamic balance

2. Brain Imaging and Neurophysiology Evidence:
   • Anatomical: cortical, subcortical, spinal cord motor neurons
   • Neurophysiology: psychophysiological interaction (PPI)
   • Structural: gray matter and white matter volumes
   • Functional: fMRI, rCBF

3. Cellular and Synaptic Evidence:
   • Presence of neuropathology
   • Cortical thickness, neuronal density, neuronal loss
   • Neural circuit connections
   • Synaptic structure and numbers
   • Biochemicals, neurotransmitters

4. Evidence from Interventional Effects on Brain/Neural Structure and Function:
   • Motor training, cognitive training, aerobic exercise
   • Vitamin D, caloric restriction

Age-Related Changes in CNS and Mobility

1. Behavioral Evidence:
   • Simple Walking (automatic) vs. Complex Walking (dual-task, brain reserve, information updating band monitoring)
   • Gait measures (length, time, speed/velocity, variability, coefficient of variation or CoV)
   • Dynamic balance

2. Brain Imaging and Neurophysiology Evidence:
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   • Synaptic structure and numbers
   • Biochemicals, neurotransmitters

4. Evidence from Interventional Effects on Brain/Neural Structure and Function:
   • Motor training, cognitive training, aerobic exercise
   • Vitamin D, caloric restriction
Structure, Neurochemistry, and Function of CNS Components Related to Mobility

Nico I. Bohnen, MD, PhD
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University of Michigan & AAVA
Ann Arbor, MI, USA

No disclosures
Except for NIH, VA, MJFF funding

HUMAN LOCOMOTION

• Erect locomotion in humans is a complex sensorimotor task requiring the dynamic interaction between spinal locomotor pattern generators and hierarchically organized supraspinal locomotion centers in the brainstem, cerebellum, and cortex: mesencephalic locomotor center (MLR), subthalamic locomotor center (SLR) and cerebellar locomotor center (CLR)

• This cerebral network is believed to modulate locomotion (e.g., gait initiation, termination, velocity, direction, and spatial orientation) and to control balance and gait by integration of multisensory information (Rossignol et al. 2006)

• Our knowledge about the hierarchical network of supraspinal locomotion centers is derived from basic science studies mainly performed in the cat, an animal with quadrupedal locomotion (Shik & Orlovsy, 1976; Mori et al. 2001).
HUMAN LOCOMOTION

- The basal ganglia, including the striatum, pallidum, subthalamic nucleus, and substantia nigra, are involved in a number of parallel, functionally segregated cortical-subcortical circuits (Alexander et al. 1998). A main role of the basal ganglia is the learning and selection of the most appropriate motor or behavioral programs (Redgrave, 2010).

- Dopaminergic signaling within the basal ganglia is clearly involved in reward-based learning and action selection (Balleine, 2010). Normal dopaminergic function is probably particularly important for establishment, selection, and sequencing of habitual patterns of action (Yin, 2006).
POSTURAL CONTROL

- Effective integration of sensory information about the visuospatial environment, body, and limb position is essential for postural control. Standing posture, for example, is affected by perturbations of visual, vestibular and proprioceptive sensory systems (Latt, 2003; Horak, 1994; Mahboobin, 2005).

- The specific role of the basal ganglia in postural control is complex and only beginning to be unraveled but is believed to be involved in several functions, including: (1) sensory channel integration; (2) selection of automatic postural reactions generated in response to motor and sensory perturbations; (3) motor control flexibility and adaptability; (4) regulation of muscle tone; and (5) modulation of the impact of cognitive factors on balance and gait (e.g. attention, multi-tasking).

Figure 1: Schematic of the Sensory Systems, Locomotor Regions, Cortical and Subcortical Regions, and Neurochemical Projections Involved in the Regulation of Balance and Gait

From Bohnen, Albin et al. 2012
The PPN is located in the dorsolateral part of the ponto-mesencephalic tegmentum (Pahapill et al. 2000).

The PPN sends profuse ascending cholinergic efferent fibers to several thalamic nuclei, particularly the intralaminar complex that is also reciprocally connected with the basal ganglia (Lee et al. 2000).

Neuropathological studies on humans have reported that ~50% of the large cholinergic neurons of the lateral part of the PPNpc degenerate in PD (Hirsch et al., 1987; Jellinger, 1988; Zweig et al., 1989; Gai et al., 1991).

PPN degeneration is associated with DA-resistant akinesia in PD (Stein, 2009) and is emerging as a DBS target for disabling gait and balance problems in PD and PSP.

Pedunculopontine Nucleus (PPN)-LDTC

Post-mortem PPN Cholinergic Losses in PD Fallers vs. PD Non-fallers

From: J Clin Invest. 2010 August 2; 120(8): 2746-2754.
Published online 2010 July 12. doi: 10.1172/JCI42642.
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Relationship between loss of PPN cholinergic neurons and balance deficits in human PD patients.
Karachi et al. JCI 2010
PPN/THALAMUS AChE in PD
FALLERS vs. NON-FALLERS:
IN VIVO vs. EX VIVO

Karachi et al. 2010

Cerebellum: DA vs. ACh

DA
ACh
What can we learn from animal lesioning studies?

Rats
Monkeys
### MPTP MONKEY STUDIES

(Karachi et al. 2010)

<table>
<thead>
<tr>
<th></th>
<th>SN DA</th>
<th>PPN ACh</th>
<th>NBM ACh</th>
<th>Clinical symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPTP young adult monkey</td>
<td>(&gt;-90%)</td>
<td>NML</td>
<td>NML</td>
<td>No balance &amp; postural deficits</td>
</tr>
<tr>
<td>MPTP old monkey</td>
<td>(&gt;-90%)</td>
<td>(&gt;-30%)</td>
<td>/ ?</td>
<td>Balance &amp; postural deficits</td>
</tr>
</tbody>
</table>

MPTP old monkey

Significant *akinesia* (decrease in global activity) in arm speed, in step speed during locomotion. The animals also displayed a *cogwheel* rigidity of the extremities, a decrease in step length and speed and an increase in the back curve, as in monkeys after PPN lesion. Symptoms were significantly reversed by apomorphine treatment.

PPN diphtheria toxin monkey*

Significant changes in *gait and posture* included a decrease in the angle of the knee and in step length and speed, an increase in the back curve, deviation of the hindquarters and of the head, modification of the tail position (*axial rigidity*), and arm and leg rigidity. Importantly, no major modification of global motor activity was detectable. No improvement with apomorphine.
### SINGLE vs. DUAL DA/ACh RAT LESION STUDIES (M. Sarter)

<table>
<thead>
<tr>
<th>DA Type</th>
<th>SN DA</th>
<th>PPN ACh</th>
<th>NBM ACh</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-OH DA lesion only</td>
<td>↓ NML</td>
<td>NML</td>
<td></td>
<td>Little effect on flat rod traversal but these animals exhibit an increase in slips if the rotating rod is sloped at 22.5°</td>
</tr>
<tr>
<td>SAP (IgG saporin)</td>
<td></td>
<td>↓ NML (30%)</td>
<td></td>
<td>Little impairment except for an increase in the number of falls when traversing the sloped, rotating rod.</td>
</tr>
<tr>
<td>DUAL 6-OH DA &amp; SAP NMB lesions</td>
<td>↓ (30%)</td>
<td>NML</td>
<td></td>
<td>Require more time to traverse the plank and are entirely unable to traverse the rotating rod (100% falls)</td>
</tr>
</tbody>
</table>

### DUAL STRIATAL DA & NBM ACH LESIONS

- Finding indicate overlapping or converging control of cue detection in attentional contexts by fronto-striatal DA and ACh cortical inputs. Loss of both projection systems augments the impairments in attentional performance when compared with deafferentation of just one system.

- Cognitive and psychomotor impairments resulting from central ACh decline interact synergistically with the cognitive and motor deficiencies caused by early striatal DA deafferentation.

*Courtesy of M. Sarter*
ABOUT 2/3 OF PD WITHOUT DEMENTIA HAVE NORMAL RANGE NEOCORTICAL OR THALAMIC AChE ACTIVITY

DA/ACh Loss and Walking Time in PD and Normal Elderly

<table>
<thead>
<tr>
<th>DA (Cortex)</th>
<th>ACh (Cortex)</th>
<th>Walking time</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL</td>
<td>NL</td>
<td>7.46 ± 1.30s</td>
</tr>
<tr>
<td>↓</td>
<td>NL</td>
<td>7.92 ± 1.72s</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
<td>9.34 ± 2.75s</td>
</tr>
</tbody>
</table>

Bohnen et al. Neurology 2009;73:1670-6
• Gait speed is not significantly slower than normal in subjects with PD with relatively isolated nigrostriatal dopaminergic denervation.

• Comorbid neocortical cholinergic denervation is a more robust marker of slowing of gait in PD than nigrostriatal denervation alone and may reflect failing (motor control) cognitive processing abilities during ambulation.

OLIGOSYSTEM vs. MULTISYSTEM DEGENERATION

Augmentation of Attentional and Cognitive Motor Deficits with Dual DA/ACh Pathology
• Normal aging is associated with 5%-8% loss of DA nerve terminals per adult decade.

• Co-morbid non-dopaminergic CNS changes (leukoaraiosis, cortical β-amyloid, anti-cholinergicity of polypharmacy) may synergistically interact with otherwise minor effects of DA-related mobility changes in “healthy” aging.

• Novel non-DA (anti-Aβ, vascular factors, cholinergic) therapies could provide new areas of mobility research in the elderly.

OLIGOSYSTEM vs MULTISYSTEM DEGENERATION: WHAT WE LEARN IN PD MAY APPLY TO “NORMAL” AGING
Mobility measures in the lab & in the field using body-worn and fixed sensor systems

Jeffrey M. Hausdorff, PhD
Laboratory for Gait & Neurodynamics, Tel-Aviv Sourasky Medical Center
Sackler Faculty of Medicine, Tel-Aviv University
Department of Medicine, Harvard Medical School
E-mail: JHAUSDOR@BIDMC.HARVARD.EDU

Isn’t gait speed enough?
In many disease states & aging, gait speed predicts:
• Health
• Function
• Utilization
• Disability
• Survival

Studenski et al., JAMA, 2011
Why study other aspects of mobility?

Key added value

Different gait & mobility properties may behave differently

Insights into mechanisms

Functional performance tests: Rationale

• Easy to implement in clinic or population studies
• Measures of physical fitness and general health
• Identification of risk factors
• Predict outcomes:
  e.g., falls, frailty, disability, nursing home admission
• Tailor exercise interventions
Performance-based tests of gait, mobility & fall risk

Timed Up and Go Test (TUG, TUGm, TUGc)
Tinetti Balance & Gait Test (aka POMA)
Dynamic Gait Index
Berg Balance Scale
BEST (mini-BEST)
Four Square Step Test
Short physical performance battery
Elderly Mobility Scale (EMS)
FICSIT-4

http://www.chcr.brown.edu/geriatric_assessment_tool_kit.pdf

Dynamic Gait Index (DGI)

<table>
<thead>
<tr>
<th>DGI items</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  walking at normal speed</td>
</tr>
<tr>
<td>2  walking at different speeds</td>
</tr>
<tr>
<td>3  walking with horizontal head movements</td>
</tr>
<tr>
<td>4  walking with vertical head movements</td>
</tr>
<tr>
<td>5  turning quickly</td>
</tr>
<tr>
<td>6  walking around an obstacle</td>
</tr>
<tr>
<td>7  walking over an obstacle</td>
</tr>
<tr>
<td>8  climbing a flight of stairs</td>
</tr>
</tbody>
</table>

• Developed to assess fall risk (Shumway-Cook & Woollacott, 1995)

• Sensitive to vestibular deficits (Whitney, Hudak & Marchetti, 2000; Hansson, 2007)

• Equipment needed: stopwatch, shoe boxes, stairs
DGI scores among 278 community living older adults

The DGI scores differed (p=0.029) in fallers (22.5±1.8) and non-fallers (23.0±1.4)
And differed in men and women

But there was a ceiling effect


Four Square Step Test

A timed test of abilities to step over & in different directions
Dite & Temple, 2002
Four Square Step Test: Responds to intervention

Effect of functional balance training in frail nursing home residents


Bio-engineering technology for assessing mobility: Rationale

- Quantitative
- Less floor / ceiling effects
- More reliable
- More sensitive
- Able to focus on distinct properties
- Episodic and continuous changes
Options for gait & mobility assessment using technology

• Fixed, lab-based systems
  • Motion capture systems
  • Balance platforms (static & dynamic)
  • Instrumented gait mats

• Wearable systems
  • Insoles
  • Accelerometers
  • Gyroscopes
  • Magnometers
  • Goniometers
  • Actigraphs

• Combined with physiologic monitoring

Laboratory, fixed-systems examples
Optical motion capture systems

- Gait analysis is the major application of motion capture in clinical medicine
- Clinicians can evaluate kinetics & kinematics across several biometric factors
- Enables surgeons to make decisions about muscle transfers (e.g., children with CP)

TE Lockhart et al., Effects of age-related gait changes on the biomechanics of slips and falls. Ergonomics. 2003

Stance time variability and mobility disability in older adults (n=544)

Brach et al, 2007
Hazard ratios for incident mobility disability associated with stance time variability

<table>
<thead>
<tr>
<th>Model</th>
<th>HR (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.27 (1.16, 1.39)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2</td>
<td>1.15 (1.03, 1.28)</td>
<td>.01</td>
</tr>
<tr>
<td>3</td>
<td>1.11 (1.00, 1.24)</td>
<td>.05</td>
</tr>
<tr>
<td>4</td>
<td>1.13 (1.01, 1.27)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Model 1: Stance time variability
Model 2: Model 1 + gait speed
Model 3: Model 2 + age, gender, and race
Model 4: Model 3 + chronic conditions, medications, health status, physical activity

Brach et al, 2007

Stance time variability related to CNS / cognitive function
Step width variability related to vision and sensation

Brach et al, 2008
Variability of gait and fall risk in The Einstein Aging Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fall risk</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed (cm/s)</td>
<td>1.05</td>
<td>0.25</td>
</tr>
<tr>
<td>Stride length (cm)</td>
<td>1.00</td>
<td>0.67</td>
</tr>
<tr>
<td>Swing phase (%)</td>
<td>0.90</td>
<td>0.64</td>
</tr>
<tr>
<td>Stride length variability (%)</td>
<td>1.13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Stride length variability had the best fit in the final models of predicting falls

J Verghese et al. JGMS 2009

Wearable systems examples
Increased DT gait variability predict future falls in older adults (n=250)

Predicting Falls over 2 Years

<table>
<thead>
<tr>
<th>Rate Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DT Gait Variability</td>
<td>1.14</td>
</tr>
</tbody>
</table>

Predicting Falls over 5 Years

<table>
<thead>
<tr>
<th>Rate Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic Gait Index</td>
<td>.88</td>
</tr>
<tr>
<td>DT Gait speed</td>
<td>.40</td>
</tr>
</tbody>
</table>

Common & distinct gait alterations in neurological diseases

Hausdorff et al., J Appl Physiol., 2000
Effects of **healthy aging** on gait: 
Sensitivity of fractal dynamics

**Hausdorff et al., J Appl Physiol., 1997**

---

**Post-stroke patients**
Impairments in bilateral coordination of gait:

PCI is independent of speed, variability & asymmetry

**R Meijer et al. JNER 2011**
Instrumenting functional-performance tests:
Example TUG (or iTUG)

A Weiss et al. Physio Meas, 2011

Gait changes associated with aging

Continuous
- Short stride
- Slow
- Shuffling
- Stooped
- Unsteady
- Fearful
- Reduced arm swing
- Asymmetric

Episodic
- Freezing (e.g., problems with gait initiation)
- Festination
- Near falls / missteps
- Falls
Quantifying mobility and near falls in at-home & daily life settings

Near Fall

Does gait measured in the lab really reflect gait in real life?
Does the context matter?

"Describing the adaptations made to suit the different environmental conditions ... is in its infancy.
The use of treadmill ... is clearly not suitable.
Even the traditional gait labs with ... straight even walkways ... may not suffice.
To simulate various environmental conditions ... will require creativity and new technology."

Aftab E. Patla (1991)

Curved path & straight line walking related to different cognitive constructs in older adults

Table 3: Linear Regression Model Summary for Straight- and Curved-Path Walking (N=106)

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Straight-Path Walking</th>
<th>Curved-Path Walking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (P)</td>
<td>β (P)</td>
</tr>
<tr>
<td>Age</td>
<td>- .324 (.001)</td>
<td>.363 (&lt;.001)</td>
</tr>
<tr>
<td>Sex</td>
<td>- .178 (.053)</td>
<td>.204 (.028)</td>
</tr>
<tr>
<td>DSST</td>
<td>236 (.015)*</td>
<td>-.171 (.077)</td>
</tr>
<tr>
<td>TMT-B-A</td>
<td>-.093 (.321)</td>
<td>.074 (.429)</td>
</tr>
</tbody>
</table>

A look into the horizon

Towards automated, at-home assessment of mobility

A Weiss et al. NNR, 2011
Automated assessment of mobility

**Long term raw acceleration**
- Gait variability measures
- Sensitive to pathology
- Quality of activity (not just quantity)
- Overall activity (not just specific event detection)

**Fallers vs. Non-Fallers**
**Quantity:** NS

**Quality:**
- Fallers gait more impaired,
- less balance control

**Different balance control strategies:**
- Fallers: higher ML, lower V variability

Quantifying mobility & fall risk in daily life using 3-day continuous accelerometer signals
Quantifying mobility & fall risk in daily life using 3-day continuous accelerometer signals

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Non-Fallers</th>
<th>Fallers</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method 1</td>
<td>5.9 ± 2.7</td>
<td>9.2 ± 4.0</td>
<td>0.008</td>
</tr>
<tr>
<td>Method 2</td>
<td>3.0 ± 1.1</td>
<td>3.1 ± 0.8</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Mean # missteps detected in 72 hours (SM windows/Gait windows)*100

Wearable device / Smart phone for detection and assistance +/- physiologic sensors

Increase in heart rate during freezing of gait

Bachlin et al., 2010

Maidan et al., 2010
Summary:
Gait has many distinct properties

- Speed
- Rhythm
- Variability
  - Stance width vs. stride time vs. ....
  - Medial-lateral vs. vertical (and anterior-posterior)
- Fractal dynamics
- Asymmetry
- Bi-lateral coordination
  (and this is focusing only on Center of Mass movement)

Summary & conclusions

- Many tools for quantifying gait and mobility.
- Technology & functional-performance tests offer “Added Value” in addition to gait speed.
- Multiple aspects of gait
  - With distinct properties and mechanisms
- Need to choose the appropriate features & tools based on:
  - Questions of interest
  - Cost (equipment, manpower)
  - Population
- Future: Need to further incorporate physiology, imaging and multi-parameter modeling; & real-world data

Charting New Frontiers in Aging
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Gal Sasson
Prof. Talma Hendler

Talia Herman
Moran Dorfman
Marina Brozgol
Aner Weiss
Leor Grundlinger
Eran Gazit
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Dr. Avram Schweiger (TA)
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Prof. Gammon Earhart (Wash U)
Prof. David Bennet (Rush)

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Laboratory for Gait & Neurodynamics
Department of Neurology
Tel Aviv Sourasky Medical Center

2012 CNS Workshop: Session 3
Tuesday, November 13, 2012
Using neuropsychological measures, dual-task paradigms and functional near infrared spectroscopy to determine cognitive and brain mechanisms of mobility

Roee Holtzer, PhD
Ferkauf Graduate School & Albert Einstein College of Medicine of Yeshiva University

Epidemiology & Public Health Consequences of Mobility Impairments in Aging

Gait impairment and falls result in:
- Loss of functional independence
- Increase risk of hospitalization, nursing home placement, and death
- Annual expenditures estimated to be 32 billion dollars by year 2020

(Verghese et al., 2006)
Mobility in Aging Is NOT Automatic

Identifying modifiable mechanisms of mobility-related decline and disability can lead to improved risk assessment and intervention procedures.

Multi-level Complementary Approach to Determine Cognitive Control of Mobility

Dual-task paradigms

Neuropsychological tests

fNIR
Gait performance: ability to walk in uninterrupted conditions

Gait adaptability: ability to maintain locomotion in the presence of cognitive and environmental perturbations

Dual-Task Paradigms: Causal Relationship Between Attention Resources and Gait

Dual-task cost \((100_{x,T} - 70_{x,T}) = 30\)

(Holtzer et al., 2006; 2012)
1. Lack of standardization and normative data but see:

Walking while talking: Investigation of alternate forms
Tamar C. Brandt 1, Moonyeon Oh-Park 2,6, Cuiling Wang 3, Rhee Holtzer 4, Joe Verghese 5,6
(Gait and Posture, 2012)

2. Practice and task order effects – often not adequately controlled for or described

3. Task selection and design – brief detour

4. Dual-task strategy and prioritization

5. Using dual-task performance to predict functional outcomes
Dual-Task Paradigms: Task Design & Selection

(Holtzer et al., Memory & Cognition, 2004)

Memory

Attention/EF

(Holtzer et al., Neuropsychology, 2005)

Orthogonalized CI:
β = .764, p = 0.004

(Holtzer & Foley; Journal of Neurological Sciences, 2009)
Dual-Task Paradigms: Task Design & Selection

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-T vs. D-T Letters</td>
<td>-35.13</td>
<td>-37.67</td>
<td>-32.60</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>S-T vs. D-T Serial 7s</td>
<td>-4.98</td>
<td>-6.94</td>
<td>-3.03</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>D-T Letters vs. D-T Serial 7s</td>
<td>-10.15</td>
<td>-12.69</td>
<td>-7.62</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

It is critical to evaluate:
1. Performance on the cognitive interference task
2. Relationship of the decline in performance between the cognitive and gait
**Dual-Task: Strategies & Prioritization**

Changing instructions while maintaining the same cognitive and motor tasks on WWT in older adults result in task prioritization effects (Verghese et al., 2007)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WWR Velocity (cm/s)</td>
<td>20.77 *</td>
<td>5.03</td>
<td>36.52</td>
<td>.010</td>
</tr>
<tr>
<td>Stride Length Variability</td>
<td>-3.92 *</td>
<td>-6.34</td>
<td>-1.50</td>
<td>.002</td>
</tr>
</tbody>
</table>

(Yoge Seligmann et al., Movement Disorders, 2012)

---

**Dual-Task Paradigms: Predicting Outcomes**

Mobility Stress Test Approach to Predicting Frailty, Disability, and Mortality in High-Functioning Older Adults

Joe Verghese, MBBS, * Rose Holtzer, PhD, + Richard B. Lipton, MD, ++ and Cading Wang, PhD

*Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA
+Department of Neurology, University of California, San Francisco, CA
++Department of Neurology, University of California, San Francisco, CA

Table 2. Association Between Study Predictors and Frailty, Disability, and Death

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% Confidence Interval), P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hazard Rate (95% Confidence Interval), P Values</strong></td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td>Adj. for Age, Sex, &amp; Education, Multivariate Adjustment*</td>
</tr>
<tr>
<td>WWT speed (10 cm/s change)</td>
<td>1.12 (1.06-1.18), &lt;.001</td>
</tr>
<tr>
<td>PPDR (1-point change)</td>
<td>1.19 (1.10-1.30), &lt;.001</td>
</tr>
<tr>
<td>Disability</td>
<td>Adj. for Age, Sex, &amp; Education, Multivariate Adjustment*</td>
</tr>
<tr>
<td>WWT speed (10 cm/s change)</td>
<td>1.13 (1.03-1.23), &lt;.007</td>
</tr>
<tr>
<td>PPDR (1-point change)</td>
<td>1.23 (1.11-1.36), &lt;.001</td>
</tr>
<tr>
<td>Death</td>
<td>Adj. for Age, Sex, &amp; Education, Multivariate Adjustment*</td>
</tr>
<tr>
<td>WWT speed (10 cm/s change)</td>
<td>1.13 (1.01-1.27), .04</td>
</tr>
<tr>
<td>PPDR (1-point change)</td>
<td>1.23 (1.09-1.40), .04</td>
</tr>
</tbody>
</table>

(Verghese et al., 2002)
**Neuropsychological Approach**

Neuropsychological tests: (1) standardized administration; (2) established reliability, validity and normative samples; (3) optimal for replication studies

<table>
<thead>
<tr>
<th>NP Tests</th>
<th>verbal IQ</th>
<th>executive attention</th>
<th>memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocabulary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block Design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Symbol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails A (time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails B (time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FCSRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C - Fluency</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

61%-65% of the variance of the NP battery

Holtzer et al, Neuropsychology, 2006
Holtzer et al, Neuropsychology, 2007
Holtzer et al, Archives of Clinical Neuropsychology, 2008
Holtzer et al, JAMA, 2008
Holtzer et al, Neurobiology of Aging, 2010
Holtzer et al, Motor Control, 2012

**Neuropsychological Approach**

<table>
<thead>
<tr>
<th>Normal Pace Walk</th>
<th>Factor</th>
<th>B</th>
<th>B</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive/attention</td>
<td>.20</td>
<td>4.6</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>.16</td>
<td>3.8</td>
<td>.015</td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>.16</td>
<td>3.9</td>
<td>.016</td>
<td></td>
</tr>
<tr>
<td>Walking While Talking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive/attention</td>
<td>.18</td>
<td>4.6</td>
<td>.011</td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>.15</td>
<td>3.7</td>
<td>.022</td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>.074</td>
<td>1.8</td>
<td>.303</td>
<td></td>
</tr>
</tbody>
</table>

(Adjusted for demographic & medical covariates & gait abnormality)

### Neuropsychological Approach

| Factor              | Single falls | Recurrent falls | | | |
|---------------------|--------------|----------------|----|----|
| Executive/attention | .52          | .31 - .88      | <.01 | .34 | .18 - .77 | <.05 |
| Memory              | 1.5          | .93 - 2.4      | ns  | 1.03 | .51 – 2.1 | ns  |
| Verbal IQ           | 1.02         | .54 -1.9       | ns  | .21  | .08 - .56 | <.05 |

(Adjusted for demographic & medical covariates & gait abnormality)

(Holtzer et al., Neuropsychology, 2007)

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### Neuropsychological Approach

<table>
<thead>
<tr>
<th></th>
<th>Velocity</th>
<th>Cadence</th>
<th>CV Stride Length</th>
<th>Secondary task</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S/T</td>
<td>D/T</td>
<td>S/T</td>
<td>D/T</td>
</tr>
<tr>
<td>Executive/Attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Adjusted for demographic & medical covariates & falls history)

(Holtzer, et al. Motor Control, 2012)
Neuropsychological Approach

Who are the individuals who benefit from or utilize more effectively attention resources to slow down gait decline?
Cognitive reserve as a moderator

(Holtzer et al., JAGS 2012)
Functional Neuroimaging During Mobility: fNIRS

Structural MRI studies suggest that frontal and subcortical regions and their connections are related to mobility in older adults (Rosano et al., 2006; 2007; 2012)

However, the functional brain correlates of normal pace walking and walking while talking are poorly understood

---

Functional Neuroimaging During Mobility: fNIRS

Portable, safe, affordable and negligibly intrusive monitoring system, which enables the study of cortical activation-related hemodynamic changes in natural environments and various field conditions
Physical Principles of fNIR: Hemodynamic Response & Near Infrared Light

Photons that enter the tissue undergo two types of interaction:

- Scattering (cell membranes)
- Absorption (Hb, HbO2, water)

CW-fNIR System Monitoring Areas

PFC Brodman's Areas: 10, 9, 45, 46
Functional Neuroimaging During Mobility: fNIRS

Increased oxygenation levels in the PFC during WWT compared with NW provide first evidence that the PFC plays a key role in monitoring and allocating cognitive resources during attention-demanding locomotion tasks.

Future Directions

fMRI: imagery paradigm

WWT>T

- Left Inferior Frontal Gyrus (VLPFC)
- Right Middle Frontal Gyrus (DLPFC)

WWT>W&T

- Right Superior Frontal Gyrus (DLPFC), but also extends into Supplementary Motor, Frontal Eye Fields, and Anterior Cingulate
- Right Superior & Middle Frontal Gyres (DLPFC)
Contributors and Support for This Work

- National Institute on Aging and AFAR Paul B. Beeson Award (K23 AG030857) and grant R01AG036921
- Joe Verghese, Albert Einstein College of Medicine
- Jeannette Mahoney, Albert Einstein College of Medicine
- Helena Blumen, Albert Einstein College of Medicine
- Optical Brain Imaging group at Drexel University
- The Einstein Aging Study is supported by the National Institute on Aging program project grant (AG03949)
- Our research team & graduate students
- Wen Chen: NIA
- THE PARTICIPANTS
Statistical and Mathematical Modeling Approaches to Multisystem Studies

Heather Allore, PhD
Yale School of Medicine

Outline

• Single-system studies
• Multisystem studies
  – Structural equation models
  – Joint models
  – Network models
Session 3: Tools and Methods

What is the current state of tools and methods for assessing the relationship between CNS and mobility in the elderly?

What are new directions?

Speakers
Nicolaas I. Bohnen, MD, PhD: University of Michigan
Jeffrey M. Hausdorff, PhD: Harvard Medical School
Roee Holtzer, PhD: Albert Einstein College of Medicine
Heather Allore, PhD: Yale School of Medicine

Moderator
Howard Aizenstein, MD, PhD: University of Pittsburgh

N. Bohnen: Structure, neurochemistry, and function of CNS components related to mobility

PET imaging and animal lesion studies allow for detailed description of the relationships of dopamine and Ach circuits to mobility impairments.

DA-related changes appear to interact with other non-dopaminergic CNS changes (WMH, amyloid, ACh).

Underscores importance of multimodal studies that take into account multiple pathways to mobility impairment.
J. Hausdorff: Mobility measures in the laboratory and in the field using body-worn and fixed sensor systems

Bio-engineering methods for measuring gait and mobility properties

Added value over gait speed, and insight into mechanism

Context matters, so important to simulate environmental conditions, and development of wearable devices

R. Holtzer: Using neuropsychological measures, dual-task paradigms and fNIRS to determine cognitive and brain mechanisms of mobility

Multi-level complementary approach to determine cognitive control of mobility.

Dual task: allows study of interaction of attention and gait

Neuropsychological testing provides standardized and normed performance measures

Functional near infrared spectroscopy (fNIRS) is non-intrusive method for measuring cortical activity
H. Allore: Statistical and mathematical modeling approaches to multisystem studies

Single-system studies ignore potential interrelationships among multiple simple systems

Several approaches for multiple-system studies:

- Structural equation: hypothesis driven diagram of potential interrelationships
- Joint models: association structure among responses, combines univariate mixed-effects models
- Network models: biologically plausible models versus artificial neural networks used as an engineering optimization tool

Importance of proper multiple comparisons correction.

Thank You
Additional Resources


Junior Investigator Late Breaker Travel Awardees and Semi-Finalists

**Benjamin D. Capistrant, ScD**  
Postdoctoral Fellow  
Carolina Population Center  
University of North Carolina, Chapel Hill  
Chapel Hill, North Carolina

Late Breaker Abstract: Cognitive Status and Mobility in Low- and Middle-Income Countries: Evidence From the Study on Ageing and Adult Health (SAGE)

**Yi-Fang Chuang, MD, PhD**  
Research Fellow  
Department of Mental Health  
Johns Hopkins Bloomberg School of Public Health  
Columbia, New York

Late Breaker Abstract: The Association Between Aggregate Cardiovascular Risk and Regional Brain Volume Changes in Older Adults

**Jason R. Gerstner, PhD**  
Research Fellow  
Center for Sleep and Circadian Neurobiology  
Perelman School of Medicine  
University of Pennsylvania Translational Research Laboratories  
Philadelphia, Pennsylvania

Late Breaker Abstract: Fabp Expression Rescues Amyloid-beta Induced Sleep Fragmentation in *Drosophila*

**Gurtej Singh Grewal, PhD**  
Research Fellow  
Interdisciplinary Consortium on Advanced Motion Performance  
Southern Arizona Limb Salvage Alliance  
University of Arizona College of Medicine  
Tucson, Arizona

Late Breaker Abstract: Virtual Reality — An Objective and Safe Tool for Early Diagnosis of Peripheral Neuropathy Virtualization of Exercise: An Innovative Ankle Exercise Paradigm Based on Virtual Reality for Improving Balance in Diabetes
**Azizah J. Jor’dan, PhD**  
Research Fellow  
Syncope and Falls in the Elderly (SAFE) Laboratory  
Harvard Medical School  
Beth Israel Deaconess Medical Center  
Boston, Massachusetts  

Late Breaker Abstract: The Impact of Cerebral Vasoreactivity on Gait Speed in Older Adults With and Without Type 2 Diabetes Mellitus

---

**Jeannette R. Mahoney, PhD**  
Neuropsychology Instructor  
Division of Cognitive and Motor Aging  
Albert Einstein College of Medicine  
Bronx, New York  

Late Breaker Abstract: Visual-Somatosensory Integration in Aging: Linking RT Facilitation to Balance

---

**Ha Nguyen, PhD, MPH**  
Assistant Professor  
Department of Family and Community Medicine  
Wake Forest School of Medicine  
Winston-Salem, North Carolina  

Late Breaker Abstract: Gait Velocity and Cognitive Function in Older Hispanic Americans and Adults in Vietnam: A Cross-Cultural Study

---

**Michael Schwenk, PhD**  
Research Fellow  
Interdisciplinary Consortium on Advanced Motion Performance  
Southern Arizona Limb Salvage Alliance  
Arizona Center on Aging  
University of Arizona College of Medicine  
Tucson, Arizona  

Late Breaker Abstract: Sensor-Derived Physical Activity Parameters Predict Future Falls in Individuals With Dementia Association Between In-Clinic Physical Performance Measures and Spontaneous Daily Physical Activity in Older Adults

---

**Sarinnapha (Fah) Vasunilashorn, PhD**  
Postdoctoral Research Associate  
Office of Population Research  
Princeton University  
Princeton, New Jersey  

Late Breaker Abstract: Overweight in Adolescence Is Associated With Later Life Functional Limitations
Late Breaker Abstract: Animal Frolics: Acceptability and Benefits in a U.S. Sample

Semi-Finalists

David Clark  
Malcom Randall VA Medical Center and University of Florida

Christine Gould  
VA Palo Alto Health Care System, Geriatric Research Education and Clinical Center

Christina Hugenschmidt  
Wake Forest School of Medicine, Section on Gerontology & Geriatric Medicine, Sticht Center on Aging

Bryan James  
Rush Alzheimer’s Disease Center

Brad Manor  
Harvard Medical School

Neelesh Nadkarni  
University of Pittsburgh

Paula Rist  
Brigham and Women’s Hospital, Harvard Medical School
Optimal Aging
Through Research

GSA Annual Scientific Meeting

NOVEMBER 20–24, 2013
Sheraton New Orleans • New Orleans Marriott

This Continuing Educational activity is jointly sponsored by The Annenberg Center for Health Sciences at Eisenhower and The Gerontological Society of America.